A Phase 1B Dose-escalation Trial of Human Anti-4-1BB Agonistic Antibody Utomilumab (PF-05082566) in Combination with Ado-trastuzumab Emtansine or Trastuzumab in Patients with HER2-postive Advanced Breast Cancer

CONFIDENTIAL

21 September 2020

Protocol Director / Principal Investigator / IND-holder

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IRB-37299 **BRS0070** **NCT03364348**

Participating Investigators and Center:

The participating Clinical Center is Stanford University, Stanford (USA).

Details of the Principal Investigators, Sub-investigators, and other key study personnel are recorded on the Participating Investigators and Centers list Trial Master File.

IND:	IND 131822
IRB number:	IRB-37299
Initial IRB approval:	25 October 2016
Initial SRC approval:	25 May 2017

PROTOCOL VERSION AND AMENDMENT HISTORY:

Protocol Amendment No.	Date of Issue	Reason for Protocol Amendment
Amendment 1	1 Nov 2016	Incorporation of comments from FDA and Stanford Cancer Institute Scientific Peer Review Committee (See Appendix 8 Change Summary Tables)
Amendment 2	16 Nov 2017	• Objectives and Endpoints re-stated and re-organized to enable revised expression of ClinicalTrials.gov outcomes consistent with ClinicalTrials.gov requirements • Clarify duration of treatment
Amendment 3	11 Mar 2019	1. The name used for study agent PF-05082566 is updated to utomilumab. For ease of review, this is only tracked in presentations of the protocol title. 2. Updates clinical experience and safety profile of utomilumab. 3. Eligibility criteria and Eligibility Checklist harmonized to a single instance at Section 3.1. Note: the move of the checklist is not tracked in track document, changes to the eligibility are tracked. 4. Eligibility criteria are simplified and edited for clarity, and revised to improve eligibility of appropriate candidate subjects 5. Clarifies that cohort accrual, ie, to utomilumab in combination with ado-trastuzumab emtansine (T-DM1) or trastuzumab, will be in parallel. 6. The sample size has been decreased to not exceed the first step of the Simon two-step study design. 7. References to the sponsor-investigator, other investigators, and the utomilumab manufacturer have been aligned to those roles. 8. Information regarding oversight of possible additional clinical sites has been added throughout. 9. Performance windows defined for procedures. 10. Collection of blood samples for pharmacokinetics harmonized to other procedures 11. Treatment beyond 24 cycles (about 18 months) will be allowed by investigator discretion. 12. Study identifiers, including NCT number, added to title page 13. CTCAE reference updated to version 5 14. Verbatim change summary table (Appendix 8 and 9) deleted. 15. Other changes as indicated.

Amendment 4	25 Jul 2019	Clarifies/harmonizes the response evaluation criteria as the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 rather than immune-related RECIST. Removes reference to extended treatment after 24 cycles (te3xt for Study Schema), and clarifies rationale for continued dosing (Section 8.9). Clarifies Inclusion Criteria regarding prior treatment, for Cohort 1 and 2 (Section 3, Inclusion Criteria 1) Removes unnecessary details in Exclusion Criteria regarding venous thromboembolism (Section 3, Exclusion Criteria 14) Harmonizes study schema at Figure 9 to correct version (see pg 12). Clarifies window for administration of ado-trastuzumab emtansine and trastuzumab (Section 5.5) Clarifies timing and requirements for tumor assessments (Section 5.5)
Amendment 5	6 Mar 2020	• Makes the study a single-center study. • Close enrollment in Cohort 2 (utomilumab plus trastuzumab) with a total of 5 subjects enrolled. • For Cohort 1 (utomilumab plus ado-trastuzumab-emtansine), specify a maximum enrollment of 17 subjects to received 100 mg ado-trastuzumab-emtansine • Total protocol enrollment is up to 25 subjects

SIGNATURE PAGE

SPONSOR-INVESTIGATOR SIGNATURE

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP),[1] the Declaration of Helsinki,[2] the Code of Federal Regulations (CFR) Title 21,[3] the applicable regulations of the relevant entities (Stanford University, Stanford Hospitals and Clinics), and the clinical trial protocol. I agree to conduct the trial according to these regulations and guidelines and to appropriately direct and assist the staff under my control, who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Investigator's Name:	George W Sledge, Jr, MD
Name of Site:	Stanford Hospitals and Clinics, Stanford University

Investigator's Signature: _____

1 FDA Guidance for Industry: E6 Good Clinical Practice Guidelines, April 1996.

2 World Medical Association , Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Patients.

3 United States Code of Federal Regulations (CFR), Title 21, Food and Drugs.

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1. PROTOCOL SYNOPSIS

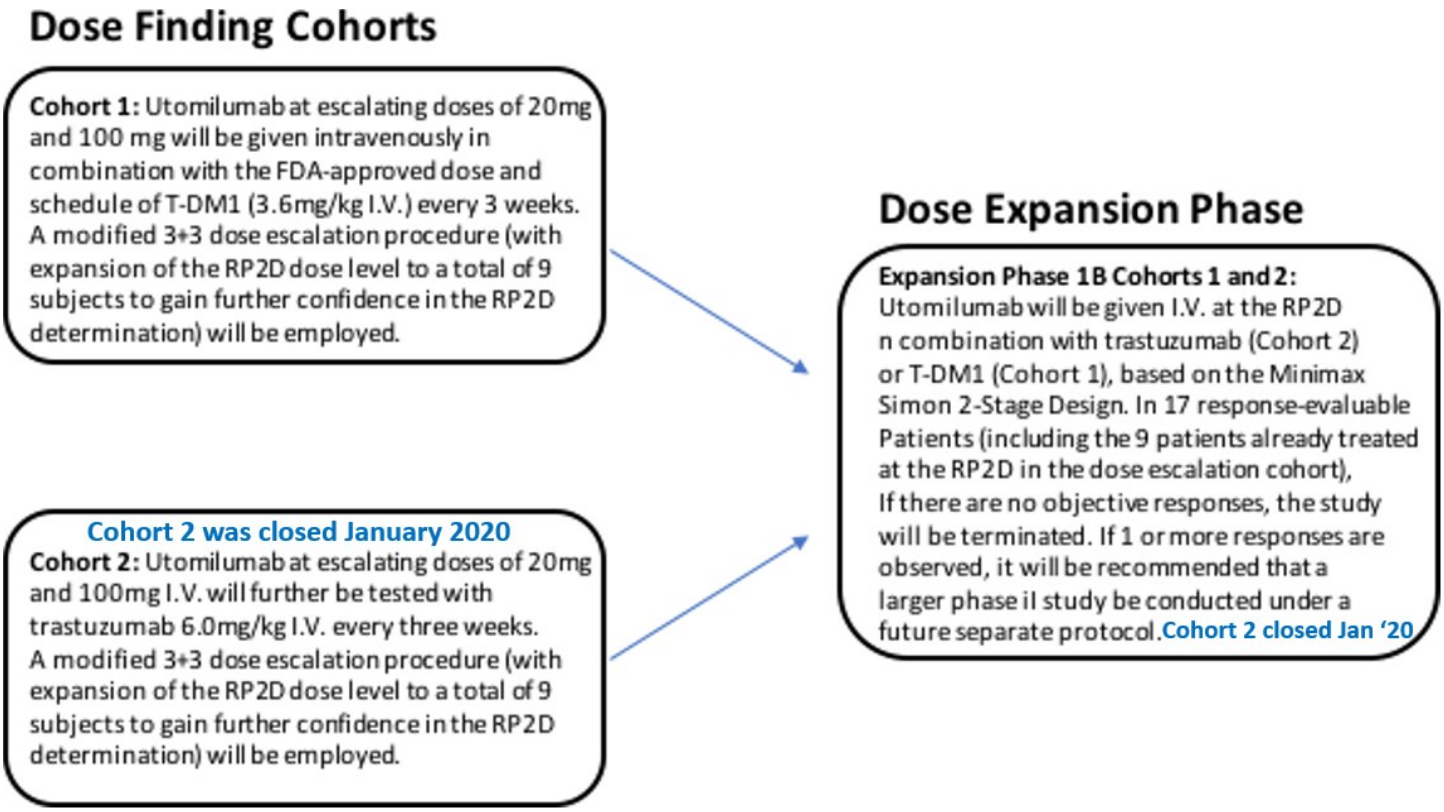
FULL TITLE	**A Phase 1B Dose Escalation Trial of human anti-4-1BB agonistic antibody utomilumab (PF-05082566) in combination with ado-trastuzumab-emtansine or trastuzumab in patients with HER2-positive advanced breast cancer**
SHORT TITLE	Phase 1B Trial of Utomilumab (PF-05082566) in Combination with Ado-trastuzumab emtansine or Trastuzumab in HER2-positive Advanced Breast Cancer
STUDY PHASE	1B
INVESTIGATIONAL PRODUCT	Fully human anti-4-1BB agonistic antibody utomilumab
PRIMARY OBJECTIVES	Estimate the maximum-tolerated dose (MTD) and determine the recommended phase 2 dose (RP2D) of utomilumab in combination with ado-trastuzumab emtansine (T-DM1) in subjects with HER2-positive advanced breast cancer.
SECONDARY OBJECTIVES	1) Determine the objective tumor response rate (ORR) 2) Determine the time-to-tumor response (TTR) 3) Determine the duration of response (DR) 4) Determine progression-free survival (PFS) 5) Assess the safety and tolerability of utomilumab in combination with ado-trastuzumab emtansine or trastuzumab
EXPORATORY OBJECTIVES	1) Evaluate the pharmacokinetics (PK) of utomilumab and ado-trastuzumab emtansine or trastuzumab when given in combination 2) Evaluate the immunogenicity of utomilumab and ado-trastuzumab emtansine or trastuzumab when given in combination 3) Assess the presence of CD8+ T-cells in HER2-positive tumors 4) To evaluate the modulation of immune activity biomarkers by utomilumab in combination with ado-trastuzumab emtansine or trastuzumab Analysis of samples from subjects who received utomilumab and trastuzumab is optional.
ClinicalTrials.gov PRIMARY OUTCOME	Incidence of dose-limiting toxicities (DLTs) within the first 2 cycles (up to about 2 months) reported for Dose-finding Cohorts 1 (ado-trastuzumab emtansine) and 2 (trastuzumab). Subjects lost to follow-up before completion of first 2 cycles due to reasons unrelated to treatment-related adverse events are not evaluable for DLT.

ClinicalTrials.gov SECONDARY OUTCOMES	• Objective tumor response rate (ORR) after 2 cycles for subjects in Expansion Phase 1B Cohort 1 (ado-trastuzumab emtansine), per RECIST v1.1 (for solid tumors per Appendix 1) • Time-to-event measures, for subjects in Expansion Phase 1B Cohort 1 (ado-trastuzumab emtansine) who have at least 1 on-study tumor assessment: o Time-to-tumor response (TTR), per RECIST v1.1 (see Appendix 1), in subjects that respond within 4 months. o Duration of response (DR), per RECIST v1.1 (see Appendix 1), in subjects that respond, through up to 5 years after treatment. o Progression-free survival (PFS) of subjects (percentage) who initiate treatment, reported as the number who remain alive without progression 6 months after treatment. Subjects withdrawn for treatment-related AEs, or lost to follow-up before 6 months, will report as the last date known alive • Incidence of all adverse events (not including laboratory abnormalities) while receiving treatment and within 30 days, reported by treatment group for severity (as graded by NCI CTCAE v5), seriousness (YES/no), and relationship to the study treatments • Incidence of laboratory abnormalities reported by treatment group for severity (as graded by NCI CTCAE v5)
KEY ELIGIBILITY CRITERIA	Eligibility criteria are extensive. Eligible subjects are cancer patients in otherwise general good health (ECOG 0 to 1), with a history of biopsy-proven HER2-overexpressing breast cancer and radiographic evidence of metastatic disease, or locally recurrent unresectable disease. Acceptable methods of contraception required. See Eligibility Criteria and Participant Eligibility Checklist at Section 3.1.

TREATMENT SUMMARY	**Study Rationale** Utomilumab is a new molecular entity that binds to human 4-1BB with high affinity and specificity. *In vitro* and *in vivo* data demonstrated significant immunomodulatory activity and anti-tumor activity of utomilumab when dosed as a single agent and in combination with ADCC-inducing antibodies. Preclinical and the ongoing phase 1 first-in-human studies have shown favorable PK properties and safety profiles suggest that it may be well-tolerated when administered IV. Based upon the above considerations, this phase 1B study will assess the safety and identify the recommended phase 2 dose (RP2D) of utomilumab in subjects with advanced/metastatic HER2-overexpressing breast cancer in combination with ado-trastuzumab emtansine or trastuzumab. During dose-escalation, consecutive dose cohorts of subjects will receive utomilumab (20 or 100 mg) administered once every 3 weeks as an IV infusion in conjunction with ado-trastuzumab emtansine or trastuzumab. During dose-expansion, 2 cohorts (one for each combination regimen) will accrue subjects to the selected dose of utomilumab. Treatment with study drugs will continue until completion of 24 cycles of treatment (up to about 18 months), confirmed disease progression, subject refusal, unacceptable toxicity, whichever occurs first, or the study is prematurely terminated by the Sponsor, or one of the other reasons for subject withdrawal as specified in Section 4.8 will occur. Treatment beyond 24 cycles (18 months) will be allowed only if reviewed and approved by the Principal Investigator. Based on preclinical studies and the ongoing phase 1 trial, the utomilumab dosing will begin at 20 mg, then step to 100 mg. Given the scientific rationale and preclinical data suggesting synergistic effect of utomilumab given in combination with ADCC-inducing mAbs, this study will primarily assess the safety and determine the utomilumab RP2D given in combination with trastuzumab or ado-trastuzumab emtansine. In both dose-escalation and expansion cohorts, subjects will be assessed for DLTs for the first 2 cycles of treatment. PK and immunogenicity of utomilumab and ado-trastuzumab emtansine or trastuzumab will be assessed, and pharmacodynamic (PD) markers of immunomodulatory activity will be examined.

SAMPLE SIZE	Up to 30 subjects, to achieve 25 evaluable subjects. • Up to a maximum of 20 subjects in Cohort 1 (utomilumab plus ado-trastuzumab emtansine), consisting of 3 subjects who receive utomilumab 20 mg IV, and up to 17 who receive utomilumab 100 mg IV. Subject replacement shall not exceed 5 additional subjects. • 5 subjects in Cohort 2 (utomilumab and trastuzumab). Cohort 2 closed in January 2020.

Study Schema



It is to note that other more complex adaptive trial designs were considered, however as just 2 doses of utomilumab will be tested in combination with ado-trastuzumab emtansine or trastuzumab, and as the safety of utomilumab IV has been well tolerated to date in combination with other ADCC-inducing mAbs (with defined PK), the following dosing scheme has been devised as an efficient means to arrive at the RP2D:

Due to differences in eligibility between Cohort 1 and Cohort 2, dose-finding and dose-escalation are not dependent between cohorts, and may occur at different times. Accrual to both cohorts for dose-finding and dose-escalation will occur in parallel to optimize efficiency in dose-finding.

Cohort 1 ado-trastuzumab emtansine:

Dose Level 1 – Utomilumab 20 mg IV + ado-trastuzumab emtansine (T-DM1) 3.6 mg/kg IV every 3 weeks. 3 subjects will be treated at this dose level. If no DLT events are recorded, then utomilumab dose will be increased to 100 mg (Dose Level 2, below). If 1 DLT is observed amongst the first 3 subjects, then Dose Level 1 will be expanded to 6 subjects. If no further DLTs are observed, then utomilumab will proceed to 100 mg (Dose Level 2). If 2 (or more) DLTs are recorded at Dose Level 1, enrollment in the ado-trastuzumab emtansine + utomilumab cohort will be terminated.

Dose Level 2 – Utomilumab 100 mg IV + ado-trastuzumab emtansine 3.6 mg/kg IV every 3 weeks. 3 subjects will be dosed initially. If one DLT is observed, Dose Level 2 will be expanded to 6 subjects. If no further DLTs are observed, then utomilumab 100mg IV + ado-trastuzumab emtansine 3.6 mg/kg IV will be expanded to 9 subjects to gain further confidence in the RP2D determination. If no DLTs are observed in the first 3 subjects, then Dose Level 2 will also be expanded to 9 subjects total to define the RP2D. If more than 2 DLTs are recorded in Dose Level 2, then by definition the MTD will be exceeded, and dosing will be decreased to utomilumab 20 mg/kg IV (Dose Level 1), with enrollment to the Dose Level 1 cohort to a total of 9 subjects. If ≤ 2 DLTs are observed in 9 subjects at Dose Level 1 (utomilumab = 20 mg/kg IV), then utomilumab 20 mg/kg IV in combination with ado-trastuzumab emtansine 3.6 mg/kg IV will be the RP2D.

Cohort 2 trastuzumab (closed January 2020 with 5 subjects enrolled)

Dose Level 1 – Utomilumab 20 mg IV + trastuzumab 6 mg/kg IV every 3 weeks. 3 subjects will be treated at this dose level. If no DLT events are recorded, then utomilumab dose will be increased to 100 mg (Dose Level 2, below). If 1 DLT is observed amongst the first 3 subjects, then Dose Level 1 will be expanded to 6 subjects. If no further DLTs are observed, then utomilumab will proceed to 100 mg (Dose Level 2). If 2 (or more) DLTs are recorded at Dose Level 1, enrollment in the trastuzumab + utomilumab cohort will be terminated.

Dose Level 2 – Utomilumab 100 mg IV + trastuzumab 6 mg/kg IV every 3 weeks. 3 subjects will be dosed initially. If one DLT is observed, Dose Level 2 will be expanded to 6 subjects. If no further DLTs are observed, then utomilumab 100 mg IV + trastuzumab 6 mg/kg IV will be expanded to 9 subjects to gain further confidence in the RP2D determination. If no DLTs are observed in the first 3 subjects, then Dose Level 2 will also be expanded to 9 subjects total to define the RP2D. If more than 2 DLTs are recorded in Dose Level 2, then by definition the MTD will be exceeded, and dosing will be decreased to utomilumab 20 mg/kg IV, with enrollment to the Dose Level 1 cohort to a total of 9 subjects. If ≤ 2 DLTs are observed in 9 subjects at Dose Level 1 (utomilumab = 20 mg/kg IV), then utomilumab 20 mg/kg IV in combination with trastuzumab 6 mg/kg IV will be the RP2D.

Expansion Phase 1B Cohort 1 (ado-trastuzumab emtansine) – Utomilumab given IV at the RP2D in combination with ado-trastuzumab emtansine 3.6 mg/kg IV, will be based on Minimax Simon 2 Stage Design. The null hypothesis that the true response rate is 5% will be tested against a one-sided alternative. In 17 response-evaluable subjects, if there are no responses, the study will be terminated. If 1 or more responses are observed, it will be recommended to conduct a future formal phase 2 trial of the combination under a separate study protocol.

Expansion Phase 1B Cohort 2 (trastuzumab) – Utomilumab given IV at the RP2D in combination with trastuzumab 6.0 mg/kg IV, will be based on Minimax Simon 2 Stage Design. The null hypothesis that the true response rate is 5% will be tested against a one-sided alternative. In 17 response-evaluable subjects, if there are no responses, the study will be terminated. If 1 or more responses are observed, it will be recommended to conduct a future formal phase 2 trial of the combination under a separate study protocol.

Additional considerations in the design and conduct of this trial:

Subjects will continue treatment at the assigned dose level and schedule until unacceptable toxicity, subject's voluntary withdrawal, or documentation of progressive disease as determined by RECIST v1.1 criteria (see Section 7.2 regarding clinical interpretation of potential "flare" tumor responses seen with immunotherapeutic drugs, such as utomilumab). If ado-trastuzumab emtansine (T-DM1) or trastuzumab must be discontinued (eg, for toxicity), the patient may remain on single-agent utomilumab until disease progression. The converse is also true (ie, if utomilumab is discontinued, the patient may remain on ado-trastuzumab emtansine or trastuzumab until disease progression. Administration of the study drug utomilumab may continue for up to 24 cycles (18 months).

1. BACKGROUND

1.1. 4-1BB Target Biology and Mechanism of Action

4-1BB (CD137, TNFRSF9), first identified as an inducible costimulatory receptor expressed on activated T-cells, is a membrane spanning glycoprotein of the tumor necrosis factor (TNF) receptor superfamily. Current understanding of 4-1BB indicates that expression is generally activation dependent and encompasses a broad subset of immune cells including activated NK and NKT cells; regulatory T-cells; dendritic cells (DC) including follicular DC; stimulated mast cells, differentiating myeloid cells, monocytes, neutrophils, eosinophils (Wang, *et al*, 2009), and activated B-cell s (Zhang, *et al*, 2011)(Figure 1). 4-1BB expression has also been demonstrated on tumor vasculature (Broll, *et al*, 2001, Seaman, *et al*, 2007) and atherosclerotic endothelium (Olofsson, *et al*, 2008). The ligand that stimulates 4-1BB (4-1BBL) is expressed on activated antigen-presenting cells (APCs); myeloid progenitor cells; and hematopoietic stem cells.

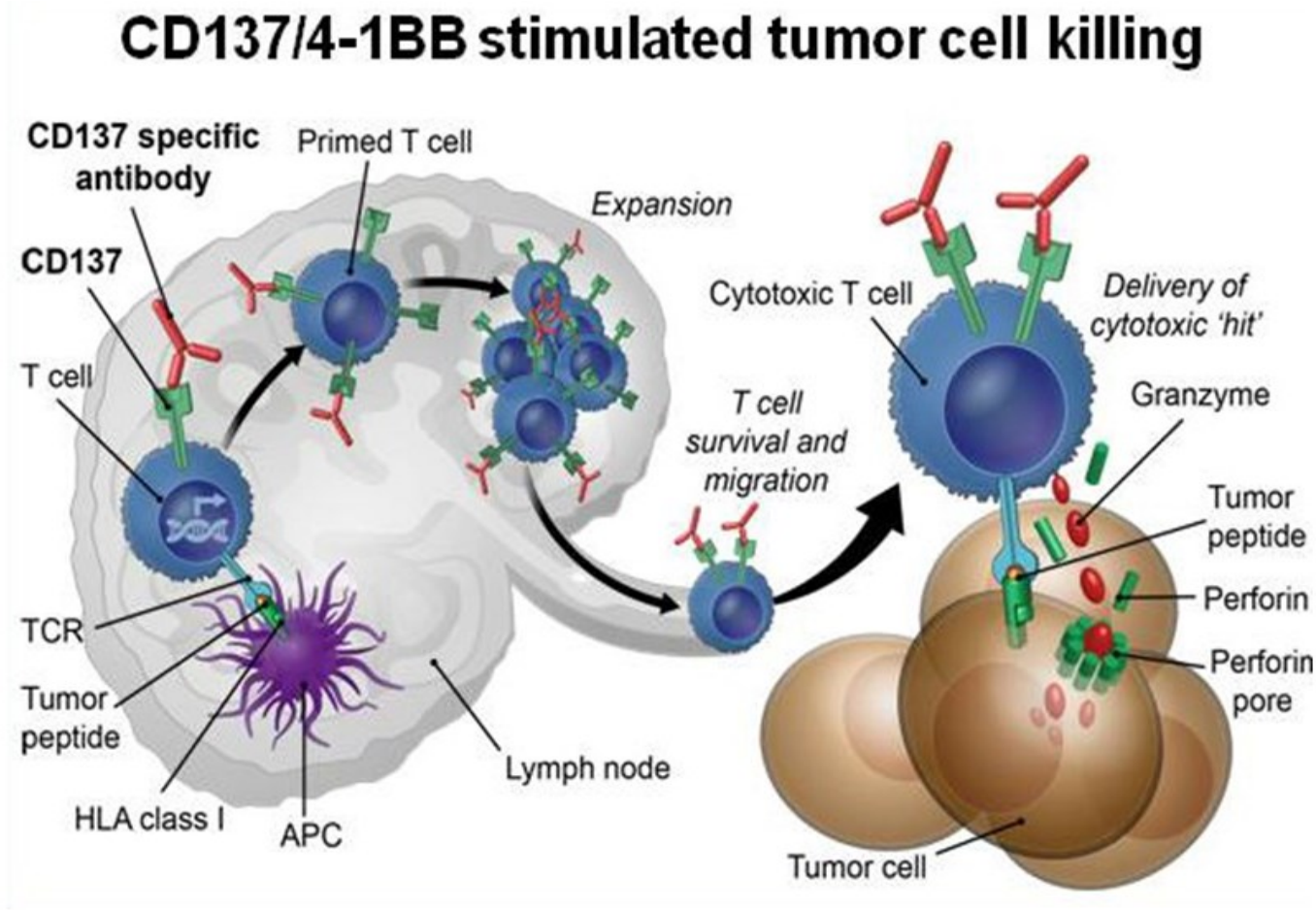


Figure 1. Mechanism of CD137, 4-1BB modulation

4-1BB is undetectable on the surface of naive T-cells but expression increases upon activation. Based on homology to other members of the TNFRSF, ligand binding is expected to induce receptor trimerization resulting in activation (Chan, *et al*, 2007). Some members of the TNFRSF can cleave the extracellular domain from the cell surface and exist in a soluble form. Soluble

4-1BB and soluble 4-1BBL have been demonstrated in the serum of some patients with autoimmune diseases and cancers (Michel, *et al*, 1998; Furtner, *et al*, 2005; Hentschel, *et al*, 2006). Upon 4-1BB activation, TRAF1 and TRAF2, pro-survival members of the TNFR-associated factor (TRAF) family are recruited to the 4-1BB cytoplasmic tail resulting in downstream activation of NFkB and the Mitogen Activated Protein (MAP) Kinase cascade including Erk, Jnk, and p38 MAP kinases. NFkB activation leads to upregulation of Bfl-1 and Bcl-XL, pro-survival members of the Bcl-2 family. The pro-apoptotic protein Bim is downregulated in a TRAF1 and Erk dependent manner (Sabbagh, *et al*, 2008).

Numerous studies of murine and human T-cells indicate that 4-1BB promotes enhanced cellular proliferation, survival, and cytokine production (Croft 2009). Reports have shown that 4-1BB agonist mAbs increase costimulatory molecule expression and markedly enhance cytolytic T lymphocyte responses, resulting in anti-tumor efficacy in various models. 4-1BB agonist mAbs have demonstrated efficacy in prophylactic and therapeutic settings and both monotherapy and combination therapy tumor models and have established durable anti-tumor protective T-cell memory responses (Lynch 2008). 4-1BB agonists also inhibit autoimmune reactions in a variety of autoimmunity models (Vinay, *et al*, 2006). This dual activity of 4-1BB offers the potential to provide anti-tumor activity while dampening autoimmune side effects that can be associated with immunotherapy approaches that break immune tolerance.

utomilumab, an intravenous (IV) fully-human IgG2 monoclonal antibody (mAb), binds to the extracellular domain of human 4-1BB with high affinity and specificity and is capable of 4-1BB agonism. Injection with utomilumab has been shown to correlate with tumor cell line growth inhibition in xenogenic tumor models as a single agent. In addition, 4-1BB agonist mAbs demonstrate significant combinatorial efficacy with ADCC antibodies in lymphoma and breast cancer models. Preclinical studies support the use of this 4-1BB agonist mAb as a promising candidate for treatment of cancer, alone or in combination with ADCC-inducing mAbs.

1.2. Preclinical Profiles of Utomilumab

1.2.1. *In vitro* Data

Utomilumab has shown immunomodulatory activity in various *in vitro* assays. In concert with a signal through the T-cell receptor, utomilumab has been shown to mediate ligation of 4-1BB, which results in release of soluble 4-1BB (sCD137), activation of NFkB, production of cytokines and chemokines (including IL2 and CCL22) and proliferation of antigen-specific CD8+ T-cells (Fisher *et al*., 2012).

Interaction of 4-1BB on activated normal human B-cell s with its ligand at the time of B-cell receptor engagement stimulates proliferation and enhances survival (Zhang, *et al*, 2011). The potential impact of 4-1BB engagement in B-cell lymphoma has been investigated in 2 published studies. Evaluation of several types of human primary NHL samples indicated that 4-1BB was expressed predominantly on infiltrating T-cells rather than the lymphoma cells (Houot, *et al*, 2011). The addition of 4-1BB agonists to *in vitro* cultures of B lymphoma cells with rituximab and NK cells resulted in increased lymphoma killing (Kohrt, *et al*, 2010). In addition, B-cell immunophenotyping was performed in two experiments using utomilumab in cynomolgus monkeys with doses from 0.001-100 mg/kg; in these experiments peripheral blood B-cell numbers were either unchanged or decreased.

1.2.2. *In vivo* Data

In pre-clinical studies, utomilumab has exhibited the ability to increase lymphocyte proliferation. In small animal models developed to test the *in vivo* function of utomilumab, utomilumab was able to enhance expansion of human leukocytes in a dose-dependent manner as evidenced by an increase in the proportion of human CD45+ cells in the peripheral blood of engrafted mice. Similarly, a dose-dependent increase in the proportion of human leukocytes expressing the proliferation marker Ki-67 was noted. In addition, utomilumab treatment of cynomolgus monkeys in single or multiple dose studies increased proliferation among cytotoxic central memory T-cells (CD8 TCM) in PBMC samples. Taken together, these data demonstrate evidence of utomilumab's ability to enhance lymphocyte response *in vivo* with human PBMC from a healthy volunteer donor prior to injection in all cases. Once tumors were established, animals were treated with utomilumab. Utomilumab was found to be efficacious against all 3 tumor types. An example growth curve demonstrating the response to a prostate carcinoma is shown in Figure 2. (Fisher, *et al*, 2012).

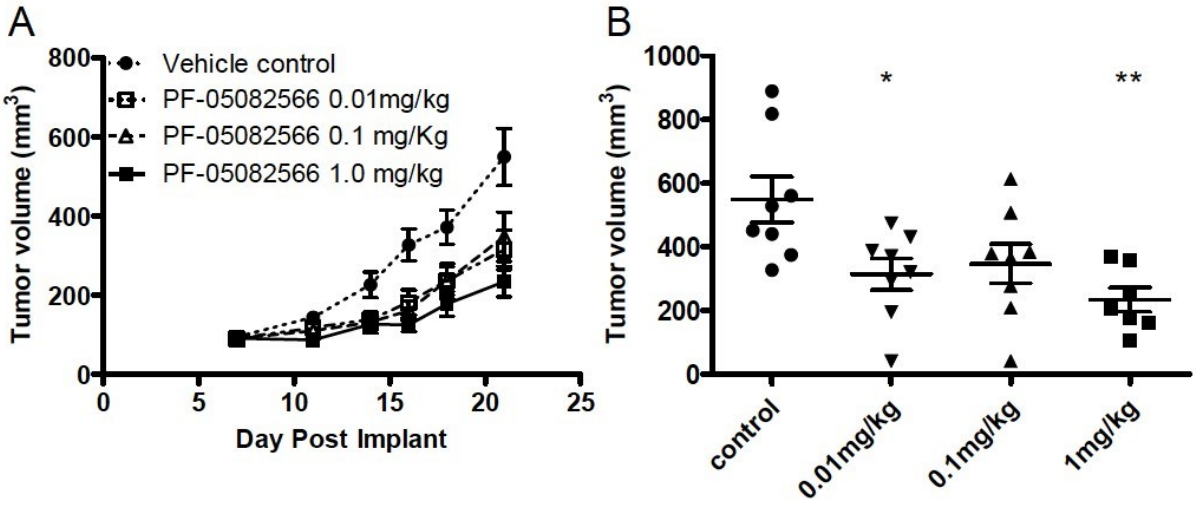


Figure 2. Effect of PF-05082566 (utomilumab) on the growth of PC3 prostate carcinoma in a huPBL SCID model PF-05082566 (utomilumab) inhibits the growth of the PC3 prostate carcinoma *in vivo*. **Panel A**: Mean tumor volume at each time point measured. **Panel B**: Volume of each tumor on the final study day (Day 21). The mean and SEM are indicated by bars. *$p < 0.05$, ** $p < 0.005$.

1.2.3. Clinical Experience

Utomilumab has been administered to a total of 390 subjects (see Table 1).

In Study B1641001, 180 subjects with advanced solid tumors and hematological malignancies received utomilumab in a dose range between 0.006 and 10.0 mg/kg. In this study, 114 subjects, mainly with advanced solid tumors, received single-agent utomilumab and 66 subjects with non-Hodgkin's lymphoma (NHL) received utomilumab in combination with rituximab.

In Study B1641003, utomilumab has been administered to 23 subjects with advanced solid tumors in a dose range between 0.45 mg/kg and 5.0 mg/kg in combination with pembrolizumab.

In Study B1641004, utomilumab has been administered to 24 subjects with advanced solid tumors, in a dose range between 1.2 mg/kg and 5 mg/kg in combination with mogamulizumab.

In Study B9991004, 153 subjects received utomilumab at dose levels of 20 mg, 100 mg, and 500 mg in combination with avelumab.

In Study B0601002, utomilumab has been administered to 10 subjects at 20 mg in combination with PF-04518600.

The ongoing first-in-patient clinical Study B1641001 is a phase 1, open–label, dose-escalation study. In study Portion A, utomilumab is administered as a single agent in subjects with advanced solid tumors or relapsed or refractory B-cell lymphoma, and in study Portion B, utomilumab is given in combination with rituximab in subjects with relapsed or refractory CD20+ NHL. The key study parameters assessed include: safety, tolerability PK/PD markers of activity, and preliminary utomilumab anti-tumor activity.

Study B1641003, a phase 1, open-label, dose-escalation study designed to evaluate the safety, and PK/PD of utomilumab administered in combination with pembrolizumab to adults with advanced solid tumors, has been completed. The study also aimed to: assess preliminary anti-tumor activity, estimate the MTD and select the RP2D for the combination. The study was halted following completion of the dose-escalation phase. The dose expansion phase of the study was not conducted. The decision to terminate the study was made for strategic reasons, and was not due to any safety or efficacy concerns related to the combination treatment. A completed CSR is available for Study B1641003.

The ongoing clinical Study B1641004 is a phase 1b, open label, multi-center, multi-dose, dose-escalation study designed to evaluate the safety, and PK/PD of utomilumab administered in combination with mogamulizumab to adults with defined advanced solid tumors. The study will assess preliminary anti-tumor activity, and will estimate the MTD and RP2D for the combination.

The ongoing clinical Study B9991004 is a phase 1b/2, open label, multi-center, multiple dose, study designed to evaluate the safety, clinical activity, PK/PD of avelumab in combination with increasing dose levels of other immune modulators in adult subjects with locally advanced or metastatic solid tumors. Combination A of this study includes utomilumab in combination with avelumab. The study aims to determine the RP2D(s) of the combination of utomilumab and avelumab in subjects with NSCLC. The phase 2 component of the study evaluates efficacy and further evaluates safety of the combination in subjects with NSCLC, melanoma, head and neck cancer, triple negative breast cancer, and small cell lung cancer.

The ongoing clinical Study B0601002 is a phase 1, open label, multi-center, multiple-dose, dose-escalation, safety, and PK/PD study that in Part A evaluates the single agent activity of PF-04518600 (OX-40 agonist) and in Part B evaluates the combination of PF-04518600 and utomilumab in subjects with select locally-advanced or metastatic carcinomas. The primary objective is to assess safety and tolerability at increasing dose levels of PF-04518600 in combination with utomilumab and to estimate the MTD of the combination. Secondary objectives include the overall safety profile, PK/PD, and anti-tumor effects of the combination.

The clinical data reported in the following sections are based on all available data as of the data cut-off of 06 July 2017 for Studies B1641001, B1641003, and B1641004.

Table 1. Clinical Studies of Utomilumab (PF-05082566)

Protocol	Title	Subjects Planned	Subjects Treated	Status
B1641001	A Phase 1 Study of PF-05082566 as a Single Agent in Patients with Advanced Cancer, and in Combination with Rituximab in Patients with Non-Hodgkin's Lymphoma (NHL)	72 to 161	180	Ongoing
B1641003	A Phase 1 Study of the 4-1BB Agonist PF-05082566 in Combination With the PD-1 Inhibitor MK-3475 in Patients with Advanced Solid Tumors	45 to 75	23	Completed
B1641004	A Phase 1b Study of PF-05082566 in Combination With Mogamulizumab (KW-0761) in Patients With Advanced Solid Tumors	70	24	Ongoing
B9991004	A Phase 1b/2 Open-Label Study to Evaluate Safety, Clinical Activity, Pharmacokinetics and Pharmacodynamics of Avelumab (MSB0010718C) in Combination with Other Cancer Immunotherapies in Patients with Advanced Malignancies (Avelumab IB version 7, 31 March 2017)	317	153	Ongoing
B0601002	A Phase 1 Open Label, Dose Escalation Study of PF-04518600 as a Single Agent and in Combination with PF-05082566 in Patients with Selected Locally Advanced or Metastatic Carcinomas (PF-04518600 IB December 2016)	190	10	Ongoing

Safety and Efficacy

As of the data cut-off date of 06 July 2017, the safety and efficacy of utomilumab are being evaluated in 3 studies within the utomilumab clinical program, 2 of which are ongoing (B1641001 and B1641004) and 1 is completed (B1641003). Utomilumab is being evaluated both as a single agent (B1641001 Portion A) and in combination with other anti-cancer treatments (B1641001 Portion B, B1641003, and B1641004).

For B1641001, safety and efficacy data were recorded for 114 subjects in Portion A (74 [64.9%] male and 40 [35.1%] female; mean age of 60.9 years) treated with utomilumab in dose levels between 0.006 and 10 mg/kg, and 66 subjects in Portion B (37 [56.0%] male and 29 [43.9%] female; mean age of 62.1 years) treated with utomilumab in dose levels between 0.03 and 10 mg/kg in combination with rituximab at 375 mg/m^2.

For B1641003, safety and efficacy data were recorded for 23 subjects (14 [60.9%] males and 9 [39.1%] females; mean age of 58.0 years) treated with utomilumab in dose levels between 0.45 and 5.0 mg/kg in combination with 2 mg/kg of pembrolizumab.

For B1641004, safety and efficacy data were recorded for 24 subjects (19 [79.1%] males and 5 [20.8%] females; mean age of 63.9 years) treated with utomilumab in dose levels between 1.2 and 5 mg/kg, in combination with 1 mg/kg of mogamulizumab.

Since Studies B1641001 and B1641004 are ongoing, the available data are subject to change. Study B1641003 is completed and the final clinical study report (CSR) is available.

Dose-limiting Toxicities

There were no dose-limiting toxicities (DLTs) in Study B1641001 either for utomilumab as a single agent in Portion A or in combination with rituximab in Portion B.

There were no DLTs reported in Studies B1641003 nor B1641004.

A summary of treatment emergent adverse events (TEAEs) occurring or worsening during the time from the first dose of study treatment to at least 30 days after the last dose of study treatment by System Organ Class (SOC), Medical Dictionary for Regulatory Activities (MedDRA), Preferred Term (PT), and maximum CTCAE Grade (all-causality and treatment-related) for Portion A is as follows. The most commonly reported TEAEs (88.6% of subjects, all grades), regardless of causality, were in the SOCs of gastrointestinal disorders (51.8%); general disorders and administration site conditions (46.5%); nervous system disorders (28.9%); musculoskeletal and connective tissue disorders (24.6%); metabolism and nutrition disorders (22.8%); respiratory; thoracic and mediastinal disorders (19.3%); skin and subcutaneous tissue disorders (17.5%); infections and infestations (15.8%); investigations (14.0%); and blood and lymphatic system disorders (13.2%). The most frequently reported TEAEs (≥ 10% of all subjects, all grades) regardless of causality were: fatigue (29.8%); nausea (21.1%); abdominal pain (14.9%); decreased appetite (14.9%); vomiting (14.0%); diarrhea (12.3%); dizziness (12.3%); pyrexia (11.4%); anemia (10.5%); and constipation (10.5%). There were four Grade 5 AEs reported (disease progression [2 subjects], respiratory failure and malignant neoplasm progression [1 subject each]), which were considered to be not related to the study drug.

The most commonly reported TEAEs (≥ 10% of all subjects; all grades) that were considered treatment-related were in the SOCs of general disorders and administration site conditions (21.1%); gastrointestinal disorders (17.5%); and skin and subcutaneous tissue disorders (10.5%). The most frequently observed treatment-related TEAE (41.2% of subjects; all grades) was fatigue (14.0%). Treatment-related TEAEs were mostly Grade 1 or 2 with only four Grade 3/4 AEs reported (colitis; diarrhea; fatigue; hyperbilirubinemia and hyponatremia); Grade 3/4 colitis and diarrhea were observed in the same subject. No Grade 5 treatment-related AEs were observed.

A summary of TEAEs by SOC, MedDRA PT, and maximum CTCAE Grade (all-causality and treatment-related) for Portion B is as follows. The most commonly reported TEAEs (≥10% of subjects; all grades), regardless of causality, were in the SOCs of general disorders and administration site conditions (48.5%); gastrointestinal disorders (45.5%); musculoskeletal and connective tissue disorders (39.4%); respiratory; thoracic and mediastinal disorders (36.4%); injury; poisoning and procedural complications and nervous system disorders (30.3% each); infections and infestations (27.3%); skin and subcutaneous tissue disorders (25.8%); investigations (24.2%); blood and lymphatic system disorders (16.7%); psychiatric disorders (12.1%). The most frequently reported TEAEs (≥10% of subjects; all grades) regardless of causality were: fatigue (28.8%); infusion-related reaction (21.2%); cough (16.7%); pyrexia (13.6%); upper respiratory tract infection (13.6%); diarrhea (12.1%); headache (10.6%); and blood creatinine increased (10.6%). There was one Grade 5 AE (death) reported (due to disease progression), which was considered not-related to the study drug.

The most commonly reported TEAEs (all grades) that were considered treatment-related were in the SOCs of general disorders and administration site conditions (28.8%); gastrointestinal disorders (25.8%); injury, poisoning and procedural complications (24.2%); nervous system disorders (16.7%); and skin and subcutaneous tissue disorders (15.2%). The most commonly reported treatment-related TEAEs (75.8% of subjects; all grades) that were considered treatment-related were infusion-related reaction (21.2%) and fatigue (19.7%). Note that all of the infusion reactions were associated with rituximab infusion. Treatment-related TEAEs were mostly Grade 1 or Grade 2. Grade 3/4 AEs were reported in 6 subjects: infusion-related reaction and neutropenia (2 subjects each), lymphocyte count decreased and neutrophil count decreased (1 subject each). All Grade 3/4 AEs were related to rituximab treatment only, per Investigator assessment. Two of the Grade 3 AEs were related to PF-05082566 (diarrhea and neutropenia). No Grade 5 treatment-related AEs were observed.

Twenty-three (23) solid tumor subjects were treated with the combination of PF-05082566 and pembrolizumab at the fixed dose of 2 mg/kg. PF-05082566 was administered at different dose levels as follows: 5 subjects received 0.45 mg/kg, 3 subjects each received 0.9 mg/kg; 1.8 mg/kg; and 3.6 mg/kg; and 9 subjects received 5 mg/kg.

A summary of TEAEs by SOC, MedDRA PT, and maximum CTCAE grade (all-causality and treatment-related) for B1641003 is as follows. The most commonly reported TEAEs, regardless of causality, were in the SOCs of gastrointestinal disorders (69.6%); general disorders and administration site conditions (65.2%); skin and subcutaneous tissue disorders (60.9%); respiratory; thoracic and mediastinal disorders (56.5%); metabolism and nutrition disorders; and musculoskeletal and connective tissue disorders (52.2% each); infections and infestations (43.5%); nervous system disorders (39.1%); investigations (34.8%); blood and lymphatic system disorders (26.1%); injury, poisoning and procedural complications (21.7%); endocrine disorders (17.4%); ear and labyrinth disorders (8.7%); cardiac disorders; eye disorders; hepatobiliary; neoplasms benign; malignant and unspecified (includes cysts and polyps); product issues; reproductive system and breast disorders; and vascular disorders (4.3% each). The most frequently reported TEAEs (100% of subjects; all grades) regardless of causality, were fatigue (43.5%); cough; nausea (34.8% each); decreased appetite (30.4%); constipation; pruritus; rash maculo-papular and vomiting (26.1% each); anemia; pyrexia (21.7% each); back pain; dyspepsia; rash; and upper respiratory tract infection (17.4% each); alanine aminotransferase increased; arthralgia; asthenia; dry mouth; dry skin; dyspnea; fall; hemoptysis; hypokalemia; hyponatremia; muscle spasms; musculoskeletal chest pain; edema peripheral; pleural effusion; pneumonia; sinusitis; and stomatitis (13.0% each). There was one Grade 5 AE (death) reported, (due to disease progression), which was considered not related to the study drug.

The most frequently observed treatment-related TEAEs (all grades) were in the SOCs of skin and subcutaneous tissue disorders (52.2%); general disorders; and administration site conditions (47.8%); gastrointestinal disorders (34.8%); and metabolism and nutrition disorders (21.7%). The most frequently observed treatment-related TEAEs (78.3% of subjects; all grades) were fatigue (34.8%); rash maculo-papular (26.1%); pruritus (21.7%); pyrexia (17.4%); nausea; decreased appetite; dry skin; dry mouth (13.0% each). Treatment-related TEAEs were mostly Grade 1 or Grade 2. There were only 2 treatment-related (PF-05082566 and pembrolizumab) Grade 3 AEs reported in 2 subjects:

adrenal insufficiency (no evidence of associated hypophysitis reported) and hypokalemia (1 subject each). No Grade 4 or 5 treatment-related AEs were observed.

Twenty four (24) solid tumor subjects were treated with the combination of PF-05082566 and mogamulizumab at 1 mg/kg. PF-05082566 was administered at 4 dose levels as follows: 11 subjects received 1.2 mg/kg; 4 subjects received 2.4 mg/kg; 3 subjects received 5 mg/kg; and 6 subjects received 100 mg.

A summary of TEAEs by SOC, MedDRA PT, and maximum CTCAE Grade (all-causality and treatment-related) for B1641004 is as follows. The most frequently observed TEAEs, regardless of causality, were in the SOCs of general disorders and administration site conditions (66.7%), gastrointestinal disorders (62.5%), skin and subcutaneous tissue disorders (58.3%), respiratory, thoracic and mediastinal disorders (54.2%), infections and infestations (45.8), metabolism and nutrition disorders (41.7%). The most frequently observed TEAEs (100% of subjects; all grades) regardless of causality, were fatigue (41.7%); rash (29.2%); constipation; nausea; diarrhea and pyrexia (20.8% each); decreased appetite, pruritus, anemia, dyspnea, and headache (16.7% each); abnormal dreams, chills, cough, dehydration, infusion related reaction, insomnia, lymphocyte count decreased, and rhinorrhea (12.5% each). There were no Grade 5 AEs reported in this study.

The most frequently observed treatment-related TEAEs (all grades) were in the SOCs of skin and subcutaneous tissue disorders (50%), general disorders and administration site conditions (41.7%), gastrointestinal disorders (37.5%), metabolism and nutrition disorders (25.0%). The most frequently observed treatment-related TEAEs (83.3% of subjects; all grades) were fatigue; rash (25.0% each); diarrhea (20.8%); nausea; pyrexia; abnormal dreams; infusion related reaction and pruritus (12.5% each). Most treatment-related TEAEs were Grade 1/2 in severity. No Grade 5 treatment-related AEs were observed.

Discontinuations Due to Adverse Events

In Portion A, there were 15 adverse events reported in 13 subjects that led to permanent discontinuation from treatment with utomilumab. Only 1 subject with metastatic melanoma treated at 1.2 mg/kg permanently discontinued treatment with utomilumab for a Grade 2 AE of enterocolitis that was considered related to study drug per Investigator assessment.

There were no AEs leading to permanent treatment discontinuation reported for subjects treated in Portion B.

No subject permanently discontinued from the study treatment due to a treatment-related AE in the pembolizumab plus utomilumab trial.

In the utomilumab and mogamulizumab at 1 mg/kg trial, 1 subject permanently discontinued from the study treatment due to treatment-related Grade 3 pneumonitis.

Serious Adverse Events

A total of 41 SAEs (all-causality) were reported in the safety database for 34 subjects who received utomilumab in Portion A or Portion B.

One (1) event each of colitis, diarrhea, enterocolitis, hyperbilirubinemia, decreased appetite, dehydration and pneumonitis were reported as treatment-related in 5 subjects.

In one case, Pfizer (the manufacturer of utomilumab) does not consider a reasonable possibility that hyperbilirubinemia may be attributed to the study drug. The event occurred approximately 43 days after the first dose of study drug in a subject who had an ongoing abdominal ascites. Significant tests, including baseline bilirubin and liver enzyme levels, abdominal imaging results, were not available to determine the causality of the event. Progression of the underlying disease may provide the most plausible cause; of note, recent MRI showed brain metastases.

A total of 14 SAEs (all-causality) were reported in the safety database for 10 subjects 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.

The MTD of utomilumab once every 3 weeks (q3wks) in combination with 2 mg/kg of pembrolizumab q3wks was determined to be at least 5 mg/kg (the highest dose evaluated). Doses up to utomilumab 5 mg/kg q3wks when combined with pembrolizumab 2 mg/kg q3wks were safe and well-tolerated in subjects with advanced solid cancer. The dose expansion phase of the study was not initiated by Pfizer for strategic reasons and therefore, there was insufficient information to determine the RP2D.

In the utomilumab plus mogamulizumab at 1 mg/kg trial, a total of 13 SAEs (all-causality) in 10 subjects were reported in the safety database. None of these SAEs were considered treatment-related.

Deaths

A total of 13 deaths were reported in the safety database for subjects in Portion A or in Portion B who received treatment with utomilumab. One (1) subject in Portion B died of disease progression after receiving the first dose of rituximab but was not dosed with utomilumab. None of the deaths were attributed to study treatment.

A total of 5 deaths were reported in the safety database in the pembrolizumab plus utomilumab trial. None of these were considered related to the treatment with utomilumab.

In the utomilumab plus mogamulizumab trial, a total of 3 deaths were reported in the safety database. None of these deaths were considered related to the treatment with utomilumab. One (1) subject died of sepsis and 2 subjects died due to neoplasm progression. None of the deaths were attributed to study treatment.

Laboratory Abnormalities

Note: As many abnormal laboratory values are not necessarily considered as AEs, the numbers presented in this section do not precisely match those in the corresponding AE sections above. For subjects who received utomilumab in Portion A, Grade 3 hematology laboratory test abnormalities reported were: lymphopenia (21 subjects; 18.9%), anemia (3 subjects; 2.7%), neutrophils (absolute) (1 subject; 0.9%). The Grade 4 hematology laboratory test abnormalities reported were: lymphopenia (2 subjects; 1.8%), neutrophils (absolute) (0 subjects; 0.0%), and white blood cells (0 subjects; 0.0%). The Grade 3 abnormal serum chemistry abnormalities reported were: hyponatremia (7 subjects; 6.3%), hypophosphatemia (4 subjects; 3.8%), hyperglycemia (3 subjects; 2.7%), alkaline phosphatase increased, hypokalemia, and

hypoalbuminemia (2 subjects each; 1.8%), and hypomagnesemia (1 subject each; 0.9%). The only Grade 4 abnormal serum chemistry values were: hypercalcemia (1 subject; 0.8%) and hypokalemia (1 subject; 0.9%).

In Portion B, Grade 3 hematology laboratory test abnormalities reported were: lymphopenia (22 subjects; 34.9%), neutrophil count decreased (4 subject each; 6.3%), white blood cell count decreased (3 subjects; 4.7%), platelet count decreased (1 subject; 1.5%). The Grade 4 hematology laboratory test abnormalities reported were: lymphopenia (4 subjects; 6.3%), and neutrophil count decreased (3 subjects; 4.7%).

The Grade 3 abnormal serum chemistry values reported were: hyperglycemia and hypophosphatemia (2 subjects each; 4.4%); ALT increased, hyperkalemia, hypomagnesemia, hypoglycemia, and hyponatremia (1 subject each; 1.5%).

Laboratory test abnormalities for subjects who received utomilumab and pembrolizumab are summarized by maximum CTCAE Grade, as follows. The Grade 3 hematology laboratory test abnormalities reported were: lymphopenia (6 subjects; 26.1%) and anemia (3 subjects; 13.0%). The only Grade 4 hematology laboratory test abnormalities reported was lymphopenia (1 subject; 4.3%). This was not reported as an AE by the Investigator. The Grade 3 abnormal serum chemistry abnormalities reported were: hypoalbuminemia and hyponatremia (3 subjects each; 13.0%), hyperglycemia, hypokalemia, and hypophosphatemia (2 subjects each; 8.7%), alkaline phosphatase increased and bilirubin increased (1 subject each; 4.3%). Both alkaline phosphatase increased and bilirubin increased were considered related to metastatic disease. The only Grade 4 abnormal serum chemistry values reported was hyponatremia (1 subject; 4.3%). This hyponatremia occurred in the subject with adrenal insufficiency.

Laboratory test results for subjects who received utomilumab and mogamulizumab in B1641004 is summarized by maximum CTCAE Grade. The Grade 3 hematology laboratory test abnormalities reported were: lymphopenia (7 subjects; 29.2%) and anemia (2 subjects; 8.3%); and in Grade 4 only lymphopenia (1 subject; 4.1%) was reported. The Grade 3 serum chemistry abnormalities reported were: hyperglycemia (3 subjects; 12.5%), hypophosphatemia (2 subjects; 8.3%), and hyponatremia (1 subject; 4.1%). There were no Grade 4 hematology or Grade 3/4 serum chemistry abnormalities reported.

ECG and Vital Signs

In both Portion A and B, as well as the pembrolizumab plus utomilumab combination, and in the utomilumab plus mogamulizumab combination, there were no observed QTc prolongations (≥ 500 msec) or changes from baseline QTcF (≥ 60 msec) that were considered clinically significant per Investigator assessment.

In both Portion A and B, as well as the utomilumab plus pembrolizumab combination, there were no observed heart rates (< 50 bpm and > 120 bpm) or change in heart rate (decrease/increase from baseline ≥ 30 bpm) that were considered clinically significant, per Investigator assessment. In both Portion A and B, there were no observed blood pressure measurements (decrease/increase baseline systolic ≥ 30 m Hg or baseline diastolic blood pressure ≥ 20 mm Hg) that were considered clinically significant per Investigator assessment.

Safety Summary

In summary, the observed safety profile, based on a data cut-off date of 06 July 2017 for B1641001, support the use of utomilumab both as a single agent and in combination with rituximab. Treatment-related AEs were generally mild or moderate with four Grade 3/4 AEs (colitis; diarrhea; hyponatremia; hyperbilirubinemia; and fatigue) reported as related to PF-5082566 in Portion A. The observed safety profile supports utomilumab use in combination with pembrolizumab. Treatment-related AEs were generally mild or moderate, with only two Grade 3 AEs reported as treatment-related to both utomilumab and pembrolizumab. In addition, the observed safety profile, based on a data cut-off date of 06 July 2017 for B1641004, supports utomilumab in combination with mogamulizumab. Treatment-related AEs were generally mild or moderate and Grade 1 or Grade 2 in severity.

Pharmacokinetics and Product Metabolism in Humans

Study B1641001: A Phase I Study of PF-05082566 As A Single Agent In Subjects With Advanced Cancer, And In Combination With Rituximab In Patients With Non-Hodgkin's Lymphoma (NHL).

The phase 1 first in human (FIH) study of utomilumab is currently ongoing. This is an open-label, multi-center, multiple-dose study of single agent utomilumab in subjects with solid tumors or relapsed or refractory B-cell lymphoma (Portion A) and of utomilumab in combination with rituximab in subjects with relapsed or refractory CD20 positive NHL (Portion B).

Preliminary median utomilumab concentration versus time profiles for subjects in Portion A (utomilumab alone) and Portion B (utomilumab + rituximab) after single dose (Cycle 1) are depicted in Figure 3. The utomilumab exposure after single dose appeared to increase with increasing doses. The utomilumab terminal half-life (t1/2) ranged from 208 to 349 hours in Portion A and from 274 to 550 hours in Portion B, respectively. The utomilumab AUCinf was slightly higher in Portion B than that in Portion A at corresponding dose levels.

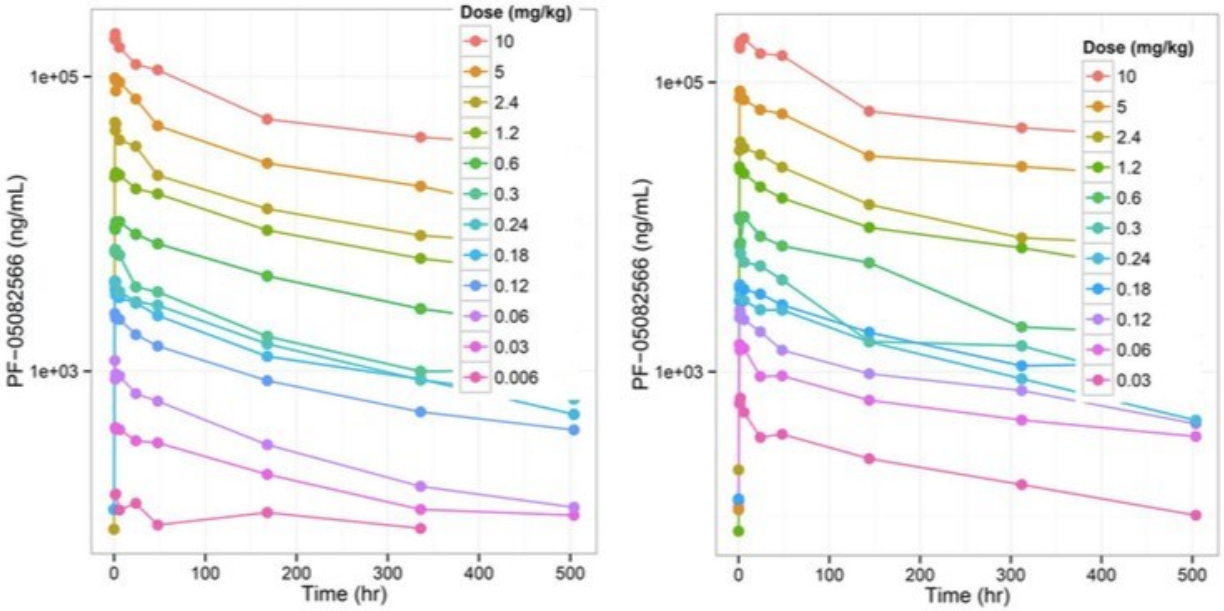


Figure 3. Left Panel: Portion A (utomilumab alone); **Right Panel**: Portion B (utomilumab + rituximab). Utomilumab exposure appeared to increase with increasing doses.

Population Pharmacokinetic Modeling

Preliminary population PK analysis has been conducted using data from 68 subjects (n = 41 in Portion A and n = 27 from Portion B) receiving doses from 0.006 to 5 mg/kg Q4W using serial and sparse PK samples in Study B1641001. A two-compartment model with linear elimination best described these data. Among the covariates tested, both baseline body weight and treatment portion had statistically significant effect on clearance (CL). Baseline body surface area and gender were found to significantly correlate with central volume of distribution (Vc). No other covariates had a statistically significant effect on either CL or Vc. Simulations were performed at various dosing schedules which indicated that the exposure at dose levels higher than 0.12 mg/kg was above the assumed efficacious concentration (Ceff, 1730 ng/mL) with both once every 3 weeks (Q3W) and once Q4W schedule. Although body weight was identified as a significant covariate on CL, it accounted for only a small percentage (~< 7%) of the inter-individual variability in serum utomilumab exposure. In addition, simulations indicated that utomilumab exposure is similar between body weight based and fixed dosing regimens. Therefore, this suggests the possibility of using a fixed dosing regimen in future utomilumab clinical studies.

Immunogenicity

Anti-drug antibodies (ADA) to utomilumab in human serum were determined by a validated, quasi-quantitative bridging electro chemi-luminescence method. Preliminary analyses based on quality-controlled, non-quality-assured data are presented.

In Portion A, 9 of 61 subjects (14.8%) exhibited positive ADA prior to treatment with utomilumab. 35 of 61 subjects (57.4%) were positive for ADA for at least 1 time point

regardless of baseline ADA status. Among 35 ADA-positive subjects, 7 (20%) exhibited positive neutralizing antibody (Nab) against utomilumab.

In Portion B, 2 of 41 subjects (4.9%) exhibited positive ADA against utomilumab prior to treatment with utomilumab plus rituximab. 3 of 41 subjects (7.3%) were positive for ADA for at least 1 time point regardless regardless of baseline ADA status when administered in combination with rituximab. Among 3 ADA-positive subjects, 1 (33.3%) exhibited positive Nab against utomilumab.

The impact of ADA on PK of utomilumab was characterized. ADA-negative subjects were defined as those with negative antibody status for all samples collected during the study including baseline (pre-treatment). ADA-positive subjects were defined as those with at least 1 positive ADA sample anytime during the study including baseline (pre-treatment).

Utomilumab clearance (CL) was similar in ADA-negative and ADA-positive subjects suggesting that ADA status had minimal impact on the PK of utomilumab (see Figure 4).

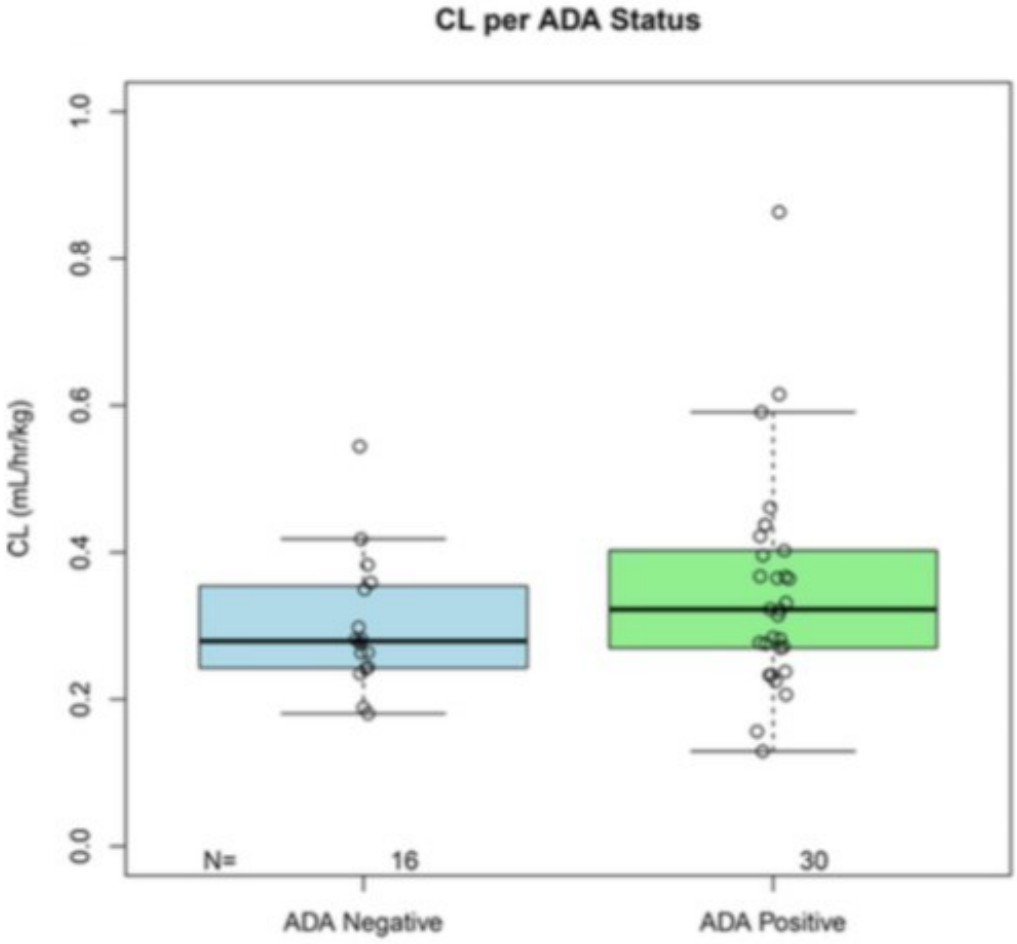


Figure 4. Effect of ADA on utomilumab Clearance (Study B1641001 Portion A)**.**

In study B1641003, 2 out of 23 (8.7%) subjects exhibited positive ADA against utomilumab prior to treatment with utomilumab plus pembrolizumab. The presence of positive ADA at baseline was likely due to pre-existing host antibodies that were cross-reactive with utomilumab.

Seventeen out of 23 subjects (73.9%) were positive for ADA for at least 1 time point regardless of baseline ADA status when administered in combination with pembrolizumab. The overall incidence of treatment-induced ADA was 65.2% (15/23 subjects); 7 out of 23 (30.4%) subjects exhibited positive Nab against utomilumab. Similar utomilumab exposure (eg, AUCtau (dn) and Cmax (dn)) was observed in subjects with treatment-induced ADA and ADA-negative subjects. While mean Cmax (dn) appeared to be lower in subjects with positive NAb, AUCτ (dn) was similar in subjects with positive and negative NAb.

There were 2 (13.3%) out of 15 ADA-positive subjects and 1 (12.5%) out of 8 ADA-negative subjects who experienced treatment-emergent, all causalities hypersensitivity/infusion reactions. There was 1 (14.3%) out of 7 NAb-positive subjects and there were 2 (12.5%) out of 16 NAb-negative subjects who experienced treatment-emergent, all causalities hypersensitivity/infusion reactions.

In addition, the presence of ADA against utomilumab did not preclude subjects from responding to the combination treatment. The response rate was 25% (2 responders out of 8 ADA-negative subjects) and 26.7 % (4 responders out of 15 ADA-positive subjects) for ADA-negative and ADA-positive subjects, respectively. The response rate was 25% (4 responders out of 16 NAb-negative subjects) and 28.6% (2 responders out of 7 NAb-positive subjects) for NAb-negative and NAb-positive subjects, respectively. Overall, there was no detectable impact of ADA/NAb on PK, safety and efficacy.

In study B1641004, among 10 subjects tested for ADA analysis, none of them exhibited positive ADA against utomilumab prior to treatment with utomilumab plus mogamulizumab. Five out of 10 subjects (50%) were positive for ADA against utomilumab for at least 1 time point when administered in combination with mogamulizumab.

Efficacy

Study B1641001: The anti-tumor activity of single-agent utomilumab in subjects with advanced malignancies and utomilumab in combination with rituximab in subjects with CD20-positive NHL is being assessed in the Study B1641001. In this study, tumor responses are reported by Investigators per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for Portion A subjects and irRECIST for subjects enrolled in the expansion cohort of Portion A or International Working Group (IWG) criteria for Portion B.

For Portion A, BOR observed was 1 CR (0.24 mg/kg; MCC) and 2 PR in MCC subjects (1 at 0.24 mg/kg, and 1 at 0.60 mg/kg). One of the PR observed in MCC subject had prior IO-experience (0.24 mg/kg). In the 59 melanoma subjects there were no CR but 1 PR (0.24 mg/kg) was observed. There were no confirmed PR and CR in NSCLC subjects. The irRECIST exploratory analysis was consistent with analysis using RECIST 1.1.

For Portion B, in NHL subjects 4 CR (1 at 0.03 mg/kg, 1 at 0.12 mg/kg, and 2 at 1.20 mg/kg) and 9 PR (2 at 0.18 mg/kg, 3 at 1.20 mg/kg, 1 and 1 at 5.0 mg/kg) were observed. In follicular lymphoma subjects, 4CR (1 at 0.03 mg/kg, 1 at 0.12 mg/kg, and 2 treated at 1.20 mg/kg) and 6 PR (2 at 0.18 mg/kg, 5 at 1.20 mg/kg, 1 at 2.40 mg/kg and 1 at 5.0 mg/kg) was observed.

Study B1641003: The anti-tumor activity of utomilumab in combination with pembrolizumab in subjects with advanced solid tumors was assessed in B1641003. In this study, tumor responses are reported by Investigators per RECIST 1.1 (Eisenhauer, *et al*, 2009). The tumor responses reported below were confirmed by the Investigator on at least 2 consecutive scan evaluations.

Among the 23 subjects treated, 6 had confirmed objective response providing an objective response rate (ORR) of 26.1%. Two (2) subjects had a confirmed CR (1 subject with RCC treated at 1.8 mg/kg and 1 subject with SCLC treated at 5.0 mg/kg). Four (4) subjects achieved a PR: 1 subject with RCC and 1 subject with NSCLC treated at 0.45 mg/kg; 1 subject with anaplastic thyroid disease treated at 3.6 mg/kg, and 1 subject with SCCHN treated at 5 mg/kg.

Study B1641004: Efficacy assessments are ongoing for Study B1641004. Out of 24 subjects evaluated during the utomilumab dose-escalation phase of the study, no RECIST-defined complete responses were observed. One (1) subject had BOR of PR and 9 subjects achieved a BOR of SD.

1.3. Trastuzumab and Ado-Trastuzumab Emtansine

Trastuzumab is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity in a cell-based assay (Kd = 5 nM) to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. The antibody is an IgG1 kappa that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2. The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the epidermal growth factor receptor (EGFR, aka HER1). HER2 protein overexpression is observed in 25% to 30% of primary breast cancers. HER2 protein overexpression can be determined using an immunohistochemistry-based assessment of fixed tumor blocks, and HER2 gene amplification status can be measured by fluorescence in situ hybridation (FISH) in archival formalin-fixed, paraffin-embedded breast tumor tissue specimens. Trastuzumab has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2. Trastuzumab is a mediator of antibody-dependent cellular cytotoxicity (ADCC). *In vitro*, trastuzumab-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

In HER2+ metastatic breast cancer trastuzumab is indicated: 1) in combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer, or 2) as a single-agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

Ado-trastuzumab emtansine is a HER2-targeted antibody-drug conjugate. The antibody is the humanized anti-HER2 IgG1, trastuzumab. The small molecule cytotoxin, DM1, is a microtubule inhibitor that is covalently linked to trastuzumab via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate). Upon binding to sub-domain IV of the HER2 receptor, ado-trastuzumab emtansine undergoes receptor-mediated internalization and subsequent lysosomal degradation, resulting in intracellular release of DM1-containing cytotoxic catabolites. Binding of DM1 to tubulin disrupts microtubule networks in the cell, which results in cell cycle arrest and apoptotic cell death. In addition, *in vitro* studies have shown that similar to trastuzumab, ado-trastuzumab emtansine inhibits HER2 receptor signaling, mediates

antibody-dependent cell-mediated cytotoxicity and inhibits shedding of the HER2 extracellular domain in human breast cancer cells that overexpress HER2.

Ado-trastuzumab emtansine as a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for metastatic disease, or developed disease recurrence during or within six months of completing adjuvant therapy.

1.4. Study Rationale

1.4.1. Rationale for the Combination of Utomilumab with Ado-Trastuzumab and Trastuzumab

Preclinical Combination Studies

Antibody dependent cellular cytotoxicity (ADCC) has been hypothesized as a mechanism of tumor destruction resulting in direct antigen presentation and in the induction of tumor antigen specific T-cell responses ('cross-priming"). This is supported by preclinical experiments demonstrating that the therapeutic efficacy of an anti-HER2/neu antibody depends on both innate and adaptive immunity (Park, *et al*, 2010).

The combinatorial anti-tumor activity of ADCC inducing mAb with 4-1BB agonist mAbs was assessed in both lymphoma and HER2+ breast cancer models. A mouse anti-mouse CD20 antibody with ADCC inducing activity was selected as a surrogate mAb for rituximab. MAB9371 was selected as a surrogate for utomilumab, as utomilumab does not cross react with murine 4-1BB. MAB9371 is a commercially available rat anti mouse 4-1BB agonist mAb (R & D Systems, Minneapolis MN). The binding affinity of MAB9371 for murine 4-1BB is similar to the affinity of utomilumab for human 4-1BB. In both models, treatment with a combination of surrogate mAbs at concentrations with limited single agent efficacy, showed significant tumor growth inhibition (A20 model) and/or enhanced survival (Em-myc model) (Figure 5).

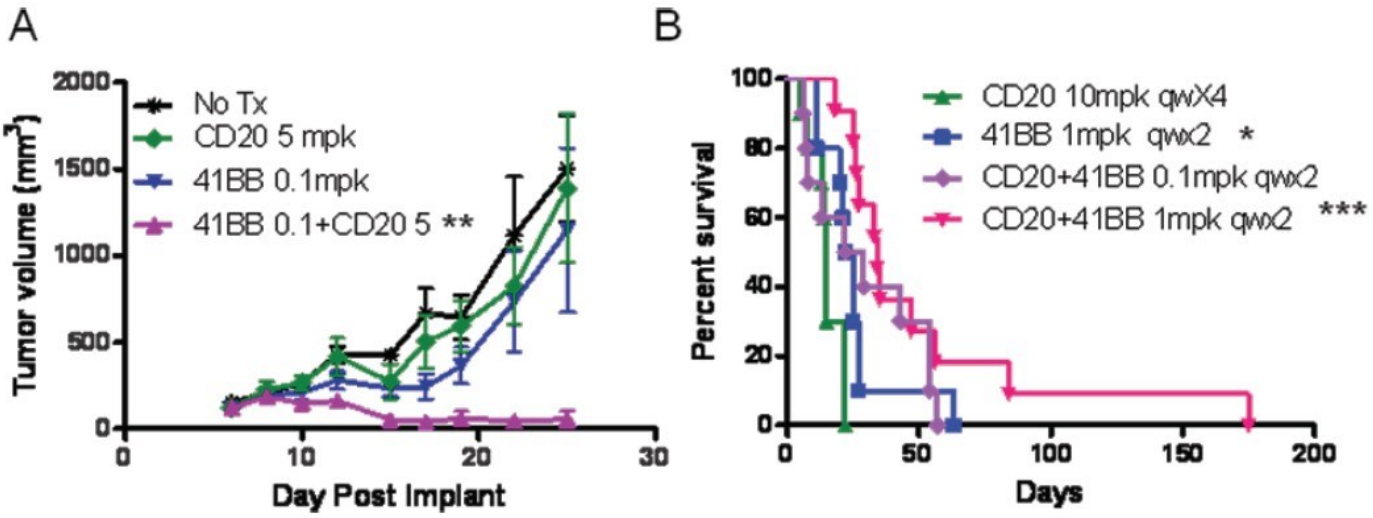


Figure 5. Combinatorial Efficacy of 4-1BB and CD20 Surrogate mAbs in Lymphoma Models 4-1BB agonist antibodies demonstrate significant combinatorial efficacy with ADCC antibodies in transplantable and

spontaneous lymphoma models. **A)** A20 murine lymphoma cells were implanted on the flank of Balb/C mice. Group mean tumor volume measurements at the indicated times are shown above. Error bars represent SEM. Untreated vs single agent p = not significant, untreated vs combination $p < 0.01$. **B)** Survival days post treatment. Median survival was calculated using Graph Pad Prism CD20 = 15 days, 1mpk 4-1BB = 23.5 days, CD20+0.1mpk 4-1BB = 25.5 days, CD20+1mpk 4-1BB = 34 days. Statistical significance of the 4-1BB treatment or combination treatment versus CD20 group was determined using a Log Rank (Mantel-Cox) test using Graph Pad Prism software, CD20 vs 4-1BB $p < 0.02$, CD20 vs CD20 + 0.1mpk 4-1BB p = not significant, CD20 vs CD20 + 1mpk 4-1BB $p < 0.001$.

Anti-4-1BB agonistic mAb enhances anti-breast cancer activity of trastuzumab *in vivo* (Kohrt, *et al*, 2012). The *in vivo* ability of anti-4-1BB mAbs to enhance trastuzumab's activity was tested in a xenotransplanted human breast cancer (BT474M1 cell line) model in athymic mice. These mice have fully competent NK cells while lacking functional T-cells. Anti-4-BB mAb alone had no effect on tumor growth, while trastuzumab had a modest effect (Figures 6A and 6C). Simultaneously, Kohrt explored the effect of trastuzumab and anti-4-1BB mAb in various schedules. Since maximal upregulation of CD137 required 24 hours of NK cell exposure to trastuzumab-coated cells *in vitro*, investigators aimed to determine the importance of injection sequence. Trastuzumab was injected on Day 3 (post-tumor inoculation) and anti-4-1BB mAb was injected either on Day 2, 3 or 4. Treatment was repeated in all groups 14 days following the first injection. Of the three combination sequences tested, trastuzumab followed by anti-4-1BB mAb resulted in the greatest reduction in tumor size and mortality with the opposite order, anti-4-1BB mAb followed by trastuzumab having the least effect both in tumor growth (Figure 6A) and survival (Figure 6B).

Since trastuzumab followed by anti-4-1BB antibodies demonstrated more potent antitumor activity *in vivo*, this injection schedule was chosen for subsequent experiments. When the treatment regimen was repeated weekly for 3 weeks the combination treatment resulted in prolonged control of tumor growth and a significant improvement in survival (Figures 6C and 6D).

Enhancement of the therapeutic activity of trastuzumab by anti-4-1BB mAb is specific to HER2-expressing tumors. To determine if the synergy between anti-HER2 and anti-4-1BB mAbs requires specific recognition by the anti-tumor antibody, two tumors differing in HER2 expression were inoculated subcutaneously in individual mice. On the left flank, mice were inoculated with MCF7 cells, which are HER2 low to negative. On the right flank, mice were inoculated with HER18 cells, a transduced derivative of MCF7 cells that stably overexpress HER2 (Figure 7A)(12). Mice then received either trastuzumab monotherapy on Day 3 or the combination of trastuzumab on Day 3 and anti-4-1BB mAb on Day 4. This sequential therapy was repeated weekly for 3 successive weeks. As expected, only the HER2-overexpressing tumors responded to monotherapy with trastuzumab. The addition of anti-4-1BB mAb resulted in an enhanced therapeutic effect but only against the HER2-positive tumor that could be targeted by the anti-HER2 mAb (Figures 7B-C).

Anti-4-1BB mAb enhances the therapeutic activity of trastuzumab against a human HER2-overexpressing primary breast tumor. Since the combination of trastuzumab and anti-4-1BB antibodies demonstrated increased efficacy against HER2-overexpressing cell lines, we next aimed to assess efficacy of the combination therapy using a primary patient

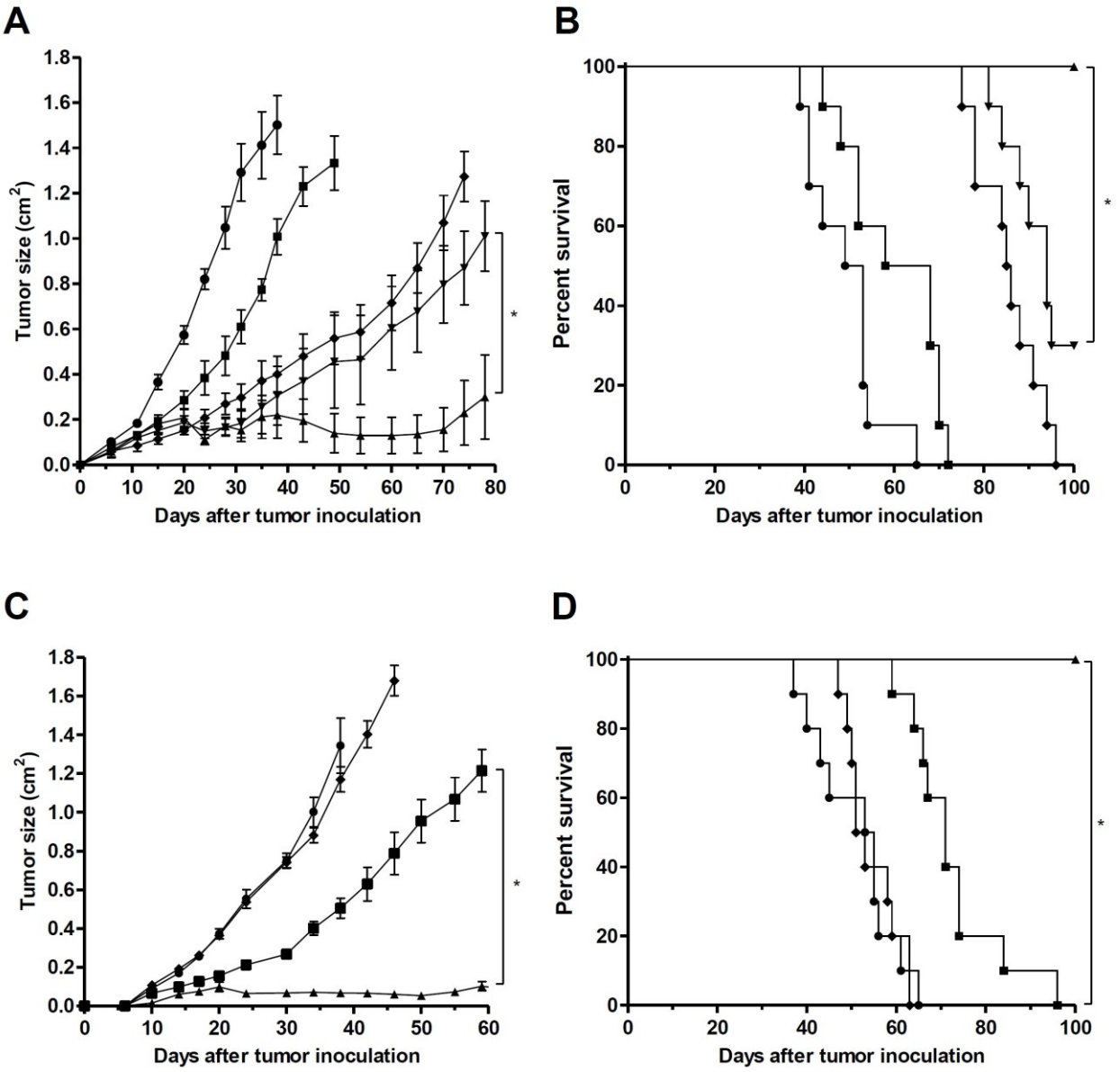


Figure 6. Anti-4-1BB agonistic mAb enhances anti-breast cancer activity of trastuzumab *in vivo*. *Nu/nu* mice were inoculated with 5×10^6 BT474M1 breast tumor cells, subcutaneously, on the abdomen 1 day after subcutaneous injection of 0.72mg/60 day release beta-estradiol pellet (A-D). **(A-B)** Post-tumor inoculation, mice then received two cycles of treatment separated by 14 days with either Rat IgG control on Days 3 and 17(●), trastuzumab antibody on Days 3 and 17(■), trastuzumab antibody on Days 3 and 17 and anti-4-1BB antibody on Days 2 and 16 (♦), trastuzumab antibody on Days 3 and 17 and anti-4-1BB antibody on days 3 and 17 (▼), or trastuzumab antibody on Days 3 and 17 and anti-4-1BB antibody on Days 4 and 18 (▲). Mice (10 per group) were then monitored for tumor growth (A, $*p < .001$) and overall survival (B, $*p = .001$). **(C-D)** To determine if increased frequency of treatment using the superior combination regimen mice received 3 weekly treatment with either Rat IgG control starting on Day 3(●), trastuzumab antibody starting on Day 3(■), anti-4-1BB antibody starting on day 4(♦), or trastuzumab antibody starting on Day 3 and anti-4-1BB antibody starting on Day 4 (▲) with treatment repeated weekly for a total of 3 weeks. Mice (10 per group) were then monitored for tumor growth (C, $*p < .001$) and overall survival (D, $*p = .003$).

xenotransplant model. A primary HER2-overexpressing-breast tumor was successfully engrafted into sub-lethally irradiated SCID mice. After tumors were established the mice were randomized into treatment groups that received either: rat IgG control, trastuzumab, anti-4-1BB mAb, or trastuzumab followed 24 hours later by anti-4-1BB mAb and repeated weekly for a total of 3 weeks. The combination of trastuzumab and anti-4-1BB mAb was superior to trastuzumab alone, significantly reducing tumor growth and prolonging survival (Figures 7D-E).

The enhanced efficacy of trastuzumab in combination with anti-4-1BB has been recently confirmed with ado-trastuzumab emtansine, which has been previously shown to retain ADCC capacity as a mechanism of action *in vitro* and *in vivo* (Junttila, *et al*, 2011; Barok, *et al*, 2011; English, *et al*, 2014). Two murine models have been performed which confirm the synergy observed with anti-4-1BB and ado-trastuzumab emtansine combination therapy including a HER18 xenograft model and an SU-258 primary breast model (data not shown).

Overexpression of HER2 is observed in approximately 20% of human breast cancers and is implicated in the aggressive growth and poor clinical outcomes associated with these tumors. While the development of trastuzumab, pertuzumab, lapatinib and ado-trastuzumab emtansine provided patients with HER2-positive tumors a markedly better outcome than with chemotherapies, virtually all patients with HER2-positive MBC will eventually progress despite these available therapies, leading to mortality. Opportunities remain to improve outcomes for patients with MBC. Ado-trastuzumab emtansine and trastuzumab have individually demonstrated activity in patients *with HER2-positive MBC*, and additionally, nonclinical data showing synergy with the combination of ado-trastuzumab emtansine and anti-4-1BB mAb, and between trastuzumab and anti-4-1BB mAb, suggest that investigation of ado-trastuzumab emtansine or trastuzumab in combination with anti-4-1BB mAb in patients with HER2-positive, locally advanced (unresectable) or metastatic breast cancer is warranted. Such patients represent the patient population eligible for study enrollment.

1.4.2. Rationale for Utomilumab and Ado-Trastuzumab/Trastuzumab Doses

1.4.2.1. Utomilumab

Preliminary population PK analysis showed that body weight accounts for only a small percentage (~7%) of the variability in drug exposure. Simulations indicated that utomilumab exposure profiles are similar in both body weight and flat utomilumab dosing regimens. Therefore, it is suggested a fixed dosing regimen be utilized for ease of use and to minimize potential medication errors.

Active doses for utomilumab ranged from 0.24 mg/kg to 0.6 mg/kg (approximately 20 to 50 mg) in Merkel cell carcinoma (MCC) as a single agent. It is not clear if higher doses might be active as limited number of MCC patients were treated at higher doses. Responses were also observed with the combination of utomilumab and rituximab (R) in R-refractory NHL as low as 0.03 mg/kg with highest active dose of 2.4 mg/kg. These data suggest that the active dose range of utomilumab is quite broad, spanning an approximate 100-fold dose range.

Flat utomilumab doses of 20 (approximately 0.24 mg/kg), 100 (approximately 1.2 mg/kg), and 500 mg (approximately 6 mg/kg) are being tested in Pfizer Study B9991004. In this study, two dose levels of utomilumab (20 mg IV, and 100mg IV) will be tested in combination with ado-trastuzumab or trastuzumab.

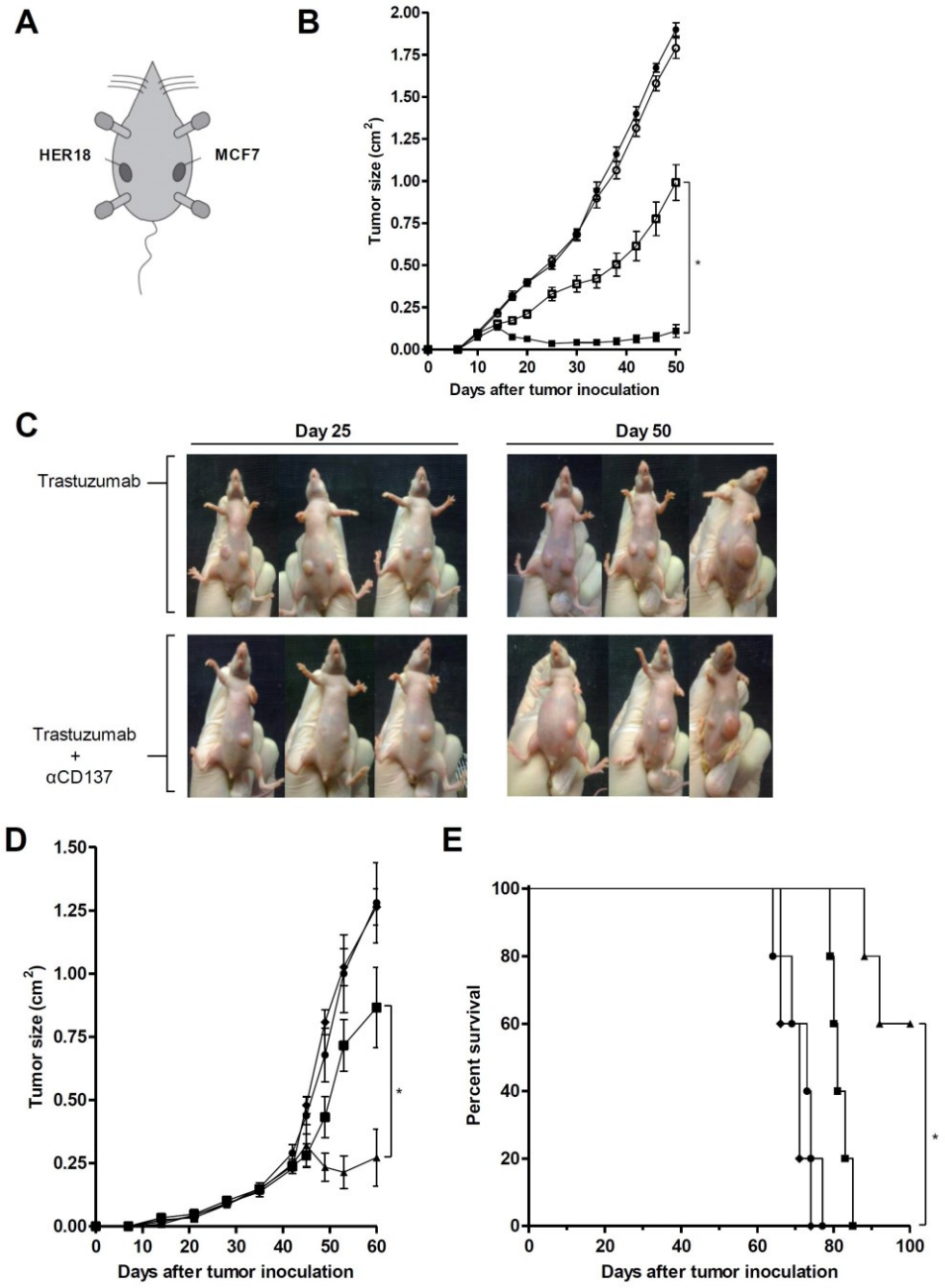


Figure 7. Anti-4-1BB agonistic mAb enhances anti-breast cancer activity of trastuzumab *in vivo* while retaining HER2 specificity against HER2-overexpressing breast cancer cell lines and a primary breast tumor. *Nu/nu* mice were inoculated with 5×10^6 MCF7 breast tumor cells subcutaneously on the left flank and 5×10^6 HER18 breast tumor cells subcutaneously on the right flank **(A, Schema)**. **(A-C)** Post-tumor inoculation, mice received either trastuzumab on Day 3, or trastuzumab on Day 3 and anti-4-1BB antibody on Day 4 with each treatment repeated weekly for a total of 3 weeks. **(B)** Mice (10 per group) were monitored for tumor growth of MCF7 on the left flank (○) and HER18 on the right flank (□) in mice treated with trastuzumab, and MCF7 on the left flank (●) and HER18 on the right flank (■) in mice treated with trastuzumab and anti-4-1BB mAbs (*$p < .001$).
(C) Representative mice (3 of 10 per group) at 25 and 50 days post-tumor inoculation. SCID mice were inoculated with 1×10^6 HER2$^+$ primary breast tumor cells (SU-258) by intramammary injection 24 hours after 200 cGy total body irradiation (TBI) **(D-E)**. On Day 40 mice were randomized to 1 of 4 groups (5 mice per group) including IgG control with treatment on Day 40 (●), trastuzumab on Day 40 (■), anti-4-1BB mAb on Day 41 (♦), or trastuzumab on Day 40 and anti-4-1BB mAb on Day 41 (▲). Treatment was repeated weekly in each group for a total of 3 treatments. Mice were monitored for tumor growth (D, *$p = .016$) and overall survival (E, *$p = .002$).

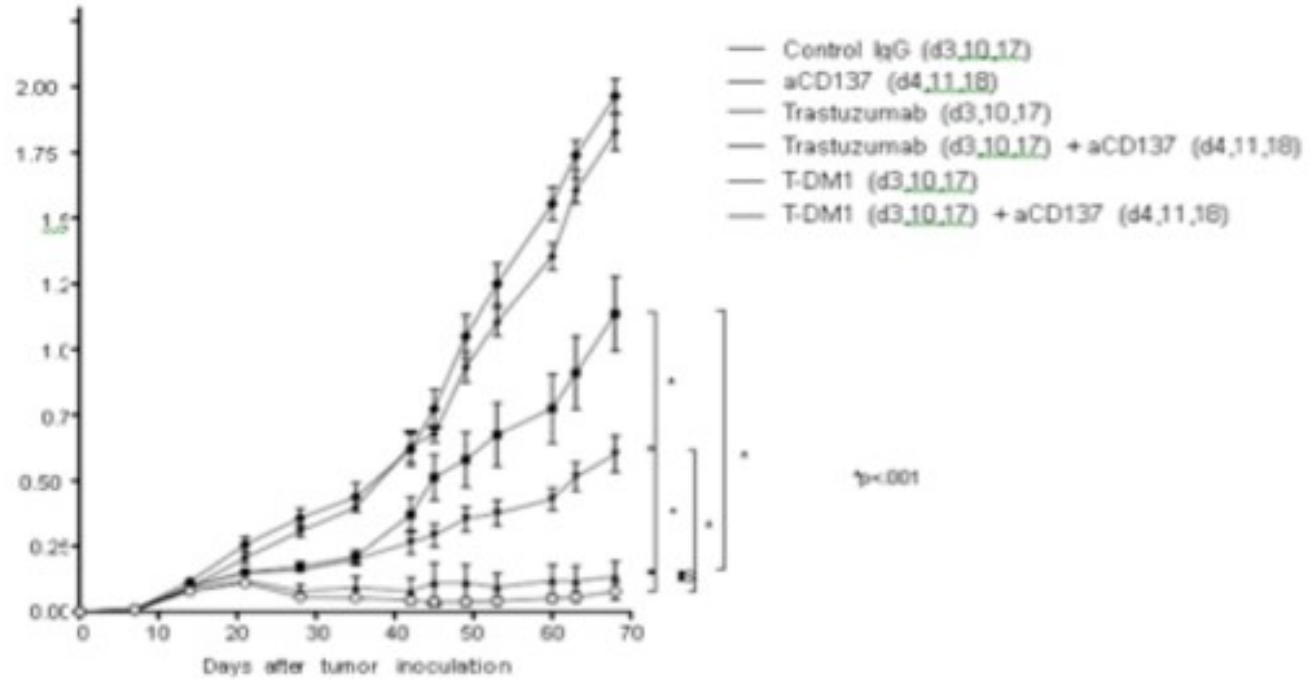


Figure 8. TDM-1 retains potency against and demonstrates synergistic activity with anti-4-1BB mAb therapy against HER2-overexpressing breast cancer, including a HER18 xenograft model (shown), and an SU-258 primary breast model (data not shown). In the HER18 model, Nu/nu mice were inoculated with 1×10^6 $HER2^+$ HER18 tumor cells by subcutaneous injection. On Day 3, mice were randomized. In the SU-258 primary model, SCID mice were inoculated with 1×10^6 $HER2^+$ primary breast tumor cells (SU-258) by intramammary injection 24 hours after 200 cGy total body irradiation (TBI).

1.4.2.2. Ado-Trastuzumab/Trastuzumab

The dose selection for ado-trastuzumab emtansine (3.6 mg/kg IV q 3 weeks) in this protocol is the full FDA-approved dose for patients with HER2+ metastatic breast cancer, and the dose selection of trastuzumab (6 mg/kg IV q3 weeks) is the full FDA-approved drug dose for treatment of HER2+ metastatic breast cancer.

2. STUDY OBJECTIVES; ENDPOINTS; AND OUTCOMES

2.1. Objectives

Primary Objective:

- Estimate the maximum tolerated dose (MTD) and determine the recommended dose (RP2D) of utomilumab in combination with ado-trastuzumab emtansine (T-DM1) in subjects with HER2-positive advanced breast cancer.

Secondary Objectives:

- Determine the objective tumor response rate (ORR)
- Determine the time-to-tumor response (TTR)

- Determine the duration of response (DR)
- Determine progression-free survival (PFS)
- Assess the safety and tolerability of utomilumab in combination with ado-trastuzumab emtansine or trastuzumab

Exploratory Objectives:

- Evaluate the pharmacokinetics (PK) of utomilumab and ado-trastuzumab emtansine or trastuzumab when given in combination
- Evaluate preliminary evidence of antitumor activity of utomilumab in combination with ado-trastuzumab emtansine or trastuzumab
- Evaluate the immunogenicity of utomilumab and ado-trastuzumab emtansine or trastuzumab when given in combination
- Assess the presence of CD8+ T-cells in HER2-positive tumors
- Evaluate the modulation of immune activity biomarkers by utomilumab in combination with ado-trastuzumab emtansine or trastuzumab.

Analysis of samples from subjects who received utomilumab and trastuzumab is optional.

2.2. Endpoints

Primary Endpoint

- First 2 cycles dose-limiting toxicities (DLTs)

Secondary Endpoints

- Objective tumor response rate (ORR) per RECIST v1.1
- Time-to-event measures:
  - Time-to-tumor response (TTR)
  - Duration of response (DR)
  - Progression-free survival (PFS)
- Adverse events (not including laboratory abnormalities) as characterized by types, severity (as graded by NCI CTCAE v5), timing, seriousness, and relationship to study treatments
- Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v5) and timing

Exploratory Endpoints:

- C_{trough} and C_{max} of utomilumab, ado-trastuzumab emtansine, or trastuzumab
- Anti-drug antibody level and incidence
- Tumor tissue biomarkers (including number and percentage of CD8+ T-cells)
- Peripheral blood and additional tumor tissue biomarkers consisting of the levels of cells, DNA, RNA or proteins, such as CD8 T-cells, PD-L1, TCR sequence changes, and

biomarkers of the IFN© pathway, that may be related to anti-tumor immune response and/or response to or disease progression on utomilumab in combination with trastuzumab or ado-trastuzumab emtansine.

Analysis of samples from subjects who received utomilumab and trastuzumab is optional.

2.3. ClinicalTrials.gov Outcomes

Primary Outcome

Incidence of dose-limiting toxicities (DLTs) within the first 2 cycles (up to 2 months) reported for the Dose-finding Cohorts 1 (ado-trastuzumab emtansine) and 2 (trastuzumab). Subjects lost to follow-up before completion of first 2 cycles due to reasons unrelated to treatment-related adverse events are not evaluable for DLT.

Secondary Outcomes

1. Objective tumor response rate (ORR) after 2 cycles for subjects in Expansion Phase 1B Cohort 1 (ado-trastuzumab emtansine), per RECIST v1.1 (see Appendix 1)
2. Time-to-event measures, for subjects in Expansion Phase 1B Cohort 1 (ado-trastuzumab emtansine) who have at least 1 on-study tumor assessment:
    - Time-to-tumor response (TTR), per RECIST v1.1 (see Appendix 1), in subjects that respond within 4 months
    - Duration of response (DR), per RECIST v1.1 (see Appendix 1), in subjects that respond, through up to 5 years after treatment
    - Progression-free survival (PFS) of subjects (percentage) who initiate treatment, reported as the number who remain alive without progression 5 years after treatment. Subjects withdrawn for treatment-related AEs, or lost to follow-up before 5 years, will report as the last date known alive
3. Incidence of adverse events (not including laboratory abnormalities) while receiving treatment and within 30 days, reported by treatment group for severity (as graded by NCI CTCAE v5), seriousness (YES/no), and relationship to the study treatments
4. Incidence of laboratory abnormalities reported by treatment group for severity (as graded by NCI CTCAE v5)

3. PARTICIPANT SELECTION

The Inclusion and Exclusion Criteria are provided on the Participant Eligibility Checklist following, which must be completed in its entirety for each subject prior to registration (see Section 10.4 Subject Registration). The checklist may be extracted from this document for use in screening potential subjects. The completed, signed, and dated checklist must be retained in the subject's study file, and the study's Regulatory Binder.

Pursuant to Stanford Medicine SOP "Confirmation of Participant Eligibility in Clinical Trials," the treating Physician (investigator); the Study Coordinator; and an Independent Reviewer will verify that the subject's eligibility is accurate; complete; and legible in source records. A description of the eligibility verification process should be included in the EPIC or other Electronic Medical Record progress note.

Protocol Title:	A Phase 1B Dose Escalation Trial of human anti-4-1BB agonistic antibody Utomilumab (PF-05082566) with ado-trastuzumab-emtansine or trastuzumab in patients with HER2-positive advanced breast cancer
Protocol Number:	IRB-37299 / BRS0070
Principal Investigator:	George W Sledge, Jr, MD

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC-Approved ☒ IRB-Approved ☒ Contract signed ☐

IV. Inclusion / Exclusion Criteria

Inclusion Criteria (From IRB-approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. History of biopsy-proven HER2-overexpressing breast cancer and radiographic evidence of metastatic disease, or locally-recurrent unresectable disease. The HER2 status can be determined either by immunohistochemistry (IHC) [IHC score, 3+] or by fluorescence *in situ* hybridization (FISH) [as defined by HER2/CEP-17 ratio ≥ 2.0, or HER2 copy number ≥ 6], or as otherwise defined by 2018 ASCO/CAP guidelines. o Cohort 1 subjects must have received trastuzumab and a taxane separately or in combination. o Subjects in Cohort 2 (**closed January 2020**) must have received at least 1 prior therapy, including ado-trastuzumab emtansine. o Subjects who discontinued prior trastuzumab or ado-trastuzumab emtansine due to progressive or refractory disease ***are*** eligible for enrollment.	☐	☐	

Inclusion Criteria (From IRB-approved protocol)	**Yes**	**No**	**Supporting Documentation***
2. Available tumor samples. For eligibility, if no unstained slides remain, stained pathology slides may be reviewed at the treating institution. However, a tumor sample is required for research evaluations per the following (any of Item 1; 2; or 3, in order of preference). 1. A FFPE tumor tissue block from a *de novo* fresh tumor biopsy obtained during screening will be requested, though not mandated. 2. A recently-obtained archival FFPE tumor tissue block (or 10 to 15 unstained slides) from a primary or metastatic tumor resection or biopsy if the following criteria are met: A. The biopsy or resection was performed within 1 year of enrollment **OR** B. The subject has not received any intervening systemic anti-cancer treatment from the time the tissue was obtained and enrolled onto the current study. **OR** 3. Any archival FFPE tumor tissue block (or unstained slides) from primary tumor resection specimen (if not provided per above). The archival sample may have been collected at any time prior to the current study, regardless of any intervening therapy. If an FFPE tissue block cannot be provided, a minimum of 10 unstained slides (15 preferable) will be acceptable.	☐	☐	
3. Subjects must have evaluable OR measurable disease, as defined by RECIST v1.1.	☐	☐	
4. Women or men, age ≥ 18 years old.	☐	☐	
5. Performance status 0 to 1 (by Eastern Cooperative Oncology Group [ECOG] scale).	☐	☐	

Inclusion Criteria (From IRB-approved protocol)	**Yes**	**No**	**Supporting Documentation***
6. Laboratory parameters (must satisfy all): Absolute neutrophil count (ANC) ≥ 1.5×10^9/L (≥ 1500/μL) Platelet count ≥ 100×10^9/L (≥ 100,000/μL) Hemoglobin ≥ 9.0 g/dL; subjects on therapeutic anticoagulation are eligible if there is no bleeding and they are on a stable dose of anticoagulation therapy (eg, on Coumadin with an INR of 2 to 3) for at least 7 days before registration (prior to the start of therapy, or stable heparin or Factor Xa inhibitor dose) Serum creatinine ≤ 1.5 × the ULN or calculated creatinine clearance (by Cockcroft-Gault formula) ≥ 60 mL/min Aspartate aminotransferase (AST) ≤ 2.5 × ULN Alanine aminotransferase (ALT) ≤ 2.5 × ULN Bilirubin ≤ 1.5 × ULN	☐	☐	
7. Subjects must not be pregnant or breastfeeding. A pregnancy test will be obtained if the subject is a woman of child-bearing potential, defined as a sexually-mature woman who has not undergone a hysterectomy or and/or bilateral oophorectomy or who has not been naturally postmenopausal for at least 24 consecutive months (ie, who has had menses at any time in the preceding 24 consecutive months) with 2 pregnancy tests, one at screening, and another immediately preceding the initiation of treatment.	☐	☐	
8. Subjects must have signed an informed consent document stating that they understand the investigational nature of the proposed treatment	☐	☐	
9. Left ventricular ejection fraction determined by echocardiogram or multiple-gated acquisition scan (MUGA) (cardiac scan) must be 50% or higher	☐	☐	

Exclusion Criteria (From IRB-approved protocol)			
1. Previously discontinued either trastuzumab or ado-trastuzumab emtansine due to intolerance.	☐	☐	
2. Received any other investigational agents within 30 days of registration.	☐	☐	
3. Central nervous system (CNS) metastases, unless previously treated by either radiation therapy and/or surgical resection, clinically-stable for at least 60 days and on a stable corticosteroid dose of ≤ 4 mg/day decadron (or equivalent steroid regimen) for at least 1 month. Subjects with a history of CNS metastases that are both treated and stably-controlled are eligible if all of the following apply: o Therapy has been administered (surgery and/or radiation therapy); o There is no additional treatment planned for brain metastases; o The subject is clinically-stable; o The subject is on a stable corticosteroid dose of ≤ 4 mg/day decadron (or equivalent steroid regimen) for at least 1 month.	☐	☐	
4. Prior malignancy (other than *in situ* cervical cancer, or basal cell or squamous cell carcinoma of the skin), unless treated with curative intent and without evidence of disease for 3 years or longer	☐	☐	
5. Administration of other prior anticancer therapies within 4 weeks of enrollment, except ongoing administration of a bisphosphonate drug or denosumab as treatment for bone metastasis	☐	☐	
6. Toxicities related to prior anticancer treatment (except alopecia) that have not resolved to ≤ Grade 1 according to common terminology criteria for adverse events (CTCAE v5) before registration or prior to start of therapy	☐	☐	
7. Currently receiving systemic antibiotic, antiviral, or antifungal therapy for the treatment of an active infection	☐	☐	

Exclusion Criteria (From IRB-approved protocol)			
8. Systemic corticosteroid therapy at doses of greater than prednisone 5 mg daily (or dose-equivalent chronic steroid regimen) for therapeutic and not adrenal replacement indications (maintenance steroid use for adrenal insufficiency is permitted). Acute emergency administration, topical applications, inhaled sprays, eye drops or local injections of corticosteroids are allowed.	☐	☐	
9. History of bleeding diathesis	☐	☐	
10. Any co-morbid medical condition deemed by the treating or principal investigator to possibly put the subject at significant risk for toxicity.	☐	☐	
11. Subject has known sensitivity to any of the products to be administered during dosing	☐	☐	
12. Subject has any kind of disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures	☐	☐	
13. Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements	☐	☐	
14. History of venous thromboembolism within prior 6 months.	☐	☐	
15. Subject with reproductive potential who will not agree to use, during the study and for 60 days after the last dose of utomilumab or 6 months for ado-trastuzumab emtansine or trastuzumab 2 highly effective method of contraceptive such as: o Implants o Injectables o Intrauterine devices (IUDs) such as copper T or levonorgestrel-releasing intrauterine system (LNG-IUS) o Sexual abstinence o Vasectomized partner o Condom or occlusive cap (diaphragm or cervical/vault cap) supplemented with the use of a spermicide during treatment.	☐	☐	

*All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Stanford Designate Signature:	Date:
Printed Name:	

3.3. Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

3.4. Study Timeline

It is anticipated that the study will reach primary completion (final subject enrollment and treatment) within 48 months from the time the study opens to accrual. The study is estimated to reach completion 60 months from the time the study opens to accrual.

Treatment with study drugs will continue until completion of 24 cycles of treatment (up to about 18 months), confirmed disease progression, subject refusal, unacceptable toxicity, whichever occurs first, or the study is prematurely terminated by the investigator, or one of the other reasons for subject withdrawal as specified in Section 4.8 will occur.

4. STUDY DESIGN

This is a parallel cohort, open-label, non-randomized treatment study. The cohorts are:

1. Ado-trastuzumab emtansine 3.6 mg/kg IV Q3W plus utomilumab (Cohort 1, with utomilumab administered at 20 mg or 100 mg), or
2. Trastuzumab 6 mg/kg IV Q3W plus utomilumab (Cohort 2, with utomilumab administered at 20 mg or 100 mg. Cohort closed January 2020)

4.1. Starting Dose Selection Strategy

In the ongoing first-in-human phase 1 study B1641001, utomilumab has been well-tolerated up to 10 mg/kg once every 4 weeks with no dose-limiting toxicity.

However, in order to minimize the potential risk of synergistic toxicity due to the combination, a starting dose of utomilumab 20 mg (0.24 mg/kg) [which is 41.6-fold lower than the 10 mg/kg dose found to be well-tolerated with no dose-limiting toxicity in protocol B1641001] was chosen for this protocol, as this dose is 1) safe, and 2) exposure is adequate based on the cumulative data in the B1641001 study.

The starting dose for ado-trastuzumab emtansine (3.6 mg/kg IV q 3 weeks) in this protocol is the full FDA-approved dose for subjects with HER2+ metastatic breast cancer, and the starting dose of trastuzumab (6 mg/kg IV q3 weeks) is the full FDA-approved drug dose for treatment of HER2+ metastatic breast cancer.

4.2. Criteria for Dose Escalation

For Cohort 1, utomilumab at escalating doses of 20 mg and 100 mg will be given intravenously in combination with the FDA-approved dose and schedule of ado-trastuzumab emtansine (3.6 mg/kg IV) every 3 weeks. On Cycle 1, ado-trastuzumab emtansine will be administered on Day 0, followed by utomilumab on Day 1. On all subsequent cycles (because of the known long half-life of ado-trastuzumab emtansine), ado-trastuzumab emtansine and

utomilumab will be administered on the same day, with utomilumab being administered following the end of ado-trastuzumab emtansine infusion. Initially, 3 subjects will be treated at each dose level. For the first 3 subjects at each utomilumab dose level, there will be a minimum 7-day window between the first dose of subject 1 and the first dose of subject 2. For all subsequent subjects enrolled in dose-escalation stages, a minimum 72-hour window will apply between first doses. For the expansion cohort combination of ado-trastuzumab emtansine plus utomilumab at the RP2D dose, no fixed time interval between subject enrollment and treatment need apply.

As indicated in the Protocol Synopsis Schema section above, it is to note that other more complex adaptive trial designs were considered, however as just 2 doses of utomilumab will be tested in combination with ado-trastuzumab emtansine or trastuzumab, and as the safety of utomilumab IV has been well tolerated to date in combination with other ADCC-inducing mAbs (with defined PK), the present dosing scheme has been devised as an efficient means to arrive at the RP2D. Accordingly, the criteria for dose-escalation will be based on a modified 3+3 dose-escalation procedure (with expansion of the RP2D dose levels to a total of 9 subjects to gain further confidence in the RP2D determination).

However, if a DLT is observed in 1 of the initial 3 treated subjects, 3 additional subjects will be enrolled and treated at the same dose level.

If no further DLT is observed, the next dose level will be opened.

Subsequent dose levels will not be opened until all subjects entered at the current dose level have been treated and observed for at least 21 days after the 1st dose in Cycle 2 is given, and the number of DLTs among those subjects in their first two cycles has been determined. If a subject in a cohort drops out of study during the DLT observation period due to reasons other than a dose limiting toxicity (eg, progression of disease; no longer willing to participate; etc), another subject (ie, replacement) will be enrolled.

Dose-escalation will continue until DLTs are observed in at least 2 of the 3 to 6 subjects treated at a dose level, leading to the conclusion that the MTD has been exceeded and thereby ending dose-escalation (or until utomilumab 100 mg IV dose cohorts with ado-trastuzumab emtansine and trastuzumab are filled). Doses of utomilumab higher than 100 mg will not be tested in either Cohort 1 or Cohort 2, even if the MTD of utomilumab in combination with either ado-trastuzumab emtansine or trastuzumab is not exceeded. If a dose exceeding the MTD has been identified, the next lower dose is declared the MTD, provided that 6 subjects have already been treated at that dose with 0 or 1.

DLTs experienced in total. [3 additional subjects may need to be enrolled at this dose level for a total of 6]. If 2 or more subjects are deemed to have DLTs, the dose will be further de-escalated and the dosing interval will be adjusted based on the observed DLTs.

When 6 subjects have been treated at the MTD dose, the MTD dose cohort will be further expanded to a total N = 9 subjects in order to further characterize the safety at that dose level. If 3 or more subjects at the expanded MTD experienced DLT, the dose will be de-escalated. The MTD/RP2D will be defined as the utomilumab dose in combination with standard dose ado-trastuzumab emtansine in which no more than 2 of 9 subjects experience DLT. The expansion cohort may be selected at this dose or at a lower dose based on observed clinical activity.

For Cohort 2, Dose Level 1 – Utomilumab 20 mg IV + trastuzumab 6 mg/kg IV every 3 weeks. 3 subjects will be treated at this dose level. If no DLT events are recorded, then utomilumab dose will be increased to 100 mg (Dose Level 2, below). If 1 DLT is observed amongst the first 3 subjects, then Dose Level 1 will be expanded to 6 subjects. If no further DLTs are observed, then utomilumab will proceed to 100 mg (Dose Level 2). If 2 (or more) DLTs are recorded at Dose Level 1, enrollment in the trastuzumab + utomilumab cohort will be terminated.

Dose Level 2 – Utomilumab 100 mg IV + trastuzumab 6 mg/kg IV every 3 weeks. 3 subjects will be dosed initially. If 1 DLT is observed, Dose Level 2 will be expanded to 6 subjects. If no further DLTs are observed, then utomilumab 100 mg IV + trastuzumab 6 mg/kg IV will be expanded to 9 subjects to gain further confidence in the RP2D determination. If no DLTs are observed in the first 3 subjects, then Dose Level 2 will also be expanded to 9 subjects total to define the RP2D. If more than 2 DLTs are recorded in Dose Level 2, then by definition the MTD will be exceeded, and dosing will be decreased to utomilumab 20 mg/kg IV, with enrollment to the Dose Level 1 cohort to a total of 9 subjects. If ≤ 2 DLTs are observed in 9 subjects at Dose Level 1 (utomilumab = 20 mg/kg IV), then utomilumab 20 mg/kg IV in combination with trastuzumab 6 mg/kg IV will be the RP2D.

Due to differences in eligibility between Cohort 1 and Cohort 2, dose-finding and dose-escalation are not dependent between cohorts, and may occur at different times. Accrual to both cohorts for dose-finding and dose-escalation will occur in parallel to optimize efficiency in dose-finding.

On Cohort 2, Cycle 1, trastuzumab will be administered on Day 0, followed by utomilumab on Day 1. On all subsequent cycles, trastuzumab and utomilumab will be administered on the same day, with utomilumab being administered following the end of trastuzumab infusion. Initially, 3 subjects will be treated at each dose level (utomilumab at RP2D). For the first cohort (utomilumab given at RP2D), there will be a minimum 7-day window between the first dose of subject 1 and the first dose of subject 2. For all subsequent subjects enrolled, a minimum 72-hour window will apply between first doses. Utomilumab doses above 100 mg will not be tested in this protocol, even if an MTD in combination with trastuzumab 6 mg/kg every 3 weeks is not observed. If a subject in a cohort drops out of study during the DLT observation period due to reasons other than a dose-limiting toxicity (eg, progression of disease, no longer willing to participate, etc), another subject (ie, replacement) may be enrolled. For reference, the study schema is presented again in Figure 9.

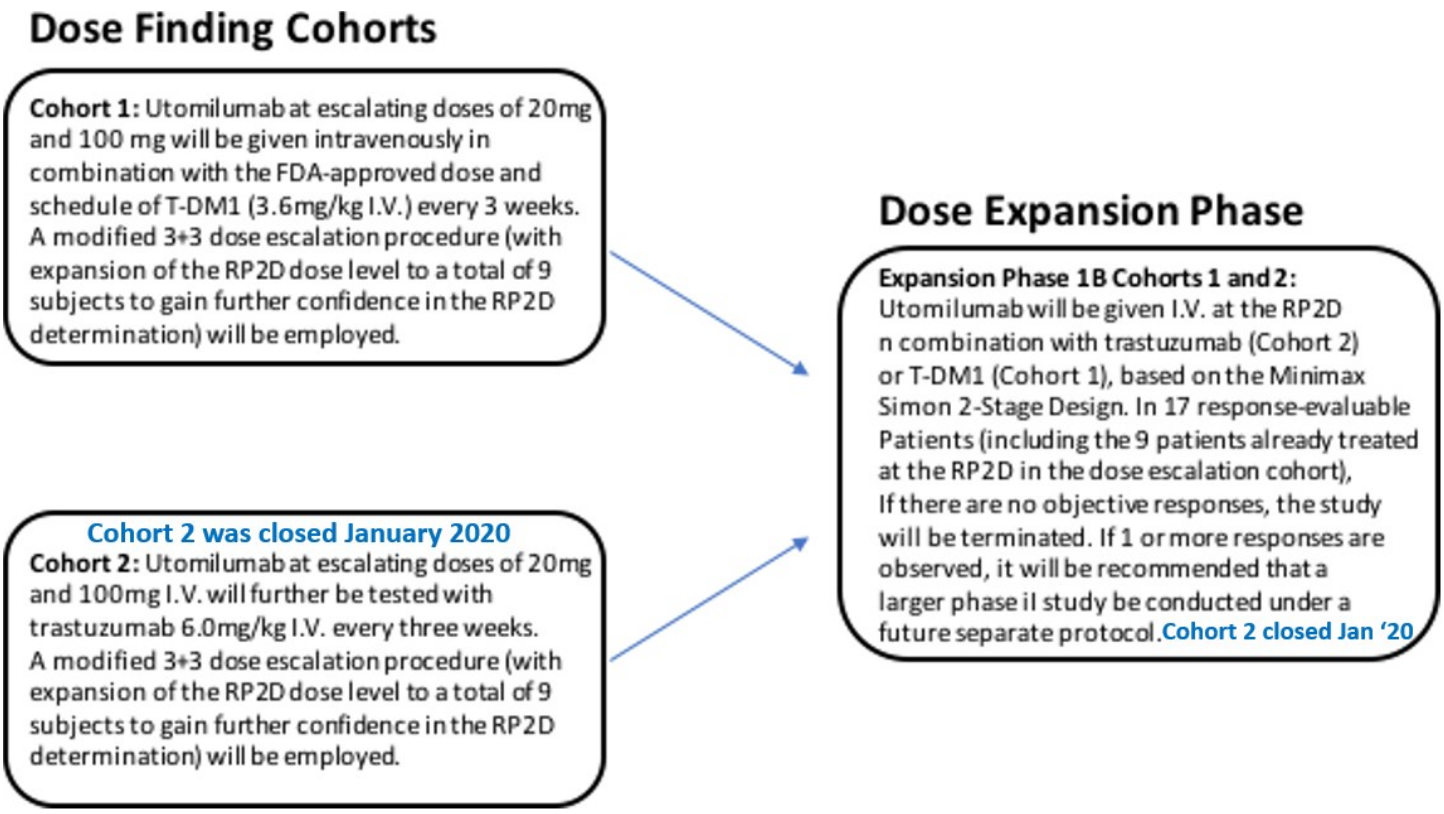


Figure 9. Protocol Schema

4.3. Expansion Phase 1B Cohorts 1 and 2

Utomilumab will be given IV at the RP2D in combination with ado-trastuzumab emtansine (Cohort 1) or trastuzumab (Cohort 2, closed January 2020), based on Minimax Simon 2 Stage Design. The null hypothesis that the true objective response rate is 5% will be tested against a one-sided alternative. In 17 response-evaluable subjects (including the 9 subjects already treated at the RP2D in the dose-escalation stage), if there are no objective responses the study will be terminated. If 1 or more responses are observed, it will be recommended to conduct a future formal phase 2 study of the utomilumab combination under a separate protocol document.

4.4. Dose-limiting Toxicity (DLT) Definition

Severity of AEs will be graded according to CTCAE version 5. For the purpose of dose-escalation, any of the following adverse events occurring during the DLT observation period (first 2 Cycles, ie, 6 weeks) that are attributable to one or both study drugs will be classified as DLTs:

Hematologic

- Grade 4 neutropenia lasting > 7 days
- Febrile neutropenia, defined as absolute neutrophil count (ANC) < 1000/mm^3 with a single temperature of > 38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than 1 hour;

- Grade ≥ 3 neutropenic infection
- Grade ≥ 3 thrombocytopenia with bleeding
- Grade 4 thrombocytopenia. Non-Hematologic:
- Grade ≥ 3 non-laboratory toxicities, except for nausea, vomiting and diarrhea that has been treated and recovered to < Grade 2 within 48 hours.
- Grade ≥ 3 laboratory abnormalities [other than aspartate aminotransferase/ alanine aminotransferase (AST/ALT)] if:
    - Medical intervention is required to treat the subject, or
    - The abnormality leads to hospitalization, or
    - Lasts more than 24 hours
- Grade 4 AST and ALT increase
- Criteria for Hy's Law is met:
    - ALT or AST > 3 × ULN
    - Total bilirubin > 2 × ULN, with no elevation of alkaline phosphatase
    - No other reason for these abnormalities or pre-existing liver disease

4.5. Maximum-tolerated Dose (MTD) Definition

The MTD estimate is the highest dose associated with the occurrence of DLTs, as pre-specified in the DLT Definition section, in < 33% of DLT-evaluable subjects.

In practice using the modified 3+3 design, the MTD estimate is the dose level at which 0 of 6; 1 of 6; or 2 of 9 DLT-evaluable subjects experience a DLT during the first two cycles with the next higher dose having at least 2 of 3 to 6 or at least 3 of 9 DLT-evaluable subjects experiencing DLTs.

4.6. Recommended Phase 2 Dose (RP2D) Definition

The recommended phase 2 dose (RP2D) is the dose chosen for further study based on phase 1 results. If the MTD proves to be clinically feasible for long term administration in a reasonable number of subjects, such dose usually becomes the RP2D. Further experience with the MTD may result in a RP2D dose lower than the MTD.

4.7. Concomitant Medication and Supportive Care Guidelines

Administration of other prior anticancer therapies within 4 weeks of enrollment, except ongoing administration of a bisphosphonate drug or denosumab as treatment for bone metastasis, is prohibited. Additionally, the concurrent use of vitamins or herbal supplements should be considered with caution.

Concomitant treatment considered necessary for the subject's well-being may be given at discretion of the treating physician. All concomitant medications, blood products, as well as interventions (eg, paracentesis, etc) received by subjects from screening until the end of study visit will be recorded in the CRF.

Palliative radiotherapy on study is permitted for the treatment of painful bony lesions providing the lesions were known at the time of study entry and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of utomilumab with radiotherapy, utomilumab treatment should be interrupted during palliative radiotherapy, resuming utomilumab treatment after recovery to ≤ Grade 1 radiotherapy-related toxicity.

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during the first two cycles of treatment but they may be used to treat treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines. (*J Clin Oncol*. 2006;24(19):3187-3205).

Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia.

Chronic, systemic corticosteroid use of more than 5 mg/day prednisone (or equivalent corticosteroid regimen) for palliative or supportive purpose is not permitted. Use of short course corticosteroids as symptomatic treatment for acute medical conditions may be allowed on individual basis, if no acceptable alternatives are available. Acute emergency administration, topical applications, inhaled sprays, eye drops or local injections of corticosteroids are allowed.

4.8. Criteria for Removal From Study

Subjects may withdraw from treatment at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral, or administrative reasons.

Reasons for subject discontinuation of study treatment may include:

- Objective disease progression according to RECIST criteria v1.1;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity which may also be an adverse event;
- Significant protocol violation;
- Lost to follow-up;
- Subject refused further treatment;
- Study terminated by the investigator or Pfizer;
- Death;
- Pregnancy

Reasons for subject withdrawal from study follow-up may include:

- Completed study follow-up;
- Study terminated by the PI or Pfizer;
- Lost to follow-up;
- Refusal for further follow-up for survival;
- Start of an alternative treatment regimen;
- Death.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return for a final visit, and follow-up with the subject regarding any unresolved adverse events. The early termination final visit should include all assessments listed for the End of Treatment visit. If the subject withdraws consent for disclosure of future information, no further study specific evaluations should be performed, and no additional data should be collected. The PI may retain and continue to use any data collected before such refusal for further follow-up.

4.9 Alternatives to study participation

For patients assigned to the ado-trastuzumab emtansine cohort, the current FDA-approved standard of care is single agent ado-trastuzumab emtansine. For patients assigned to the trastuzumab cohort, the current standard of care is trastuzumab plus chemotherapy. There are numerous chemotherapy options commonly used in combination with trastuzumab in this clinical setting (eg, vinorelbine, capecitabine, gemcitabine, taxanes, and eribulin).

5. INVESTIGATIONAL AGENT INFORMATION

5.1 Physical, Chemical, and Pharmaceutical Properties and Formulation

Name:	Utomilumab
Laboratory Nomenclature:	PF-05082566
Molecular Weight:	145 kDa
Antibody Type:	Recombinant fully-human IgG2 monoclonal antibody
Physical Description:	Clear to opalescent solution

5.2 Formulation of utomilumab Solution for Intravenous administration

Utomilumab Injection, 10 mg/ml is presented as a sterile solution for intravenous administration in a 10 mL clear glass vial with an appropriate stopper and aluminum overseal. The formulation contains of the active substance utomilumab in a buffered solution containing precedented excipients. The drug product should be stored at 2 to 8ºC (36-46ºF). Protect from light.

Each vial contains nominal 100 mg of utomilumab in a 10 mL solution. To ensure that the exact volume can be withdrawn by syringe, there is a small amount of overfill in the vial.

5.3 Agent Accountability

Utomilumab drug product will be supplied by Pfizer. Utomilumab drug product is a solution and should be stored refrigerated at 2 to 8°C. Utomilumab drug product will be supplied in glass vials at a 10 mg/mL concentration and labeled as open supplies. Each vial is packed in an individual carton. Each vial has a unique container number.

For packaging and labeling information on ado-trastuzumab emtansine and trastuzumab, refer to the most recent version of the local product labeling. Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment will undertake the preparation, handling, and safe disposal of investigational and cytotoxic (or monoclonal antibody) agents. Specific preparation and dispensing instructions are provided in the Dosage Administration Instruction located in the Study Manual. Refrigerated

utomilumab drug product will be equilibrated to ambient temperature before preparation and administration.

5.4 Drug Storage and Accountability

Utomilumab will be shipped and stored at a temperature between 2° and 8°C. Ado-trastuzumab-emtansine and trastuzumab should be stored according to product instructions. The storage conditions stated in the investigator brochure may be superseded by the label storage. The storage conditions and stability of the reconstituted product are detailed in the Dosing Administration Instructions. If a deviation to the storage condition occurs, contact Pfizer.

The Investigator or an approved representative (eg, research pharmacist) will ensure that all investigational product is stored in a strictly controlled, secure area, at appropriate temperatures and in accordance with applicable regulatory requirements.

The Investigator or designated personnel must maintain adequate records documenting the receipt, use, loss or other disposition of the investigational product(s). Pfizer *may* supply drug accountability forms that must be used or may approve use of standard institution forms. In either case, the forms must identify the investigational product, including batch or code numbers, and account for its disposition on a subject by subject basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug and copies must be provided to Pfizer when directed.

At the end of the trial, Pfizer will provide instructions as to disposition of any unused investigational product. If Pfizer authorizes destruction at the trial site, the Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy and any special instructions provided by Pfizer. Destruction must be adequately documented.

5.5 Drug Administration

Subjects will receive doses of utomilumab on Day 1 every 3 weeks (one cycle). A cycle is defined as the time from Day 1 dose to the next Day 1 dose. If there are no treatment delays, a cycle will be 3 weeks in duration.

An every 3-week schedule of utomilumab (instead of every 4 weeks in prior studies) is deliberately chosen for 1) clinical feasibility to match the treatment schedule for ado-trastuzumab emtansine in Cohort 1 and trastuzumab in Cohort 2, and 2) to avoid a staggered dosing schedule (every 4 week) of utomilumab as compared to the trastuzumab and ado-trastuzumab emtansine (which are every 3 weeks), which would add considerable complexity to the PK analysis.

Pre-medication is allowed for all subjects, and may include an antihistamine, an antiemetic, an anti-inflammatory agent and/or pain reliever.

The anticipated duration of utomilumab infusion is 1 hour (± 15 minutes). The infusion rate should be reduced or interrupted in the case of symptoms of infusion reaction, and symptomatic treatment administered. The infusion may be continued at one-half the previous rate upon improvement of symptoms. If symptoms persist or worsen, the infusion should be discontinued.

For the administration of ado-trastuzumab emtansine and trastuzumab, refer to the most recent version of the FDA-approved product labeling.

Ado-trastuzumab emtansine or trastuzumab administration: Treatment will be administered in a 3-week cycle (ie, 21-day cycle), by intravenous infusion. The first infusion of ado-trastuzumab emtansine or trastuzumab on-study will be over 90 minutes (± 30 minutes), on Cycle 1 Day 0. Subsequent infusions will be administered over 30 ± 15 minutes as tolerated (see Appendix 3, Study Schedule of Activities, footnote 16).

Given the known side effects of ado-trastuzumab emtansine and trastuzumab, and the pre-clinical safety data for utomilumab, it is not anticipated that overlapping severe side effects will occur. Subjects will be treated with ado-trastuzumab emtansine (Cohort 1) or trastuzumab (Cohort 2) one day prior to the initiation of utomilumab on Cycle 1 to assess for ado-trastuzumab emtansine-or trastuzumab-specific side effects. Subjects should be monitored carefully, however, for potential infusion reactions, particularly for the earlier cycles of utomilumab. The safety monitoring as dictated per protocol is consistent with that recommended for subjects receiving ado-trastuzumab emtansine or trastuzumab.

6. DOSE MODIFICATIONS

Every effort should be made to administer study treatment on the planned dose and schedule. In the event of significant toxicity dosing may be delayed and/or reduced as described below.

In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Subjects are to be instructed to notify Investigators at the first occurrence of any adverse symptom.

Subjects who experience an adverse event meeting the definition of a DLT should be removed from treatment.

Dose modifications may occur in 3 ways:

- Within a cycle: dose interruption/reduction until adequate recovery during a given treatment cycle;
- Between cycles: next cycle administration may be postponed due to toxicity in the previous cycle;
- In the next cycle: dose reduction based on worst toxicity in the previous cycle.

Ado-trastuzumab emtansine dose should not be re-escalated after a dose reduction is made.

The infusion rate of ado-trastuzumab emtansine or trastuzumab should be slowed or interrupted as stated in the label if the subject develops an infusion-related reaction. Permanently discontinue ado-trastuzumab emtansine or trastuzumab for life-threatening infusion-related reactions.

Management of increased serum transaminases, hyperbilirubinemia, left ventricular dysfunction, thrombocytopenia, pulmonary toxicity or peripheral neuropathy may require temporary interruption, dose reduction or treatment discontinuation of ado-trastuzumab emtansine as per guidelines provided in Tables 2 to 5.

Table 2. Recommended Ado-trastuzumab Emtansine (Kadcyla) Dose Reduction Schedule for Adverse Events

Dose Reduction Schedule	Dose Level
Starting dose	3.6 mg/kg
First dose reduction	3 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Discontinue treatment

Hepatotoxicity

A reduction in the dose of ado-trastuzumab emtansine is recommended in the case of hepatotoxicity exhibited as increases in serum transaminases and/or hyperbilirubinemia (see Tables 3 and 4).

Table 3. Dose Modification Guidelines for Increased Serum Transaminases (AST/ALT)

Grade 2 (> 2.5 to ≤ 5 × ULN)	Grade 3 (> 5 to ≤ 20 × ULN)	Grade 4 (> 20 × ULN)
Treat at same dose level.	Do not administer KADCYLA until AST/ALT recovers to Grade ≤ 2, and then reduce one dose level.	Permanently discontinue KADCYLA.

ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal.

Table 4. Dose Modification Guidelines for Hyperbilirubinemia

Grade 2 (> 1.5 to ≤ 3 × ULN)	Grade 3 (> 3 to ≤ 10 × ULN)	Grade 4 (> 10 × ULN)
Do not administer KADCYLA until total bilirubin recovers to Grade ≤ 1, and then treat at same dose level.	Do not administer KADCYLA until total bilirubin recovers to Grade ≤ 1, and then reduce one dose level.	Permanently discontinue KADCYLA.

Permanently discontinue ado-trastuzumab emtansine treatment in subjects with serum transaminases > 3 × ULN and concomitant total bilirubin > 2 × ULN.

Permanently discontinue ado-trastuzumab emtansine in subjects diagnosed with nodular regenerative hyperplasia (NRH).

Thrombocytopenia

A reduction in dose is recommended in the case of Grade 4 thrombocytopenia (platelets < 25,000/mm^3 (see Table 5).

Table 5. Dose Modification Guidelines for Thrombocytopenia

Grade 3	Grade 4
PLT 25,000/mm^3 to < 50,000/mm^3	**PLT < 25,000/mm^3**
Do not administer KADCYLA until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), and then treat at same dose level.	Do not administer KADCYLA until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), and then reduce one dose level.

PLT = Platelets

Pulmonary Toxicity

Ado-trastuzumab emtansine should be permanently discontinued in subjects diagnosed with interstitial lung disease (ILD) or pneumonitis.

Peripheral Neuropathy

Ado-trastuzumab emtansine should be temporarily discontinued in subjects experiencing Grade 3 or 4 peripheral neuropathy until resolution to ≤ Grade 2.

Left Ventricular Dysfunction

Dose Modifications for Left Ventricular Dysfunction

For symptomatic congestive heart failure, ado-trastuzumab emtansine, trastuzumab and Utomilumab will be permanently discontinued and subjects removed from the study. If the left ventricular ejection fraction decreases to less than 50% and is ≥ 10% points from baseline, ado-trastuzumab emtansine, trastuzumab, and utomilumab should be held, with repeat LVEF assessment within 3 to 4 weeks. If the LVEF has not recovered to within 10% points from baseline, ado-trastuzumab emtansine, trastuzumab and utomilumab will be permanently discontinued and subjects removed from the study. If the LVEF decreases to less than 50%, but is within 10% points from baseline and the subject is asymptomatic with respect to cardiac signs/symptoms, continue medical treatment with reassessment of the LVEF within 3 weeks.

Dose Interruptions/Delay

A new cycle of treatment may begin only if:

- ANC ≥ 1,000/μL;
- Platelets count ≥ 75,000/μL;
- Non-hematologic toxicities have returned to baseline or Grade ≤ 2 severity. If these conditions are not met, treatment must be delayed by 1 week. If, after a 1-week delay, all toxicities have recovered within the limits described above treatment with utomilumab or ado-trastuzumab emtansine or trastuzumab, as applicable, can be resumed. Both study drugs should be delayed simultaneously if applicable. If the subject has not recovered after 1 week of delay, treatment may be delayed by 1 more week. However, initiation of the next cycle can only be delayed by a maximum of 2 weeks. Therefore, if persisting toxicity does not allow for the resumption of treatment, the subject will be permanently discontinued.

Dose Reductions

Subjects who experience a DLT will be removed from the study. After the first two cycles dose reductions may be required based on the worst toxicity experienced in the previous cycle. Subjects experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the next lower dose level once recovery to ≤ Grade 1 or baseline is achieved.

Dose reduction for utomilumab-related serious adverse events is not allowed. In such cases the subject should discontinue treatment with this drug. In Cohort 2, no dose reductions of trastuzumab will be allowed.

Once a subject has a dose reduction for a drug-related toxicity, the dose for that drug will not be re-escalated. For subjects requiring more than 2 dose reductions of ado-trastuzumab emtansine for treatment-related toxicity, ado-trastuzumab emtansine will be discontinued as per the approved package insert. At the investigator's discretion, utomilumab may be continued until disease progression or cumulative dose-limiting toxicity.

Infusion-Related Reactions, Hypersensitivity Reactions in Cohort 1

Treatment with ado-trastuzumab emtansine has not been studied in subjects who had trastuzumab permanently discontinued due to infusion-related reactions (IRR) and/or hypersensitivity; treatment with ado-trastuzumab emtansine is not recommended for these subjects. Infusion-related reactions, characterized by one or more of the following symptoms − flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia have been reported in clinical trials of ado-trastuzumab emtansine. In a randomized FDA-registrational trial, the overall frequency of IRRs in subjects treated with ado-trastuzumab emtansine was 1.4%. In most subjects, these reactions resolved over the course of several hours to a day after the infusion was terminated. Ado-trastuzumab emtansine treatment should be interrupted in subjects with severe IRR. Ado-trastuzumab emtansine treatment should be permanently discontinued in the event of a life-threatening IRR. Subjects should be observed closely for IRR reactions, especially during the first infusion. One case of a serious, allergic/anaphylactic-like reaction has been observed in clinical trials of single-agent ado-trastuzumab emtansine. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.

Management of Infusion Reactions, Cohort 2: During the first infusion with trastuzumab, a symptom complex most commonly consisting of chills and/or fever was observed in about 40% of subjects in clinical trials. The symptoms were usually mild to moderate in severity and were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of trastuzumab infusion). Trastuzumab discontinuation was infrequent. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, rash and asthenia. The symptoms occurred infrequently with subsequent trastuzumab infusions.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the

safety and well being of the subject. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The IRB will be informed of these incidents in a timely fashion, according to governing IRB requirements.

7.1 Safety Assessment

Safety assessments will include collection of AEs, SAEs, vital signs and physical examination, ECG (12 lead), laboratory assessments, including pregnancy tests and verification of concurrent medications.

7.1.1 Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 5) timing, seriousness, and relatedness.

Baseline signs and symptoms will be recorded at baseline and then reported as adverse events during the trial if they worsen in severity or increase in frequency.

Adverse events will be collected at every study visit, whether scheduled or unscheduled; at end-of-treatment; and through the Day 60 follow-up. In addition, if subjects continuing to experience toxicity (ie, treatment-related adverse events) following discontinuation of study treatment, adverse events will be collected at least every 3 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. Adverse events will not be collected after resolution of treatment-related toxicities or 60 days after last dose of study treatment, whichever is later.

Due to pre-clinical results and human experience with compounds of a similar nature, subjects will be assessed at baseline and as medically-indicated by medical history, physical examination, and routine laboratory parameters (eg, blood chemistries) for endocrine function (including but not limited to TSH, ACTH, and cortisol levels, and may include assessment for hypopituitarism and hypoadrenalism) and hepatic events. Laboratory evaluation of hypopituitarism or hypoadrenalism should be considered in subjects who develop signs and symptoms that may include unexplained loss of body and facial hair, decreased blood pressure, and hyponatremia with hyperkalemia. In the presence of clinical suspicion, laboratory testing should include one or more of the following: TSH, ACTH, and cortisol levels before and 30 to 60 minutes after corticotrophin stimulation. Referral to an endocrinologist should be considered.

7.1.2 Laboratory Safety Assessments

Blood and/or urine for hematology, chemistry, coagulation, hepatitis B and C, endocrine function (as clinically indicated), urinalysis and pregnancy testing will be collected at the time points described in the Schedule of activities (Appendix 3), and analyzed at local laboratories.

7.1.3 Vital Signs and Physical Examination

Subjects will have a physical exam to include weight, blood pressure, heart rate, assessment of ECOG status and height; height will be measured at baseline only. Physical examinations will be performed at the time points described in the Schedule of activities (Appendix 3).

7.1.4 ECG Assessments

Electrocardiogram (ECG): A 12-lead tracing in the supine position will be used for all ECGs at each time point (see the Schedule of Activities, Appendix 3). It is preferable that the machine used has a capacity to calculate the standard intervals automatically. If the QTc is prolonged (> 500 msec, ie, ≥ CTCAE Grade 3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTc of > 500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTc interval) should be performed at the discretion of the treating physician. In addition, repeat ECGs should be performed until the QTc interval falls below 500 msec. If QTc interval reverts to less than 500 msec, and in the judgment of Investigator(s) is determined to be due to cause(s) other than study drug, treatment may be continued with regular ECG monitoring. If in that timeframe the QTc intervals rise above 500 msec the study drug will be held until the QTc interval decreases to ≤ 500 msec. Subjects will then re-start the study drug at the next lowest dose level. If the QTc interval has still not decreased to < 500 msec after 2-weeks, or if at any time a subject has a QTc interval > 515 msec or becomes symptomatic, the subject will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

Prior to concluding that an episode of prolongation of the QTc interval is due to study drug, thorough consideration should be given to potential precipitating factors (eg, change in subject clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

If subject experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), an ECG should (ideally) also be obtained at the time of the event.

7.2 Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans; brain CT or MRI scan for subjects with known or suspected brain metastases; bone scan; PET scan; CT/PET scan; and/or bone x-rays for subjects with known or suspected bone metastases.

During screening period within 28 days of Cycle 1 Day 0, tumor assessment is required using CT scan with contrast (chest, abdomen, + pelvis), plus radionuclide bone scan or CT/PET with contrast. If central nervous system (CNS) metastasis are present, CNS imaging is required by CT or MRI.[17]

The same imaging technique used to characterize each identified and reported lesion at baseline should ideally be employed in the following tumor assessments. However, in certain clinical circumstances (eg, IV contrast allergy or nephrotoxicity from IV contrast), the most suitable imaging modality for an individual patient may be used at the discretion of the treating physician.

Antitumor activity will be assessed through radiological tumor assessments conducted at baseline, during treatment as specified in the Schedule of Activity (Appendix 3), whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from the study (if not done in the previous 6 weeks). Subjects will be followed up

to 6 months from the date of the last dose of the study drug, with follow-up ending at death; disease progression; or initiation of a new anticancer therapy. During this follow-up period, subjects will have disease assessments performed every 9 weeks (± 7 days).

Utomilumab is thought to stimulate patients' immune systems to attack their tumors, rather than to have a direct and immediate effect on tumor cells. In addition, drugs with a similar mechanism have been observed to have a delayed effect on tumors. It is possible that new lesions may appear early after treatment begins, before an effective immune response is induced. In addition, it is postulated that there may be initial increase in size of lesions due to infiltration of inflammatory cells, which is later followed by tumor regression. In some cases, this inflammation could make an undetectable lesion increase in size so that it appears to be a new lesion. In addition, subjects may have mixed responses, in which some lesions respond while other lesions progress or new lesions appear. There may be cases where, in the judgment of the Sponsor-investigator, a patient with a mixed response appears to be deriving benefit from the treatment. In such cases, at the discretion of the Sponsor-investigator, subjects may continue treatment until clinical benefit is no longer present in the opinion of the Investigator.

Assessment of response will be made using RECIST v1.1 (for solid tumors).

All subjects' files and radiologic images must be available for source verification and for potential peer review.

7.3 Pharmacokinetic Assessment

PK samples will be collected as specified in the Schedule of Activity (Appendix 3), and assayed for utomilumab, ado-trastuzumab emtansine or trastuzumab using a validated analytical assay. Analysis of samples from subjects who received utomilumab and trastuzumab is optional. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the Laboratory Manual.

All efforts will be made to obtain the pharmacokinetic samples at the scheduled nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within ± 6 minutes of a 60-minute sample) will be considered protocol compliant, and the exact time of the sample collection noted on the CRF.

Wherever possible or applicable, blood samples for utomilumab concentrations should be collected at as close to the same time a pharmacodynamic biomarker samples or tumor biopsy is collected.

7.4 Immunogenicity Assessment

Blood samples will be collected as specified in the Schedule of Activity (Appendix 3), and assayed for anti-drug antibodies (ADA) including, anti-utomilumab, and anti-ado-trastuzumab-emtansine or anti-trastuzumab using a validated analytical method. Analysis of samples from subjects who received utomilumab and trastuzumab is optional. Samples that are positive for ADA may also undergo characterization for neutralizing antibodies.

7.5 Pharmacodynamic Assessments

7.5.1. Blood for Immunomodulation/Cytokine Release Biomarkers

Blood will be analyzed for immune-related biomarkers that may include TNFα; IFNγ; IL10; IL-8; IL-6; IL-4; IL-2; IL-1b; IL-12p70; sFasL; CRP; sCD25; CXCL9; CXCL10; and Neopterin, etc. The specific biomarkers in the immunomodulation/cytokine release biomarker panel is subject to change based upon technical updates to the panel made by the Stanford Human Immune Monitoring Core Facility. Analysis of samples from subjects who received utomilumab and trastuzumab is optional.

7.5.2. Pharmacodynamic Assessment of Lymphocyte Subpopulations

Blood and available tumor will be analyzed for biomarkers indicative of key immune cell populations, including T-cell, NK cells, and B-cells. Analysis of samples from subjects who received utomilumab and trastuzumab is optional.

7.5.3. T-cell receptor assessment

Blood and available tumor will be collected for future analysis of T-cell receptor frequencies using targeted sequencing. Analysis of samples from subjects who received utomilumab and trastuzumab is optional.

7.6 Tumor Biopsies

Tumor biopsies will be requested, though not mandated, pre-treatment and after at least one dose of utomilumab (as clinically feasible) for CD8+ T-cells and other markers of tumor infiltrating lymphocytes, such as CD3; CD4; PD-1; 4-1BB; FoxP3; and PD-L1.

8. ADVERSE EVENT REPORTING

Adverse events will be graded according to CTCAE v5. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study-specific Case Report Forms (CRFs). The Principal Investigator or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochure, and related to the investigation. All Serious Adverse Events (SAEs) will be tracked until resolution, or until 30 days after the last dose of the study treatment.

SAEs CTCAE Grade 3 and above, and all subsequent follow-up reports will be reported to the Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) using the study specific CRF regardless of the event's relatedness to the investigation. Following review by the DSMC, events meeting the IRB definition of "Unanticipated Problem" will be reported to the IRB using eProtocol within 10 working days of DSMC review, or within 5 working days for deaths or life-threatening experiences.

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all adverse events, the local Principal Investigator (treating physician) must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate

notification to the Sponsor-investigator (IND-holder or designate). For all adverse events, sufficient information should be obtained by the local Principal Investigator to determine the causality of the adverse event. The local Principal Investigator and/or the Sponsor-investigator will assess causality. Follow-up by the local Principal Investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator.

8.1 Reporting Period

For serious adverse events, the active reporting period begins from the time that the subject provides signed informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product or including 60 calendar days after the last administration of the investigational product if no other therapy is administered. Should an investigator be made aware of any serious adverse event occurring any time after the active reporting period, it must be promptly reported.

Adverse events (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of study treatment through last subject visit.

If a subject begins a new anticancer therapy, the adverse event reporting period for non-serious adverse events ends at the time the new treatment is started. Death must be reported if it occurs during the serious adverse event reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.2 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity/allergy;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasations;
- Exposure during pregnancy;

- Exposure via breastfeeding;
- Medication error.

Worsening of signs and symptoms of the malignancy under study should be reported as adverse events in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as adverse events.

8.3 Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

8.4 Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as serious adverse event. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an adverse event and as a serious adverse event with CTCAE Grade 5. Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious. Examples of such events are intensive treatment in an

emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.5 Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes. If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines a serious adverse event is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements.

8.6 RISKS ASSOCIATED WITH TRASTUZUMAB

Note: Cohort 2, utomilumab plus trastuzumab, was closed in January 2020.

Trastuzumab is a recombinant monoclonal antibody that binds specifically and with high affinity to the extracellular domain of HER2. Trastuzumab has been shown to inhibit the proliferation of human tumor cells overexpressing HER2 both *in vitro* and *in vivo*.

The clinical benefit of trastuzumab in women with MBC has been demonstrated in two pivotal studies.

A phase 2 trial (H0649g) assessed the activity of single-agent trastuzumab in 222 women with HER2-overexpressing MBC with progressive disease after one or more chemotherapy regimens (Cobleigh, *et al*, 1999). An independent response evaluation committee identified 8 complete and 26 partial responses, for an objective response rate of 15% in the intent-to-treat population (95% confidence interval [CI]: 11% to 21%). The median duration of response was 9.1 months, and the median duration of survival was 13 months. The most common adverse events, which occurred in approximately 40% of subjects, were mild to moderate infusion-associated fever and/or chills. The most clinically significant event was cardiac dysfunction, which occurred in 4.7% of subjects.

An open-label, randomized, phase 3 study (H0648g) in 469 subjects with HER2-positive MBC was conducted to evaluate the efficacy of trastuzumab in combination with chemotherapy as first-line treatment. Subjects who were anthracycline-naïve were randomized to receive either anthracycline plus cyclophosphamide (AC) or trastuzumab plus AC. Subjects who had received prior anthracyclines in the adjuvant setting were randomized to receive either paclitaxel or trastuzumab plus paclitaxel. As determined by an independent response evaluation committee, trastuzumab prolonged median time to disease progression from 4.6 months to 7.4 months ($p < 0.001$), improved the overall response rate (complete and

partial responses) from 32% to 50% ($p < 0.001$), and increased median duration of response from 6.1 to 9.1 months ($p < 0.001$). Compared to chemotherapy alone, the addition of trastuzumab significantly lowered the incidence of death at one year from 33% to 22% ($p = 0.008$) and increased median overall survival 24% from 20.3 months to 25.1 months ($p = 0.046$) (Slamon, *et al*, 2001). The observed survival advantage remained despite crossover of 66% of subjects initially randomized to chemotherapy alone who elected to receive trastuzumab upon disease progression (Tripathy, *et al*, 2000). Fever/chills were observed with the initial trastuzumab infusion in approximately 25% of subjects. Class III or IV cardiac dysfunction was observed in 16% of the trastuzumab + AC subgroup; increasing age was an associated risk factor for the development of cardiotoxicity in this treatment cohort (Slamon, *et al*, 2001).

Based on these data, trastuzumab was approved by the US Food and Drug Administration (FDA) for use in HER2-overexpressing MBC in combination with paclitaxel for first-line treatment and as a single agent for patients failing prior chemotherapy for metastatic disease.

Trastuzumab is also currently approved in the early breast cancer setting.

See the trastuzumab (Herceptin®) prescribing information for additional information.

8.7 RISKS ASSOCIATED WITH ADO-TRASTUZUMAB EMTANSINE

The following summarizes the experience with ado-trastuzumab emtansine in multiple breast cancer studies to date. The usual dose used in the studies was 3.6 mg/kg every 3 weeks. Trastuzumab emtansine has demonstrated a favorable toxicity and tolerability profile to date across multiple studies.

In a phase 1, TDM3569g, trastuzumab emtansine was administered every 3 weeks. The MTD of trastuzumab emtansine administered every 3 weeks was 3.6 mg/kg. DLTs consisted of Grade 3 and 4 thrombocytopenia that prevented retreatment in 2 of 3 subjects treated at 4.8 mg/kg on the every-3-week schedule. Grade ≥ 2 adverse events at the MTD were infrequent and manageable. The most common adverse events ($\geq 25\%$ incidence) seen in this study were thrombocytopenia, fatigue, nausea, anemia, constipation, headache, increased liver function tests, and cough. Every-3-week trastuzumab emtansine schedules are well tolerated and associated with significant clinical activity. In addition, the phase 2 studies, TDM4258g and TDM4374g, have shown similar tolerability of trastuzumab emtansine at a dose of 3.6 mg/kg administered every 3 weeks.

Reversible thrombocytopenia has been commonly observed in completed and ongoing studies with trastuzumab emtansine. Most events were Grade 1 or 2; with Grade 3 or 4 thrombocytopenia has been observed less commonly. The incidence of Grade 1 thrombocytopenia gradually increased over successive cycles; however, there was no increase in the proportion of Grade 3 abnormalities. The number of subjects who experienced platelet count recovery to normal levels by Day 1 of the subsequent cycle decreased with successive cycles, suggesting a modest cumulative effect of trastuzumab emtansine on platelet count. There was no clear association between thrombocytopenia and *severe* hemorrhagic events; however, the use of platelet transfusions has been reported.

Transient and reversible increases in serum AST and ALT have been observed across the trastuzumab emtansine studies. Grade 1 and 2 events have been observed frequently; Grade 3 to 4 events have been observed much less commonly. The incidence of increased AST was substantially higher than that for ALT. Increases in AST and ALT were commonly observed by Day 8 of each cycle and generally returned to baseline by Day 21. The proportion of subjects with Grade 1 and 2 increases in transaminases increased with successive cycles; however, no increase in the proportion of Grade 3 abnormalities over time was observed. To date, there have been no cases meeting Hy's Law criteria for drug-induced liver injury caused by trastuzumab emtansine. Although significant hepatotoxicity has rarely been seen in clinical trials with trastuzumab emtansine to date, the relationship to trastuzumab emtansine has not been established. Nevertheless, severe liver injury remains an important potential risk.

Infusion-related reactions are known to occur with the administration of monoclonal antibodies and have been reported with trastuzumab emtansine. Infusion reaction adverse events occurred rarely and were mostly Grade 1 or 2. Non-specific symptoms that occurred on the first day of trastuzumab emtansine infusion that could be associated with an infusion reaction included fatigue; nausea; chills; pyrexia; and less commonly, headache; hypertension; vomiting; and cough.

Pneumonitis has been rarely reported with trastuzumab emtansine. Signs, symptoms, and clinical findings include dyspnea, cough, fatigue, and pulmonary infiltrates. There were no fatalities among the cases of pneumonitis reported with trastuzumab emtansine.

In clinical trials with trastuzumab emtansine, peripheral neuropathy has been reported, mainly as Grade 1 toxicity. Hypokalemia and decreases in serum potassium have been reported in completed and ongoing studies with trastuzumab emtansine. Most of these adverse events were Grade 1 or 2.

Although significant cardiac events have been infrequent in clinical trials with trastuzumab emtansine to date, severe cardiotoxicity remains an important potential risk. Treatment with trastuzumab, a component of trastuzumab emtansine, has resulted in subclinical and clinical cardiac failure manifesting as CHF, decreased LVEF, and cardiac death. The incidence and severity of cardiac dysfunction was highest in subjects who received trastuzumab concurrently with anthracycline-containing chemotherapy regimens. Cardiotoxicity, manifesting as a decline in left ventricular ejection fraction (LVEF) or congestive heart failure (CHF), is being closely monitored in the current study. Rare cases of Grade 3 cardiac dysrhythmias have been reported among subjects receiving trastuzumab emtansine, although a direct relationship to study drug remains unclear.

Given the potential for trastuzumab emtansine, and trastuzumab to cause cardiac toxicity, only subjects without significant cardiac history, with acceptable anthracycline exposure, and with an LVEF determined to be ≥ 50% by screening ECHO or MUGA scan are eligible for participation in this study. Repeat ECHO or MUGA scans will be performed at baseline and the beginning of Cycle 5 and then every 4 cycles thereafter, using the same noninvasive monitoring technique each time, to determine if therapy should be held or discontinued in asymptomatic subjects on the basis of local assessment of declines in LVEF. Any subject with symptomatic cardiac dysfunction or a significant decline in LVEF as detected by noninvasive cardiac imaging will discontinue all study treatment but will continue to be

followed for 30 days for adverse events and serious adverse events and every 6 weeks for disease progression until the initiation of another anti-cancer therapy, subject- or investigator-initiated withdrawal from the study, or study termination.

8.8 Infusion-Related Symptoms with Hypersensitivity Reactions

Infusion-related reactions consisting of fever and/or chills have been observed in ≤ 40% of patients during their first infusions of either trastuzumab or ado-trastuzumab emtansine. The symptoms have usually been mild to moderate and controlled with acetaminophen, diphenhydramine, or meperidine. These symptoms are uncommon with subsequent infusions. However, in the post-approval setting, more severe adverse reactions to trastuzumab have been reported. These have been categorized as hypersensitivity reactions (including anaphylaxis), infusion reactions, and pulmonary events. In rare cases, the reaction culminated in a fatal outcome.

Administration of ado-trastuzumab emtansine, trastuzumab and utomilumab will be performed in a setting with emergency equipment and staff who are trained to monitor and respond to medical emergencies. Subjects will be monitored during each study medication infusion, for 60 minutes after the first infusion, and for 30 minutes after subsequent infusions in the absence of infusion-related adverse events. If infusion-associated symptoms occur, the subject will be monitored until symptoms completely resolve or are considered by the investigator to be clinically insignificant.

Subjects who experience infusion-related symptoms during the administration of ado-trastuzumab emtansine, trastuzumab or utomilumab may be pre-medicated for subsequent infusions. Subjects who experience a Grade ≥ 3 allergic reaction or acute respiratory distress syndrome will discontinue all study treatment but will continue to be followed for 30 days for adverse events and serious adverse events and every 6 weeks for disease progression until the initiation of another anti-cancer therapy, subject- or investigator-initiated withdrawal from the study, or the study termination.

8.9 RATIONALE FOR CONTINUED DOSING

Subjects who meet the criteria for ongoing clinical benefit will be allowed to continue study treatment in the absence of disease progression, unacceptable toxicity, or the initiation of other anti-cancer therapy, unless the study is terminated early for one of the reasons described in Sections 4.8 and 11.

9. CORRELATIVE/SPECIAL STUDIES

9.1 BIOMARKERS

Serum and intratumoral biomarkers linked to immunomodulation and cytokine release, exploratory PD biomarkers expressed by PBMC and intratumoral lymphocytes, markers of T- and NK-cell phenotype, quantitation of T-cell receptor sequences, and tumor biopsy for analysis of exploratory mechanistic biomarkers such as IHC assessment of tumor-infiltrating lymphocytes and quantitation of T-cell receptor sequences will be collected as indicated in the Schedule of Activity (Appendix 3). A more detailed accounting of the biomarker collection/analysis is provided in Appendix 5.

10. REGULATORY CONSIDERATIONS

Throughout this document, reference to the "Sponsor-investigator" includes designates. Sponsor-investigator retains all defined responsibilities of the IND-holder, unless specifically delegated or transferred.

10.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (eg, advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). The Protocol Director will disseminate the protocol amendment information to all participating investigators.

One version of the protocol document should be used at all times. Prior to implementation, the Stanford IRB and SRC will prospectively approve of any amendment to the protocol, except where necessary to eliminate an immediate hazard(s) to trial subjects. With the exception of actions to protect the safety and welfare of human subjects, any changes to the protocol will be submitted as a modification to the IRBs of record for the clinical site, and will be approved by the IRB of record prior to implementation.

10.4 Subject Registration

Subjects may be registered to participate in this study when they have confirmed to meet all eligibility requirements (see Eligibility Criteria in Section 3 Participant Selection), and that eligibility has been reviewed (Eligibility Triple-check, see Eligibility Checklist in Appendix 6).

All study participants will be entered into OnCore.

10.5 Data and Safety Monitoring Plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities approximately once per year to determine whether the study has been conducted in accordance with the protocol; local standard operating procedures; FDA regulations; and Good Clinical Practice (GCP). This may include review of the following types of documents: regulatory binders, case report forms, eligibility checklists, and source documents.

In addition, the DSMC will regularly review serious adverse events and protocol deviations to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

10.6 Data Management Plan

The Principal Investigator, or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study-specific Case Report Forms (CRFs) will be created in the Online Collaborative Research Environment (OnCore).

All electronic data systems and devices should maintain a security system that prevents unauthorized access. All participants must be registered in the OnCore database, allowing the Stanford SRC to judge the aggregate accrual and stopping rules for the study.

10.7 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonization guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

11. STUDY DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in the opinion of the IRB/IEC, drug safety problems, or at the discretion of utomilumab manufacturer Pfizer. In addition, Pfizer retains the right to discontinue development of utomilumab at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the Sponsor-investigator. As directed by Pfizer, all study materials must be collected and all CRFs completed and submitted to the Sponsor-investigator to the greatest extent possible.

12. Publications by Investigators

To ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, the Sponsor-investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The Sponsor-investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the Sponsor-investigator agrees to delay the disclosure for a period not to exceed an additional 60 days. The Sponsor-investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

13. DATA ANALYSIS/STATISTICAL METHODS

13.1 Analysis Sets

All clinical research data generated by this protocol will be captured in electronic case report forms (CRFs) generated using REDCap software.

1. Full Analysis Set

The full analysis set includes all enrolled subjects.

2. Safety Analysis Set

The safety analysis set includes all enrolled subjects who receive at least one dose of study medication.

3. DLT Evaluable Set

All enrolled subjects who are eligible, receive study treatment and who either experience DLT during the first 2 cycles, or complete the 2-cycle observation period. Subjects who are lost to follow-up before completion of first 2 cycles due to reasons unrelated to treatment related adverse events are not evaluable for DLT.

4. Response Analysis Set

All enrolled subjects who are eligible for the study and receive study treatment, have adequate baseline tumor assessments and at least 1 on-study tumor assessment. Subjects who are treated and removed from study prior to on-study tumor assessment because of disease progression will be considered evaluable for efficacy and counted as failures.

5. Pharmacokinetic/Immunogenicity Sets

The pharmacokinetic/ADA concentration population is defined as all enrolled subjects who have been treated and have at least one post-dose concentration measurement of either utomilumab or ado-trastuzumab emtansine or trastuzumab.

6. Biomarker Analysis Set

Treated subjects who have baseline and at least 1 on-study biomarker assessment.

13.2 Statistical Methods and Sample Size Determination

Overall study population is up to 30 subjects, to achieve 25 evaluable subjects.

Statistical analyses of this non-randomized, phase 1B study will be primarily descriptive in nature. Formal statistical methods will not be used to determine the number of subjects per cohort in this phase 1B study. Summary statistics for discrete variables will be provided as frequencies and for continuous variables as the mean, standard deviation, median, and ranges. In Cohort 1 Expansion, utomilumab will be given IV at the RP2D (utomilumab 100 mg IV) in combination ado-trastuzumab emtansine up to a total of 17 evaluable subjects who received utomilumab plus ado-trastuzumab emtansine (up to 5 inevaluable subjects may be replaced). Cohort 2 (utomilumab plus trastuzumab) was closed in January 2020 with 5 total subjects enrolled. If 1 or more responses are observed, it will be recommended to conduct a future formal phase 2 trial under a separate protocol.

13.2.1 Accrual Considerations

There are approximately 600 new breast cancer patients seen annually at the Stanford Cancer Institute. It is estimated that half of these cases are metastatic and 20% are HER2-positive.

13.3 Efficacy Analysis

Tumor response will be presented in the form of subject data listings that include, but are not limited to, tumor type, received (maximum) dose, overall tumor response at each visit, and best overall response. In addition, disease progression date, death date, date of first response,

and last tumor assessment date will be listed, together with DR and PFS for the expansion cohort. Kaplan-Meier plot will be created for DR, TTR and PFS in the expansion cohort.

13.4 Analysis of Pharmacokinetics and Pharmacodynamics

13.4.1 Analysis of Pharmacokinetics of Study Drugs

C_{trough} and C_{max} for utomilumab and ado-trastuzumab emtansine or trastuzumab will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% confidence interval) by dose, cycle, and day.

Dose normalized parameters (eg, C_{max}, C_{trough}) will be reported as appropriate.

The trough concentrations for utomilumab and ado-trastuzumab emtansine or trastuzumab will be plotted for each dose using a box whisker plot by cycle and day in order to assess the attainment of steady state.

13.4.2. Analysis of Immunogenicity Data of Study Drugs

ADA/neutralizing antibody (Nab) data will be listed and summarized for each dosing interval for utomilumab, ado-trastuzumab emtansine, or trastuzumab. The percentage of subjects with positive ADA and neutralizing antibodies each will be summarized by dose. For subjects with positive ADA, the magnitude (titer), time of onset, and duration of ADA response may also be described, if data permit. The effect of ADA on utomilumab, ado-trastuzumab emtansine or trastuzumab concentrations will be evaluated if data permit.

13.4.3. Analysis of Biomarker Endpoints

For CD8 and HER-2 as wells other exploratory biomarkers in tumor biopsy, summary statistics (eg, the mean and standard deviation, median, and minimum/maximum levels of continuous, and frequencies and percentages of categorical biomarker measures) will be determined at baseline and post-treatment as appropriate. For each pair of specimens, the percent change from baseline of these same parameters will also be calculated.

Data from biomarker assays may be analyzed using graphical methods and descriptive statistics such as linear regression, t-test, and analysis of variance (ANOVA). The statistical approach will examine correlations of biomarker results with pharmacokinetic parameters and measures of anti-tumor efficacy.

13.4.4. Population Pharmacokinetic Analysis or Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling

Pharmacokinetic and pharmacodynamic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between utomilumab and ado-trastuzumab emtansine/trastuzumab exposure and biomarkers or significant efficacy/safety endpoints. The results of these analyses, if performed, may be reported separately.

13.5 Safety Analysis

13.5.1 Analysis of the Primary Endpoint

DLT is the primary endpoint of the study. Analyses of DLT are based on the DLT-evaluable set. The occurrence of DLTs and Adverse Events constituting DLTs will be summarized and listed per dose for subjects.

13.5.2 Analysis of Secondary Safety Endpoints

Adverse Events

Adverse Events (AEs) will graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study treatment. The number and percentage of subjects who experienced any AE, serious AE (SAE), treatment-related AE, and treatment-related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1).

The Sponsor-investigator will report all unanticipated problems involving risks to human subjects or others to the IRB of record and to the Stanford SCI Data and Safety Monitoring Committee (DSMC).

Laboratory Test Abnormalities

The number and percentage of subjects who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). Shift tables will be provided to examine the distribution of laboratory toxicities.

For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

14. REFERENCES

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Appendix 1. Determination of Efficacy – Solid Tumors

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5 to 8 mm).
- Lesions with longest diameter at least 20 mm when assessed by chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease**:** Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions**:** Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.
- Normal nodes**:** Nodes with short axis < 10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target

lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared;; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to < 10 mm (normal), the actual measurement should still be recorded.

Non-target disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION.

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis < 10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.
- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.
- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.
- Indeterminate. Progression has not been documented; and
    - One or more target measurable lesions have not been assessed; or
    - Assessment methods used were inconsistent with those used at baseline; or

- One or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure); or
- One or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.
- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.
- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective progression

Subjects requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Objective Response Status at each Evaluation			
Target Lesions	**Non-target Lesions**	**New Lesions**	**Objective status**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR		No	
	Indeterminate or Missing		PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Adapted from: Eisenhauer EA, Therasse P, Bogaerts J, *et al*. "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)." *Eur J Cancer*. Jan 2009;45(2):228-247.

Appendix 2: ECOG Performance Status

Score	Definition
0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work or office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

From: Oken MM, Creech RH, Tormey DC, *et al*. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649–655.

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Appendix 3: Schedule of Activities

Protocol Activity (Cycle Day relative to utomilumab dosing)	Screening	On Treatment (1 Cycle = 21 days)								Post-Treatment	
	(Within 28 days of Cycle 1, Day 0)	Cycle 1				Cycle 2			Cycles ≥ 3	End of Treatment / withdrawal (within 28 days from final dose) [28]	Follow-Up [30]
		Day 0 (± 2 business days)	Day 1 (± 2 business days)	Day 8 (± 2 business days)	Day 15 (± 2 business days)	Day 1 (± 2 business days)			Day 1 (± 2 business days)		
Baseline documentation											
Informed Consent [1]	X										
Medical/Tumor History [2]	X										
Physical Examination (within 24 hours prior to start of each cycle) [3]	X	X				X			X	X	(X)
ECOG Performance Status (± 3 days) [4]	X	X				X			X	X	(X)
Safety Labs/ Measurements											
Vital signs (BP and pulse, within 24 hours prior to start of each cycle) [5]	X	X	X	X	X	X			X	X	(X)
12 lead ECG (± 3 days) [6]	X		X			X				X	(X)
Hematology (CBC, differential, platelets) [7]	X	X		X	X	X			X	X	(X)
Coagulation (PT/INR and PTT) [8]	X	X				X			X	X	(X)
Blood Chemistry [9]	X	X		X	X	X			X	X	(X)
Urinalysis [10]	X									X	(X)
Hepatitis B and C testing [11]	X										
Pregnancy test [12]	X	X				X			X	X	(X)
Endocrine function [13]	X										
LVEF assessment [14]	X								Cycle 5 Day 1, then every 4th cycle (± 7 days)	X	
Registration [1]	≤ 7 days before Cycle 1, Day 0										
Treatment											
Administration of utomilumab [15]			X			X			X		
Administration of ado-trastuzumab emtansine or trastuzumab [16]		X				X			X		

Protocol Activity (Cycle Day relative to utomilumab dosing)	Screening	On Treatment (1 Cycle = 21 days)								Post-Treatment	
	(Within 28 days of Cycle 1, Day 0)	Cycle 1				Cycle 2			Cycles ≥ 3	End of Treatment / withdrawal (within 28 days from final dose) [28]	Follow-Up [30]
		Day 0 (± 2 business days)	Day 1 (± 2 business days)	Day 8 (± 2 business days)	Day 15 (± 2 business days)	Day 1 (± 2 business days)			Day 1 (± 2 business days)		
Tumor Assessment											
CT scan with contrast (chest, abdomen, + pelvis) plus radionucleide bone scan or CT/PET with contrast. CNS imaging by CT or MRI if CNS metastasis present [17]	**X**								Cycle 4 Day 1, then every 3rd cycle **(± 7 days)** while on treatment	X	
Pharmacokinetic, Pharmacodynamic Assessments											
Blood for utomilumab PK [6, 18]			**X**			**X**			**X**	**X**	
Blood for ado-trastuzumab emtansine / trastuzumab PK [6, 19]		**X**				**X**			**X**	**X**	
Blood for biomarkers linked with immunomodulation / cytokine release [20]	**X**	**X**	**X**	**X**	**X**	**X**				**X**	
Pharmacodynamic assessment of lymphocyte subpopulation [21]	**X**					**X**				**X**	
T cell receptor assessment [22]	**X**					**X**				**X**	
Blood for utomilumab immunogenicity (ADA) testing [23]			**X**			**X**			**X**	**X**	**X**
Blood for ado-trastuzumab emtansine / trastuzumab immunogenicity (ADA) testing [24]		**X**				**X**			**X**	**X**	**X**
Blood for exploratory biomarkers [25]	**X**					**X**				**X**	
Optional tumor biopsy for biomarker assessment [26]	**X**								**X** (Cycle 4)		
Other Clinical Assessment											
Adverse event [27]	**X**	Monitor and record **at every study visit**								**X**	**X**
Concomitant medication [28]	**X**	Monitor and record **at every study visit**								**X**	

Note: 1 cycle = 21 days ± 2 business days

1. Informed Consent: Must be obtained prior to undergoing any study specific procedure and may occur prior to the 28-day screening period. Registration will considered to be signed informed consent with triple-signed eligibility checklist, with the final signature being the Stanford Principal Investigator or his designee.

2. Medical History/Tumor History: To be collected within 28 days prior to registration (registration is defined as signed informed consent plus PI-signed confirmation of all eligibility criteria). Includes history of other diseases (active or resolved) and concomitant illnesses. Include oncology history; information on prior regimens (including dosing and duration of administration, description of best response observed, recurrence date), surgery and radiation therapy.

3. Physical Examination: Includes an examination of major body systems. Weight for the purposes of dose calculation will be recorded at screening and within 7 days pre-dose Day 1 of each cycle. Weight may not be collected at End of Treatment. Height will be measured at baseline.

4. ECOG PS: ECOG performance scale is available as Appendix 6 in the full protocol.

5. Blood pressure (BP) and pulse rate to be recorded in supine or sitting position.

6. 12-lead ECG and pharmacokinetics: At each time point, a 12-lead ECG will be performed to determine QTc. ECGs and blood sample draws for PK and other research assessments should be done at 2 separate time points prior and post-infusion when applicable, with no preference to the order of performance. ECGs will be performed at screening, on Day 1 of Cycles 1 and 2 before and at the end of utomilumab infusion. If the QTc interval is prolonged (> 500 msec), then the ECGs should be reevaluated by a qualified person at the center for confirmation. Additional ECGs may be performed as clinically indicated.

7. Hematology: No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. On treatment, to be performed prior to dosing with study medications unless otherwise indicated. If during the first cycle of treatment a Grade 4 hematologic event is evident, the hematology assessment should be repeated at least on or after 7 days later to assess for events qualifying as DLT.

8. Coagulation: No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. On treatment, to be performed prior to dosing with study medications unless otherwise indicated.

9. Blood Chemistry: Blood chemistry collection as shown for first cycle; thereafter, blood chemistry collection required only within 72 hours prior to beginning of each cycle.

10. Urinalysis: Conducted for all subjects at screening. During the treatment period to be performed only when clinically indicated. If protein ≥ 2+ by semiquantitative method (eg, urine dipstick), protein will be quantified by 24-hour urine collection. Urine reflex microscopy is recommended whenever urine multitest dipstick is positive for blood or protein.

11. Hepatitis B and C Testing: Conduct tests for hepatitis B surface antigen, core antibody, and anti-hepatitis C. Other standard tests may be conducted to confirm an active hepatitis infection.

12. Pregnancy Test: For female subjects of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, and assayed in a certified laboratory, will be performed on 2 separate occasions prior to starting study treatment: once at the start of screening and once at the baseline visit (**except if screening and baseline are within 2 days of each other**). Negative results for the baseline pregnancy must be obtained and documented before ado-trastuzumab emtansine administration. Following a negative pregnancy result at screening, appropriate contraception must be commenced. Pregnancy tests to be routinely repeated at every cycle (eg, on Day 1) during the active treatment period. Additional pregnancy test to be repeated whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected.

13. Endocrine Function: Assessed by medical history, physical examination, and routine laboratory parameters (eg, blood chemistries) for endocrine function (including but not limited to TSH, ACTH, and cortisol levels), and as medically appropriate may include assessment for hypopituitarism and hypoadrenalism. Conducted for all subjects at screening/baseline, and when clinically indicated during the treatment period.

14. LVEF Assessment: Performed at screening; at Cycle 5 Day 1 (± 7 days); every 4 cycles (± 7 days) thereafter; and at end of treatment.

15. 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 (± 15 minutes) on Day 1 of each cycle. When both utomilumab and ado-trastuzumab emtansine/trastuzumab are administered, ado-trastuzumab emtansine/trastuzumab will be administered first, followed within 30 minutes (± 15 min) by utomilumab infusion.

16. Ado-trastuzumab emtansine or trastuzumab Administration: Treatment will be administered in a 3-week cycle (ie, 21-day cycle), by intravenous infusion. The first infusion of ado-trastuzumab emtansine or trastuzumab on-study will be over 90 minutes (± 30 minutes) on Cycle 1 Day 0. Subsequent infusions will be administered over 30 ± 15 minutes as tolerated.

17. Tumor assessment: Assessment of response will be made using RECIST v1.1. Antitumor activity will be assessed through radiological tumor assessments conducted a baseline, on treatment every 9 weeks and whenever disease progression is suspected (eg, symptomatic deterioration). To be repeated at End of Treatment/Withdrawal only if not done in the previous 9 weeks. Confirmation of response (CR/PR) should be done at least 4 weeks after the initial response. The allowable time window for disease assessments is ± 7 business days, on treatment, starting from C1D1. Timing should follow calendar days and should not be adjusted for delays in cycle starts. Tumor assessments performed after the screening period should consist of 1) CT and/or MRI of the chest/abdomen/pelvis; 2) bone scan or PET scan if bone metastases identified during the screening period are clinically indicated by the treating physician; and 3) CNS imaging clinically indicated by the treating physician.

18. Blood for utomilumab pharmacokinetics: Blood samples (tube type and quantity per lab manual) 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 subjects discontinuing from the study, a PK sample should be collected at the End of Treatment assessment.

19. Blood for ado-trastuzumab emtansine or trastuzumab pharmacokinetics: Blood samples (tube type and quantity per lab manual) will be collected as follows: Cycle 1 on Day 0 at pre-dose and a the end of ado-trastuzumab emtansine or trastuzumab infusion; Cycle 2 to 3 on Day 1 at pre-dose and at the end of ado-trastuzumab emtansine or trastuzumab 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 subjects discontinuing from the study, a PK sample should be collected at the End of Treatment assessment.

20. Blood for Immunomodulation/Cytokine Release Biomarkers: Blood samples (tube type and quantity per lab manual) will be collected as follows: at Screening, Cycles 1 on Day 0 at pre-dose and at the end of infusion of ado-trastuzumab emtansine or trastuzumab; 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.

21. Blood for Pharmacodynamic Assessment of Lymphocyte Subpopulation: Blood samples (tube type and quantity per lab manual) for the isolation and analysis of lymphocytes subpopulation will be collected at screening, on Cycle 2 Day 1 at pre-dose, and at end of treatment.

22. Blood for T cell Receptor Assessment: Blood samples (tube type and quantity per lab manual) for the isolation and analysis of T-cell receptors will be collected at screening, on Cycle 2 Day 1 at pre-dose, and at end of treatment.

23. Blood for utomilumab Immunogenicity Testing: Blood samples (tube type and quantity per lab manual) for 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 subjects 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.

24. Blood for ado-trastuzumab emtansine/trastuzumab Immunogenicity Testing: Blood samples (tube type and quantity per lab manual) for ado-trastuzumab emtansine or trastuzumab immunogenicity testing will be collected on Cycles 1 on Day 0 at pre-dose and on Cycle 2 and 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 subjects 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.

25. Blood for Exploratory Biomarkers: Blood samples (tube type and quantity per lab manual) will be collected at Screening, on Cycle 2 Day 1 at pre-dose, and at end of treatment.

26. Tumor Biopsy for Biomarker Assessment: See Appendix 4. A recent tumor biopsy is requested be provided at enrollment. An archival biopsy may be acceptable per eligibility criteria (see inclusion criteria). Tissue blocks are preferred, but if not available at least 20 unstained slides are suggested. For eligibility, if no unstained slides remain, stained pathology slides should be reviewed at the treating institution. A tumor biopsy at Day 1, Cycle 4 (± 14 days) is requested unless clinically not feasible.

27. Adverse Event (AE) Assessments: Adverse events should be documented and recorded at each scheduled or unscheduled visit, including at end-of-treatment and during follow-up, using NCI CTCAE v5. Subjects must be followed for AEs for 28 days after the last treatment administration or until all drug-related toxicities have resolved, whichever is later; or earlier than 28 days should the subject commence another anticancer therapy in the meantime. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 60 calendar days after the last administration of the investigational products and before initiation of a new anti-cancer treatment. The prolonged follow up is due to the pharmacokinetic properties of the investigational product utomilumab. SAEs experienced by a subject after the active reporting period has ended should be reported to the Sponsor if the Investigator becomes aware of them; at a minimum, all SAEs that the Investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor. AEs (serious and non-serious) should be recorded on the Case Report Form (CRF) from the time the subject has taken at least one dose of study treatment through last subject visit (Day 28 after last dose). If a subject begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Pregnancy or breast feeding that occur during the trial, within 28 days after the cessation of utomilumab if the subject begins a new anticancer therapy, whichever is earlier, should be reported as SAE.

28. Concomitant Medications: Concomitant medications will be recorded from 28 days prior to the start of study treatment and up to 28 days after the last dose of study treatment. Concomitant medications will be collected at each scheduled or unscheduled visit, including at end-of-treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).

29. End of Treatment: To be performed 28 days (± 7 days) after the last dose of study drug. Obtain these assessments if not completed during the previous week on study, (during the previous 9 weeks on study, for tumor assessments).

30. Follow-Up: Subjects should be evaluated, including for adverse events, up to 60 days after last dose of study treatment. Subjects continuing to experience toxicity following discontinuation of study treatment will continue to be followed including for adverse events, at least every 3 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. Adverse events will not be collected after resolution of treatment-related toxicities or 60 days after last dose of study treatment, whichever is later. Subjects whose disease has not progressed at the end of treatment will enter into disease follow-up. During this follow up period, subjects will have disease assessments performed every 9 weeks (± 7 days). Once subjects

have exhibited disease progression or began a new anticancer therapy, or 6-month follow-up from the date of the last dose of the study drug, whichever occurs first, they will be withdrawn from the study.

Appendix 4: Tumor Biopsy Recommendations

Optional tumor biopsies for subjects with accessible tumors are strongly encouraged. Suggested time points are as follows: Baseline pre-treatment, and on Cycle 4 Day 1 ± 14 days. These are suggested time points; but tissue sample collection may be obtained at any time point as feasible (eg, during drainage of pleural fluid for symptom relief, etc).

Tissue collection kits will be provided:

1. Tumor specimens will be obtained from accessible tumor sites as follows:
    a. Fine Needle Aspiration (FNA) -- to be used only if core biopsy is not allowed or if not feasible. The needle aspirate biopsies will be apportioned by pathology into multiple types of media for assessment. Portions of specimen must be prioritized in the following order at the discretion of the pathologist involved in the case/responsible for the trial:
        i. Smears for histology and diagnosis
        ii. Tissue frozen at -80ºC for RNA/DNA isolation/analysis
        iii. Fresh frozen tissue for optimum cutting temperature (OCT) compound.
    b. Core biopsy: 2 to 3 large bore (3 mm) needle biopsies of accessible, involved sites will be made at the time points suggested above. The needle aspirate biopsies will be apportioned by pathology into multiple types of media for assessment. Portions of specimen must be prioritized in the following order at the discretion of the pathologist reviewing the case /responsible for the trial:

i. Portion of core submitted for formalin-fixed, paraffin-embedded (FFPE) processing to be used for histology and diagnosis, for FFPE compatible immunohistochemistry and in situ hybridization
        ii. Tissue frozen at -80ºC for RNA/DNA isolation/analysis
        iii. Fresh frozen tissue embedded in optimum cutting temperature (OCT) compound for immunohistochemistry and in situ hybridization that requires fresh frozen tissue, and for Western blot analysis.
        iv. Viably frozen tumor cells, dissociated for other cellular experimentation and for flow analysis to determine percentage of tumor cells vs infiltrating lymphocytes, etc.
    c. Excisional biopsy: Tissue will be taken and apportioned by pathology into multiple types of media for assessment. Portions of specimen must be prioritized in the following order and will be at the discretion of the pathologist reviewing the case/responsible for the trial:
        i. Portion of the specimen will be submitted for FFPE processing to be used for histology and diagnosis, determination of treatment effect (degree of necrosis compared to original diagnostic material), determination of local variations (periphery of tumor vs center) for FFPE compatible immunohistochemistry and in situ hybridization.
        ii Tissue frozen at -80ºC for RNA/DNA isolation/analysis
        iii. Fresh frozen tissue embedded in optimum cutting temperature (OCT) compound for immunohistochemistry and in situ hybridization that requires fresh frozen tissue, and for Western blot analysis.
        iv. Viably frozen tumor cells, dissociated for other cellular experimentation and for flow analysis to determine percentage of tumor cells vs infiltrating lymphocytes, etc.

v. Fresh viable (non-frozen) tissue for consideration for implantation into mice to develop xenograft models and extend tumors for further experimentation.

d. Paracentesis/thoracocentesis/lumbar puncture: Cells in the fluid obtained from paracentesis/thoracentesis/lumbar puncture will be spun down and cell count taken. Tissue will be taken and apportioned by pathology into multiple types of media for assessment. Portions of specimen must be prioritized in the following order and will be at the discretion of the pathologist reviewing the case/responsible for the trial:

   i. Smear for histology and diagnosis, eg, determination of percentage of tumor cells vs inflammatory cells.

   ii. Fresh cells for flow analysis to determine percentage of tumor cells vs infiltrating lymphocytes, vs mesothelial cells, etc.

   iii. Tissue for RNA/DNA analysis

   iv. Fresh frozen tissue embedded in optimum cutting temperature (OCT) compound for immunohistochemistry and in situ hybridization that requires fresh frozen tissue, and for Western blot analysis.

   v. Viably frozen tissue for other cellular experimentation

   vi. Remainder of the cell pellet will be submitted for FFPE for FFPE compatible immunohistochemistry and in situ hybridization.

Appendix 5: Correlative / Special Studies – Biomarkers

- Serum and intratumoral biomarkers linked to immunomodulation and cytokine release such as: TNFα; IL-6; IFNγ; CXCL9; CXCL10; IL10; IL-8; IL-4; IL-2; IL-1b; IL-12p70
- Exploratory PD biomarkers expressed by PBMC and intratumoral lymphocytes, such as Ki67, soluble CD137, and markers of T and NK cell phenotype (such as CD3; CD4; CD8; CD25; HLA-DR; CCR7; ICOS; Eomesodermin; CD45RA; CD45RO; CD16; CD56; CD25; CXCR6; TNFSF4; TNFSF7; ITGA2; ITGB7; VCAM1) and quantitation of T-cell receptor sequences;
- Tumor biopsy for analysis of exploratory mechanistic biomarkers such as IHC assessment of tumor-infiltrating lymphocytes and quantitation of T-cell receptor sequences;
- (Optional blood and intratumoral sample) Pharmacogenomic (RNA) analysis of subject PBMC to explore expression of genes that would influence subject response to utomilumab and TDM-1 or trastuzumab, such as EOMES; CDKN2D; TIMP1; FCGR2B; IL1RN; SOCS3; CXCL9; CXCL10; IL1B; IFI16; CCR5; FASLG; CXCR3; IFNG; ICOS; CD40LG; IL2RA; CD80; CCL5; FOXP3; CDC25A,GZMA; IL23A; SOCS1; IL10;
- (Optional blood and intratumoral sample) Pharmacogenetic (DNA) analysis of subject PBMC to explore polymorphisms in genes such as FCGR2A and FCGR3A that could affect response to utomilumab and TDM-1 or trastuzumab

Appendix 6. List of Abbreviations:

4-1BB	CD137, a member of the tumor necrosis factor (TNF) receptor family. Alternative names are tumor necrosis factor receptor superfamily member 9 (TNFRSF9) and induced by lymphocyte activation (ILA).
AC	Adriamycin plus cyclophosphamide chemotherapy
ADA	Anti-drug antibody
ADCC	Antibody dependent cellular cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
APC	Antigen-presenting cell
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ANC	Absolute neutrophil count
CFR	Code of Federal Regulations
CL	Clearance
CNS	Central nervous system
CRF	Case report form
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DC	Dendritic cell
DLT	Dose-limiting toxicity
DR	Duration of response
DSMC	Data safety and monitoring committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin embedded
FIH	First-in-human
FISH	Fluorescence *in situ* hybridization
FL	Follicular lymphoma
FNA	Fine needle aspirate
GCP	Good clinical practice
HER2	Human epidermal growth factor receptor 2
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IRB	Institutional review board
IRR	Infusion related reaction
IV	Intravenous
LNG-IUS	Levonorgestrel-releasing intrauterine system
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MAP	Mitogen activated protein
MCC	Merkel Cell Carcinoma

MCL	Mantle cell lymphoma
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition
NCI	National cancer institute
NHL	Non-Hodgkin's lymphoma
OCT	Optimum cutting temperature
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PET	Positron emission tomography
PF-05082566	Utomilumab, a humanized anti-CD137 monoclonal antibody
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SRC	Scientific review committee
TBI	Total body irradiation
T-DM1	Ado-trastuzumab emtansine, a antibody-drug conjugate of trastuzumab and maytansine 1
TNF	Tumor necrosis factor
TRAF	Tumor necrosis factor receptor-associated factor
TTR	Time-to-treatment response
Vc	Volume of distribution