Are you participating in any other research studies? _____ Yes _____No

PURPOSE OF RESEARCH

You are being asked to take part in this research study because you have advanced cancer that is no longer responsive to standard anti-cancer therapies of proven effectiveness and for which new therapies need to be developed.

There are two parts to this study, Cohort 1 and Cohort 2. Cohort 2 has closed. Only Cohort 1 is active, which will be explained throughout this consent form. In Cohort 1, the study team hopes to learn if utomilumab (also known as PF-05082566), plus ado-trastuzumab emtansine (referred to in this document as T-DM1, also known as Kadcyla), is safe at several doses of utomilumab, and if there is any beneficial effect of the combination at those doses.

Utomilumab is a new investigational drug. An investigational drug is one that is currently not approved for sale in this country. Utomilumab is an antibody, a type of protein, which has been shown in animal studies to stimulate the immune system. Because this is a research study, utomilumab will be given to you only during this study and not after the study is over.

There may be up to about 25 people enrolled into this study. At this time, participants are only enrolling to Cohort 1, utomilumab 100 mg in combination with T-DM1 (3.6 mg/kg). The study is being performed at Stanford University, but other sites may eventually participate.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

DURATION OF STUDY INVOLVEMENT

Your participation will last up to about 24 cycles, including up to 18 months of treatment. There will be a 28-day screening period, up to 24 cycles of treatment (each cycle is about 21 days) of treatment and a follow-up period for up to 60 days after the last dose of study drug. Additional treatment after 24 cycles (about 18 months) may be allowed based on the doctor's judgment. Overall, this research study will be conducted over about 3 years.

PROCEDURES

The study will begin with a screening visit. The purpose of the screening visit is to find out if you meet all of the requirements to take part in this research study. The screening visit procedures will be made within the 28 days before the first day of study treatment. A summary of the procedures included in the screening visit is included in the assessments listed below. By the end of the screening visit, the study doctor will determine if you are eligible to continue into the study. If you will not be able to continue in the study, the study doctor will explain why and will discuss with you other treatment options.

Study Treatment

In this study, you will receive 100 mg of utomilumab plus T-DM1 3.6 mg/kg.

Assessments During the Study

The following tests/procedures will be done during this study:

- Informed Consent: You will be asked to sign this consent form (performed at Screening).
- Medical and Tumor History: The study staff will ask you questions about your medical history including oncology history, information on prior treatment regimens. (performed at Screening)
- Physical Exam: Includes an exam of major body systems. Height will be recorded only one time at first exam. Weight will be recorded at Screening, within 7 days before the dose on Day 1 of each treatment cycle (performed at Screening; Day 0 of Cycle 1 and above; End of Treatment visit; Follow-up visit.)
- A measure of your activity level (performed at Screening; Day 0 of Cycle 1 and above; End of Treatment visit; Follow-up visit.)
- Vital signs including blood pressure and pulse (Performed at Screening; Cycle 1 Days 0, 1, 8 and 15; Cycle 2 Day 1; Cycle ≥ 3 Day 1; End of Treatment visit; Follow-up.)
- ECG: Measures the electrical activity in your heart. (Performed at Screening; Cycle 1 Day 0; Cycle 2, Day 1; End of Treatment Visit; Follow-up.)
- Blood tests for hematology and chemistry are considered “safety lab tests” to make sure your organs are functioning properly. (Performed weekly. Specific visits include Screening; Cycle 1 Days 0, 1, 8 and 15; Cycles 2 Day 1, 8, 15; Cycle ≥ 3 and above at Day 1; End of Treatment visit; and Follow up visit. About 1 tablespoon (15 mL) will be collected each time.
- Blood tests for coagulation are to measure your blood’s ability to clot and will also be included in the hematology and chemistry blood draws (Screening; Cycle 1 and above: Days 1; End of Treatment visit; and Follow-up visit.
- Urine Test (Screening, End of Treatment Visit, and Follow Up).
- Blood test for Hepatitis B and C will be taken at screening (2 teaspoons).
- Pregnancy Test (Performed at Screening; Cycle 1 above: Day 1; End of Treatment Visit; Follow Up and additional whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected).
- Blood test for endocrine function. It will be 1 teaspoon (5 mL). (Screening. If your doctor believes it is necessary it may be measured again during the study).

- Left ventricular ejection fraction (LVEF) assessment. LEVF is a test of heart function, and will be performed at screening; at Cycle 5 Day 1 (± 7 days); every 4 cycles (± 7 days) thereafter; and at end of treatment.
- Utomilumab administration: Treatment will be administered in a 3-week cycle (ie, 21-day cycle). Utomilumab will be administered as a 1-hour intravenous infusion on Day 1 of each cycle. When both utomilumab and T-DM1 are administered, T-DM1 will be administered first, followed within 30 minutes (± 10 minutes) by utomilumab infusion.
- T-DM1 administration: Treatment will be administered in a 3-week cycle (ie, 21-day cycle). The first infusion of T-DM1 on-study will be over 90 minutes (± 30 minutes), on Cycle 1 Day 0. Subsequent infusions at the beginning of each cycle will be administered over 30 ± 15 minutes as tolerated.
- An MRI or a CT scan is to be done approximately every 9 weeks starting at screening. An MRI or CT will be repeated at the end of the study if more than 9 weeks have passed since the last evaluation. MRIs are a series of pictures taken while you lie on a narrow bed inside of a large magnet. CTs or "CAT" scans are a series of X-rays that will be passed through your body while you lie inside a machine.
- Blood tests to see how fast your body eliminates utomilumab. Blood samples [about ½ teaspoon (2 mL) whole blood at each time point] will be collected as follow: Cycles 1 to 3 on Day 1 at pre-dose and at the end of utomilumab infusion; From Cycle 4 onwards, it will be collected on Day 1 at pre-dose of every 3 cycles (eg, Cycle 4; Cycle 7; Cycle 10; etc). For patients discontinuing from the study, a blood sample to determine the levels of study drug in the blood (pharmacokinetics, PK) should be collected at the End of Treatment assessment.
- Blood tests to see how fast your body eliminates TDM1. Blood samples will be collected as follows: Cycle1 on Day 0 at pre-dose and at the end of T-DM1 infusion; Cycle 2 to 3 on Day 1 at pre-dose and at the end of T-DM1 infusion. From Cycle 4 onwards, it will be collected on Day 1 at pre-dose of every 3 cycles (eg, Cycle 4; Cycle 7; Cycle 10; etc). For patients discontinuing from the study, a PK sample should be collected at the End of Treatment assessment.
- Blood tests to assess the level of immune activation within your body at screening, cycles 1 on Day 0, at pre-dose and at the end of infusion of T-DM1, Cycles 1 on Day 1 at pre-dose and at the end of infusion of utomilumab, on Day 8 and Day 15 of Cycle 1, on Day 1 of Cycle 2 at pre-dose; at end of treatment.
- Blood for Exploratory Biomarkers: About 2 tablespoons (28 mL) blood will be collected at Screening, on Cycles 2 on Day 1 at pre-dose, and at end of treatment.
- Blood for Pharmacodynamic Assessment of Lymphocyte Subpopulations: Blood samples [about 1½ teaspoons (7.5 mL) whole blood at each time point] will be collected at Screening, on Cycles 2 on Day 1 at pre-dose, and at end of treatment.

- Blood for utomilumab Immunogenicity Testing: Blood samples [about ½ teaspoon (2 mL) whole blood at each time point] for test to determine if you are making antibodies against the study drug utomilumab ("immunogenicity testing") will be collected on Cycles 1 to 3 on Day 1 at pre-dose. From Cycle 4 onwards, blood samples will be collected on Day 1 at pre-dose every 4 cycles (eg, Cycle 8, Cycle 12, Cycle 16, etc.). For patients discontinuing study drug treatment, immunogenicity samples should be collected at the End of Treatment and at Follow Up. If anti-drug antibodies (ADAs) are detected, additional samples may be collected approximately every 9 weeks (coinciding with disease assessment visit) until ADA levels return to baseline.
- Blood for T-DM1 Immunogenicity Testing: Blood samples [about ½ teaspoon (2 mL) whole blood at each time point] for T-DM1 immunogenicity testing will be collected on Cycles 1 on Day 0 at pre-dose and on Cycle 2 to 3 on Day 1 at pre-dose. From Cycle 4 onwards, blood samples will be collected on Day 1 at pre-dose every 4 cycles (eg, Cycle 8, Cycle 12, Cycle 16, etc.). For patients discontinuing study drug treatment, immunogenicity samples should be collected at the End of Treatment and at Follow Up. If ADAs are detected, additional samples may be collected approximately every 9 weeks (coinciding with disease assessment visit) until ADA levels return to baseline.
- Optional tumor biopsy for biomarker assessment: A recent tumor biopsy must be provided at enrollment. An archival biopsy may be acceptable if it is recent and no anti-tumor therapy has been administered between collection and enrollment in this study. (See below section on Optional Tumor Biopsy for Research).
- Signs and symptoms of adverse side effects: You will be asked about changes to your health and any toxicities you may experience due to the study drugs. This will be done continuously throughout the study.
- Review of your medications will be done continuously throughout the study from 28 days prior to the start of the study treatment and up to 28 days after the last dose of the study treatment.

<u>End of Treatment Assessments</u>

Within 28 days after the last dose of the study drug you will have a series of assessments described in the list above. This is to assess your health and any toxicities you may be experiencing as a result of the study procedures.

<u>Follow-Up Assessments</u>

Once your treatment is discontinued, you will enter into a follow-up period. An MRI or CT scan will be done approximately every 9 weeks, until your disease has progressed or you begin any anti-cancer therapy. If you have any toxicities that are continuing at this point, you will continue to be followed at least every 4 weeks until resolution or until your doctor decides. You will then be contacted to assess how you are doing. The follow-up period will last from 60 days to 6 months from the date of the last dose of the study drug if you do not have disease progression or a new anticancer therapy.

Optional Tumor Biopsy for Research

Research using tissue and blood samples is an important way to try to understand human disease. The investigators want to include your tumor samples in additional research. There are several things you should know before allowing your tissues to be studied.

Participation in the additional research is voluntary. You do not have to provide any reason for your decision, no matter what that decision is. You may also continue to participate in the main study if you decide not to include your blood and tissue in this research.

The tumor tissue taken will be used to evaluate DNA, RNA, protein or metabolite (a metabolite is produced by the action of proteins or the break-down of food, drugs and naturally occurring substances) patterns among patients with cancer. This can help us understand how different patients respond to utomilumab. One tumor sample be collected at the start of the trial. Another tumor sample will be collected at Cycle 3, Day 1 if feasible.

Your blood will be stored under a unique code number associated with the study and linked to your personal identifiers, such as your name or medical record number. Because the samples are linked, you have the right to withdraw consent for the usage of these samples at any time. You may withdraw from this study at any time. The investigators might retain the identified samples, eg, as part of your routine clinical care, but not for additional research. Any samples left over will be destroyed at the end of the study.

Any tissues you have donated which are used in research may result in new products, tests or discoveries. In some instances, these may have potential commercial value and may be developed and owned by the Investigators, Stanford University and/or others. However, donors of tissues do not retain any property rights to the materials. Therefore, you would not share in any financial benefits from these products, tests or discoveries.

<u>Tissue Sampling and Genetic Testing</u>

As part of the research studies on your tumor samples, the Investigators will do genetic testing. Genetic testing is research that studies genes, including gene characteristics and gene versions that are transmitted by parents to children. Your genes can affect how your body responds to a medication or how it converts it.

Genetic research raises certain questions about informing you of any results. Possible risks of knowing results include: anxiety; other psychological distress; and the possibility of insurance and job discrimination. A possible risk of not knowing includes being unaware of the need for treatment. These risks can change depending on the results of the research and whether there is a treatment or cure for a particular disease.

Sometimes patients have been required to furnish information from genetic testing for health insurance, life insurance, and/or a job. A Federal law, the Genetic Information Nondiscrimination Act of 2008 (GINA), generally makes it illegal for health insurance companies, group health plans, and employers with 15 or more employees to discriminate against you based on your genetic information. This Federal law does not protect you against

genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

The results of the genetic testing of your blood sample from this project will be used for research purposes only, and you will not be told the results of the tests. You will not directly benefit from your participation in this genetic testing, but you might help scientists understand why people respond differently to the study medication or convert it differently. The study could also help to identify the type of person who is most likely to benefit from the study medication or develop side effects.

Please indicate your wish to participate in these optional tumor sample by checking the appropriate yes or no box.

☐ **I choose to participate in the optional tumor sample for DNA, RNA, Protein and Metabolite Evaluation.**

☐ **I choose NOT to participate in the optional tumor sample for DNA, RNA, Protein and Metabolite Evaluation.**

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Tell the Protocol Director or research staff if you believe you might be pregnant or gotten your partner pregnant.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

While participating in this research study, you should not take part in any other research project without approval from the Protocol Directors of each study. This is to protect you from possible injury arising from such things as extra blood drawing, extra X-rays, the possible interaction(s) of research drugs, or other similar hazards.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify George Sledge, MD at XXX-XXX-XXXX.

The Protocol Director may also withdraw you from the study and the study medication may be stopped without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff;
- The study doctor decides that the study is not in your best interest;
- The study is stopped by the study investigator, the institutional review board (IRB) (a group of people who review the research to protect your rights), by a regulatory agency, or by the drug manufacturer, Pfizer;
- You become pregnant, intend to become pregnant or are nursing a child during this study;
- You need treatment not allowed in the study;
- Unanticipated circumstances.

If you leave the study for any reason, the study doctor may ask you to have tests before you are released from the study for your safety. They are designated as "End of Treatment Visit" above.

If you withdraw or are removed from the study, biological samples (for example, blood or urine samples) that have been collected from you can be withdrawn if they have not yet been analyzed or destroyed. If you want your samples withdrawn, you must tell the study team before or at the time you leave the study.

We will tell you if we learn new information that could change your mind about taking part in this research study. If you want to drop out, you should tell us. We will make sure you can end the study in the safest way. We will also talk to you about follow-up care, if needed.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

Any research has some risks, which may include things that could make you sick, make you feel uncomfortable, or hurt you. You might experience negative effects related to the study drug while participating in the study. All research participants taking part in the study will be watched carefully for any negative effects; however, the study team does not know all the effects that the study drug may have on you. The study team may give you medicines to help reduce negative effects. These effects may be mild or serious. Many side effects go away when treatment is stopped, but in some cases, it is possible that the side effects could be serious, long lasting, permanent, or may even be life threatening or fatal. You should discuss these with your study doctor.

The negative events that are the most likely to happen to you if you take part in this study are listed below. The study drugs and procedures in this study may have risks that are not known at this time. You will be told in a timely manner of new information that may affect whether you will want to continue to participate in this study. It is important that you report all symptoms and side effects that you experience as soon as they occur, whether or not you think they are caused by the study drug. The phone numbers for the study team are listed in this document.

Potential side effects of utomilumab:

Utomilumab has been administered as a single agent or in combination to over 390 participants with advanced cancer at dose levels between 0.006 and 10.0 mg/kg. Frequent adverse events, regardless of relationship to treatment, that occurred in people receiving utomilumab in clinical studies, are listed in the following tables.

Most Common Adverse Events (occurred in 10% or more of people taking utomilumab as a single agent, regardless of causality)

• Fatigue (30%)	• Diarrhea (13%)
• Nausea (21%)	• Dizziness (12%)
• Appetite decreased (16%)	• Anemia (12%)
• Abdominal pain (14%)	• Constipation (12%)
• Fever (pyrexia) (14%)	• Labored breathing (dyspnea) (11%)
• Vomiting (13%)	• Back pain (10%)

The most commonly reported adverse events caused by utomilumab, reported in ≥ 10% of participants was fatigue (13%) (all grades). Treatment-related AEs were mostly Grade 1 or 2 with only five Grade 3/4 AEs reported (colitis; diarrhea; fatigue; hyperbilirubinemia; and hyponatremia). No fatal treatment-related AEs were observed.

There were 4 deaths during utomilumab treatment, caused by disease progression (3) and respiratory failure. These deaths were not considered related to utomilumab.

Most Common Adverse Events [occurred in 10% or more of people receiving utomilumab + rituximab (Rituxan), regardless of causality]

• Fatigue (27%)	• Diarrhea (12%)
• Infusion-related reaction (24%)	• Blood creatinine increased (10%)
• Cough (18%)	• Nausea (10%)
• Headache (15%)	• Back pain (10%)
• Fever (pyrexia) (13%)	• Muscle pain (myalgia (10%)
• Upper respiratory tract infection (13%)	

The most commonly reported adverse event caused by utomilumab + rituximab combination treatment was fatigue (9%). Treatment-related AEs were mostly Grade 1 or Grade 2. Two Grade 3 AEs were related to utomilumab (diarrhea and neutropenia). Grade 3/4 AEs were limited to a single event of neutrophil count decreased. No fatal treatment-related AEs were observed.

There was 1 death during treatment, caused by disease progression. This was not considered related to utomilumab.

Most Common Adverse Events [occurred in 10% or more of people receiving utomilumab + pembrolizumab (Keytruda), regardless of causality]

23 study participants with solid tumors were treated with the combination of utomilumab and 2 mg/kg pembrolizumab (Keytruda). Utomilumab was administered at 0.45 mg/kg; 0.9 mg/kg; 1.8 mg/kg; 3.6 mg/kg; and 5 mg/kg.

- Fatigue (44%)
- Cough (35%)
- Nausea (35%)
- Decreased appetite (30%)
- Constipation (26%)
- Pruritus (26%)
- Rash maculo-papular (26%)
- Vomiting (26%)
- Anemia (22%)
- Pyrexia (22%)
- Back pain (17%)
- Dyspepsia (17%)
- Rash (17%)
- Upper respiratory tract infection (17%);
- Alanine aminotransferase increased (13%)
- Arthralgia (13%)
- Asthenia (13%)
- Dry mouth (13%)
- Dry skin (13%)
- Dyspnea (13%)
- Edema peripheral (13%)
- Fall (13%)
- Hemoptysis (13%)
- Hypokalemia (13%)
- Hyponatremia (13%)
- Muscle spasms (13%)
- Musculoskeletal chest pain (13%)
- Pleural effusion (13%)
- Pneumonia (13%)
- Sinusitis (13%)
- Stomatitis (13%)

Most Common Treatment-related Adverse Events (occurred in 10% or more of people receiving utomilumab + pembrolizumab)

- Fatigue (35%)
- Rash maculo papular (26%)
- Pruritus (22%)
- Pyrexia (17%)
- Nausea (13%)
- Decreased appetite (13%)
- Dry skin (13%)
- Dry mouth (13%)

Treatment-related AEs were mostly Grade 1 or Grade 2. There were only 2 treatment-related Grade 3 AEs in participants receiving utomilumab + pembrolizumab combination treatment, adrenal insufficiency (1 participant) and hypokalemia (1 participant). No life-threatening or fatal treatment-related AEs were observed.

There was one Grade 5 AE (death) reported, (due to disease progression), which was considered not related to the study drug.

Most Common Adverse Events (occurred in 10% or more of people receiving utomilumab + mogamulizumab (Poteligeo), regardless of causality)

48 study participants with solid tumors were treated with the combination of utomilumab and mogamulizumab (Poteligeo), with the participants receiving either 1 mg/kg or 2 mg/kg mogamulizumab (24 participants each). Utomilumab was administered at 4 dose levels, 1.2 mg/kg; 2.4 mg/kg; 5 mg/kg; and 100 mg fixed dose.

• Fatigue (42%) • Rash (29%) • Constipation (21%) • Nausea (21%) • Diarrhea (21%) • Pyrexia (21%) • Appetite decreased (17%) • Pruritus (17%) • Anemia (17%) • Dyspnea (17%)	• Headache (17%) • Dreams abnormal (13%) • Chills (13%) • Cough (13%) • Dehydration (13%) • Infusion-related reaction (13%) • Insomnia (13%) • Lymphocyte count decreased (13%) • Rhinorrhea (13%)

Most Common Treatment-related Adverse Events (occurred in 10% or more of people receiving utomilumab + mogamulizumab)

• Fatigue (25%) • Rash (25%) • Diarrhea (21%) • Nausea (21%)	• Pyrexia (21%) • Abnormal dreams (13%) • Infusion-related reaction (13%) • Pruritus (13%)

Most treatment-related TEAEs were Grade 1 or 2 in severity. No Grade 5 treatment-related AEs were observed.

There were no fatal 5 AEs reported in this study.

Discontinuations Due to Adverse Events

Utomilumab as a single agent

15 adverse events reported in 13 participants that led to permanent discontinuation from treatment with utomilumab. Only 1 participant (metastatic melanoma) treated at 1.2 mg/kg utomilumab permanently discontinued treatment with utomilumab, due to a Grade 2 AE of enterocolitis considered related to treatment.

Utomilumab + mogamulizumab combination treatment

1 participant permanently discontinued from treatment due to treatment-related Grade 3 pneumonitis.

Serious Adverse Events

Utomilumab + rituximab combination treatment

34 participants who received utomilumab in the utomilumab + rituximab combination study experienced 41 serious adverse events (SAEs) (regardless of causality), including 1 event each of colitis, diarrhea, enterocolitis, hyperbilirubinemia, decreased appetite, dehydration and pneumonitis that were considered treatment-related. Utomilumab manufacturer Pfizer does not consider it a reasonable possibility that the event of hyperbilirubinemia was caused by utomilumab because of the presence of progressive disease (cancer metastases).

Utomilumab + pembrolizumab combination treatment

A total of 14 SAEs (all-causality) were reported in the safety database for 10 participants who received utomilumab and pembrolizumab. None of these SAEs were considered related to utomilumab per Investigator assessment. There was 1 SAE (Grade 2 inflammation) that was determined by the investigator as related to pembrolizumab treatment. There was 1 SAE of special interest, a Grade 3 hyperbilirubinemia in the utomilumab 5 mg/kg + pembrolizumab 2 mg/kg treatment group, which was considered not related to treatment.

Utomilumab + mogamulizumab combination treatment

10 participants in the utomilumab + mogamulizumab combination study experienced 13 serious adverse events (SAEs), none were considered treatment-related.

Deaths on study

13 participants died during the utomilumab plus rituximab trial, none of the events were considered related to utomilumab treatment.

5 participants died during the utomilumab plus pembrolizumab trial, none of the events were considered related to utomilumab treatment.

3 participants died during the utomilumab plus mogamulizumab trial, none of the events were considered related to utomilumab treatment.

Grade 3 Laboratory Abnormalities (occurred in people taking utomilumab as a single agent, regardless of causality)

• Lymphopenia (19%) • Hyponatremia (6%) • Hypophosphatemia (4%) • Anemia (3%) • Hyperglycemia (3%)	• Alkaline phosphatase increased (2%) • Hypokalemia (2%) • Hypoalbuminemia (2%) • Neutrophils, absolute count (ANC) (1%) • Hypomagnesemia (1%)

The only Grade 4 abnormal laboratory test abnormalities were lymphopenia (2%), hypercalcemia (1%), and hypokalemia (1%).

Grade 3 Laboratory Abnormalities (occurred in people receiving utomilumab + rituximab, regardless of causality)

• Lymphopenia (35%) • Neutrophil count decreased (6%) • White blood cell (WBC) count decreased (5%) • Hyperglycemia (4%) • Hypophosphatemia (4%) • Platelet count decreased (2%)	• ALT (liver enzyme) increased (2%) • Hyperkalemia (2%) • Hypomagnesemia • Hypoglycemia (2%) • Hyponatremia (2%)

The only Grade 4 laboratory test abnormalities reported were lymphopenia (6%) and neutrophil count decreased (5%).

Grade 3 Laboratory Abnormalities (occurred in people receiving utomilumab + pembrolizumab, regardless of causality)

• Lymphopenia (26%) • Anemia (13%) • Hypoalbuminemia (13%) • Hyponatremia (13.0%)	• Hyperglycemia (9%) • Hypokalemia (9%) • Hypophosphatemia (9%) • Bilirubin increased (considered related) (4%)

The only Grade 3 laboratory test abnormality that was considered related to treatment was Alkaline phosphatase increased (4%).

The only Grade 4 laboratory test abnormalities reported were lymphopenia (4.3%) and hyponatremia (4.3%).

Grade 3 Laboratory Abnormalities (occurred in people receiving utomilumab + mogamulizumab, regardless of causality)

• Lymphopenia (29%) • Hyperglycemia (13%) • Anemia (8%)	• Hypophosphatemia (8%) • Hyponatremia (4%)

The only Grade 4 laboratory test abnormalities reported was lymphopenia (4%).

Antibodies to Utomilumab

A small number of patients receiving utomilumab treatment developed antibodies to utomilumab. Some patients have antibodies at baseline, ie, before utomilumab treatment. The clinical significance of antibodies to utomilumab is unclear. In some instances, these antibodies may be pre-existing against other biological entities. No serious or significant clinical effects have been observed, including that the presence of antibodies to utomilumab did not affect response to combination treatment.

Potential side effects of Ado-trastuzumab emtansine (Kadcyla, T-DM1)

Ado-trastuzumab emtansine (Kadcyla, T-DM1) is an FDA-approved drug. The drug package insert for this product provides a complete listing of warnings and precautions.

Most Common Grade 1 to 2 (mild to moderate) Side Effects (occurred in more than 20% of people taking T-DM1)

• Upset stomach (nausea) • Tiredness (fatigue) • Body pain (musculoskeletal pain) • Bleeding (hemorrhage) • Decrease in blood levels of platelets, may cause bleeding or bruising (thrombocytopenia)	• Increased blood levels of liver enzymes (increased transaminases) • Headache • Constipation • Diarrhea • Bloody nose (epistaxis) • Numbness, pain, or weakness, usually in hands and feet (peripheral neuropathy)

Less-likely Grade 1 to 2 Side Effects (occurred in more than 10% to 20% of people taking T-DM1)

• Vomiting • Joint pain (arthralgia) • Abdominal pain • Fever (pyrexia) • Cough • Physical weakness or lack of energy (asthenia)	• Dry Mouth • Decreased levels of red blood cells may cause tiredness and fatigue (anemia) • Soreness and inflammation of the mouth, may affect eating, talking and sleeping (stomatitis)

Unlikely Grade 1 to 2 Side Effects
(these side effects occurred in 1% to 10% of people taking T-DM1)

• Urinary tract infection • Indigestion, including abdominal fullness, heartburn, nausea, belching (dyspepsia) • Bad taste in the mouth (dysgeusia) • Chills • Swelling in the limbs (peripheral edema) • Decreased levels of neutrophils, a type of infection-fighting cell (neutropenia) • Rash or itching (pruritus) • Increased blood pressure (hypertension) • Increased blood level of alkaline phosphatase • Vision blurred	• Dry eye • Eye infection, “pink eye” (conjunctivitis) • Increased tear production (lacrimation increased) • Increased sensitivity to other drugs (drug hypersensitivity) • Heart problems (left ventricular dysfunction) • Infusion-related reaction, can include flushing, rash, fever, rigors, chills, difficulty breathing, decreased blood pressure, or heart problems • Inflammation in the lungs (pneumonitis)

Grade 3 to 4 (severe or life-threatening) adverse events (these side effects occurred in 1 to 15% of people taking T-DM1)

• Decrease in blood levels of platelets, may cause bleeding or bruising (thrombocytopenia) • Increased blood levels of liver enzymes (increased transaminases) • Decreased levels of red blood cells may cause tiredness and fatigue (anemia) • Decreased levels of potassium in the blood (hypokalemia)	• Tiredness (fatigue) • Numbness, pain, or weakness, usually in hands and feet (peripheral neuropathy) • Decreased levels of neutrophils, a type of infection-fighting cell (neutropenia) • Body pain (musculoskeletal pain) • Bleeding (hemorrhage) • Diarrhea • Increased blood pressure (hypertension)

Rare but Serious / Severe Side Effects
(these side effects occurred in less than 1% of people taking T-DM1)

• Abdominal pain • Vomiting • Upset stomach (nausea) • Headache • Shortness of breath; unpleasant; or uncomfortable breathing (dyspnea) • Urinary tract infection • Muscle pain (myalgia) • Joint pain (arthralgia) • Constipation • Physical weakness or lack of energy (asthenia)	• Increased blood level of alkaline phosphatase • Dizziness • Difficulty sleeping (insomnia) • Heart problems (left ventricular dysfunction) • Soreness and inflammation of the mouth, may affect eating, talking and sleeping (stomatitis) • Fever (pyrexia) • Increase in the blood pressure in the liver and other internal organs (portal hypertension) • Cough • Bloody nose (epistaxis) • Rash or itching (pruritus)

Specific Warnings for T-DM1

Liver toxicity

Liver toxicity, usually elevated levels of liver enzymes in the blood, have occurred. Serious liver toxicity, including at least two fatal cases of severe drug-induced liver injury have been reported.

Heart toxicity

People treated with T-DM1 are at increased risk of developing a specific kind of heart problem, called left ventricular dysfunction, although this may be more or less than the amount observed with other treatments.

Lung Toxicity

Lung problems, some leading to acute respiratory distress syndrome or death have been reported in clinical trials with T-DM1. Patients with breathing difficulties may be at increased risk.

Infusion-related reactions

At least one case of anaphylaxis, a serious allergic reaction, has occurred in a patient receiving single-agent T-DM1. Anaphylaxis can be fatal.

Hemorrhage

Cases of hemorrhagic events, including in the brain and central nervous system, lungs, and gastrointestinal track, have been reported, some bleeding events were fatal.

Decreased levels of platelets

Decreased platelet count (thrombocytopenia) was reported over 30% of people receiving T-DM1, most events were mild to moderate (Grade 1 to 2). The incidence and severity of thrombocytopenia may higher in Asian patients.

Nerve toxicity

Nerve toxicity in the limbs, hands and feet (peripheral neuropathy) has been reported in over 20% of people receiving T-DM1. The events were mainly mild (Grade 1), but can be severe or worse.

Effects on pregnancy

T-DM1 can cause fetal harm when administered to a pregnant woman.

Risks and possible discomforts you might experience from the study procedures include:

Risks of the Blood Collection and IV

You may have pain, swelling, or bruising around the vein where your blood is collected/IV inserted. There may be risk of infection. You may feel dizzy or you may faint. You may get an infection at the place on your body from which the blood is collected and/or IV insertion.

Risks of the ECG

Placement of the leads may cause skin irritation, redness, or burning of the skin at the site where the leads were attached.

Risks of the CT Scan

When the contrast medium is injected during the CT scan, you may experience nausea, flushing, warmth and a salty taste. You might be allergic to the contrast medium. You must not move during the test, but relax and breathe normally. You might be uncomfortable while you are in the tunnel-shaped machine. Some subjects have felt claustrophobic during this test.

This research study involves exposure to radiation from up to two CT scans. This radiation exposure is not necessary for your medical care and is for research purposes only. The additional amount of radiation exposure is about 30 mSv, which is approximately equal to 60% of the limit that radiation workers (for example, a hospital X-ray technician) are allowed to receive in 1 year. This amount of radiation involves minimal risk and is necessary to obtain the research information desired.

Risks of MRI

MRI (Magnetic Resonance Imaging)

MRI machines use a strong magnet and radiofrequency magnetic fields to make images of the body interior. The scanning procedure is very much like an X-ray or CT scan. You will be asked to lie on a long narrow couch for a certain amount of time approximately 30 to 60 minutes while the machine gathers data. During this time you will not be exposed to X-rays, but rather a strong magnetic field and radiofrequency magnetic fields, which you will not feel. You will, however, hear repetitive tapping noises that arise from the Magnetic Resonance scanner. We will provide earplugs or headphones that you will be required to wear. The space within the large magnet in which you lie is somewhat confined, although we have taken many steps to relieve the "claustrophobic" feeling.

Risks:

Magnetic fields do not cause harmful effects at the levels used in the MRI machine. However, the MR scanner uses a very strong magnet that will attract some metals and affect some electronic devices. If you have a cardiac pacemaker or any other biomedical device in or on your body, it is very important that you tell the operator/investigator immediately. As metallic objects may experience a strong attraction to the magnet, it is also very important that you notify the operator of any metal objects (especially surgical clips), devices, or implants that are in or on your body before entering the magnet room. All such objects must be removed (if possible) before entering the magnet room. In some cases, having those devices means you should not have an MRI scan performed. In addition, watches and credit cards should also be removed as these could be damaged.

- If you have an artificial heart valve; a pacemaker; or any other biomedical device in or on your body, these devices could malfunction when exposed to the very strong magnetic field.
- If you have a metal plate; pin; screws; surgical clips; metallic fragments; or any other metallic implant in your body, these pieces of metal could move while in your body, causing possible serious injury or death.
- If you have tattoos, these could become warm and irritated during the scan and remain so for several days.

If you have a history of severe allergies (eg, bee-sting reaction, food, shellfish, or nut reactions), or have previously had a reaction to medications or contrast agents, in particular Gadolinium-based contrast agents, you may be at risk of a serious reaction, which can be severe and/or life-threatening, including breathing difficulty; sweating; numbness; or heart palpitations. Tell the study team or technician **immediately if you experience these.**

It has been observed that deposits of Gadolinium-based contrast agent (GBCA) remain in the brains of some people who undergo four or more contrast enhanced MRI scans, long after the last administration. It is not yet known whether these Gadolinium deposits are harmful or can lead to adverse health effects. You should talk to the study doctor if you have any questions about the use of GBCAs with MRIs.

IF YOU FEEL DISCOMFORT AT ANY TIME, NOTIFY THE OPERATOR AND YOU CAN DISCONTINUE THE EXAM AT ANY TIME.

Pregnancy Related Risks / Use of Birth Control

The effects of utomilumab on sperm, a pregnancy, or a nursing child are not known. The study doctor will instruct you in the correct use of your selected birth control methods and how to use them consistently and correctly.

Women of Childbearing Potential

If you are a woman who is able to become pregnant, it is expected that you will use two effective methods of birth control consistently and correctly during and for 60 days after you have stopped taking the study drug to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are currently pregnant, planning to become pregnant or father a child, you should not take part in this study. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to an unknown risk.

To confirm to the extent medically possible that you are not pregnant, you agree to have a pregnancy test done before beginning this research study. You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of reliable methods of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

Birth control methods, even when used consistently and correctly, are not perfect. If you become pregnant during the study or you want to stop your required birth control during the study, you should tell your doctor immediately. You may be withdrawn for safety reasons if you discontinue birth control or you become pregnant.

If you are a man participating in this study and your partner is able to become pregnant, you and your partner must use adequate contraception while you are participating in the study and for at least 90 days after you stop taking the study medication. Your doctor will discuss with you what methods of birth control are considered adequate.

POTENTIAL BENEFITS

It is possible that your condition or health may improve because of study treatment or because of your visits to the research site. Information from this study may benefit others in the future. **We cannot and do not guarantee or promise that you will receive any benefits from this study.**

ALTERNATIVES

You do not have to be in this study to receive treatment for your cancer. Instead of taking part in this study, you may choose to receive treatment with other anti-cancer drugs and/or surgery that have been approved for use in this country. Your study doctor will be able to discuss alternative treatments and their risks/benefits with you.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

ClinicalTrials.gov

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US 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.

The description of this clinical trial is at https://clinicaltrials.gov/ct2/show/NCT03364348.

CONFIDENTIALITY

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be

disclosed except as authorized by you or as required by law. However, there is always some risk that even de-identified information might be re-identified.

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The purpose of this research study is to obtain data or information on the safety and effectiveness of utomilumab alone or in combination with ado-trastuzumab emtansine or trastuzumab. The results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required.

Authorization to Use Your Health Information for Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?

The purpose of this research study is to learn about the effects of the safety and effectiveness of utomilumab alone or in combination with ado-trastuzumab emtansine or trastuzumab and to find the best dose for treating advanced breast cancer.

Your health records will be used to gather information about your disease, your response to the treatment and any side effects that may occur. The information obtained from this study may be used in a publication or an application to the FDA for approval of this drug.

In addition, during and after your participation in the study your study doctor will be required to report to the sponsor information related to any serious adverse effect that you may experience due to your participation in the study.

Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study including receiving any research-related treatment. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?

If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your

information (eg, necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to: Dr. George Sledge, Stanford University Medical Center, 269 Campus Drive, CCSR, Room 1115, Stanford, CA 94305, telephone XXX-XXX-XXXX.

What Personal Information Will Be Used or Disclosed?

You will be identified by name, medical record number, address, telephone number, and other direct personal identifiers to persons directly involved with your medical care and to those involved in the conduct and monitoring of the study. Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to, blood and other tissue samples and related records, physical examinations, CT scans, MRIs and other diagnostic test results.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director, Dr. George Sledge and his associates at Stanford Medical Center who are involved in your medical care including study coordinators, research nurses and clinic and laboratory employees.
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Other research personnel at Stanford University and Medical Center.

Who May Receive or Use the Information?

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the US Department of Health and Human Services

- Government health agencies (such as the Food and Drug Administration and the National Institute of Health) in the US or other countries
- Pfizer Inc, the manufacturer of the study drug.
- The Food and Drug Administration
- Researchers who are conducting this study at other research sites

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?

Your authorization for the use and/or disclosure of your health information will end on December 31, 2050 or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?

To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (eg, if included in your official medical record).

_____ _____
Signature of Adult Participant Date

_____
Print Name of Participant

Participant ID:

_____ _____
Signature of Legally Authorized Representative (LAR) Date
(eg, parent, guardian or conservator)

_____
Print Name of LAR

_____
LAR's Authority to Act for Participant
(eg, parent, guardian or conservator)

FINANCIAL CONSIDERATIONS

Payment

You will not be paid to participate in this research study.

Costs

If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with the study that are not a part of your routine medical care. However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the study visits. You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. **You will also be responsible for any co-payments and/or deductibles as required by your insurance.** Participation in this study is not a substitute for health insurance.

Pfizer is providing financial support and material for this study. The study drug, utomilumab will be provided free of charge while you are participating in this study.

The National Institutes of Health are providing some financial support for the facility and staff where part or all of the study is taking place.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

Consultative or Financial Relationships

Dr. Melinda Telli is a paid advisor to Pfizer Pharmaceuticals, the company sponsoring this research study.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director, George Sledge, MD, at XXX-XXX-XXXX. You should also contact him at any time if you feel you have been hurt by being a part of this study.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at XXX-XXX-XXXX or toll free at XXX-XXX-XXXX. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

Signing your name means you agree to be in this study and that you were given a copy of this signed and dated consent form.

Signature of Adult Participant	Date
Print Name of Adult Participant	
Signature of Legally Authorized Representative (LAR) (eg, parent, guardian or conservator)	Date
Print Name of LAR	
LAR's Authority to Act for Participant (eg, parent, guardian, or conservator)	
Signature of Person Obtaining Consent	Date
Print Name of Person Obtaining Consent	

Participant ID:

The following witness line is to be signed only if the consent is provided as a summary form and accompanied by a short form foreign language consent.

_____ _____
Signature of Witness Date

_____
Print Name of Witness

(eg, staff, translator/interpreter, family member)

- *Translated short form must be signed and dated by both the participant (or their LAR) AND the witness.*
- *The English consent form (referred to as the "Summary Form" in the regulations):*
  - *Must be signed by the witness AND the Person Obtaining Consent (POC).*
  - *The non-English speaking participant/LAR does not sign the English consent.*
  - *The non-English speaking participant/LAR should not sign the HIPAA participant line*
  - *If the participant or the LAR is non-English speaking, the Person Obtaining Consent (POC) must ensure that 1) the LAR's Description of Authority is completed and 2) that any questions or options presented by the consent form are documented and initialed by the POC on the Summary Form, per the participant's wishes, as they are understood during the consent process.*