A RANDOMIZED, PHASE II STUDY COMPARING TRASTUZUMAB AND VINORELBINE IN COMBINATION WITH AVELUMAB OR AVELUMAB AND UTOMILUMAB (41BB/CD137 AGONIST), IN PATIENTS WITH HER2-POSITIVE METASTATIC BREAST CANCER WHO HAVE PROGRESSED ON PRIOR TRASTUZUMAB AND PERTUZUMAB:
The "AVIATOR" Study

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Agent(s)	Avelumab, Utomilumab, *supplied by Pfizer* Trastuzumab, Vinorelbine, *commercially supplied*

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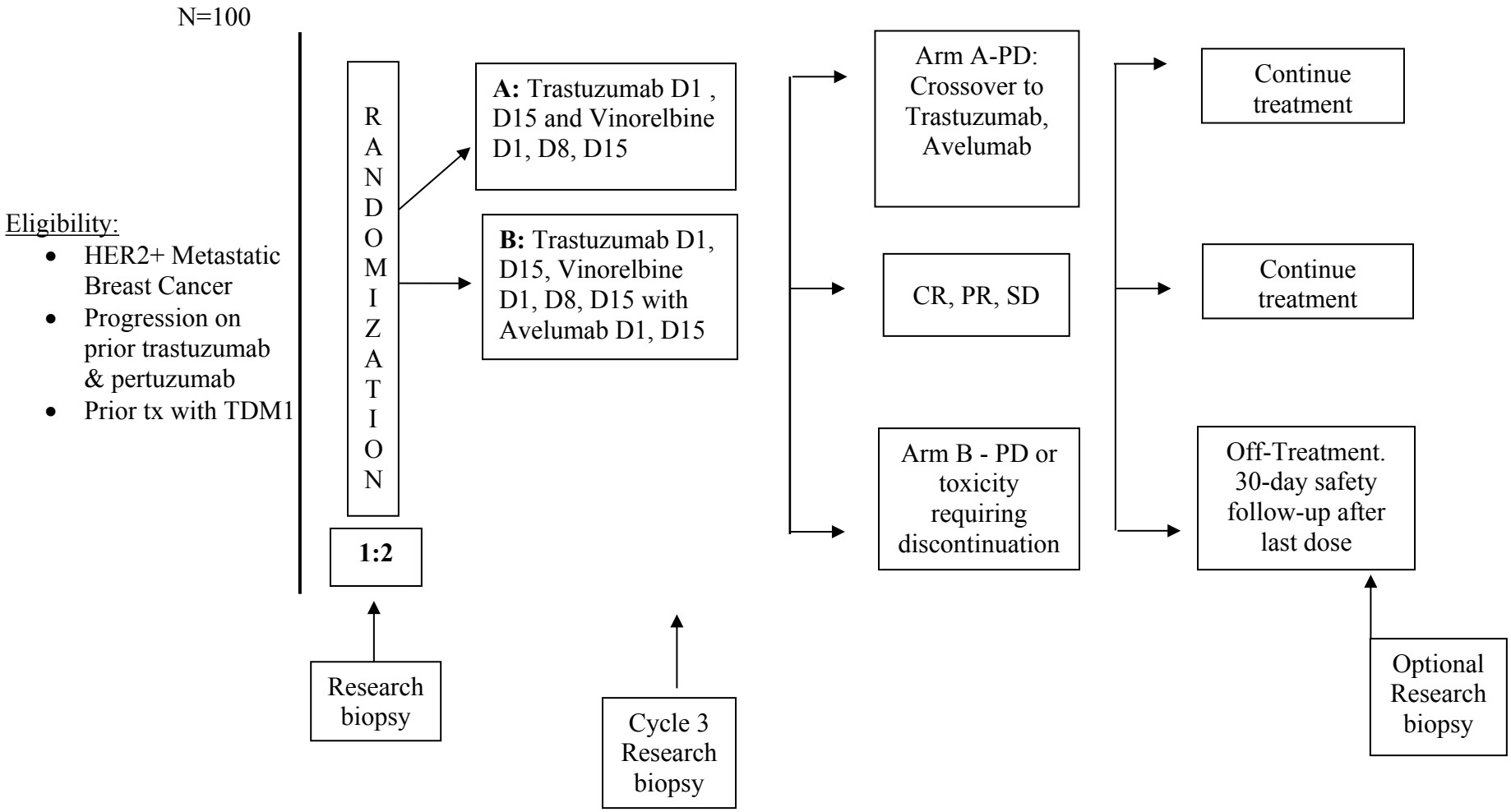
Revised SCHEMA



*Arm C was permanently discontinued in February 2021.

Stratification Factors

1. Lines of Prior Metastatic Therapy (<3 vs. 3+)
2. Hormone Receptor Status (ER+ vs. ER-)
3. Presence of Liver Metastases (yes or no)

1. OBJECTIVES AND ENDPOINTS

1.1 Study Design

This is a randomized phase II study designed to evaluate the safety and efficacy of trastuzumab and vinorelbine alone, in combination with an anti-PD-L1 monoclonal antibody (avelumab) or in combination with both avelumab and an anti 41BB/CD137 agonist mAb (utomilumab) in patients with advanced HER2+ breast cancer that has progressed on prior trastuzumab, pertuzumab and TDM-1 therapy.

At least 100 eligible patients will be randomized 1:2:2 to receive trastuzumab/vinorelbine (Arm A: approximately 20 patients), trastuzumab/vinorelbine plus avelumab (Arm B: approximately 40 patients), or trastuzumab/vinorelbine plus avelumab plus utomilumab (Arm C: approximately 40 patients).

Because of an interim futility analysis in January 2021 that met the criteria for utomilumab inefficacy**, Arm C has been closed to further enrollment and the crossover arm will now be trastuzumab and avelumab (Sponsor Amendment 4/Protocol Version 5).** Going forward, all newly enrolled patients will be randomized 1:2 to receive trastuzumab/vinorelbine (Arm A: approximately 20 patients) or trastuzumab/vinorelbine plus avelumab (Arm B: approximately 40 patients).

- **Arm A (n=20)**
  - trastuzumab 4mg/kg IV D1, D15
  - vinorelbine 25mg/m^2 IV D1, D8, D15
  - *NOTE: Crossover option to trastuzumab and avelumab upon progression.*

- **Arm B (n=40)**
  - trastuzumab 4mg/kg IV D1, D15
  - vinorelbine 25mg/m^2 IV D1, D8, D15
  - **avelumab 10mg/kg IV** D1, D15

- **Arm C (n=40) (Closed with protocol version 5/Sponsor Amendment 4)**
  - trastuzumab 4mg/kg IV D1, D15
  - vinorelbine 25mg/m^2 IV D1, D8, D15
  - **avelumab 10mg/kg IV** D1, D15
  - **utomilumab 100mg IV** D1

Patients will be stratified by lines of prior metastatic therapy (< 3 vs. 3+), ER status (positive vs negative) and presence of liver metastases (yes vs no).

1.2 Primary Objectives

- To determine whether the addition of avelumab to the combination of trastuzumab and vinorelbine will improve progression-free survival (PFS) compared to the trastuzumab

and vinorelbine combination alone in patients with advanced HER2-positive breast cancer.

- To determine whether the addition of utomilumab to the combination of avelumab, trastuzumab, and vinorelbine will improve progression-free survival (PFS) compared to the avelumab, trastuzumab, and vinorelbine combination alone in patients with advanced HER2-positive breast cancer.

1.3 Secondary Objectives

The secondary objectives of the study are to evaluate efficacy of the no immunotherapy arm (Arm A), single immunotherapy (Arm B) and doublet immunotherapy (Arm C) using the following endpoints:

- Objective response (ORR), defined as Complete Response or Partial Response by RECIST 1.1
- Duration of response (DOR)
- Overall survival, defined as time from randomization to death from any cause
- Preliminary assessment of the clinical activity, as measured by ORR and PFS, of the cross-over regimen of trastuzumab, avelumab and utomilumab in patients who progress on vinorelbine/trastuzumab
- Safety and tolerability using NCI-CTCAE version 5.0. In particular, emphasis will be on cardiac, hepatic and pulmonary events (nature, severity and timing of these adverse events)

1.4 Exploratory Objectives

The exploratory objectives in this study are to determine efficacy of the combinations using the following endpoints:

- PFS measures according to PD-L1 immunohistochemistry (IHC) status
- PFS measures according to tumor infiltrating lymphocytes (TILs) level (baseline absolute levels and change)
- PFS measures as defined by immune modified RECIST
- ORR by PD-L1 IHC status and various categories
- Estimate two-year overall survival rate according to treatment arm

1.5 Correlative Objectives

- To assess if baseline PD-L1 IHC expression is associated with responders and if this differs by treatment arm
- To assess if baseline TIL (as determined on H&E slides) levels are associated with responders and if this differs by treatment arm
- To assess if baseline “activated” immune status (defined by high TILs/ high PD-L1 expression, mRNA enrichment of interferon signaling) is associated with responders and if this differs by treatment arm
- To assess the above (1.3.6-1.3.8) by ER status

- To determine if mutational profiles of material from baseline tumor biopsies are associated with efficacy and if this differs by treatment arm
- To determine if baseline levels or change in IHC or gene expression levels of immune biomarkers are associated with efficacy and if this differs by treatment arm
- To determine if clonality and diversity derived from sequencing of the T cell receptor (TCR) in tumor and blood are associated with efficacy
- To track mutations in plasma to understand biomarkers of responders and non-responders
- To determine if levels of T cell phenotypes (activated effector T cells in blood) are associated with efficacy
- To determine if any biomarkers are associated with safety signals

1.6 Endpoints

1.6.1 Primary Endpoint

- Progression-Free Survival (PFS): Both median PFS and 12 month PFS will be estimated from the PFS distribution.

1.6.2 Secondary Endpoints

- Objective Response (ORR: Complete Response or Partial Response)
- Duration of Response (DOR)
- Overall Survival (OS)
- ORR and PFS in the crossover arm
- Safety and Tolerability (by NCI CTCAE Version 5.0)

2. BACKGROUND

2.1 HER2-Positive Breast Cancer

Breast cancer is the most common cancer, other than skin cancer, in women and is one of the leading causes of cancer deaths among women in the United States. The introduction of trastuzumab into the treatment of HER2- overexpressing breast cancer has significantly changed the natural history of this disease, especially in the adjuvant setting. Trastuzumab treatment in the adjuvant setting in combination with chemotherapy has now resulted in high cure rates [16-18]. However, the prevalence of metastatic breast cancer is still significant and is not currently considered curable. For the HER2-positive disease subtype, studies now suggest that at least 50-70% of patients with a new diagnosis of metastatic disease are presenting de novo [19,20]. Hence even as adjuvant cure rates are increasing, the number of patients being diagnosed with de novo advanced HER2-positive disease is static or even increasing. Therefore, this group of patients still remains in high need of efficacious therapies that can improve survival.

The current standard first line treatment for advanced HER2-positive disease is combination trastuzumab, pertuzumab and docetaxel [20]. This combination significantly improved both progression free and overall survival compared with trastuzumab and docetaxel alone. Trastuzumab emtansine (T-DM1) has subsequently shown superiority in

the 2nd and later settings after failure of trastuzumab, or trastuzumab and lapatinib [21,22]. There is no standard in the 3rd line setting and after, so therapy beyond this point remains suboptimal. While treatment in the advanced setting is thought to be palliative, an increase in survival is still an important objective for these patients, highlighting the need for new and effective therapies in this group of patients.

Increasing preclinical and correlative clinical data suggest that HER2-positive breast cancer is immunogenic [23,24]. These data suggest that successful treatment of HER2-positive breast cancer with anti-HER2 therapies relies on intact and functional host anti-tumor immunity. Thus, we believe that HER2-positive breast cancer is potentially highly amenable to immunotherapeutic approaches. Relatively high rates of TILs in this subtype, and the observation that TIL levels correlate with prognosis and higher responses to anti-HER2 therapy, as well as knowledge that one of the main mechanisms of action of trastuzumab is ADCC and generation of adaptive immunity, together all support immune evasion as a critical requirement for tumor progression in HER2-positive cancers.

Due to the competitive therapy landscape in HER2-positive breast cancer, there are not many studies evaluating immunotherapy in this breast cancer subtype. However, the preclinical and correlative data suggest that HER2-positive disease may be the most amenable subtype to immune modulation due to partially effective reinstatement of immunosurveillance by trastuzumab, the presence of a strong tumor antigen (HER2) as well as a higher mutational load [23].

At present, the advanced setting remains the optimal setting to evaluate new approaches given the high cure rates of many early-stage HER2-positive patients. Nearly all patients with advanced disease will suffer disease progression and die from their disease. Hence, there is a still a critical need to develop more efficacious therapies that may prolong survival in this subgroup. In addition, successful approaches in the advanced setting may also lead to more tailored approaches and de-escalation of chemotherapy in the early-stage setting.

2.2 Study Agent(s)

2.2.1 Avelumab

Avelumab is a fully human anti-PD-L1 mAb of the IgG1 isotype that is FDA approved for the treatment of patients with metastatic Merkel cell carcinoma (MCC) or metastatic previously treated urothelial carcinoma. It is also currently being investigated in combination with other immunotherapies in patients with locally advanced or metastatic solid tumors.

Avelumab selectively binds to PD-L1 and competitively blocks its interaction with PD-1. Compared with anti-PD-1 antibodies that target T-cells, avelumab targets tumor cells, and is therefore expected to have fewer side effects, including a lower risk of autoimmune-related toxicity, as blockade of PD-L1 leaves the PD-L2/PD-1 pathway intact to promote peripheral self-tolerance.

Avelumab has 2 main mechanisms of action for exerting its anti-tumor effects:

- PD-L1 on tumor cells can interact with PD-1 or B7-1 on activated T cells. These interactions have been shown to significantly inhibit T cell activities. Therefore, blocking PD-L1 interaction with PD-1 or B7-1 by anti-PD-L1 can release T cells from immunosuppression, and lead to elimination of tumor cells by T cells.
- Tumor cells may express high levels of PD-L1 on their surface compared with normal tissues. As a fully human IgG1 MoAb, avelumab has antibody-dependent cellular cytotoxicity (ADCC) potential. Upon binding to PD-L1 on tumor cells and binding with their Fcpart to Fc-gamma receptors on leukocytes, avelumab can trigger tumor-directed ADCC.

A dose of 10 mg/kg of avelumab, intravenous (IV) once every 2 weeks is the FDA approved adult dosing of avelumab and is the dose used in the ongoing Phase III trials based on the preliminary pharmacokinetic(PK),target occupancy, and preliminary clinical safety data collected in the clinical trials.

Avelumab plasma levels leading to full programmed death ligand 1 (PD-L1) receptor target occupancy (TO) on PBMCs resulted in tumor growth inhibition in a murine disease model. Therefore, full TO on PBMCs can be considered a PD marker for the ability of avelumab to act on its target and to show clinical activity.

Preliminary PK data from EMR 100070-001 show that the concentration at the end of dose interval (Cmin) increased more than proportionally to dose between 1 to 10 mg/kg, but proportionally for doses above 10 mg/kg. Consistently the t1/2 also increased with the dose. However, the average value was 102 and 120 hours for 10 mg/kg and 20 mg/kg, respectively, with no significant difference between these two dose groups. This PK characteristic suggests that target mediated drug disposition is involved in the clearance of avelumab and a high PD-L1 TO is likely achieved at the trough concentration for doses of 10mg/kg and 20mg/kg.

The in vitro target occupancy data further support that a high TO is likely achieved at 10 mg/kg and above.

Target occupancy was measured ex vivo by flow cytometry on peripheral blood CD3+ T cells from patients (n=9) treated with avelumab. After the first dose of the initial dose-escalation portion of Trial EMR 100070-001, the observed mean target occupancy reached a plateau of about 90% on Day 15 pre-dose for dose levels of 3 mg/kg and above.

In addition, in vitro target occupancy was measured using flow cytometry on peripheral blood CD3+ T cells from 8 healthy volunteers after spiking avelumab over a concentration range of 0.003 to 10 µg/mL. A 50% target occupancy was observed at a drug concentration (standard deviation [StD]) of 0.122 (0.042) µg/mL, and a concentration of 1 µg/mL avelumab was required for > 95% target occupancy. Based on these data and the trough serum levels observed in EMR 100070-001, target occupancy was projected to reach or

exceed > 95% throughout the entire dosing interval for 10/13 subjects at 3 mg/kg, and for all (15/15) subjects at 10 mg/kg group from dose escalation group in EMR1000700-001.

Based on the ex-vivo peripheral blood CD3+ T cell and in vitro target occupancy results, the dose of 10 mg/kg every 2weeks is expected to achieve target saturation during the entire dosing interval in the majority of patients.

As of the safety cutoff date of 05 November 2015, 1353 subjects have received at least 1 dose of avelumab at doses ranging from 1.0 to 20 mg/kg in the Phase I Trial EMR 100070-001, of which 1315 have received the proposed dose of 10mg/kg (15 in the dose escalation part of the study and 1300 subjects in the pooled expansion cohort).

In the dose escalation portion of the Phase I study, there was no evidence of differences in the safety profile across all administered dose levels from 1 mg/kg to 20 mg/kg. The MTD was not reached. Ongoing review of the safety data by the Safety Monitoring Committee (SMC) suggests an acceptable safety profile of avelumab administered at the 10 mg/kg every 2 weeks dose and schedule. Treatment-related treatment-emergent adverse events (TEAEs) were observed in 813 (62.5%) subjects in the pooled expansion cohort. The most frequently observed treatment related TEAEs (incidence > 5%) were fatigue (212 subjects, 16.3%), infusion-related reaction (209 subjects, 16.1%), nausea (108 subjects, 8.3%), chills (102 subjects, 7.8%), diarrhea (79 subjects, 6.1%), and pyrexia (72 subjects, 5.5%).Grade ≥ 3 treatment-related TEAEs were observed in 124 subjects (9.5%) in the pooled expansion cohort. The most frequently reported Grade ≥ 3 treatment related TEAEs were gamma-glutamyl transferase increased (GGT) and infusion-related reaction (each occurred in 9 subjects; 0.7%). Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions have been identified as expected adverse drug reactions of avelumab. The safety profile of avelumab is consistent with findings reported for other anti-PD-1 or anti-PD-L1 antibodies.

In conclusion, preliminary data from EMR 100070-001 showed that avelumab at doses up to 20mg/kg Iv every 2 weeks was well tolerated, and the dose of 10 mg/kg Iv every 2 weeks was considered to have an acceptable safety profile for further investigation in clinical studies.

Avelumab is currently in clinical development across Phases I, II, and III. These include:

- EMR 100070-001: A Phase I, open-label, multiple ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab in subjects with metastatic or locally advanced solid tumors and expansion to selected indications
- EMR 100070-002: A Phase I trial to investigate the tolerability, safety, pharmacokinetics, biological and clinical activity of avelumab in Japanese subjects with metastatic or locally advanced solid tumors, with expansion part in Asian subjects with gastric cancer
- EMR 100070-004: A Phase III open-label, multicenter trial of avelumab versus docetaxel in subjects with non-small cell lung cancer that has progressed after a platinum-containing doublet

EMR 100070-001 is a Phase I, open-label, multiple ascending dose trial to investigate the safety, tolerability, PK, biological and clinical activity of avelumab in subjects with metastatic or locally advanced solid tumors and expansion to selected indications. This trial consists of 2 parts. In the dose escalation part, sequential cohorts of subjects were enrolled at progressively higher dose levels (ranging from 1.0, 3.0, 10.0, and 20.0 mg/kg once every 2 weeks) with a 3 + 3 algorithm design for determination of the maximum tolerated dose (MTD) of avelumab; in the treatment expansion phase, subjects in different tumor cohorts are being treated with 10 mg/kg of avelumab once every 2 weeks until, confirmed progression, unacceptable toxicity, or any reason for withdrawal occurs. More than 1500subjects have been enrolled in the EMR100070-001 trial. The 3 + 3 dose escalation algorithm to determine the MTD is complete and a dose of 10 mg/kg once every 2 weeks was determined for the tumor expansion cohorts on the basis of safety, PK, and PD observations. The treatment expansion part of the trial consists of 16tumor treatment cohorts. As of 05 November 2015 (data cutoff for a pre-planned safety data review by the study Safety Monitoring Committee [SMC]), 53 subjects in the dose escalation part had received avelumab (4, 13, 15, and 21 subjects had received 1.0, 3.0, 10.0, and 20.0mg/kg of avelumab, respectively) and 1300 subjects in the pooled expansion part had received 10 mg/kg avelumab and were followed up for at least 4weeks.

The safety summary summarizes data from 1300 subjects treated in the pooled treatment expansion cohort from the ongoing Phase I Trial EMR100070-001 (as of 05 November 2015). The pooled data included subjects treated in all tumor expansion cohorts, including non-small cell lung cancer (NSCLC), metastatic gastric cancer, breast cancer, colorectal cancer, castrate-resistant prostate cancer, adrenocortical carcinoma, melanoma, mesothelioma, urothelial carcinoma, ovarian cancer, renal cell carcinoma, and squamous cell cancer of the head and neck. Safety data are also summarized for 52 subjects in the ongoing Phase I Trial EMR 100070-002 and for 88 subjects in the ongoing Phase II Trial EMR100070-003 (as of 17December 2015). For TrialEMR100070-004, an overview of the serious adverse events (SAEs) is provided.

Most of the observed adverse events (AEs) were either in line with those expected in subjects with advanced solid tumors or with class effects of monoclonal antibody (mAb) blocking the PD-1/PD-L1 axis. Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions (immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related endocrinopathies (thyroid disorders, adrenal insufficiency, new onset type I diabetes mellitus, pituitary disorders), immune-related nephritis and renal dysfunction and other immune-related AEs (myositis, myocarditis, Guillain-Barré syndrome, uveitis). Guidelines for the management of immune-mediated adverse reactions and infusion-related reactions are implemented in all ongoing clinical studies with avelumab.

The clinical efficacy information summarized in the Investigator's Brochure includes data from the following expansion cohorts of the ongoing Phase I Trial EMR100070-001, NSCLC (second line and first line cohorts), ovarian cancer, GC/GEJ, UC, mesothelioma,

and adrenocortical carcinoma. In addition, efficacy results for 20 subjects in the gastric cancer expansion cohort of the ongoing Phase I Trial EMR 100070-002 and 88 subjects in Part A of the ongoing Phase 1 Trial EMR 100070-003 in mMCC are summarized.

The NSCLC expansion cohort in the ongoing Phase I Trial EMR100070-001 had a cutoff date of 15 January 2015, 6 months after start of avelumab treatment of the last subject in this expansion cohort (a total of 184 treated subjects). The objective response rate (ORR) based on confirmed and unconfirmed responses for subjects treated in the NSCLC expansion cohort was 14.1% (26 of 184 NSCLC subjects). Progression free survival (PFS) and overall survival (OS) were all evaluated for all NSCLC subjects treated in the expansion phase. As of 15 January 2015, the median PFS and OS for the NSCLC treatment expansion cohort were 11.6 weeks and 8.4 months, respectively.

The clinical activity of avelumab was also evaluated by subjects' tumor PD-L1 expression status in the NSCLC expansion cohort. An objective response was observed in 20 of 122 subjects (16.4%) who were PD-L1 positive (defined as having at least 1% PD-L1 positive tumor cells) compared with 2 of 20 subjects (10.0%) who were considered PD-L1 negative (defined as having less than 1% PD-L1 positive tumor cells). A longer median PFS (12.0vs 5.9 weeks) and OS (8.9 vs 4.6months) were both observed in PD-L1 positive compared with PD-L1 negative subjects.

The ovarian cancer expansion cohort had a data cutoff of 13 February 2015, approximately 13 weeks after the start of avelumab treatment on the last subject who was included in this pre-planned interim analysis on this expansion cohort. The ORR based on confirmed and unconfirmed responses for subjects treated in the ovarian cancer expansion cohort was 10.7% (8 of 75 subjects). The median PFS for the ovarian cancer expansion cohort was 11.4 weeks (95%confidence interval (CI): 6.3 to 12.0weeks).

The preliminary efficacy data for the ongoing Phase I Trial EMR 100070-002 are based on a data cutoff of 11 March 2015. As of the data cutoff, 3 of 20 subjects responded to trial treatment (all responses were partial responses [PRs] and all responses were confirmed responses), and the best overall response (BOR) was 15.0% (95%CI: 3.2%to 37.9%). The median PFS of this group was 11.9 weeks (95% CI: 6.0 to 12.3weeks).

The results of a Phase I cohort expansion trial in patients with metastatic breast cancer were presented at the 2015 San Antonio Breast Cancer meeting (Dirix et al, SABCS 2015). In this trial, 168 patients with metastatic breast cancer with up to 3 prior lines of therapy in the metastatic setting were treated with avelumab 10 mg/kg every 2 weeks until disease progression. Overall, treatment was well tolerated, with the primary grade >3 clinically significant toxicities including autoimmune hepatitis (3 patients, 1.8%), GGT increase (3 patients, 1.8%) and fatigue (3 patients, 1.8%). Eight patients (4.8%) experienced grade 1/2 hypothyroidism, and one patient each experienced grade 3 pneumonitis, or grade 4 thrombocytopenia. The overall response rate in this unselected population was 4.8% (95% CI 2.1, 9.2) with one complete and 7 partial responses. An additional 23.2% of patients had stable disease. The median time to response was 11.4 weeks (range, 5.7-17.7 weeks), the median duration of response was 28.7 weeks (95%

CI: 6.1, ne), and responses were ongoing in 5/8 patients at time of the analysis. Tumor shrinkage of ≥30% was observed in 16 patients (9.5%), including 2 patients with progressive disease by RECIST who had partial responses by modified Immune RECIST Criteria (irRC). Responses were seen in all molecular subtypes. PD-L1 status in 136 evaluable patients did not appear to correlate with response, although small numbers and varying cut-offs make this data difficult to interpret.

For additional details, refer to the Avelumab Investigator's Brochure.

2.2.2 Utomilumab

Utomilumab is a novel full humanized IgG2 mAb agonist of 4-1BB (*CD137, TNFRSF9*)

A membrane spanning glycoprotein of the Tumor Necrosis Factor (TNF) receptor superfamily, 4-1BB was first identified as an inducible costimulatory receptor expressed on activated T cells. 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 and activated B cells [4]. 4-1BB expression has also been demonstrated on tumor vasculature [5,6]. The ligand that stimulates 4-1BB (4-1BBL) is expressed on activated antigen-presenting cells (APCs), myeloid progenitor cells and hematopoietic stem cells.

Interaction of 4-1BB on activated normal human B cells with its ligand at the time of B cell receptor engagement stimulates proliferation and enhances survival [4]. The potential impact of 4-1BB engagement in B cell lymphoma has been investigated in two 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. The addition of 4-1BB agonists to in vitro cultures of B lymphoma cells with rituximab and NK cells resulted in increased lymphoma killing [7]. 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.

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 [8]. 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 [9-11].

Upon 4-1BB activation, TRAF 1 and TRAF 2, 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.

Numerous studies of murine and human T cells indicate that 4-1BB promotes enhanced cellular proliferation, survival, and cytokine production [12]. 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 [13]. 4-1BB agonists also inhibit autoimmune reactions in a variety of autoimmunity models [14]. 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.

2.2.2.1 Preclinical and clinical development of Utomilumab

Utomilumab (PF-05082566), 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. Treatment with Utomilumab as a single agent results in tumor cell line growth inhibition in xenogeneic tumor models. In addition, 4-1BB agonist mAbs demonstrate significant combinatorial efficacy with antibody-dependent cell-mediated cytotoxicity (ADCC) in lymphoma 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.
It is thought that tumor expression of PD-L1 can limit the ability of cytotoxic T cells to directly kill the tumor cells. Therefore, even if a 4-1BB agonist is used to stimulate cytotoxic T cells, capable of recognizing such tumors, PD-L1 expressed on the tumor cells may down-modulate the activity of these stimulated T cells. A 4-1BB agonist antibody resistant mouse MC38 colon cancer tumor model that expresses PD-L1 was used to provide evidence for improved anti-tumor activity using the combination of a 4-1BB agonist antibody with PD-1 antagonist antibody compared with either single agent. In immunocompetent mouse models of colon carcinoma (MC38), melanoma (B16F10) and triple negative breast cancer (AT3-ova), statistically significant anti-tumor activity versus the vehicle control is observed in the cohort of mice that received a combination of a PD-1 antagonist antibody with a 4-1BB agonist antibody, but not with either antibody administered as a single agent (see IB for further information). Consistent with the proposed mechanism for the combination, significant increases in CD8+ effector memory cells and tumor responsive IFN-gamma producing cells were found in the spleens of mice treated with the combination (data not shown). In addition, preliminary toxicology data in mice suggest that the toxicity of an anti-4-1BB agonist is not increased by addition of an anti-PD-1 antagonist (data not shown).

As of October 2015 (see IB), utomilumab has been administered as a single agent to 47 patients with advanced cancerat dose levels between 0.006 and 10.0 mg/kg, in 40 patients at dose levels between 0.03 and 10.0 mg in combination with rituximab and in 23 patients

at dose levels between 0.45mg/kg and 5.0 mg/kg in combination with pembrolizumab for a total of 110 patients treated.

The ongoing first in-patient clinical Study B1641001 is a Phase 1, open–label, dose-escalation study to evaluate the safety and tolerability, in one study arm, of PF- 05082566 given as a single agent in subjects with solid tumors or relapsed or refractory B-cell lymphoma, and in another study arm, of Utomilumab given in combination with rituximab in patients with relapsed or refractory CD20 positive Non-Hodgkin's Lymphoma (NHL). Key study parameters assessed included pharmacokinetics of PF-05082566, pharmacodynamic markers of activity, and preliminary anti-tumor activity.

No dose limiting toxicities have thus far been seen. The most frequently occurring treatment related AEs were pyrexia (10.6%) which was generally mild, followed by fatigue (8.5%). One case of grade 3 thrombocytopenia was observed which lasted less than 7 days and was not considered a serious adverse event.

For additional details, refer to the Utomilumab Investigator's Brochure.

2.2.3 Trastuzumab and Biosimilars

Refer to the Full Prescribing Information for trastuzumab or biosimilars for complete safety information: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ in addition to information provided in Sections 7 and 8 of the protocol.

2.2.4 Vinorelbine

Refer to the Full Prescribing Information for trastuzumab for complete safety information: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ in addition to information provided in Sections 7 and 8 of the protocol.

2.3 Rationale

2.3.1 Rationale for combination administration of avelumab and utomilumab

As noted above, the combination of a 4-1BB agonist antibody with a PD-1 antagonist antibody shows significant inhibition of tumor growth in preclinical models of colon carcinoma, melanoma model and triple negative breast cancer compared with either agent alone. In addition, the combination of a 4-1BB agonist antibody with an anti-HER2 agent also shows synergy in preclinical models of HER2-positive disease [15]. Patients previously progressing on anti-PD-1 therapy have responded to utomilumab monotherapy suggesting a viable alternative mechanism of relief of T cell exhaustion. The core hypothesis to be evaluated in this study is that a 4-1BB agonist antibody will synergize with anti PD-L1 to activate cytolytic T cells and synergize with trastuzumab to increase ADCC. Hence the combination of avelumab and Utomilumab is a rational combination to evaluate in HER2-positive disease.

The benefit-risk relationship has been carefully considered in the planning of this study. Avelumab demonstrated clinical activity in patients with advanced solid tumors as well as breast cancers. The clinical safety data available to date, with single-agent avelumab in patients with advanced solid tumors, suggest an acceptable safety profile of the compound. Most of the observed events were either in line with those expected in patients with advanced solid tumors or with similar class effects of monoclonal antibodies blocking the PD-1/PD-L1 axis. Infusion-related reactions including hypersensitivity and immune related (ir) AEs/autoimmune disorders have been identified as important risks for avelumab. Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab, including this clinical trial protocol. These include guidelines for treatment interruption and discontinuation in case of irAEs, as well as mandatory pretreatment with a histamine H1 receptor (H1) blocker and acetaminophen.

The anti-4-1BB mAb, utomilumab, has also demonstrated clinical activity as monotherapy in patients with advanced solid tumors and in combination with rituximab in patients with NHL in an ongoing Phase 1 study. The clinical safety profile of Utomilumab supports its use as both a single agent and in combination with other monoclonal antibodies. Fatigue and skin rashes represent the most common utomilumab related AEs, although they have been generally mild to moderate in intensity. While clinically significant irAEs have not been observed with PF-05082566, risk mitigation measures have been implemented in ongoing clinical studies with PF-05082566, including this clinical trial protocol. These include guidelines for treatment interruption and discontinuation in case of treatment related irAEs. Based on the nonclinical and Phase 1 data available to date for both avelumab and PF-05082566, the conduct of this trial is considered justifiable using the dose and frequency of administration of avelumab and the dose and frequency of administration of utomilumab as specified in this clinical trial protocol. Of note, the highest utomilumab dose to be administered in this study is considerably lower than the highest dose tested as a single agent and in combination with rituximab, where no severe treatment related toxicities were observed. In addition, toxicity data from the ongoing phase Ib study of avelumab and utomilumab will provide additional information regarding the safety of this combination and these data will inform this protocol as warranted. Lastly, this study shall be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit relationship that would render continuation of the trial unjustifiable.

Thus, the projected benefit/risk of avelumab given in combination with Utomilumab is anticipated to be favorable for investigation in this population of patients.

2.3.2 Rationale for combination with chemotherapy and dual immunotherapeutic approaches

Anti-HER2 therapies, in particular trastuzumab and T-DM1, have been shown to require and also induce anti-tumor immunity which likely contributes to an effective clinical response. In preclinical studies, the combination of trastuzumab or T-DM1 with checkpoint blockade have enhanced tumor regressions in immunocompetent mouse models [15,25,26]. Given the strong positive prognostic associations of inducing an immune

response as evidenced by tumor immune cell infiltration, we hypothesize that therapies that can induce or enhance an immune response could be beneficial in improving survival of advanced HER2-positive disease.

Certain chemotherapy agents given weekly or metronomically (i.e., paclitaxel, vinorelbine) have always synergized well with anti-HER2 therapy and this mechanism of action may be through enhancement of immune responses through apoptosis, inflammation and presentation of MHC I/II [27]. Hence the rationale to combine with chemotherapy in HER2-positive breast cancer is compelling.

Trials with trastuzumab in combination with an anti-PD-1 antibody in advanced HER2-positive patients are currently ongoing (NCT02129556). To date, early efficacy data suggest that whilst there are some patients who respond very well to PD-1 blockade as monotherapy with durable responses, these represent a minority of patients. This could be due to lower levels of pre-existing immunity (as evidenced by lower levels of TILs) in the advanced setting. Hence it is plausible that combination immunotherapy approaches (i.e. with chemotherapy or targeting other checkpoints) will be needed to reinstate immunosurveillance in most patients in the advanced setting in order to improve survival.

Early data in other solid tumor types support that combination immunotherapies look promising. Combination CTLA-4 and PD-1 blockade in both melanoma and non-small cell lung cancer (NSCLC) have shown higher objective response rates as well as longer progression free survival. These responses seem independent of baseline PD-L1 levels if one considers PD-L1 as a surrogate for a pre-existing immune response (T effector/IFN-gamma type signature)[28]. Melanoma and NSCLC are considered more “immunogenic” than breast cancer, with almost 10-fold higher mutational loads. In preclinical models combination checkpoint blockade increases T effector cell infiltration, reduces T-regulatory cells and increases IFN-gamma production.

Our preliminary data analyzing the composition of TILs in breast cancer suggest that CD137/4-1BB is involved in the generation of an effective T cell anti-tumor response. Furthermore, we and others have shown the importance of adaptive immunity in trastuzumab response as well as synergism of checkpoint modulation (4-1BB /PD-1) with anti-HER2 therapy in preclinical immunocompetent mice models. 4-1BB has also been shown to be upregulated on NK cells post trastuzumab treatment-- hence strategies that can enhance ADCC may also increase response rates in an immunosuppressive microenvironment. Together the data suggests that the anti-tumor immune response could be enhanced by combination T cell agonist (4-1BB) and checkpoint blockade (PD-L1) together with anti-HER2 therapy. This combination may also have less toxicity than dual checkpoint (CTLA-4 and PD-1/L1) blockade as preclinical models suggest that 4-1BB may play a role in reducing autoimmunity side effects of checkpoint blockade. Pre-clinical data also supports a role for 4-1BB agonists in protecting T cells from detrimental actions of agents such as chemotherapy and MEK inhibition (personal communication S Loi).

In view of the low mutational burden of breast cancer relative to other immunogenic tumor types, the lower frequency of PD-L1 protein expression and TILs observed in advanced breast cancer to date, we propose that the combination of a 4-1BB agonist with PD-L1 blockade could be a suitable treatment strategy in advanced HER2 breast cancer as a means to enhance T cell infiltration and activity. This may be most relevant to HER2-positive patients who are ER-positive vs. negative as the former have lower levels of immune infiltrate. Patients who progress post pertuzumab and T-DM1 based regimens still have poor survival and are hence a population requiring novel and efficacious therapies to be developed. If efficacy is observed with the strategy of combination checkpoint blockade, then this approach can be applied to earlier line and/or stage settings, particularly in patients who lack TILs, given that TILs are strongly associated with improved survival in both early and late stage settings.

This study will provide proof of concept data for two important clinical and translational questions. First, whether PD-1/L1 blockade (single immunotherapy) can improve the efficacy of a standard-of-care chemotherapy/trastuzumab combination in PD-L1-unselected patients. Second, can dual immunotherapy further enhance efficacy compared to single immunotherapy regimen in the same patient population. Lastly, the study's biomarker work may allow us to begin to determine which patients particularly need the combination regimens.

2.3.3 Rationale for using a vinorelbine/trastuzumab backbone

Vinorelbine is a microtubule inhibitor, similar to the taxanes. These agents interfere with mitosis and as such promote polyploidization. Such stress in chromosomal content has been linked to an endoreticulum stress response that favors calreticulin exposure and hence facilitates the recognition and elimination of malignant cells by the immune system. In non-small cell lung cancer, treatment with vinorelbine has been shown to increase the levels of cytoxic T cells over T regs. Both vinorelbine and the taxanes have demonstrated strong synergistic clinical activity with trastuzumab [1]. This synergy can be hypothesized to be due in part to promotion of immune effects in combination with trastuzumab. In randomized studies, the combination of vinorelbine and trastuzumab has shown comparable or potentially superior efficacy compared to taxane and trastuzumab, typically with lower rates of severe toxicity [2,29,30]. Vinorelbine, unlike taxanes, does not require the use of prophylactic steroids, which may be an advantage in the setting of immunotherapy. Vinorelbine also is not typically used in the early disease setting, therefore most patients with advanced disease are vinorelbine naïve. For these reasons, the combination of vinorelbine and trastuzumab offers a convincing alternative to taxane-based regimens in combination with immunotherapy in the advanced HER2 setting and as a non-immunotherapy standard of care control arm in this study.

2.3.4 Rationale for trial design

This trial is a comparative proof-of-concept phase II study to determine if 1) avelumab adds to the standard of care combination of trastuzumab and vinorelbine and 2) if utomilumab adds to avelumab in combination with trastuzumab and vinorelbine. It is noted that both avelumab and Utomilumab are investigational agents with no proven

benefit in HER2-positive breast cancer. Because the population that will be enrolled in this study may be heterogenous, it is challenging to accurately predict the PFS of the trastuzumab and vinorelbine control arm. Thus, it is possible that the study may be slightly underpowered to detect a benefit of avelumab when added to trastuzumab and vinorelbine. However, we will soon have the results of ongoing phase III studies evaluating the addition of PD-1/PD-L1 blockade to standard chemotherapy/trastuzumab to provide more definitive data on the benefit of PD-1/PD-L1 blockade in this context. In addition, we will also have the correlative work described below which will help determine who benefits from the addition of immunotherapy. Given the current limited efficacy data in advanced breast cancer with PD-1/PD-L1 blockade, the move in other solid tumor types towards combination approaches, and the low immunogenicity of advanced breast cancer in general, our hypothesis is that this forward-looking study design evaluating both a single immunotherapy and a combination immunotherapy regimen is warranted.

2.3.5 Rationale for allowing cross-over for patients randomized to the control arm

As noted above, at this time there is no proven benefit to either Utomilumab or avelumab in HER2+ breast cancer, therefore there is not an ethical responsibility to provide crossover in this study. However, patients enrolling on this study are likely interested in immunotherapy approaches to treating their cancer. Thus, for those patients who are randomized to the no-immunotherapy control arm, providing an option to receive an immunotherapy regimen at the time of progression is appropriate. As overall survival is not a primary endpoint of this study, allowing cross-over will not significantly compromise the study's ability to assess its objectives. Importantly, this crossover will provide an opportunity to obtain a preliminary assessment of the clinical activity of the trastuzumab, Avelumab and Utomilumab regimen in the absence of chemotherapy.

2.3.6 Safety of the proposed two investigational study arms

The safety evaluation of utomilumab is ongoing and is reported in the current Invenstigator Brochure (October 2017). Study B9991004 is a Phase 1b/2, open label, multi center, multiple dose, safety, efficacy, PK/PD study of immune modulators in combination with avelumab (PD-L1 blocking mAb) in adult patients with locally advanced or metastatic solid tumors. Utomilumab is the first agent to be evaluated in combination with avelumab in this study and is designated as Combination A. Combination A consists of three lead-in cohorts patients with advanced NSCLC randomly assigned to a utomilumab flat dose cohort of 20 mg, 100 mg, or 500 mg, administered concurrently with avelumab at 10 mg/kg on Day 1 of each 4-week cycle (avelumab is administered every 2 weeks within a 4-week cycle). Cohorts found to be safe and well tolerated are then to be expanded in the Phase 2 stage in patients with advanced NSCLC. Upon activation of the Phase 2 portion of Combination A, cohorts of patients with advanced melanoma, squamous cell carcinoma of the head and neck, and triple negative breast cancer will be treated with 100 mg utomilumab plus avelumab. In Phase 2, bothsafety and efficacy objectives will be assessed.

The combination of an anti-PD-1 inhibitor (pembrolizumab) with trastuzumab is also being evaluated in an ongoing phase 2 study with more than 60 patients enrolled thus far (NCT02129556). Again, no unexpected safety signals have been observed; the main drug related toxicity was fatigue.

PD-1/PD-L1 blockade in combination with various cytotoxic agents is currently being evaluated in large studies. The toxicity profile of these agents as monotherapy is now well established. In particular, there appears to be no cardiac toxicity which is particularly relevant when considering combinations with trastuzumab. Pfizer reports that avelumab is in phase III studies in ovarian cancer with combination with carboplatin/ paclitaxel and with pegylated liposomal doxorubicin (JAVELIN Ovarian 200: NCT02580058). Again, there has been no unexpected toxicity seen. Therefore, the combination of avelumab with the chemotherapy proposed seems feasible.

Vinorelbine has been extensively evaluated in combination with trastuzumab in phase 3 studies. In these studies, the main drug related toxicity was hematological, with predominantly grade 2 leucopenia.

Overall, we do not expect significant safety issues with the triplet and quadruple combination. However careful safety monitoring is incorporated into this study to address concerns that these combinations have not been evaluated together yet.

2.3.7 Rationale for allowing patients to continue treatment beyond initial progression per RECIST 1.1

Conventional response criteria may not be the most suitable to assess activity of immunotherapeutic agents. There are numerous documented responses of patients who progress by RECIST 1.1 criteria who then demonstrate durable anti-tumor activity. In many trials of checkpoint blockade there are patients who demonstrate tumor shrinkage even after an initial increase in tumor burden. This may be due to increase in immune infiltrates. The most commonly observed pattern was the appearance of new lesions such as FDG avid lymph nodes in the context of decreased overall tumor burden at the first or second tumor assessment. The potential for pseudo-progression or delayed anti-tumor immunity with combination chemotherapy, trastuzumab, and immunotherapy is unknown.

2.3.8 Rationale for revised study design discontinuing enrollment to utomilumab-containing regimens

In October 2020, the study team was informed that Pfizer had discontinued development of utomilumab. This decision was based on a perceived lack of efficacy observed in a study of utomilumab and avelumab in a mixed population of solid cancers that did not include HER2-positive breast cancer. There were no concerns about the safety of the combination. To address this new information, in consultation with the study's Data Safety Monitoring Board, in January 2021 an interim futility analysis for utomilumab benefit was performed on available efficacy data from the AVIATOR study. Results from this analysis indicated

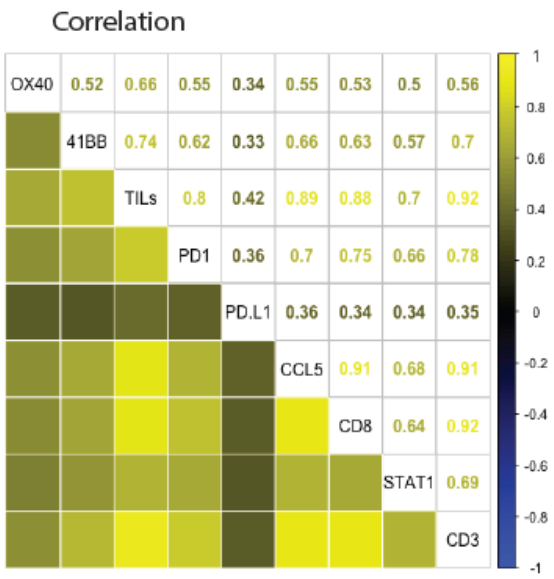
the accumulating data were inconsistent with the targeted benefit hazard ratio of 0.60. Based on this analysis, new enrollment to Arm C of this study (vinorelbine/trastuzumab/avelumab/utomilumab) has been permanently discontinued. Utomilumab has also been removed from the crossover regimen for all new patients starting that portion of the study.

Importantly, the AVIATOR trial has a co-primary objective to determine whether the PD-L1 inhibitor avelumab adds benefit to vinorelbine and trastuzumab. This important question remains unanswered in HER2+ breast cancer. Thus, there is still strong rationale to complete enrollment to Arms A (vinorelbine/trastuzumab) and B (vinorelbine/trastuzumab/avelumab) of AVIATOR. Notably this comparison was *not* part of the interim analysis.

Of note, at the time of Sponsor Amendment 4, there were no longer any active patients receiving utomilumab.

2.4 Correlative Science Background

Our preliminary data analyzing the composition of TILs in breast cancer suggest that CD137/4-1BB is involved in the generation of an effective T cell anti-tumor response (Figure below showing strong correlations with 4-1BB and TILs [by hematoxylin and eosin staining (H&E)[31]] and expression of other immune markers in the TCGA breast cohort [32]. Furthermore, we and others have shown the importance of adaptive immunity in trastuzumab response as well as synergism of checkpoint modulation (4-1BB /PD-1) with anti-HER2 therapy in preclinical immunocompetent mice models[15,33]. 4-1BB also has been shown to be upregulated on NK cells post trastuzumab treatment-- hence strategies that can enhance ADCC may also increase response rates in an immunosuppressive microenvironment[33]. Together the data suggests that the anti-tumor immune response could be enhanced by combination T cell agonist (4-1BB) and checkpoint blockade (PD-L1) together with anti-HER2 therapy. This combination may also have less toxicity than dual checkpoint (CTLA-4 and PD-1/L1) blockade.



We hypothesize that the presence of a pre-existing immune response (i.e. using PD-L1 or TILs as a proxy for a T-effector/IFN-gamma signature) will bode for higher responses to avelumab alone, but the lack of one may mean that the addition of utomilumab may be required. The other main hypothesis is that the combination will be more effective in all patients (i.e. with or without a pre-existing immune response).

Hence, the main objectives of the correlative elements of this study will be to determine

which patients need the combination of utomilumab and avelumab as opposed to avelumab alone, as well as to identify early biomarkers of responders.

2.4.1 Rationale for biomarker evaluations

TILs as measured in a semi-quantitative fashion on routine H&E slides are strongly associated with prognosis in both primary and advanced HER2 positive disease in the setting of anti-HER2 therapy and chemotherapy [31,34]. Immune gene signatures have also been strongly associated with both pCR and survival in both early and advanced disease [35-37]. PD-L1 protein expression both on tumor cells and on TILs are associated with increased responses to checkpoint blockade [38]. This study will evaluate the potential [39]prognostic and predictive effect of TILs and PD-L1 expression for treatment of HER2-positive breast cancer treated with combination trastuzumab, vinorelbine and immunotherapy. Activating *PIK3CA* mutations in HER2-positive disease has been shown to be associated with resistance to HER2-targeted therapies in prior trials. In the CLEOPATRA study, *PIK3CA* mutations were shown to be associated with a worse outcome, although the treatment benefit remained the same [39]. *PIK3CA* and other somatic mutations will be measured in the baseline tumor samples to determine associations with prognosis and relationship with immune infiltrates.

Studies have shown that chemotherapy and anti-HER2 therapies can cause increases in TILs in human breast cancer and these TILs are largely tumor effector T cells in murine models [15,25,40]. As such, an important exploratory effect of this study is to test how the doublet immunotherapy vs the avelumab alone and the control regimen can change the expression levels of TILs, T effector cells (infiltration of CD8+ T cells for example) and other immune biomarkers in the tumor and peripheral blood that suggest initiation and ongoing anti-tumor immune activation. Baseline pre-treatment and on-treatment tumor and blood samples will be collected to assist in these assessments.

2.4.2 Rationale for collection of archival and metastatic tumor specimens

For a comparative proof-of-concept phase II study, correlative investigations into tumor biology will be of high importance. The most recent tumor block will be used for evaluation of baseline HER2, TILS by H&E, and PD-L1 status. This is preferably a recently obtained sample as we know that the immune infiltrate changes over time and quantities are prognostic in the advanced setting [41]. In addition to these biomarkers other exploratory biomarkers will be evaluated in tumor specimens which may help us understand the value of adding utomilumab to avelumab by assessing tumor immune activation markers, genomics and other resistance mechanisms. These analyses may involve large panels of genes at both the RNA (gene expression) and DNA (targeted exome/genome sequencing) level. Serial HER2 levels, TILs and PD-L1 status may also be evaluated to understand changes in HER2 heterogeneity and immune status over time and on therapy.

2.4.3 Rationale for collection of mandatory on-treatment biopsy

The collection of serial biopsies from patients undergoing study treatment will contribute to the biological understanding of how the study treatments work and differences between the control arm, avelumab and the combination with utomilumab. Such biopsies may lead to the identification of novel biomarkers and/or signatures which may identify responders and those who require avelumab or the combination. Often changes in biomarkers (i.e. comparison to baseline) can be highly informative and as such, a biopsy from the patient prior to Cycle 3 day 1 will be performed (if feasible). TILs, CD8+ T cells, PD-L1, HER2 status, and other relevant biomarkers, will be evaluated on these paired samples. Increase in TILs has been reported to be significantly associated with pCR and disease free survival in the early stage setting (Loibl et al, submitted- data from NeoPhoebe study NCT1816594] [42]).

2.4.4 Rationale for collection of biopsy at time of progression.

If clinically feasible, patients will be asked to undergo an optional tumor biopsy at time of evidence of radiographic or RECIST disease progression. Analyses of biological material will include biomarkers (DNA and RNA) as well as changes in expression of biomarkers related to immunity. This knowledge will help us understand molecular changes related to resistance. Comprehensive examination of specimens on progression may help us understand important pathways. Such information will also be combined with data from other similar studies, thus increasing the power to identify important resistance mechanisms and new drug targets.

2.4.5 Rationale for collection of serial blood specimens

Plasma of cancer patients contains cell-free tumor DNA that carries information on tumor mutations and tumor burden. This information may be useful as a non-invasive way of monitoring advanced disease using cancer genetic alterations (mutations, rearrangements) that are specific to the individual's tumor[43]. This information may allow us to track and monitor tumor dynamics during the disease course as well emergence of new clones (i.e., resistance mechanisms). Individual mutations may be assessed using technologies such as digital PCR or next generation deep sequencing. Plasma samples will be collected at the same times as planned restaging imaging.

3. PARTICIPANT SELECTION

3.1 Inclusion Criteria

3.1.1 Age ≥18 years or older

3.1.2 Histologically confirmed breast cancer that is metastatic or unresectable loco-regionally advanced

3.1.3 Histologically confirmed HER-2 positive breast cancer by ASCO CAP 2013 guidelines. NOTE: Central confirmation of HER-2 status is not required:

- IHC 3+ based on circumferential membrane staining that is complete, intense

-AND/OR-

- FISH positive based on one of the three following criteria:
  - Single-probe average HER2 copy number ≥6.0 signals/cell; **OR**
  - Dual-probe HER2/CEP17 ratio ≥2.0 **OR**
  - Dual-probe HER2/CEP17 ratio <2.0 with an average HER2 copy number≥6.0 signals/cell

3.1.4 Measurable disease per RECIST v1.1 (see Section 11)

3.1.5 Participants must have previous treatment with ado-trastuzumab emtansine (Kadcyla, T-DM1) in any setting.

3.1.6 Participants must have previously received trastuzumab and pertuzumab in the metastatic setting or recurred ≤12 months after a neoadjuvant/adjuvant regimen containing trastuzumab and pertuzumab.It is not mandatory to have a trastuzumab and/or pertuzumab containing regimen as the most recent treatment.

3.1.7 Participants must have progressed on their most recent line of therapy. Progression must have been demonstrated by radiological or clinical assessment.

3.1.8 Left ventricular ejection fraction (LVEF) ≥50%, as determined by MUGA or echocardiogram

3.1.9 Eastern Cooperative Oncology Group (ECOG) performance status 0-1

3.1.10 Participants must have normal organ and marrow function as defined below:

- Absolute neutrophil count ≥ 1250/µL
- Platelet count ≥ 100,000/µL
- Hemoglobin ≥ 9 g/dL
- Serum total bilirubin ≤ 1.5 × institutional upper limit of normal (ULN). In the case of known Gilbert's syndrome, a higher serum total bilirubin (< 2 × ULN) is allowed.
- AST ≤ 2.5 × ULN or ≤ 5 × ULN if patient has liver metastases
- ALT ≤ 2.5 × ULN or ≤ 5 × ULN if patient has liver metastases
- Creatinine ≤ 1.5 ×institutional ULN or creatinine clearance ≥ 60 mL/min/1.73 m^2
- Urinary protein:creatinine (UPC) ratio < 1.0

3.1.11 International Normalized Ratio (INR) or Prothrombin Time (PT) ≤1.5 × ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulant.

3.1.12 Willingness and availability to submit FFPE tissue for research purposes. This can be from archival tissue from unresectable loco-regional or metastatic disease obtained ≤1 year prior to enrollment or new tissue material from a recently obtained surgical or diagnostic biopsy. Tissue obtained for the biopsy must not have been previously irradiated. If a patient does not have any available archival tissue ≤1 year old and the treating investigator does not feel that it would be safe to perform a fresh biopsy, the requirement for a fresh biopsy may be waived after discussion with the Protocol Chair.

3.1.13 If female of childbearing potential, must have a negative pregnancy test within 7 days of registration. Childbearing potential is defined as: those who have not been surgically

sterilized and/or have had a menstrual period in the past 12 months or who have been on ovarian suppression in the past year.

3.1.14 Participants of childbearing potential (males and females as defined above) must be willing to use effective contraception during treatment and up to 7 months after stop of trial treatment. Acceptable methods of contraception are intrauterine devices, bilateral tubal occlusion, vasectomized, or total abstinence. Oral, injectable, or implant hormonal contraceptives are not allowed.

3.1.15 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Prior therapy with vinorelbine in any setting

3.2.2 Prior therapy with any anti-PD-1, anti-PD-L1, L2, anti-4-1BB (CD137), or anti-CTLA4 therapy

3.2.3 Known Human Immunodeficiency Virus (HIV) positive (testing not required)

3.2.4 Active or chronic Hepatitis B or C (testing not required)

3.2.5 History of interstitial lung disease

3.2.6 Active central nervous system metastases, as indicated by clinical symptoms, cerebral edema, and/or progressive growth (patients with history of CNS metastases or spinal cord compression are eligible if they are clinically stable for at least 4 weeks before first dose of investigational product and do not require high-dose steroid treatment)

3.2.7 History of clinically significant or uncontrolled cardiac disease, including congestive heart failure (New York Heart Association functional classification > 3), angina, myocardial infarction or ventricular arrhythmia

3.2.8 Previous severe hypersensitivity reaction to treatment with another monoclonal antibody

3.2.9 Active infection requiring systemic therapy

3.2.10 Chronic systemic therapy with immunosuppressive agents including corticosteroids

3.2.11 Active autoimmune disease or a documented history of autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Patients with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Patients that require intermittent use of bronchodilators or local steroid injections would not be excluded from the trial. Patients with hypothyroidism stable on hormone replacement or Sjögren's syndrome will not be excluded from the trial.

3.2.12 Concurrent disease or condition that would make the patient inappropriate for trial participation or any serious medical disorder that would interfere with the patient's safety in the opinion of the treating investigator.

3.2.13 No current uncontrolled hypertension (≥180/110), unstable diabetes mellitus, dyspnea at rest, or chronic therapy with oxygen.

3.2.14 Chemotherapy, radiotherapy, and/or biological cancer therapy (excluding trastuzumab)

within 3 weeks prior to the planned treatment start date

3.2.15 Unresolved or unstable adverse events from prior therapy, except alopecia (has not recovered to CTCAE v.5 ≤grade 1 or baseline).

3.2.16 Pregnant women or women who are lactating/breastfeeding due to the teratogenic potential of the study drugs

3.2.17 Participants receiving any medications or substances that are strong inhibitors or inducers of CYP3A are ineligible. A list of medications and substances known or with the potential to interact with the CYP3A isoenzymes is provided in Appendix B. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as the Physicians' Desk Reference. As part of the enrollment/informed consent procedures, the participant will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the participant is considering a new over-the-counter medicine or herbal product.

3.2.18 Live vaccines within 30 days prior to the first dose of trial therapy and during trial treatment.

3.3 Inclusion of Underrepresented Populations

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION AND RANDOMIZATION PROCEDURES

Eligible participants will be registered in the Clinical Trials Management System (CTMS) OnCore at Dana-Farber Cancer Institute (DFCI). Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants must begin protocol therapy within 2 weeks (14 calendar days). Issues that would cause treatment delays should be discussed with the Overall Principal Investigator/Protocol Chair.

4.1 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Randomization can only occur during ODQ business hours (8:30am - 5pm Eastern Time, Monday through Friday excluding holidays).

An email confirmation of the registration and randomization will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

4.2 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the Project Manager. All sites should email or call the Project Manager to verify slot availability. The required forms in Section 4.3 should be emailed or faxed to the Project Manager.

Following registration, participants should begin protocol therapy within 2 weeks (14 calendar days days). Issues that would cause treatment delays should be discussed with the Overall PI/Protocol Chair. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Project Manager should be notified of cancellations as soon as possible.

4.3 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the research nurse or data manager and emailed to the Project Manager at CTOPM@dfci.harvard.edu or faxed to 617-632-5152:

- Clinic visit note documenting history and physical exam
- Copy of required laboratory tests including: Hematology (CBC with differential), comprehensive metabolic panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose total bilirubin, calcium, total protein, albumin, AST, ALT, and alkaline phosphatase), pregnancy testing (if necessary), T3, T4, TSH, Urinalysis, UPC ratio, LDH, Coagulation profile
- Pathology report and documentation of ER/PR status and HER2 status
- Tumor assessments by CT, PET, or MRI
- Bone Scan (If applicable)
- ECHO or MUGA report
- Signed participant consent form
- HIPAA authorization form (if separate from the informed consent document)
- Completed DF/HCC Eligibility Checklist with stratification

To complete the registration process, the Project Manager will

- follow the DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) and register the participant on the protocol
- call or email the research nurse or data manager at the participating site with the participant study number, and to confirm registration

NOTE: Registration can only be conducted during the business hours of 8:00 AM and 5:00 PM Eastern Time Monday through Friday. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Project Manager.

5. STUDY CALENDARS

Scans must be done within 30 days prior to planned start of protocol therapy. Exams and MUGAs or echocardiograms are to be done within 30 days prior to registration. Baseline bone scan is not required, but should be performed if clinically indicated.

All assessments must be performed prior to administration of any study agent unless otherwise specified. The following windows apply:

- Screening assessments performed ≤ 96 hours prior to Day 1 of Cycle 1 do not have to be repeated for Day 1 of Cycle 1.
- Day 1 study assessments for Cycle 2 and beyond must be performed within +/- 3 days of the protocol-specified date.
- Day 8 and Day 15 study assessments for all cycles must be performed within -1/+3 days of the scheduled day (e.g., Day 8 visit must occur between Day 7 and Day 11). A minimum of 6 days between D1, D8, and D15 of vinorelbine administration is required.

Restaging scans for tumor evaluation should continue on schedule if treatment is held or delayed.

In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated as soon as possible prior to initiation of the next cycle of therapy. Subjects withdrawn from study with responsive or stable disease will be followed approximately every 9-12 weeks from the date of last assessment until progression.

5.1 Required Data: Arms A, B, and C

Table 1.

	Screening	All Cycles			30-Day Follow- Up[j]	Long Term Follow-Up
	≤30 days of registration, unless otherwise noted	D1	D8	D15	30-37 days after last dose	Annually after PD
		+/- 3 days	+3/- 1 day(s)	+3/- 1 day(s)		
Medical History/Demographics	X					
Physical Exam (full at screening, limited at subsequent cycle D1), ECOG PS	X	X			X	
Vital signs, weight, height (height at baseline only)	X	X	X	X	X	
Hematology (CBC with diff)	X	X	X	X	X	
Serum Chemistry [a]	X	X	X	X	X	
Pregnancy Test (serum or urine)[b]	X				X	
Total T3 and T4, TSH and Urinalysis [c]	X	X (odd cycles)			X	
Urine Creatinine and Urine Protein	X					
LDH	X				X	
Coagulation (INR and PTT) [a]	X					
Tumor Assessments[d]	X	X				X[e]
MUGA or Echocardiogram[f]	X	X				
Research Biopsy[g]	X	X[g]			X[g]	
Research Blood[h]		X	X[i]	X[i]	X	
Archival Tissue	X					
Adverse Event Assessment	X	X			X	
Overall Survival						X[k]

a. Serum chemistry includes measurement of sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total bilirubin, calcium, total protein, albumin, AST, ALT, and alkaline phosphatase. INR and aPTT at screening only, then as clinically indicated.

b. For women of childbearing potential only. A negative pregnancy test (urine or serum β- HCG) is required prior to registration and must be repeated, if necessary, within the 7 days prior to planned treatment start. All positive urine pregnancy tests must be confirmed by a serum β-HCG test.
c. T3, T4, TSH and Urinalysis are required at Screening, prior to dosing on C3D1, and then on Day 1 of every odd cycle (e.g. C5D1, C7D1, etc.)
d. Clinical and radiological tumor assessments will be performed by CT, PET or MRI scan at baseline (within 30 days) and then every 2 cycles (i.e., within -7 days prior to Cycles 3, 5, 7, and 9) until completion of Cycle 10; and then every 3 cycles (i.e., within -7 days prior to cycles 11, 14, 17, etc.) until disease progression. Responses of CR or PR should be confirmed with a second assessment no earlier than 4 weeks, but no later than the next scheduled scan, per protocol. Bone scan will be performed if clinically indicated. Results must be reviewed by RECIST for each scan prior to dosing at next cycle. Scans must be assessed by RECIST and irRECIST criteria
e. During follow-up of patients who went off study for reasons other than PD, tumor assessments should continue every 9 to 12 weeks from the date of the last assessment until progressive disease is documented
f. Cardiac evaluation (ECHO or MUGA) will be done at screening (within 30 days of registration) and then every 12 weeks (within -14 days i.e. prior to Cycles 4, 7, etc.)
g. Research biopsy at screening is mandatory if archival tissue is not available; biopsy is preferred. Cycle 3 Day 1 biopsy is mandatory. Time of progression biopsy is optional. If feasible, progression biopsy should be of same site as Cycle 3 Day 1 biopsy. Cycle 3 biopsy should occur prior to administration of treatment on Cycle 3 Day 1 (up to 7 days prior). If possible, this biopsy should be of same site as screening biopsy. Biopsies from bone or bone marrow are not acceptable.
h. See Section 9 for detailed research blood sampling schedule
i. Cycle 1 only. See Section 9
j. Extended safety follow-up is required for Arms B and C (90 days). The extended follow-up may be performed by phone call
k. Survival status should be collected annually, either by review of the medical record or by phone call

5.2 Required Data: Crossover

Table 2.

	Pre-Crossover	All Cycles		30-Day Follow- Up[h]	Long Term Follow-Up[i]
		Day 1	Day 15	30-37 days after last dose	
		+/- 3 day(s)	+3/- 1 day(s)		
Medical History/Demographics	X				
Physical Exam, ECOG PS	X	X		X	
Vital signs, weight, height (height at baseline only)	X	X		X	
Hematology (CBC with diff)	X	X	X	X	
Serum Chemistry[a]	X	X	X	X	
Total T3 and T4, TSH and Urinalysis[b]	X	X		X	
LDH	X			X	
Coagulation (INR and PTT)[a]	X				
Tumor Assessments[c]	X	X			X[d]
MUGA or Echocardiogram[e]	X	X			
Research Biopsy[f]				X	
Research Blood[g]		X	X	X	
Adverse Event Assessment	X	X		X	
Overall Survival[h]					X

a. Serum chemistry includes measurement of sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total bilirubin, calcium, total protein, albumin, AST, ALT, and alkaline phosphatase. INR and aPTT at screening only, then as clinically indicated.

b. T3, T4, TSH and Urinalysis are required at Screening, prior to dosing on C3D1, and then approximately every 8 weeks on Day 1 of every odd cycle (e.g. C5D1, C7D1, etc.)

c. Clinical and radiological tumor assessments will be performed by CT, PET or MRI scan at baseline (within 30 days) and repeated every 2 cycles (i.e., within 7 days prior to Cycles 3, 5, 7, and 9) until completion of Cycle 10; and then every 3 cycles (i.e., within 7 days prior to cycles 11, 14, 17, etc.) until disease progression. Responses of CR or PR should be confirmed with a second assessment no earlier than 4 weeks, but no later than the next scheduled scan, per protocol. Bone scan will be performed if clinically indicated. Results by RECIST must be reviewed for each scan prior to dosing at next cycle. Scans must be assessed by RECIST and irRECIST criteria

d. During follow-up of patients who went off treatment for reasons other than PD, tumor assessments should continue every 9 to 12 weeks from the date of the last assessment until progressive disease is documented
e. Cardiac evaluation (ECHO or MUGA) will be done pre-crossover treatment and then every 12 weeks (within -14 days, i.e. prior to Cycles 4, 7, etc.)
f. Time of progression biopsy is optional. If feasible, progression biopsy should be of same site as Baseline and/or Cycle 3 Day 1 biopsy. See Section 9.
g. ctDNA and PBMCs will be collected according to the Crossover Research Specimen Table in Section 9
h. Extended safety follow-up is required for the crossover arm (90 days). The extended follow-up may be performed by phone call
i. Survival status should be collected annually, either by review of the medical record or by phone call

6. TREATMENT PLAN

Treatment cycles are defined as 28 days. Treatment will be administered on an outpatient basis unless patient is hospitalized for other reasons. Patients will be randomized to one of the following treatment regimens: Arm A or B. Patients initially assigned to Arm A (control arm), may cross over to the combination of trastuzumab and avelumab (Cross-over arm) at the time of progression. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 7.2. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy. Biosimilars may be used for trastuzumab on any arm on this study.

Randomization will be 1:2 ratio to:

- **Arm A (n=20):** trastuzumab + vinorelbine
- **Arm B (n=40)**: trastuzumab + vinorelbine **+ avelumab**

Cross-Over: Participants initially randomized to Arm A may cross over to a combination of trastuzumab and avelumab at the time of disease progression.

Patients will be stratified by lines of prior metastatic therapy (< 3 vs. 3+), ER status (positive vs negative) and presence of liver metastases (yes vs no).

6.1 Pre-Treatment Criteria

For C1D1 labs:
Patients must have adequate organ function before initiating treatment on day 1:

- absolute neutrophil count ≥1,250/mcL
- platelets ≥100,000/mcL
- hemoglobin ≥ 9 g/dl
- total bilirubin ≤ 1.5 x institutional upper limit of normal
- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal (or ≤ 5 x ULN (for subjects with documented liver metastases)
- Serum or plasma creatinine ≤ 1.5 x institutional upper limit of normal (ULN) **OR** creatinine clearance ≥ 60 mL/min/1.73 m^2 for participants with creatinine levels above institutional ULN
- Negative pregnancy test (in appropriate patients)

Day 1 of Subsequent Cycles +/- 3 days):

- absolute neutrophil count ≥1,250/mcL(if 750-1249/ mcL, can proceed with the next cycle at a reduced dose of vinorelbine (see Section 7.2.2)
- In the event of a grade 4 decrease in absolute neutrophil count without fever, CBC should be assessed at least weekly until resolution to determine the length of the

event. This bloodwork may be done at a local lab to the participant as long as the results are reviewed by a study staff member qualified to assess toxicity.

- platelets ≥100,000/mcL (if 50,000-99,000/ mcL, can proceed with the next cycle at a reduced dose of vinorelbine (see Section 7.2.2)
- hemoglobin ≥ 9 g/dl
- total bilirubin ≤ 1.5 x institutional upper limit of normal
- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal or AST and ALT levels ≤ 5 x ULN (for subjects with documented metastatic disease to the liver)
- creatinine ≤ 1.5 x institutional upper limit of normal (ULN)

6.2 Regimen Descriptions

6.2.1 Arm A Regimen Description

Table 3.

Agent	Premedications	Dose	Route	Schedule	Cycle Length
Trastuzumab or Biosimilar	No routine premedication required. May be given at the investigator's discretion.	4 mg/kg*	IV per institutional guidelines	D1, D15	28 days (4 weeks)
Vinorelbine	Optional: prochlorperazine (Compazine) 10 mg PO/IV *and/or* lorazepam (Ativan) 1 mg PO/IV *or* other anti-emetics as per local institutional standard of care.	25mg/m^2	IV over 6-10 minutes or per institutional guidelines	D1, D8, D15	

*if > 6 weeks from last trastuzumab dose, patients will receive loading dose of 6 mg/kg of trastuzumab on C1D1 and then 4 mg/kg for subsequent doses

Order of administration of study agents will be as written above.

Treatment visits should occur within +/- 3 days for Day 1 of the cycle and +3/-1 for Day 8 or Day 15days of the scheduled day (e.g., Day 8 visit must occur between Day 7 and Day 11). A minimum of 6 days between D1, D8, and D15 of vinorelbine administration is required.

Day 8 of vinorelbine therapy for may be administered at a non-participating institution and should be administered per protocol or per institutional standards.

6.2.2 Arm B Regimen Description

Table 4.

Agent	Premedications	Dose	Route	Schedule	Cycle Length
Trastuzumab or Biosimilar	No routine premedication required. May be given at the investigator's discretion.	4 mg/kg*	IV institutional guidelines**	D1, D15	28 days (4 weeks)
Vinorelbine	Optional: prochlorperazine (Compazine) 10 mg PO/IV *and/or* lorazepam (Ativan) 1 mg PO/IV *or* other anti-emetics as per local institutional standard of care.	25 mg/m^2	IV over 6-10 minutes or per institutional guidelines	D1, D8, D15	
Avelumab	Premedicate with antihistamine and acetaminophen, or per local guidelines 30-60 minutes prior to the first 4 infusions.Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/ severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate; however, the prophylactic use of systemic corticosteroids is not permitted.	10 mg/kg	IV over 60 minutes (a +20/-10 minutes window is permissible i.e. infusion time is 50-80 minutes)	D1, D15	

*if > 6 weeks from last trastuzumab dose, patients will receive loading dose of 6 mg/kg of trastuzumab on C1D1 and then 4 mg/kg for subsequent doses

Order of administration of study agents will be as written above (i.e. standard of care agents prior to investigational agents).

Treatment visits should occur within +/- 3 days for Day 1 of the cycle and +3/-1 for Day 8 or Day 15 (e.g., Day 8 visit must occur between Day 7 and Day 11). A minimum of 6 days between D1, D8, and D15 of vinorelbine administration is required.

Day 8 of vinorelbine therapy for may be administered at a non-participating institution and should be administered per protocol or per institutional standards.

6.2.3 Arm C Regimen Description (CLOSED TO NEW ENROLLMENT)

Table 5.

Agent	Premedications	Dose	Route	Schedule	Cycle Length
Trastuzumab or Biosimilar	No routine premedication required. May be given at the investigator's discretion.	4 mg/kg*	IV per institutional guidelines**	D1, D15	28 days (4 weeks)
Vinorelbine	Optional: prochlorperazine (Compazine) 10 mg PO/IV *and/or* lorazepam (Ativan) 1 mg PO/IV *or* other anti-emetics as per local institutional standard of care.	25 mg/m^2	IV over 6-10 minutes or per institutional guidelines	D1, D8, D15	
Utomilumab	No routine premedication required. May be given at the investigator's discretion.	100 mg	IV over 60 minutes (a +15/-5 minutes window is permissible i.e. infusion time is 55-75 minutes)	D1	
Avelumab	Premedicate with antihistamine and acetaminophen, or per local guidelines 30-60 minutes prior to the first 4 infusions. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/ severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate; however, the	10 mg/kg	IV over 60 minutes (a +20/-10 minutes window is permissible i.e. infusion time is 50-80 minutes)	D1, D15	

	prophylactic use of systemic corticosteroids is not permitted.				

*if > 6 weeks from last trastuzumab dose, patients will receive loading dose of 6 mg/kg of trastuzumab on C1D1 and then 4 mg/kg for subsequent doses

Order of administration of study agents will be as written above (i.e. standard of care agents prior to investigational agents).

Treatment visits should occur within +/- 3 days for Day 1 of the cycle and +3/-1 for Day 8 or Day 15 (e.g., Day 8 visit must occur between Day 7 and Day 11). A minimum of 6 days between D1, D8, and D15 of vinorelbine administration is required.

Day 8 of vinorelbine therapy for may be administered at a non-participating institution and should be administered per protocol or per institutional standards.

6.2.4 Cross-over Arm Regimen Description

Table 6.

Agent	Premedications	Dose	Route	Schedule	Cycle Length
Trastuzumab or Biosimilar	No routine premedication required. May be given at the investigator's discretion.	4 mg/kg (6 mg loading dose, if needed*)	IV per institutional guidelines**	D1, D15	28 days (4 weeks)
Avelumab	Premedicate with antihistamine and acetaminophen, or per local guidelines prior to the first 4 infusions. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/ severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate; however, the prophylactic use of systemic corticosteroids is not permitted.	10 mg/kg	IV over 60 minutes (a +20/-10 minutes window is permissible i.e. infusion time is 50-80 minutes)	D1, D15	

*if > 6 weeks from last trastuzumab dose, patients will receive loading dose of 6 mg/kg of trastuzumab on C1D1 and then 4 mg/kg for subsequent doses Order of administration of study agents will be as written above (i.e. standard of care agents prior to investigational agents). Treatment visits should occur within +/- 3 days for Day 1 of the cycle and +3/-1 for Day 8 or Day 15 (e.g., Day 15 visit must occur between Day 14 and Day 18).					

6.3 Agent Administration

6.3.1 Trastuzumab and Biosimilars

Trastuzumab (or biosimilar) will be administered in clinic at 4 mg/kg on Day 1 and 15 of each 28-day cycle (+/- 3days). If the patient is > 6 weeks from last trastuzumab dose, patients will receive loading dose of 6 mg/kg of trastuzumab on C1D1 and then 4 mg/kg for subsequent doses. The total dose of trastuzumab will be calculated according to the institution's standard administration guidelines. Trastuzumab dose reductions are not allowed.

All infusions of trastuzumab (or biosimilar) may be administered according to institutional guidelines.Since all participants on this study have previously tolerated trastuzumab prior to study entry, the preferred first infusion time for participants is over approximately 30-60 minutes followed by a 30-minute post-infusion observation period, or according to institutional guidelines.

Infusion Associated Symptoms (IAR): If a significant infusion reaction occurs, the infusion should be interrupted and appropriate medical therapies should be administered (see below). Permanent discontinuation should be considered in participants with severe IAR. This clinical assessment should be based on the severity of the preceding reaction and response to administered treatment for the adverse reaction.

If participants develop an IAR, participants should be treated according to the following guidelines, or according to institutional guidelines, at discretion of the study physician:

- Stop infusion and notify physician.
- Assess vital signs.
- Administer acetaminophen 650 mg PO.
- Consider administration of: Meperidine 50 mg IM, Diphenhydramine 50 mg IV, Ranitidine 50 mg IV or cimetidine 300 mg IV, Dexamethasone 10 mg IV or famotidine 20 mg IV.
- If vital signs are stable, resume trastuzumab infusion.

Participants tend not to develop infusion syndromes with subsequent cycles. No standard premedication is required for future treatments if participants have developed an infusion syndrome. Participants may be given acetaminophen prior to treatments.

Serious reactions have been treated with supportive therapy such as oxygen, beta-agonists, corticosteroids and withdrawal of study agent as indicated.

6.3.2 Vinorelbine

6.3.2.1 Pretreatment Antiemetic Medication

Recommended optional antiemetic pretreatments include the following:

- prochlorperazine (Compazine) 10 mg PO/IV and/or
- lorazepam (Ativan) 1 mg PO/IV

- Other anti-emetics may be used as per local institutional standard of care.

6.3.2.2 Dosing

The dose for weekly treatments with vinorelbine is 25 mg/m2 IV infusion. Vinorelbine doses may be adjusted for expected side effects (see Section 7.2). There must be a minimum of 6 days between doses of vinorelbine.

6.3.2.3 Administration

Vinorelbine is given after trastuzumab when both treatments are given in the same day. Vinorelbine is a vesicant, and must be infused through a free-flowing IV infusion. It is administered as an IV infusion over 6 to 10 minutes preferred or per institutional guidelines. After administration, the vein is flushed with 125 mL of NS IV solution. Leakage into surrounding tissue during intravenous administration of vinorelbine may cause considerable irritation, local tissue necrosis, and/or thrombophlebitis. If extravasation occurs, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Skin reactions may occur with accidental exposure. The use of gloves is recommended. If the solution of vinorelbine contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

Vinorelbine should not be mixed or diluted with other drugs.

No hydration required. This is no observation period for Vinorelbine.

After Cycle 1, day 8 of vinorelbine therapy may be administered at a non-participating institution. Vinorelbine should be administered per protocol or per institutional standards.

6.3.3 Utomilumab (for reference only – Utomilumab has been removed from this study)

Utomilumab will be administered in clinic at a dose of 100 mg (fixed dose) on Day 1 of each 28-day cycle (+3/- 1 days). Utomilumab is administered as a 1-hour IV infusion (a +15/-5 minutes window is permissible i.e. infusion time is 55-75 minutes), diluted with 0.9% saline solution.

No routine premedication is required, but may be given at the investigator's discretion.
There is no observation period for Utomilumab.

6.3.4 Avelumab

Avelumab will be administered as 10 mg/kg body weight IV on Day 1 (+/- 3 days)and 15 (+3/-1 day) of each 28-day cycle every 2 weeks. Avelumab is administered as a 1-hour IV infusion (a +20/-10 minutes window is permissible i.e. infusion time is 50-80 minutes), diluted with 0.9% saline solution; alternatively, a 0.45% saline solution can be used if needed.

6.3.4.1 Premedication

In order to mitigate infusion-related reactions, a premedication with an antihistamine and with acetaminophen 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory (for example, 25-50 mg oral diphenhydramine and 500-650 mg oral acetaminophen). Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate; however the prophylactic use of systemic corticosteroids is not permitted.

6.3.4.2 Setting

Avelumab should be administered in a setting that allows for immediate administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1: 1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

6.3.4.3 Observation period

Following avelumab infusions, patients must be observed for 30 minutes post-infusion for potential infusion-related reactions. Documentation of observation time is not required.

6.4 Dose Limiting Toxicity (DLT)

Once 6 patients assigned to each investigational treatment group (Arms B, C) have received at least one cycle of assigned treatment, a safety review will be conducted before additional patients are enrolled. Based on the monitoring criteria, if ≥4 of 6 patients (or before 6, if 3/3, ≥3/4, ≥4/5 patients) experience DLT within the first cycle of treatment, then the treatment regimen will be modified or discontinued. The review will include a per-patient listing of all reported AEs to date, including actions required for dosing, to more fully review the nature, frequency, severity and timing of the events. This information combined with fewer DLTs may also result in modification of a treatment regimen.

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as suspected to be trial treatment related (possible, probable or definite) and unrelated to disease or disease progression that occurs within the *first cycle of treatment*. Toxicities and lab values will be categorized and graded according to CTCAE v5.0.

1. Any grade ≥ 3 non-hematologic, non-hepatic adverse event with the following exceptions:
    - Grade 3 nausea that resolves in ≤ 3 days,
    - Grade 3 fatigue that resolves to ≤ grade 2 in ≤ 3 days,
    - Grade 3 fever (>40C for ≤ 24 hrs),

- Grade 3 adverse event of tumor flare,
- Grade 3/4 lab values that are not considered clinically significant,
- Grade 3 rash that resolves to ≤ grade 2 in ≤ 7 days with therapy equivalent to prednisolone 10 mg/day or less,
- Grade 3 arthralgia that can be managed with supportive care that resolves to ≤ grade 2 within 7 days,
- Grade 3 autoimmune thyroiditis or other endocrine abnormality that can be managed by endocrine replacement without systemic steroids (not including replacement steroids for adrenal insufficiency.

2. Grade ≥ 4 neutropenia (ANC < 500uL) lasting > 7 days. In the event of a grade 4 decrease in absolute neutrophil count without fever, CBC should be assessed at least weekly until resolution to determine the length of the event. This bloodwork may be done at a local lab to the participant as long as the results are reviewed by a study staff member qualified to assess toxicity.

3. Grade ≥ 3 febrile neutropenia.
4. Grade ≥ 4 anemia.
5. Grade ≥ 4 thrombocytopenia or grade 3 with clinically significant bleeding.
6. Grade ≥ 3 or more elevation of serum hepatic transaminase (ALT or AST) lasting > 7 days. With patients with grade 1 elevations due to disease at baseline only grade ≥ 3 elevation that is ≥ 3 x baseline lasting >7 days will be considered a DLT.
7. ALT/AST >3 x upper limit of normal (ULN) AND total bilirubin > 2 x ULN
8. LVEF drop < 45% and/or symptomatic heart failure.
9. Grade ≥ 3 pneumonitis.

6.5 Concomitant Treatment and Supportive Care Guidelines

Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as anti-emetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed. If steroids are given at any time on trial, this should be recorded on the applicable page in the case report forms.

Supportive care medications are allowed at any time on trial. Specifically, the following agents are permitted:

- Antiemetics
- Antidiarrheal therapy
- Antiallergic measures such as corticosteroids and antihistamines

- Bone modifying agents: Subjects being treated with bisphosphonates or denosumab when they enter the study may continue the medication as long as the dose is stable. Subjects may also initiate bisphosphonate or denosumab therapy while on protocol therapy if it is thought to be medically necessary.

The use of concurrent investigational or other antitumor therapies is not permitted. Concurrent palliative radiotherapy is not allowed on trial.

Because there is a potential for interaction of vinorelbine with other concomitantly administered drugs through the cytochrome P450 system in the CYP3A subfamily, strong CYP3A inhibitors/inducers are not allowed on study. These agents include inhibitors such amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit, grapefruit juice or any product containing grapefruit. CYP3A inducers include carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort. This medication list may also be found in Appendix B.

Concomitant use of moderate CYP3A inducers and CYP3A substrates is allowable on study, however precaution should be exercised for use of any concomitant medication.

The use of herbal medicine is not recommended during protocol treatment.

Participants of childbearing potential (defined by: those who have not been surgically sterilized and/or have had a menstrual period in the past calendar year) must be willing to use effective contraception during treatment and up to 7 months after stop of trial treatment. Acceptable methods of contraception are intrauterine devices, bilateral tubal occlusion, vasectomized, or total abstinence. **Oral, injectable, or implant hormonal contraceptives are not allowed.**

6.6 Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue until one of criteria in Section 6.8 applies.

6.7 Isolated CNS progression

Patients who have demonstrated control of their extra-cranial disease (defined for this purpose as objective response or SD maintained for at least 2 cycles) from study therapy, but who have developed isolated brain metastases that are felt to be treatable with radiation will be allowed to receive radiation therapy and then continue their assigned study therapy until they either experience systemic progression of their disease and/or further progression in the brain. Patients should have their study therapy held until radiation is completed. Patients can recommence study therapy once clinically stable as deemed by the investigator.

6.8 Criteria for Taking a Participant Off Treatment

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression (except isolated CNS progression – see Section 6.7)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the study requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the electronic case report form (eCRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, treating investigators must immediately notify Dr. Adrienne Gropper Waks at 617-632-3800.

All patients who initiate protocol treatment will be included in the overall evaluation of response (intent-to-treat analysis). All reasons for discontinuation of therapy should be documented clearly in the medical record.

If a subject discontinues or withdraws from the study, every attempt will be made to get a tissue/tumor biopsy and study bloods if the subject is able and willing to do so.

6.9 Criteria for Crossover Therapy

If treatment is permanently discontinued due to disease progression (i.e. not due to toxicity) in a participant randomized to Arm A, the participant will be offered the option to crossover to receive trastuzumab and avelumab until documented disease progression per RECIST 1.1 criteria or unacceptable toxicity.

Screening does not need to be repeated, however, patients must meet the following criteria to treat Day 1 of Crossover Therapy, and eligibility must be confirmed by the treating investigator:

- ECOG performance status 0-2
- Absolute neutrophil count ≥ 1,000/mcL
- Platelets ≥ 75,000/mcL
- Total bilirubin ≤ 1.5 × institutional upper limit of normal (ULN) (or ≤ 2.0 x ULN in patients with documented Gilbert's Syndrome)
- AST(SGOT)/ALT(SGPT) ≤ 2.5 × institutional ULN or ≤ 5 × institutional ULN for

participants with documented liver metastases
- Negative pregnancy test within 7 days of planned treatment start
- LVEF ≥ 50% by MUGA or echocardiogram
- No ongoing unresolved, unstable, or serious adverse events from prior administration of protocol therapy

For DF/HCC Institutions: Documents to support the above criteria should be reviewed and signed by the treating investigator. The Crossover portion of the DF/HCC Eligibility Checklist will be completed by a Screening Staff member and confirmed by an Enrollment Monitor, per DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101). Provided the patient meets criteria, ODQ will process the request and enroll the participant on the Crossover arm. Once enrolled, the patient may begin Crossover therapy.

For Other Investigative Sites: Documents to support the above criteria should be reviewed and signed by the treating investigator/screening staff and faxed or emailed to the Project Manager at 617-632-5152 or ctopm@dfci.harvard.edu for review. The DF/HCC Project Manager confirm eligibility and submit the cross-over registration request to ODQ. The DF/HCC Project Manager will contact the participating site via email with a confirmation that registration to the Crossover arm has occurred and the participant may begin Crossover Therapy.

NOTE: Registration can only be conducted during the business hours of 8:00 AM and 5:00 PM Eastern Time Monday through Friday.

6.10 Duration of Follow-Up

For participants who went off treatment for reasons other than Progressive Disease, tumor assessments should continue every 9 to 12 weeks from the date of the last assessment until progressive disease is documented.

Participants will be followed annually until death, withdrawal of consent, or lost to follow-up.

6.11 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:
- Lost to follow-up
- Withdrawal of consent
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the electronic case report form (eCRF).

7. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the following sections and tables. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A

copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, antidiarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study, and until the final study visit. Participants continuing to experience toxicity at the off-protocol-therapy visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

In the event of significant treatment-related toxicity, dosing may be interrupted or delayed and/or reduced as described below. If treatment is held for toxicity, restaging scans should stay on schedule according to the required data table. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse sign or symptom.

7.1 Anticipated Toxicities

7.1.1 Anticipated Toxicities for Trastuzumab (or biosimilar)

The following information is from the package insert for trastuzumab (Herceptin®; Genentech, Inc.). This is a list of those adverse events most likely to occur to this study; please refer to the trastuzumab package insert for the comprehensive list of adverse events that have occurred with trastuzumab administration. The side effect profile for trastuzumab biosimilars is the same as trastuzumab.

Cardiac Failure/Dysfunction: Signs and symptoms of cardiac dysfunction, such as dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, S3 gallop, or reduced ejection fraction, have been observed in participants treated with trastuzumab. Congestive heart failure associated with trastuzumab therapy may be severe and has been associated with disabling cardiac failure, death, and mural thrombosis leading to stroke. The probability of cardiac dysfunction was highest in participants who received trastuzumab concurrently with anthracyclines. The data suggest that advanced age may increase the probability of cardiac dysfunction. Subjects entering this study will undergo a baseline cardiac assessment including history, physical exam and an echocardiogram or MUGA scan.

Anemia and Leukopenia: An increased incidence of anemia and leukopenia was observed in the treatment group receiving trastuzumab and chemotherapy, especially in the trastuzumab and adriamycin/cytoxan subgroup, compared with the treatment group receiving chemotherapy alone. The majority of these cytopenic events were mild or moderate in intensity, reversible, and none resulted in discontinuation of therapy with trastuzumab. Hematologic toxicity is infrequent following the administration of trastuzumab as a single agent, with an incidence of

Grade III toxicities for WBC, platelets, hemoglobin all <1%. No Grade IV toxicities were observed.

Diarrhea: Of participants treated with trastuzumab as a single agent, 25% experienced diarrhea. An increased incidence of diarrhea, primarily mild to moderate in severity, was observed in participants receiving trastuzumab in combination with chemotherapy.

Infection: An increased incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections was observed in participants receiving trastuzumab in combination with chemotherapy.

Infusion Reactions: During the first infusion with trastuzumab, a symptom complex most commonly consisting of chills and/or fever was observed in about 40% of participants 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.

7.1.2 Anticipated Toxicities for Vinorelbine

The following information is from the insert for vinorelbine (Navelbine®) by GlaxoSmithKline, Inc. This is a list of those adverse events most likely to occur in this study, please refer to the vinorelbine package insert for a comprehensive list of adverse events that have occurred with vinorelbine administration.

*Hematologic***:** Granulocytopenia was the major dose-limiting toxicity with vinorelbine. Dose adjustments are required for hematologic toxicity and hepatic insufficiency. Granulocytopenia was generally reversible and not cumulative over time. Granulocyte nadirs occurred 7 to 10 days after the dose, with granulocyte recovery usually within the following 7 to 14 days. Granulocytopenia resulted in hospitalizations for fever and/or sepsis in 8% of patients. Septic deaths occurred in approximately 1% of patients.

*Neurologic***:** Loss of deep tendon reflexes occurred in less than 5% of patients. The development of severe peripheral neuropathy was infrequent (1%) and generally reversible.

*Skin***:** Like other anticancer vinca alkaloids, vinorelbine is a moderate vesicant. Injection site reactions, including erythema, pain at injection site, and vein discoloration, occurred in approximately one third of patients; 5% were severe. Chemical phlebitis along the vein proximal to the site of injection was reported in 10% of patients.

Gastrointestinal: Prophylactic administration of antiemetics was not routine in patients treated with single-agent vinorelbine, but was used when given in combination.

Hepatic: Transient elevations of liver enzymes were reported without clinical symptoms.

Cardiovascular: Chest pain was reported in 5% of patients. Most reports of chest pain were in patients who had either a history of cardiovascular disease or tumor within the chest. There have been rare reports of myocardial infarction.

Pulmonary: Shortness of breath was reported in 3% of patients; it was severe in 2%. Interstitial pulmonary changes were documented.

*Other***:** Fatigue occurred in 27% of patients. It was usually mild or moderate but tended to increase with cumulative dosing. Other toxicities that have been reported in less than 5% of patients include jaw pain, myalgia, arthralgia, and rash. Hemorrhagic cystitis and the syndrome of inappropriate ADH secretion were each reported in <1% of patients. The incidence of Grade 3 and/or 4 nausea and vomiting, alopecia, and renal toxicity were reported more frequently in the cisplatin-containing combinations compared to single-agent vinorelbine. Severe local reactions occurred in 2% of patients treated with combinations containing vinorelbine.

7.1.3 Anticipated Toxicities for Utomilumab (for reference only, utomilumab therapy has been removed from this protocol)

There is limited toxicity available for utomilumab monotherapy. In a phase 1 study of Utomilumab monotherapy, the most commonly reported Treatment-Emergent Adverse Events (TEAE) (all grades) that were considered treatment-related were in the System Organ Class of general disorders and administration site conditions (18.6%), and gastrointestinal disorders (12.8%). The most frequently observed treatment-related TEAE (≥10% of patients; all grades) was fatigue (11.6%). Treatment-related TEAEs were mostly Grade 1 or Grade 2 with only three Grade 3 AEs reported (fatigue, alanine aminotransferase elevation (ALT), and hyponatremia). The reported Grade 3 fatigue was of limited duration approximately 20 days and seen at the highest dose tested of 10 mg/kg of utomilumab. Of note, after the data cut-off date causality of the Grade 3 ALT elevation was re-assessed as not related to utomilumab by the Investigator. No Grade 4 treatment-related AEs were observed.

Two immune-related AEs (irAEs) potentially related to use of utomilumab have been observed (G2 pneumonitis, G2 enterocolitis). In both cases the events were observed in the setting of immediate prior treatment with immune checkpoint inhibitors (anti-PD-1 mAb; nivolumab) utomilumab administration is considered possibly related to these irAEs.

7.1.4 Anticipated Toxicities for Avelumab

For regulatory reporting requirements during clinical development, the following AEs will be considered as expected and meet the threshold of causal association (based on comprehensive medical evaluation considering the mechanism of action and temporal relationship after excluding other possible etiologies).

The following side effects have been observed among 1738 patients treated with avelumab according to the results from studies EMR100070-001 in various solid tumors (N=1650) and

EMR100070-003 Part A in Merkel cell carcinoma (N=88) where avelumab was administered intravenously (IV) as single agent at a dose of 10 mg/kg every 2 weeks (Q2W)

Three types of risks are associated with avelumab: general signs and symptoms, reactions that occur during or following the infusion, and immune-mediated side effects:

- General signs and symptoms including fatigue, nausea, diarrhea, constipation, anorexia, weight loss, vomiting, anemia, abdominal pain, cough, shortness of breath, edema of the feet and legs, back pain, joint pain
- Infusion related symptoms including hypersensitivity reactions which may include chills, shaking, fever, back pain, belly pain, shortness of breath or wheezing, decrease in blood pressure or hives.
- Immune-mediated adverse reactions including immune-mediated colitis, pneumonitis, immune-mediated thyroid disorders including hyperthyroidism, hypothyroidism, thyroiditis and autoimmune thyroiditis; immune-mediated skin reactions including rash, pruritis, redness, blisters, pemphigoid or peeling; other immune-mediated reactions including myocarditis, hepatitis, pneumonitis, adrenal insufficiency, diabetes, uveitis, myosistis, pancreatitis and Guillain-Barre syndrome.

7.2 Dose Modification Guidelines

Patients will be assessed for toxicity prior to each dose. Patients will be instructed to notify their physician immediately for any and all toxicities. CTCAE v 5.0 must be used to grade the severity of AEs. Assessment of causality (chronology, confounding factors, concomitant medications, medical history, diagnostic tests, and previous experience with the study treatment) should be conducted by the investigator prior to dose modification and/or delay whenever possible.

As a general approach, it is suggested that all AEs be managed with supportive care when possible at the earliest signs of toxicity. If supportive care is ineffective, a dose delay or dose reduction may be considered to avoid worsening toxicity. Dosing will occur only if the clinical assessment and laboratory test values are acceptable.

In the event that any of the individual study drug(s) in a regimen is delayed because of toxicity, the administration of other agent(s) may be continued.

General guidelines on dose delays for study treatment-related toxicity, other than those specified below are as follows:

- If significant treatment–related toxicities have not recovered to Grade 1 or baseline grade, the next scheduled dose of the causative study agent(s) may be delayed for up to 28 days from the last scheduled dose. “Significant” and “related” will be based on the judgment of the investigator. For example, alopecia, even if considered related, would most likely not be considered significant. Fatigue may or may not be considered either related or significant.
- After a treatment delay, study therapy should be resumed as soon as possible and within 28 days from the last schedule dose.

7.2.1 Special Considerations

- For toxicities, which are considered by the treating investigator unlikely to develop into serious or life–threatening events (e.g. alopecia, altered taste etc.), treatment may be continued at the same dose without reduction or interruption.
- The treating investigator may reduce a subject's dose for a toxicity of any grade/duration where s/he believes it to be in the best interest of the subject.
- Any consideration to modification of the above dose modification guidelines should be discussed with the Principal Investigator for approval or disapproval in advance.

7.2.2 Vinorelbine Toxicity Management

Vinorelbine is a commonly used standard of care in this patient population and therefore management of its toxicity can be per local institutional guidelines. Alternatively, guidelines below can be utilized. In the event that a patient's vinorelbine dose is held, the patient will still proceed with other study therapy unless otherwise specified in the protocol. If vinorelbine treatment is delayed more than 4 weeks, vinorelbine will be permanently discontinued.

Hematologic Toxicity. Prior to weekly therapy, patients should be assessed for hematologic toxicity. Vinorelbine therapy will be adjusted based on local institutional standards or the following parameters in Table 7.

Table 7. Dose Adjustment of Vinorelbine for Hematologic Toxicity
(Dose Adjusted for Either ANC or Platelet Count Parameters)

Absolute Neutrophil Count (ANC)	**Platelet Count**	**Dose Adjustment**	**Vinorelbine Dose**
>1250/ mcL	≥100,000/ mcL	No change	25 mg/m^2
750-1250/ mcL	50,000-99,000/ mcL	Decrease 40%*	15 mg/m^2
< 750 / mcL	< 50,000/ mcL	Dose skipped for that week	
Delay > 4 weeks	Delay > 4 weeks	Off protocol	

*Note: dose adjustment applies to that dose only. Patients can be dosed at full dose (25 mg/m^2) in subsequent weeks if hematologic toxicity resolves.

In the event of a grade 4 decrease in absolute neutrophil count without fever, CBC should be assessed at least weekly until resolution to determine the length of the event. This bloodwork may be done at a local lab to the participant as long as the results are reviewed by a study staff member qualified to assess toxicity.

Filgrastim (Neupogen®) is to be considered under the following circumstances:

- Treatment delay of ≥ 2 weeks due to of ANC < 750 / mcL in patients who have received at least 2 weeks of vinorelbine therapy.

- Patients who previously experienced febrile neutropenia.
- Filgrastim (Neupogen®) should be administered 24 hrs after the end of chemotherapy at the discretion of the treating investigator. In the event the patient receives Trastuzumab alone, Neupogen® may be given on the same day.

Neurologic Toxicity: Patients who develop grade 2 neurologic toxicity should be treated at a dose of 15 mg/m2/week until the toxicity resolves to grade 1 or less. Vinorelbine will be held in patients who develop grade 3 neurologic toxicity until the toxicity resolves to grade 1 or less. Treatment for symptomatic neuropathy is allowed at the discretion of the treating physician. If vinorelbine treatment is delayed more than 4 weeks, vinorelbine will be permanently discontinued.

Hepatic Toxicity: Patients who develop bilirubin levels 2 mg/dl to 3 mg/dl should receive a 50% dose reduction in vinorelbine dose (to 12.5 mg/m2). Patients who develop bilirubin > 3 mg/dl should have vinorelbine held.

Gastrointestinal Toxicity: Patients who develop grade 3 GI toxicity should have vinorelbine therapy held until toxicity has resolved to ≤ grade 1. Treatment for symptomatic nausea, constipation or diarrhea is allowed at the discretion of the treating physician. If treatment is held more than 4 weeks (28 days), vinorelbine should be discontinued. Patients can be dose reduced to 40% at the discretion of the treating investigator.

Other Toxicity: Patients who develop drug related grade 3 non-hematological toxicity should have vinorelbine therapy delayed until toxicity has resolved to ≤ grade 1. If the toxicity fails to resolve with a 4-week treatment delay, vinorelbine will be permanently discontinued. Patients with grade 4 non-hematological toxicity attributed to vinorelbine will discontinue treatment unless exception is given by the Principal Investigator. Prior to retreatment, toxicity must resolve to ≤ grade 1. Patients can be dose reduced to 40% at the discretion of treating investigator.

7.2.3 Trastuzumab (or biosimilar) Toxicity Management

Cardiac toxicity: Left ventricular ejection fraction (LVEF) will be determined at baseline prior to study entry, and every 12 weeks on study. LVEF assessments will be determined by echocardiogram or MUGA scan. Among patients with asymptomatic cardiotoxicity, the algorithm in Table 8 for antibody (trastuzumab, avelumab, and utomilumab) dosing will be followed. As there is a theoretical risk that the immunotherapy agents (avelumab, and utomilumab) can contribute to trastuzumab mediated cardiotoxicity, all antibodies will be held.

Table 8. Algorithm for continuation or withdrawal of antibody therapy in asymptomatic patients based on serial measurements of left ventricular ejection fraction (LVEF)

	Asymptomatic decrease in LVEF from Baseline		
Relationship of LVEF to Radiology Facility's LLN	**Decrease of < 10 Percentage Points**	**Decrease of 10 to 15 Percentage Points**	**Decrease of ≥ 16 Percentage Points**
Within normal limits	Continue antibody	Continue antibody	Continue antibody[a]
1-5 percentage points below LLN	Continue antibody	Hold antibody[a,b]	Hold antibody[a,b]
≥ 6 percentage points below LLN	Continue antibody[a]	Hold antibody[a,b]	Hold antibody[a,b]

LLN, lower limit of normal; LVEF, left ventricular ejection fraction; MUGA, multiple gated acquisition scan
Source: Modified from Cardiac management during adjuvant trastuzumab therapy [44]
[a]Repeat MUGA/ECHO after 4 weeks (one cycle)
[b]After two consecutive holds permanently discontinue antibody

Any clinically significant cardiac adverse event should be treated according to current medical practice with the help of a cardiologist as needed.

Patients will stop receiving antibody for the following reasons:

- Grade ≥3 cardiac toxicity (symptomatic congestive heart failure).
- Ejection fraction less than 40%.

7.2.4 Avelumab and Utomilumab Toxicity Management (discussion of utomilumab is for reference only – it is no longer being used in this protocol)

There are no dose reductions for avelumab or utomilumab.

Because both avelumab and utomilumab can cause similar irAEs, it may be difficult to identify the causative agent for such an AE. Thus, in general, both agents should be adjusted concordantly for AE's as noted below. The exception to this rule is that infusion related reactions are not typically seen with utomilumab and therefore unless strong evidence is present to suggest that an infusion related reactions is caused by utomilumab, only avelumab should be modified.

In the event that the participant holds or discontinues avelumab and utomilumab, therapy with other study medications may continue.

7.2.4.1 Management of Severe Hypersensitivity Related to Avelumab

In order to mitigate infusion-related reactions, premedication with an antihistamine and with acetaminophen is mandatory prior to each dose of avelumab. Management of infusion-related reactions should follow guidelines set forth in Table 9.

Table 9: Treatment Modification for Symptoms of Infusion-Related Reactions

NCI-CTCAE Grade	Treatment Modification for Avelumab

Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated	• Decrease the avelumab infusion rate by 50% and monitor closely for any worsening
Grade 2 – moderate • Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	• Stop avelumab infusion • Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae • Grade 4: Life-threatening consequences; urgent intervention indicated	• Stop the avelumab infusion immediately and disconnect infusion tubing from the subject • Subjects must be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment

- Once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions. If a subject experiences a Grade 3 or 4 infusion-related reaction at any time, the subject must discontinue avelumab.

7.2.4.2 Severe Hypersensitivity Reactions

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. Subjects should be instructed to report any delayed reactions to the investigator immediately.

Symptoms:
- Impaired airway
- Decreased oxygen saturation (< 92%)
- Confusion
- Lethargy
- Hypotension
- Pale/clammy skin
- Cyanosis

Management:
- Epinephrine injection and dexamethasone infusion
- Subject should be placed on monitor immediately
- Alert intensive care unit for possible transfer if required

7.2.4.3 Management of Immune-Related Adverse Events (irAEs)

Since inhibition of PD-L1 or agonism of 4-1BB stimulates the immune system, irAEs may occur. Treatment of irAEs is dependent upon severity (NCI-CTCAE grade) and in general consist of:

- Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring
- Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)
- Grade 3 to 4: treat with high dose corticosteroids

7.2.4.4 Management of Tumor Lysis Syndrome

Since avelumab and utomilumab can induce ADCC, there is a theoretical risk of tumor lysis syndrome. Should this occur, subjects should be treated as per local guidelines and the management algorithm described in Howard et al 2011.

7.2.4.5 Avelumab and Utomilumab Dose modification/delays

Treatment of immune related Adverse Events (irAEs) should follow guidelines set forth in the following Tables (per Investigator's Brochure):

Table 10. Management of Avelumab and Utomilumab Related Immune-Mediated Adverse Events (discussion of utomilumab is for reference only – it is no longer being used in this protocol)

Gastrointestinal irAEs		
Severity of Diarrhea / Colitis (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab and utomilumab therapy Symptomatic treatment (for example, loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Hold avelumab and utomilumab therapy Symptomatic treatment	If improves to Grade 1: Resume avelumab and utomilumab therapy If persists > 5 to 7 days or recur: Treat as Grade 3 to 4

Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 hrs.; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Hold avelumab and utomilumab for Grade 3. Permanently discontinue avelumab and utomilumab for grade 4 or recurrent grade 3. 1.0 to 2.0 mg/kg/day methylprednisolone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until ≤ Grade 1, then taper over at least 1 month, resume avelumab and utomilumab therapy following steroids taper for initial Grade 3 If worsens or persists > 3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue avelumab and utomilumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: Withhold Avelumab and utomilumab therapy Consider skin biopsy Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper If worsens: Treat as Grade 3 to 4
Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: life threatening consequences	Hold avelumab and utomilumab for grade 3 Permanently discontinue avelumab and utomilumab for grade 4 or recurrent grade 3 Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤ 1: Taper steroids over at least 1 month; resume Avelumab and utomilumab therapy following steroids taper (for initial grade 3)

Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	hold avelumab and utomilumab therapy Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as appropriate per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab and utomilumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab and utomilumab. Guideline based supportive treatment as appropriate per cardiology consult.* Methylprednisolone 1-2 mg/kg/day or equivalent. Add prophylactic antibiotics for opportunistic infections	Once improving, taper steroids over at least 1 month If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A)
*Local guidelines, or eg. AHA guidelines		

Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	Consider holding avelumab therapy and utomilumab Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	Delay avelumab and utomilumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 to 2.0 mg/kg/day methyl-prednisolone IV or oral equivalent Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days If improves: When symptoms return to ≤ Grade 1, taper steroids over at least 1 month and then resume avelumab and utomilumab therapy following taper If not improving after 2 weeks or worsening: Treat as Grade 3 to 4
Grade 3 to 4 Grade 3: Severe new symptoms; New / worsening hypoxia; Grade 4: life-threatening	Permanently discontinue avelumab and utomilumab therapy Hospitalize Pulmonary and Infectious Disease consults 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to ≤ Grade 1: Taper steroids over at least1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 x ULN	Continue avelumab and utomilumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4

Grade 2* AST or ALT > 3.0 to ≤ 5 x ULN and / or total bilirubin > 1.5 to ≤ 3 x ULN	Hold avelumab and utomilumab therapy Increase frequency of monitoring to every 3 days	If returns to ≤ Grade 1: Resume routine monitoring, resume avelumab and utomilumab therapy If elevations persist > 5 to 7 days or worsen: Treat as Grade 3 to 4.
*AST or ALT> 3.0 to ≤ 5 x ULN in patients with documented liver mets and baseline AST or ALT> 3.0 to ≤ 5 x ULN	Continue study therapy - no modification required	
Grade 3 to 4* AST or ALT > 5 x ULN and / or total bilirubin > 3 x ULN	Permanently discontinue avelumab and utomilumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤ Grade 1: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines
*AST or ALT > 5.0 to ≤ 8 x ULN in cases with documented liver mets and baseline AST or ALT> 3.0 to ≤ 5 x ULN	Hold avelumab and utomilumab therapy Increase frequency of monitoring to every 3 days	If returns to ≤ Grade 2: Resume routine monitoring, resume avelumab and utomilumab therapy
Renal irAEs		
Grade of Creatinine Increase (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab and utomilumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Hold avelumab and utomilumab therapy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab and

	Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	utomilumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab and utomilumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to Grade ≤1: Taper steroids over at least 1 month.
Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab and utomilumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Hold avelumab and utomilumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for	Resume avelumab and utomilumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as

	hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH) Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) Hormone replacement/suppressive therapy as appropriate Perform pituitary MRI and visual field examination as indicated If hypophysitis confirmed: Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month Hold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. Add prophylactic antibiotics for opportunistic infections.	Resume avelumab and utomilumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.

The following table (Table 11) should be used for guidance on management of all other adverse drug reactions to avelumab or utomilumab not specified in Table 10.

Table 11. Adverse Drug Reactions requiring Avelumab and Utomilumab discontinuation or modification

Any avelumab or utomilumab-related Grade 4 ADRs require treatment discontinuation with avelumab and utomilumab except for single laboratory values out of normal range that are unlikely related to study treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management.

Any avelumab or utomilumab related Grade 3 ADRs require treatment discontinuation with avelumab and utomilumab except for any of the following:

- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management
- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1
- Single laboratory values out of normal range (excluding Grade ≥ 3 liver function test increase) that are unlikely related to study treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor

Any avelumab or utomilumab-related Grade 2 ADR should be managed as follows:

- If a Grade 2 ADR resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue.
- If a Grade 2 ADR does not resolve to Grade ≤ 1 by the last day of the current cycle, infusions should not be given on the following cycle. If at the end of the following cycle the event has not resolved to Grade 1, the subject should permanently discontinue treatment with avelumab and utomilumab (except for hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted).
- Upon the second occurrence of the same Grade 2 ADR (except for hormone insufficiencies that can be managed by replacement therapy) in the same subject, treatment with avelumab and utomilumab must be permanently discontinued.

8. DRUG FORMULATION/STORAGE/SUPPLY

8.1 Trastuzumab or Biosimilar

8.1.1 Description, form, and preparation

This study will use trastuzumab from commercial supply. Trastuzumab is a sterile, white to pale yellow, preservative free lyophilized powder for intravenous (IV) administration, supplied as a 150 mg vial. Each single-dose vial of trastuzumab delivers 150 mg trastuzumab, 136.2 mg α,α-trehalose dihydrate, 3.4 mg L-histidine HCl monohydrate, 2.2 mg L-histidine, and 0.6 mg polysorbate 20.

Use appropriate aseptic technique. Reconstitute each 150 mg vial of single-dose Trastuzumab with 7.4 mL of sterile water for injection (SWFI) to yield a solution containing 21mg/mL trastuzumab that delivers 7.15 mL (150 mg trastuzumab), at a pH of approximately 6.

Use of other reconstitution diluents should be avoided. Determine the dose of trastuzumab needed, based on a loading dose of 8 mg trastuzumab/kg body weight for q3wk dosing schedules or a maintenance dose of 6 mg/kg trastuzumab/kg body weight for q3w dosing schedules. Calculate the correct dose using 21 mg/mL trastuzumab solution. Withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% sodium chloride, USP. **DEXTROSE (5%) SOLUTION SHOULD NOT BE USED**. Gently invert the bag to mix the solution. The reconstituted preparation results in a colorless to pale yellow transparent solution. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.

Trastuzumab should not be mixed or diluted with other drugs. Trastuzumab should not be filtered during administration.

If a trastuzumab biosimilar is used, please refer to the manufacturer's prescribing information/ package insert for information about dosage and administration.

8.1.2 Storage Conditions

Vials of trastuzumab are stable at 2ºC–8ºC (36ºF–46ºF) prior to reconstitution. Do not use beyond the expiration date stamped on the vial. Use the Herceptin solution immediately following reconstitution with SWFI, as the 150 mg vial contains no preservative. If not used immediately, store the reconstituted Herceptin solution for up to 24 hours at 2ºC-8ºC; discard any unused Herceptin after 24 hours. DO NOT FREEZE.

The solution of trastuzumab for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% sodium chloride for injection, USP, may be stored at 2ºC–8ºC (36ºF–46ºF) for up to 24 hours prior to use. Diluted trastuzumab has been shown to be stable for up to 24 hours at room temperature 15ºC–25ºC; however, since diluted trastuzumab contains no effective preservative the reconstituted and diluted solution should be stored refrigerated (2ºC–8ºC).

If a trastuzumab biosimilar is used, please refer to the manufacturer's prescribing information/ package insert for information about storage conditions.

8.1.3 Compatibility

No incompatibilities between trastuzumab and polyvinylchloride, polyolefin or polypropylene bags have been observed. Dextrose 5% solution should not be used since it causes aggregation of the protein. Trastuzumab should not be mixed or diluted with other drugs.

If a trastuzumab biosimilar is used, please refer to the manufacturer's prescribing information/package insert for information about drug compatibility.

8.1.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

If a trastuzumab biosimilar is used, please refer to the manufacturer's prescribing information/package insert for information about handling of the agent.

8.1.5 Availability

Trastuzumab is a commercially available agent. The cost of trastuzumab will be charged to the patient and/or his/her insurance company since its use is considered standard of care for metastatic, HER2-positive breast cancer.

A biosimilar for trastuzumab may be used on this study according to the standard of care at the participating institution and/or the insurance company of the participant.

8.1.6 Administration

Trastuzumab (or biosimilar) will be administered in clinic at 4 mg/kg on Day 1 (+/- 3 days) and 15 (+3/-1 days) of each 28-day cycle.If the patient is > 6 weeks from last trastuzumab dose, patients will receive loading dose of 6 mg/kg of trastuzumab on C1D1 and then 4 mg/kg for subsequent doses. The total dose of trastuzumab will be calculated according to the institution's standard administration guidelines. Trastuzumab dose reductions are not allowed.

All infusions of trastuzumab (or biosimilar) may be administered according to institutional guidelines. Since all participants on this study have previously tolerated trastuzumab prior to study entry, the preferred first infusion time for participants is over approximately 30-60 minutes followed by a 30-minute post-infusion observation period, or according to institutional guidelines.

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If a biosimilar for trastuzumab is used, the administration of the agent should be according to the participating site's institutional policy/standard of care.

8.1.7 Ordering

Trastuzumab is a commercially available agent and therefore ordering should be performed as standard policy in the investigational site.

If a biosimilar for trastuzumab is used, the agent should be ordered according to the participating site's institutional policy/standard of care.

8.1.8 Drug Supplies and Accountability

Trastuzumab is a commercially available agent and therefore accountability should be performed as standard policy in the investigational site.

If a biosimilar for trastuzumab is used, accountability of the agent should be according to the participating site's institutional policy/standard of care.

8.2 Vinorelbine

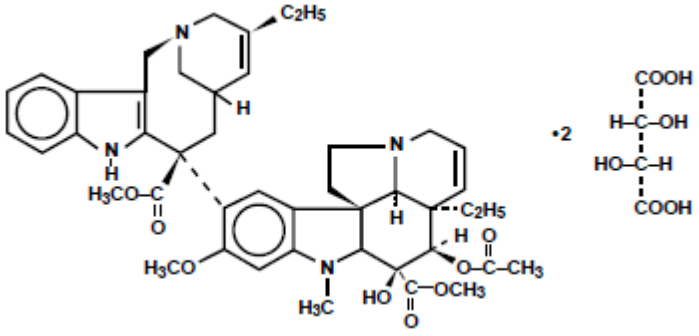
8.2.1 Description

Vinorelbine tartrate (NSC-608210) is a semi-synthetic vinca alkaloid with antitumor activity. The aqueous solubility is >1000 mg/mL in distilled water. The pH of vinorelbine tartrate injection is 3.3 to 3.8.

Chemical Name: 3',4'-Didehydro-4'-deoxy-8'- norvincaleukoblastine L-(+)-tartrate (1:2)(salt)

Molecular Formula: $C_{45}H_{54}N_40_8 \bullet 2C_4H_60_6$

Chemical Structure:



Molecular weight: 1079.12

Mechanism of clearance: The mean plasma clearance ranges from 0.97 to 1.26 L/h per kg. Vinorelbine undergoes substantial hepatic elimination in humans, with large amounts recovered in feces after intravenous administration to humans.

Mean terminal half-life: The terminal phase half-life averages 27.7 to 43.6 hours

Volume of distribution: Steady-state volume of distribution (Vss) values range from 25.4 to 40.1 L/kg.

Drug Interactions:	Acute pulmonary reactions have been reported with vinorelbine and other anticancer vinca alkaloids used in conjunction with mitomycin. Although the pharmacokinetics of vinorelbine are not influenced by the concurrent administration of cisplatin, the incidence of granulocytopenia with vinorelbine used in combination with cisplatin is significantly higher than with single-agent vinorelbine. Patients who receive vinorelbine and paclitaxel, either concomitantly or sequentially, should be monitored for signs and symptoms of neuropathy. Administration of vinorelbine to patients with prior or concomitant radiation therapy may result in radiosensitizing effects. Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP3A subfamily (Appendix B), or in patients with hepatic dysfunction. Concurrent administration of vinorelbine tartrate with an inhibitor of this metabolic pathway may cause an earlier onset and/or an increased severity of side effects.

8.2.2 Form

Please refer to vinorelbine package insert for additional details. Vinorelbine Injection USP is for intravenous administration. Each vial contains vinorelbine tartrate equivalent to 10 mg (1 mL vial) or 50 mg (5 mL vial) vinorelbine in water for injection. Vinorelbine Injection USP is a clear, colorless to pale yellow solution. No preservatives or other additives are present. The aqueous solution is sterile and nonpyrogenic. Vinorelbine tartrate is a white to yellow or light brown amorphous powder.

8.2.3 Storage and Stability

Vinorelbine Injection USP is available in single-use, clear glass vials with elastomeric stoppers and royal blue caps, individually packaged
in a carton in the following vial sizes: 10 mg/1 mL Single-Dose Vial or 50 mg/5 mL Single-Dose Vial.

Unopened vials of vinorelbine are stable until the date indicated on the package when stored under refrigeration at 2° to 8°C (36° to 46°F) and protected from light in the carton. Unopened vials of vinorelbine are stable at temperatures up to 25°C (77°F) for up to 72 hours. This product should not be frozen.

Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. If particulate matter is seen, vinorelbine should not be administered.

8.2.4 Compatibility

Vinorelbine should not be mixed or diluted with other drugs. Vinorelbine should be given after the trastuzumab infusion.

8.2.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Skin reactions may occur with accidental exposure. The use of gloves is recommended. If the solution of vinorelbine contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

8.2.6 Availability

Vinorelbine is commercially available.

8.2.7 Preparation

Vinorelbine Tartrate Injection must be diluted in either a syringe or IV bag using one of the recommended solutions. Diluted vinorelbine may be used for up to 24 hours under normal room light when stored in polypropylene syringes or polyvinyl chloride bags at 5° to 30°C (41° to 86°F).

*Syringe***:** The calculated dose of vinorelbine should be diluted to a concentration between 1.5 and 3.0 mg/mL, or per institutional standards. The following solutions may be used for dilution:

- 5% Dextrose Injection
- 0.9% Sodium Chloride Injection

IV Bag: The calculated dose of vinorelbine should be diluted to a concentration between 0.5 and 2 mg/mL, or per institutional standards. The following solutions may be used for dilution:

- 5% Dextrose Injection
- 0.9% Sodium Chloride Injection
- 0.45% Sodium Chloride Injection
- 5% Dextrose and 0.45% Sodium Chloride Injection
- Ringer's Injection
- Lactated Ringer's Injection

8.2.8 Administration

See Section 6.2.1

8.2.9 Ordering

Vinorelbine is commercially available and therefore ordering should be performed as standard policy in the investigational site.

8.2.10 Accountability

Vinorelbine is a commercially available agent and therefore accountability should be performed as standard policy in the investigational site.

8.2.11 Destruction and Return

Unused supplies of vinorelbine will be destroyed as per the site chemotherapy waste policy. Destruction will be documented per institutional standard operating procedure.

8.3 Utomilumab (PF-05082566) (for reference only – utomilumab is no longer being used in this protocol)

8.3.1 Pharmaceutical Properties

Utomilumab is a recombinant IgG2 fully human monoclonal antibody that is an agonist of 4-1BB.

Utomilumab is provided as a 10 mg/mL sterile solution for injection, in an aqueous histidine buffered solution at pH 5.5. The drug product is supplied in 20 mL Type 1 clear glass vial sealed with a coated serum stopper and aluminum seal (nominal fill volume of 5.0 mL).

8.3.2 Instructions for Storage

The following supplies must be stored at 2 to 8 °C or 36 to 46 °F.

- Utomilumab 10 mg/mL (100 mg/vial) Solution for Injection
- Do not shake.
- Protect from light until ready to use.

Utomilumab solution for Injection must be allowed to reach room temperature for 15 minutes prior to use in dose preparation. Unused vials containing utomilumab should not be left at room temperature for more than 4 hours. Discard any vials that are left at room temperature for more than 4 hours.

Minimize exposure of utomilumab 10 mg/mL (100 mg/vial) solution for injection vials and dosing solutions to room light during storage. Avoid direct sunlight and ultraviolet light exposure. From a microbiological point of view the prepared products should be used within 8 hours starting from the start of dose preparation. If the prepared utomilumab is left at room temperature for more than 8 hours, contact Pfizer.

The final IP must be administered within 8 hours of preparation if stored at room temperature 15 to 25 °C, 59 to 77 °F. The total in-use stability is a period of not more than 24 hours at 2-8 °C or 36-46 °F with no more than 8 of those hours at room temperature.

Prepared utomilumab solutions that are refrigerated must be allowed to reach room temperature prior to administration. Make sure the prepared dosing solution in its container is not cold to the touch.

No other drugs should be added to the solution for infusion containing utomilumab.

8.3.3 Preparation and Administration

- Final infusion concentrations must be between 0.2 mg/mL to 9 mg/mL.
- Dose preparation must be performed using sterile handling techniques in compliance with local, state, and national laws/regulations.
- Inspect parenteral drug products visually for particulate matter and discoloration prior to administration, whenever the solution and container permit. If particles or discoloration are observed, do not use the vial(s) and notify Pfizer.
- The final IP must be administered within 24 hours with a maximum of 8 hours at 20 to 25 °C (68 to 77 °F) and the remainder at 2 to 8 °C (36 to 46 °F). If storage of the diluted dosing solution exceeds 8 hours at room temperature or 24 hours total do not use and contact Pfizer
- The final IP must be administered within 8 hours of preparation if stored at room temperature 15 to 25 °C, 59 to 77 °F. The total in-use stability is a period of not more than 24 hours at 2-8 °C or 36-46 °F with no more than 8 of those hours at room temperature.
- Minimize exposure of vials and dosing solutions to light (e.g. room light, UV light and sunlight)
- Prepared solutions that are refrigerated must be allowed to reach room temperature, prior to administration. Make sure the prepared study solution is not cold to the touch.
- Each vial is for single-use only. Each vial is for use in a single patient, for a single dose.

8.3.4 Compatibility

No known compatibility issues exist for co-administration of utomilumab with any of the other agents

8.3.5 Availability

Utomilumab is an investigational agent and will be supplied free-of-charge from Pfizer.

8.3.6 Drug Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form.

8.3.7 Destruction and Return

All opened (i.e. aluminum overseal broken) vials (full, partially used, and empty) may be destroyed at the site by the appropriate site personnel local environmental requirements and institutional policies. Discarded volumes of IP solutions must be disposed of as pharmaceutical waste according to local site procedures. Destruction must be adequately documented.

8.4 Avelumab

8.4.1 Pharmaceutical Properties

The active pharmaceutical ingredient in avelumab drug product is a fully human antibody of the IgG1 isotype that specifically targets and blocks the ligand (PD-L1) for PD-1.

Avelumab drug product is a sterile, clear, and colorless concentrate for solution for infusion presented at the concentration of 20 mg/mL in European Pharmacopeia (Ph. Eur.) and United States Pharmacopeia (USP) type I glass vials closed with a rubber stopper and sealed with an aluminum Flip Off crimp seal closure.

8.4.2 Description of the Formulations

Each single-use vial contains 200 mg of avelumab as a preservative-free acetate-buffered solution (pH 5.2) containing Mannitol, and Polysorbate 20 (Tween 20).

8.4.3 Instructions for Storage

Avelumab drug product must be stored at 2°C to 8°C until use. The storage condition is based on data from ongoing long term stability studies with avelumab. Avelumab drug product stored at room (23 °C to 27 °C) or higher temperatures for extended periods of time might be subject to degradation. Avelumab drug product must not be frozen. Rough shaking of the solution must be avoided. For administration in clinical trials, avelumab drug product must be diluted with 0.9% saline solution (sodium chloride injection) supplied in an infusion bag. The immediate administration of the prepared solution for dosing kept at room temperature is preferred. In case the aseptically prepared dosing solution cannot be administered immediately after preparation, the acceptable holding time is: not more than 24 hours under refrigerated conditions (2-8°C, 36-46°F) with no more than 8 of those hours at room temperature (15-25°C, 59-77°F), including infusion time.

No other drugs should be added to the solution for infusion containing avelumab.

8.4.4 Handling of the Dosage Forms

For administration in clinical trials, avelumab drug product must be diluted with 0.9% saline solution (sodium chloride injection) supplied in an infusion bag; alternatively, a 0.45% saline solution can be used if needed. Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the IP Manual.

To prepare the dilutions, subsequent preparation steps must be accomplished by adequate trained personnel under a laminar flow box using aseptic techniques:

Prior to the preparation of the dilution for final infusion, allow each vial to equilibrate to room temperature for a minimum of 30 minutes. Use a disposable syringe equipped with a needle of suitable size to remove a volume of sodium chloride solution to be replaced by avelumab from the infusion bag and discard the removed solution. Use a new disposable syringe equipped with a needle of suitable size to inject a volume of avelumab drug product identical to the discarded volume of sodium chloride solution into the infusion bag. Gently invert the mixture 10 times. Infusion bags must not be shaken, in order to avoid foaming or excessive shearing of the protein solution. The preparation must be carefully inspected as it should result in a homogeneous looking clear solution, free of visible particles.

8.4.5 Compatibility

No known compatibility issues exist for co-administration of avelumab with any of the other agents.

8.4.6 Availability

Avelumab is an investigational agent and will be supplied free-of-charge from Pfizer.

8.4.7 Preparation and Administraiton

Only clinical site personnel who are appropriately trained on the procedures may perform the preparation and administration step specified in the IP Manual. Clinical site personnel involved in these procedures must comply with all applicable regulations and standards. The preparation and administration of all sterile products must be performed using aseptic technique. Utilize local site procedures as appropriate.

Avelumab) infusion solutions must be prepared in 0.9% Sodium Chloride (Normal Saline) and the final concentration of MSB0010718C (avelumab) in the infusion solutions must be between 0.016 mg/mL to 8 mg/mL. Total volume of final prepared solution must be 250 mL. Investigational drug products must be inspected visually for particulate matter and discoloration (i.e. change in color) prior to administration, whenever the solution and container permit. If particulates or discoloration are observed, do not use the vial(s) and notify the Principal Investigator or designee. Do not shake or freeze the vial(s). The final IP must be administered within 24 hours of preparation stored at room temperature 15 to 25 °C, 59 to 77 °F. Dose preparation must be performed using sterile handling techniques in compliance with local, state,

and national laws/regulations. Avelumab MUST be administered with a low protein binding 0.2 micron PES filter. Each vial is for single-use only. Each vial is for use in a single patient, for a single dose. Avelumab is administered over 1 hour (-10/+20 minutes).

8.4.8 Ordering

Qualified personnel at participating sites will order the drug directly from Pfizer.

8.4.9 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form.

8.4.10 Destruction and Return

All opened (i.e. aluminum overseal broken) vials (full, partially used, and empty) may be destroyed at the site by the appropriate site personnel local environmental requirements and institutional policies. Discarded volumes of IP solutions must be disposed of as pharmaceutical waste according to local site procedures. Destruction must be adequately documented.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Correlative Studies Background

This trial is exploring combination immunotherapy as a new therapeutic area for advanced HER2-positive breast cancer. A comprehensive collection of biological materials is requested in order to be able to understand the molecular and immune landscape of these the patients enrolled on this study. The goals of the translational research will be to determine mechanisms and biomarkers for avelumab efficacy and resistance, and where the combination of avelumab and utomilumab may further aid in enhancing immune activation and improving outcomes in HER2-positive breast cancer patients.

9.2 Specimen Submission Requirements

The following specimens are to be submitted to the indicated lab. Instructions for collection, processing, labeling, and shipment are included within the Study Manual.

Specimen Type	Collection Time Point						Shipping Condition	Ship to
	Baseline (Pre-Treatment)	C3D1	C7D1	Progression/ EOT [f]	Crossover C3D1	Crossover C7D1		
Paraffin block (or 20 unstained slides) [a]	X						Ambient temperature	DFCI AVIATOR study team

1 H&E stained slide	X						Ambient temperature	DFCI AVIATOR study team
ctDNA (two 10 mL Streck tubes) [b]	X	X	X	X	X	X	Processed for plasma, frozen and batch shipped	DF/HCC Core Blood and Tissue Bank
PBMCs (two CPT tubes) [c]	X	X	X	X	X	X	Processed for PBMCs, frozen and batch shipped	DF/HCC BTIL
Germline DNA (one 10 mL purple top EDTA tube)[d]	X						Processed for whole blood, frozen and batch shipped	DF/HCC Core Blood and Tissue Bank
Research Biopsy (Fresh and frozen tumor tissue) [e]	X	X		X			Frozen in OCT & formalin-fixed paraffin-embedded block(s)	DF/HCC Core Blood and Tissue Bank

a. If baseline biopsy is performed, archival tissue can be collected at any time point throughout the study.
b. 2 Streck tubes will be collected for ctDNA at baseline(C1D1), Cycle 3 Day 1, and Cycle 7 Day 1 PRIOR to dosing. These samples are processed locally, frozen, and batch shipped to DFCI.
c. PBMCs collected at Cycle 1: Days 1,8 and 15 PRIOR to dosing. Participants who cross-over will not have the C1D8 sample collected. These samples are processed locally, frozen, and batch shipped to DFCI.
d. Sample for germline DNA should be collected at C1D1. If missed, this sample can be drawn at any time during treatment
e. Baseline and Cycle 3 biopsies are mandatory. Off-Treatment research biopsy at time of progression or EOT is optional, but strongly encouraged. Biopsy prior to start of cross-over therapy and at time of progression/EOT on cross-over arm are both optional, but encouraged. There is no Cycle 3 biopsy on the crossover arm.
f. All time of progression/EOT samples must be collected prior to treatment on the cross-over arm. These samples are collected again at time of progression/EOT on the crossover arm.

9.3 Translational Research Blood

9.3.1 ctDNA (Streck Tubes) Blood Collection

Blood will be collected for ctDNA analysis via 2 10 mL Streck tubes prior to dosing at Cycle 1 Day 1, Cycle 3 Day 1, Cycle 7 Day 1 and at time of disease progression or treatment discontinuation, whichever comes first.

For participants who cross-over, 2 10 mL Streck tubes will also be collected during cross-over prior to dosing at Cycle 3 Day 1, Cycle 7 Day 1 and at time of disease progression or treatment discontinuation, whichever comes first.

Streck tubes will be processed for plasma at the local site where the sample was collected. Plasma is stored in cryovials at −80°C until shipment. Frozen plasma cryovials will be batch shipped on dry ice to DFCI.

Collection tubes for research blood samples will be in the research sample collection kit provided by Core Prognostex. Please see the Study Manual for detailed instructions for collection, processing, labeling and shipping of ctDNA samples.

9.3.2 Peripheral Blood Mononuclear cells (PBMCs) Blood Collection

Blood will be collected for PBMC analysis via two CPT tubes prior to dosing at Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15, Cycle 3 Day 1, Cycle 7 Day 1 and at time of disease progression or treatment discontinuation, whichever comes first.

For participants who cross-over, two CPT tubes will also be collected during cross-over prior to dosing at Cycle 3 Day 1, Cycle 7 Day 1 and at time of disease progression or study discontinuation visit, whichever comes first.

CPT tubes will be processed for at the local site where the sample was collected. Processed samples are stored in cryovials at −80°C until shipment. Frozen cryovials will be batch shipped on dry ice to DFCI.

Collection tubes for research blood samples will be in the research sample collection kit provided by Core Prognostex. Please see the Study Manual for detailed instructions for collection, processing, labeling and shipping of PBMC samples.

9.3.3 Germline DNA Blood Collection

One 10 mL Lavender top [EDTA] tube of whole blood will be collected at Cycle 1 Day 1 for extraction of germline DNA. If it is missed, the sample may be drawn at any time during treatment.

Whole blood (un-spun) from the EDTA tubes will be aliquoted into cryovials at the local site where the sample was collected. Processed samples are stored in cryovials at −80°C until shipment. Frozen cryovials will be batch shipped on dry ice to DFCI.

Collection tubes for research blood samples will be in the research sample collection kit provided by Core Prognostex. Please see the Study Manual for detailed instructions for collection, processing, labeling and shipping of PBMC samples.

9.4 Research Tumor Biopsies

Tumor Biopsy will be performed at the following time-points:

- **Mandatory** Baseline (Pre-Treatment): to be performed up to 2 weeks prior to starting treatment.
- **Mandatory** Cycle 3: to be performed prior to starting Cycle 3 treatment.

- **Optional** Off-Treatment/Disease Progression: to be performed when disease progression has been determined or treatment discontinuation (whichever comes first). If a participant will crossover, the off-treatment biopsy should be performed prior to initiation of crossover therapy. An additional Off-Treament biopsy is desired, but **optional** at time of disease progression/treatment discontinuation on the Cross-over arm.

Eligible patients should have lesions suitable for serial biopsies. If a mandatory biopsy is unsafe or not feasible, permission must be granted by the overall study PI, Dr. Adrienne Gropper Waks, to decline the mandatory biopsies.

At baseline (pre-treatment), in lieu of the mandatory baseline biopsy, previously collected tumor tissue from a metastaic or loco-regional lesion obtained $\leq$ 1 year prior to enrollment may be submitted. Availability of tissue from a metastatic biopsy/surgery must be comfirmed prior to enrollment if this will be submitted instead of the baseline biopsy.
or new tissue material from a recently obtained surgical or diagnostic biopsy.

A goal of six (6) core biopsy samples will be obtained:

- Three cores should be frozen in OCT, each core frozen in a separate cassette.
- Two additional core biopsies should be placed in a 10% neutral buffered formalin tube. These cores must be paraffin embedded with the local pathology department prior to shipment to DFCI.

Collection tubes for research biopsy samples will be in the research sample collection kit provided by Core Prognostex. Please see the Study Manual for detailed instructions for collection, processing, labeling and shipping of research biopsy samples.

9.5 Archival Tissue Collection

The following archival tissue specimens are required for gene profiling:

- 1 paraffin block (or 20 unstained charged slides 4-5µm thick)
- 1 H&E slide

Archival tissue will be collected for all participants. If a metastatic sample collected within 1 year is submitted in lieu of the baseline biopsy sample, the archival tissue sample should be submitted from a primary breast cancer surgery/biopsy. If primary tissue is unavailable, a metastatic sample may be submitted. Archival tissue sample is shipped ambient in conventional paraffin block or slide shipper to the DFCI study team with the Specimen Requisition form found in the Study Manual. The Study Manual contains additional information on labeling and shipment of archival tissue to DFCI. Paraffin blocks will be returned after completion of correlative research. Unstained slides will not be returned.

Archival tissue blocks/slides are shipped to the following address:

Dana-Farber Cancer Institute
Breast Oncology
Attn: 17-455 AVIATOR study team

9.6 Translational Research Planned Analyses

9.6.1 Biomarkers of PD-1/PD-L1

Quantification of PD-L1 and PD-1 expression will be done by a CLIA-certified IHC test in a central lab. This marker will be performed in the primary tumor and unresectable loco-regional or metastatic biopsies pre-treatment and at time of trial treatment discontinuation.

9.6.2 Multiparametric IHC

Spatial association of PD-1+ TILs and PD-L1+ cells (tumor and myeloid cells) suggests "induction" of PD-L1. Interferon-gamma production by antigen-specific PD-1+ CD8+ T cells is hypothesized to drive local intratumoral upregulation of PD-L1 on adjacent tumor and myeloid cells, leading to a "stalled Cytotoxic T Lymphocyte (CTL)" response which may be predictive of response to checkpoint blockade therapy. We will also evaluate NK cells for markers of activation (CD11). By assessing both required elements, (i.e., PD-L1 expressing cells and PD-1+ T cells) an IHC assay may be a better predictor of response than PD-L1 expression alone.

9.6.3 Characterization of HER2 and tumor infiltrating lymphocytes (TILs)

The BWH Pathology Department will determine the HER2 status for submitted biopsies retrospectively. Five 5 µm sections (FFPE) will be sent to the certified lab for PD-L1 determination by IHC. HER2 status will be quantified by copy number and FISH ratio.
Tumor infiltrating lymphocytes (TILs) will be quantified on H&E slides using a pre-defined method.

Quantification of tumor infiltrating lymphocytes will be performed independently by an experienced pathologist. The percentage infiltration in the adjacent stromal areas as previously described will be recorded [31]. This assessment will be performed in the primary tumor and metastatic biopsies pre-treatment and at time of trial treatment discontinuation.
Agreement between assessments by local and central pathologists will be analyzed.

Objective responses will be assessed as a function of TILs adjusted for other clinicopathological factors, the hypothesis being that high levels of TILs will be associated with a higher rate of objective responses in this trial.

9.6.4 Characterization of circulating tumor DNA (ctDNA)

Plasma of cancer patients contains cell-free tumor DNA that carries information on tumor mutations and tumor burden. This information may be useful as a non-invasive way of monitoring

advanced disease using cancer genetic alterations (mutations, rearrangements) that are specific to the individual's tumor. This information may allow us to track and monitor tumor dynamics during the disease course as well emergence of new clones (i.e., resistance mechanisms). Individual mutations may be assessed using technologies such as digital PCR, or next generation sequencing.

9.6.5 Characterization of peripherial blood Mononuclear cells (PBMCs)

We expect to see evidence of immune activation in peripheral blood subsets and will determine this with multiparameter FACs for T cells, T reg, NK cells and MDSC subsets. We will also examine immune suppression molecules (i.e. PD-1, TIM3) as well as activation molecules (OX40, CD137) on PB T cell subsets. NK cells will be CD3-, CD56+, CD16+ with markers of activation such as CD25, CD11 and CD54.

9.6.6 Sequencing of tumor biopsies (DNA and RNA)

FFPE biopsies will be retained for deep sequencing using next generation technologies at the completion of the trial. Nucleic acids will be extracted according to standard protocols. Sequencing will be performed using the Illumina Hi-Seq, though the technology is improving at a rapid rate. The aim of the sequencing is to understand the molecular landscape (mutations, rearrangements and copy number changes) associated with HER2-positive, PD-L1 expressing and or high TIL tumors, as well as response or resistance to the trial therapy. Specific mutational patterns may be associated with increasing PD-L1 expression or lack of TILs (i.e., chromosomal instability, certain somatic mutations) which could imply a means by which the tumor escapes and subverts host immunity. This may be amenable to targeting with another compound. Similarly, tumors may upregulate specific pathways in order to avoid immune destruction after the PD-1 pathway has been inhibited. The presence of intra-tumoral heterogeneity will be investigated for in tumor biopsies and if this correlates with tumor responses. New data are emerging that suggest we can define certain tumor types as being 'hypermutated.' There is a potential that this hypermutated state may correlate with response to avelumab therapy, and/or that the converse, 'hypomutated' state may require the combination.

Paired metastatic lesions will be compared for the changes that occur during progression and resistance to trastuzumab/vinorelbine, or the combination with Avelumab or avelumab/utomilumab. These data will be also compared with the primary tumor.
If enough RNA is able to be extracted from baseline and serial biopsies, gene expression of these tumors will be evaluated using a genome-wide, deep sequencing technology (RNA-seq). Specific markers of immune response (T-effector/IFNgamma signature, immunosuppression etc) can be then assessed for changes during the treatment course. For example, the expression of T regs (FOXP3) as well as IDO1, an immunosuppressive soluble factor may be increased at progression. Gene signatures that are published in the literature representing various aspects of immunity could also be assessed for their change during treatment.

Whole blood will be collected at baseline prior to treatment. It will be used to confirm the somatic nature of any interesting mutations found. This will not be used for analysis of germline abnormalities. DNA and RNA will be analyzed to attempt to define a gene set critical for clinical

response to either avelumab alone or the combination. The hypothesis to be tested is that avelumab alone responders will exhibit a "stalled Cytotoxic T Lymphocyte (CTL)" response within the tumor reflected in the physical proximity between PD-1 and PD-L1 expression and the presence of an aborted (e.g. weak but discernible) interferon-gamma transcriptional program will be detectable by profiling analyses. Significant alterations identified with these technologies can also be evaluated using ctDNA.

9.6.7 Further exploratory biomarkers

Other immune biomarkers will be performed using IHC evaluation, minimally to include PD-1 and PD-L1 IHC, as well as Nanostring-based gene expression analysis.

9.6.8 Not yet specified translational research

Translational research proposals not outlined in this protocol will be assessed by a trial-specific research committee for merit and feasibility. Biomarkers that are published in the future and considered to be of relevance can then also be assessed in the context of this trial.
For example, an anti-HER2 adaptive response could be assessed and monitored in plasma samples should a suitable antibody be found.

9.7 Genetic Testing

Participants will be given information as part of the informed consent process that samples will be used for research tests that will include genetic studies and testing. The intent is not to give participants (or his/her medical providers) the results of any testing done for research purposes; however, incidental germline (heritable) mutations may be identified of which a participant may or may not already be aware. In the case that an incidental genetic finding is identified, the Protocol Chair of this project will be notified. The possible decisions for handling incidental findings may include notification of the participant (and provider); recommendation for genetic counseling, which may or may not include genetic testing (e.g., if the finding was not done in a CLIA certified laboratory); or, neither. In general, a member of the participant's treating team will be given the information to help with notification. In all cases, the current policy of the Dana Farber Cancer Institute and local/participating site IRB, as applicable, will be followed and any additional approvals that may be required prior to participant notification will be secured in advance.

9.8 Additional Information

Submission of data for Genome Wide Association Studies (GWAS) is not currently planned; however, subjects will be asked for permission in the informed consent process. A revision to the protocol and/or any regulatory approvals will be secured prior to any GWAS submission or inclusions in the future, if applicable.

10. SPECIMEN BANKING

The Protocol Chair and collaborators have approval by the TBCRC to use all research bio-specimens collected during the conduct of this trial to address the research questions described in the protocol document. All future use of residual or repository specimens collected in this trial for purposes not prospectively defined will require review and approval by the TBCRC according to its established policies, whether the specimens are stored in a central site or at a local institution in a virtual repository.

Secondary use of biospecimens for new endpoints must be submitted to the TBCRC Central Office for possible review by the TBCRC Correlative Science Review Committee.

11. MEASUREMENT OF EFFECT

For the purposes of this study, patients should be re-evaluated for response per the study calendar. In the case of documented response (CR or PR), confirmation scan is required no earlier than 4 weeks, but no later than the next scheduled scan. Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) Committee (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Avelumab, like other immunotherapeutic agents, may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of image responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

For any subject who shows first radiologic evidence of progressive disease (PD) by RECIST 1.1 and is deemed clinically stable, it is at the discretion of the investigator to continue treating the subject until progression is confirmed at the next scheduled restaging. These cases should be discussed with the Principal Investigator.

- If progression is not confirmed on the subsequent scan, the subject should continue to receive treatment if the treating investigator feels that the participant is clinically stable, demonstrates improved condition, or is clearly continuing to benefit from the treatment. In this case, radiographic scans should continue to be performed according to the study calendar (i.e., every 8 weeks for the first 10 cycles; and, then every 12 weeks).
- If radiologic progression is confirmed on the subsequent scan, then the subject should be discontinued from all study treatment.

In all participants, the date of progression for the primary endpoint will be documented as the first date progression was observed.

11.1 Definitions

11.1.1 Evaluable for toxicity

All patients will be evaluable for toxicity from the time of their first treatment with Avelumab OR the combination of Avelumab and Utomilumab.

11.1.2 Evaluable for best overall objective response

Only those patients have received at least one cycle of therapy will be considered evaluable for best overall response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

11.1.3 Disease Parameters

Measurable Disease:

- A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥20 mm with chest x-ray, or as ≥10 mm with CT scan, CT component of a PET/CT, or MRI.
- A superficial non-nodal lesion is measurable if its longest diameter is ≥10 mm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- A malignant lymph node is considered measurable if its short axis is ≥15 mm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

NOTE: Tumor lesions in a previously irradiated area are only considered measurable disease in the event that there is evidence of post-radiation progression.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-Measurable Disease:
All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm, are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. “Cystic lesions” thought to represent cystic

metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <10 mm are considered non-pathological (i.e., normal) and should not be recorded or followed.

Target Lesions:
All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-Target Lesions:
All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

11.2 Guidelines for Evaluation of Disease

11.2.1 Measurement Methods

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up.
- Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

11.2.2 Modalities for Measurable Disease

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. CT is preferred; MRI is also acceptable in certain situations (e.g., for body scans).

Diagnostic quality CT is expected (with oral and IV contrast); any deviations from this must be approved by the Protocol Chair/designee in advance. (See note below regarding contrast allergy).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

NOTE: If prior to enrollment it is known a subject is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the subject at baseline and follow-up should be guided by the anatomic location(s) of the disease. For subjects who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist and Protocol Chair/designee to determine if substitution of these other approaches is possible and, if not, the subject may be considered not evaluable from that point forward.

- Chest X-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scans are preferable.
- Clinical Lesions: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern

about radiation exposure at CT, MRI may be used instead of CT in selected instances.

- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time with approval from the Protocol Chair/designee.
- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A 'positive' FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered 'negative.' New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
  - FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

NOTE: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.2.3 Additional Considerations

- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

11.3 Lesion Documentation

11.3.1 Target Lesions

- Measurable lesions: up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  NOTE: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

- Baseline Sum of Diameters (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Diameters (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the diameters (MSD) is the minimum of the BSD and the PBSD.

11.3.2 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions or non-target lymph nodes and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted

throughout follow-up.

11.4 Response Criteria

11.4.1 Overview

All target lesions, as well as non-target lesions must be measured on re-evaluation at evaluation time points. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

If CR or PR occurs at tumor evaluation timepoint within the first 10 cycles, a confirmation scan will occur no earlier than 4 weeks, but no later than the next scheduled scan, per protocol; future tumor evaluations then occur/resume at protocol-defined intervals from the date of response confirmation.

NOTE: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.4.2 Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (NOTE: The appearance of one or more new lesions is also considered progression.)
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.4.3 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

  NOTE: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

  NOTE: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened." Where possible, similar rules to those described above for target lesions for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

11.4.4 Symptomatic Deterioration

Subjects with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A subject is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss >10% of body weight
- Worsening of tumor-related symptoms
- Decline in performance status of >1 level on ECOG scale

11.4.5 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For subjects with measurable disease at baseline:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required
CR	CR	No	CR	4-8 wks Confirmation

CR	Non-CR/Non-PD	No	PR	4-8 wks Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	confirmation not required
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	
* See RECIST 1.1 for further details on what is evidence of a new lesion. ** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.				

For subjects with Non-Measurable/evaluable Disease Only at Baseline:

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD**	No	Non-CR/Non-PD
UNK/Not All Evaluated*	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

11.4.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the time from randomization until the date of objective disease progression or death (by any cause in the absence of progression). In the absence of an event, PFS is censored at last disease assessment; the statistical analysis plan will provide details of censoring rules and sensitivity analyses for the rules.

11.4.7 Objective Response

Confirmed best overall response of CR or PR on two consecutive measurements.

11.4.8 Response Review

There is no independent or central review of the radiology assessments planned for this trial. It is the responsibility of each Principal Investigator to ensure that tumor assessments are reported per

the RECIST 1.1 criteria outlined above. The Protocol Chair (or designee) may choose to review select cases.

11.4.9 Confirmatory Measurement/Duration of Response

Confirmation of Response:
To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks, but no later than the next scheduled scan, per protocol.

Duration of Response:
The duration of response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

The duration of SD is measured from randomization until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Overall Survival:
Overall survival is defined as the time from randomization to death from any cause, or is censored at date last known alive.

11.4.10 Other Response Parameters – irRECIST

Definition of Tumor Response Using Immune-Related Response Criteria (irRECIST):
The sum of the product of the longest diameter of lesions (SPD) at tumor assessment using the immune-related response criteria (irRECIST) for progressive disease incorporate the contribution of new measurable lesions. Each net Percentage Change in Tumor Burden per assessment using irRC criteria accounts for the size and growth kinetics of both old and new lesions as they appear.

Impact of New Lesions on irRECIST:
New lesions in and of themselves do not qualify as progressive disease. However, their contribution to total tumor burden is included in the SPD which in turn feeds into the irRECIST criteria for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

Definition of Target Lesions Response Using irRECIST:

- **irRECIST Complete Response (irRECIST CR):** Complete disappearance of all target lesions. This category encompasses exactly the same subjects as “CR” by the mWHO criteria.

- **irRECIST Partial Response (irRECIST PR):** Decrease, relative to baseline, or 50% or greater in the sum of the products of the two largest perpendicular diameters of all target and all new measurable target lesions (i.e., Percentage Change in Tumor Burden). Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SBD increases by ≥25% when compared to SPD at nadir.
- **irRECIST Stable Disease (irRECIST SD):** Does not meet criteria for irRECIST RC or irPR, in the absence of progressive disease.
- **irRECIST Progressive Disease (irRECIST PD):** At least 25% increase Percentage Change in Tumor Burden (i.e. taking SPD of all target lesions and any new lesions) when compared to SPD at nadir.

Definition of Non-Target Lesions Response Using irRECIST:

- **irRECIST Complete Response (irRECIST CR):** Complete disappearance of all non-target lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- **irRECIST Partial Response (irRECIST PR) or irRECIST Stable Disease (irRECIST SD):** Non-target lesion(s) are not considered in the definition of PR; these terms do not apply.
- **irRECIST Progressive Disease (irRECIST PD):** Increases in number or size of non-target lesion(s) does not constitute progressive disease unless/until the Percentage Change in Tumor Burden increases by 25% (i.e. the SPD at nadir of the target lesions increases by the required amount).

Definition of Overall Response Using irRECIST:

Overall response using irRECIST will be based on these criteria:

- **Immune-Related Complete Response (irRECIST CR):** Complete disappearance of all tumor lesions (target an non-target) together with no new measurable/unmeasurable lesions for at least 4 weeks from the date of documentation of complete response.
- **Immune-Related Partial Response (irRECIST PR):** The sum of the products of the two largest perpendicular diameters of all target lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the SPD of the two largest perpendicular diameters of all target lesions and of new measurable lesions are added together to provide the Immune Response Sum of Product Diameters (irRECIST SPD). A decrease, relative to baseline, of the irRECIST SPD compared to the previously SPD baseline of 50% or greater is considered an irRECIST PR.
- **Immune-Related Stable Disease (irRECIST SD):** irRECIST SD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease
- **Immune-Related Progressive Disease (**irRECIST **PD):** It is recommended in difficult cases to confirm PD by serial imaging. Any of the following will constitute PD:
    - At least 25% increase in the SPD of all target lesions over nadir SPD calculated

for the target lesions.

- At least 25% increase in the SPD of all target lesions and new measurable lesions (irRECIST SPD) over the baseline SPD calculated for the target lesions. Criteria for determining overall response by irRECIST are summarized as follows:

Immune-Related Response Criteria Definitions

Target Lesion Definition	Non-Target Lesion Definition	New Measurable Lesions	New Unmeasurable Lesions	Percent change in tumor burden (including measurable new lesions when present)	Overall irRC Response
Complete Response	Complete Response	No	No	–100%	irCR
Partial Response	Any	Any	Any	≥ –50%	irPR
				<–50% to <+25%	irSD
				>+25%	irPD
Stable Disease	Any	Any	Any	<–50% to <+25%	irSD
				>+25%	irPD
Progressive Disease	Any	Any	Any	≥+25%	irPD

Immune-Related Best Overall Response Using irRECIST (irRECIST BOR):
irRECIST BOR is the best confirmed overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered.

irRECIST CR or irRECIST PR determinations included in the irRECIST BOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

12. ADVERSE EVENT REPORTING REQUIREMENTS

12.1 Adverse Event Characteristics

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs and the characteristics of an observed AE will determine whether the event requires expedited reporting **in addition** to routine reporting.

This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events v5 (CTCAE*v.*5) that is available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

12.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

- **Expectedness:**
  Expected adverse events are those adverse events that are listed or characterized in the current adverse event list, the Investigator Brochure or included in the informed consent document as a potential risk.
  Unexpected adverse events are those not listed in the current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

12.2.1 Serious adverse event (SAE)

A serious adverse event is an undesirable sign, symptom, or medical condition which:

- is fatal;
- is life-threatening;
- requires or prolongs inpatient hospitalization for ≥24 hours;
- results in persistent or significant disability/incapacity to conduct normal life functions;
- constitutes a congenital anomaly or birth defect; or

- jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above;
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen, or that is required per protocol
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care
- death due to disease progression unless attributable to the study drug(s)
- a hospitalization due to an expected adverse event (e.g., hospitalization due to expected febrile neutropenia).

12.3 Expedited Adverse Event Reporting

In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.

Investigators **must** report to the Overall PI any SAE that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

For Multi-Center Trials where a DF/HCC investigator is serving as the Sponsor, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

12.3.1 DF/HCC Expedited Reporting Guidelines

The following adverse events must be reported to the DFCI IRB according to the expedited reporting guidelines:

- **CTCAE Grade 2 and Grade 3 Events** – that are *Unexpected* and there is a *Reasonable Possibility* that the *Adverse Event* is related to the study Intervention.
- **CTCAE Grade 4 Events –** Report all events that are *Unexpected*. Events that are *Expected* and listed within the protocol and/or current consent form do not need to be reported to the DFCI IRB. Please note, an event that presents at a higher severity than what is currently listed within the protocol and/or current consent as expected would be considered unexpected and reportable.

- **ALL CTCAE Grade 5 Events.**

Investigative sites within DF/HCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy. For all events that meet the expedited reporting criteria, a full written adverse event report must be submitted to the DFCI IRB **within 10 working days** from notification of the event.

Other investigative sites will report SAEs to their respective IRB according to their local IRB's policies and procedures for reporting adverse events. A copy of the submitted institutional AE form will be forwarded to the Coordinating Center.

The Coordinating Center will submit AE reports from outside institutions to the DFCI IRB according to DFCI IRB policies and procedures in reporting adverse events.

12.3.2 Participating Sites Reporting Requirement of SAEs to Pfizer

Participating sites will report related SAEs to Pfizer **within 1 business day** of first awareness of the event using the Pfizer or MedWatch SAE Reporting Form. Follow-up information will be provided to Pfizer as reasonably requested. A copy of these reports should also be sent to the lead site at the time of reporting.

Via fax: Pfizer U.S. Clinical Trial Department; Fax 1-866-997-8322 or
Via email: USA.AEReporting@pfizer.com

A copy of the Pfizer or MedWatch SAE Reporting Form and the email correspondence or fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow up events should be reported in the same manner as above, stating that this is a follow-up to the previously reported SAE and providing the follow-up number if appropriate. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation.

12.3.3 Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (e.g., because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product. An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (e.g., because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the Pfizer Drug Safety Unit on a Serious Adverse Event (SAE) Form and Exposure in Utero (EIU) Supplemental Form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (e.g., a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU Form. This must be done irrespective of whether an AE has occurred and **within 24 hours** of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EIU Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study patient with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

12.3.4 Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to the drug safety unit within 24 hours of the Investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a Case Report Form (eCRF); however, a copy of the completed SAE Report form is maintained in the investigator site file.

12.4 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

12.5 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

12.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. Abnormal laboratory results deemed to be not-clinically significant (NCS) by a treating investigator do not need to be entered as an adverse event in the case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

12.7 IND Safety Reports

Pfizer will provide to the Overall PI IND safety reports from external studies that involve the study drug(s) per their guidelines. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required).

13. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 12.0

13.1 Data Reporting

13.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

13.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms in accordance with DF/HCC SOPs.

13.2 Data and Safety Monitoring Board

The Dana-Farber/Harvard Cancer Center (DF/HCC) Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The board is chaired by a medical oncologist from outside of DF/HCC and has external and internal representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Overall PI, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; adverse events and serious adverse events reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

13.3 Supplemental Monitoring of Safety

The safety plan has been developed considering the risk measures for each investigational agent as well as the potential overlapping toxicities. While the safety profile of trastuzumab and vinorelbine is generally well understood given its approval for treatment of HER2-positive advanced disease, avelumab and Utomilumab are currently in clinical development and human experience is limited with the entire safety profile of both agents not known at this time. Please refer to the latest versions of the avelumab and Utomilumab IBs for a complete summary of safety information. The safety considerations are based on results from nonclinical and ongoing clinical studies and published data on similar molecules.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities from study participation. Guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided.

Safety monitoring reported to the DSMB will be supplemented by 1) a formal, prespecified safety monitoring guidance for pausing study accrual to more fully evaluate safety in case of unexpectedly high dose-limiting toxicities; 2) a pause of study accrual after the first 6 patients in

each investigational treatment group (Arms B, C) to more fully review safety, regardless of the number of dose-limiting toxicities observed.

13.3.1 Monitoring of dose-limiting toxicity (DLT)

Please reference section 6.4 for more information regarding the definition of DLTs.

Throughout enrollment, DLTs (defined below) of each investigational treatment group separately (Arms B, C) will be summarized with pre-specified criteria based on sequential boundaries to pause enrollment to more fully review safety if excessive numbers of DLTs are observed. The criteria are such that the probability of pausing is at most 0.05 if the true DLT rate is equal to 15%, and the probabilities of pausing will be 0.66 or 0.95 if the true DLT rate is equal to 30% or 40% [45].

Separately by treatment, the cumulative number of patients (X) experiencing DLT will be compared with the number of safety-evaluable patients (N), i.e., in the safety population (defined in Section 15.8), at that time, and an associated cutoff of safety-evaluable patients (Nx). If the number of patients N is greater than Nx then enrollment will continue; if the number of patients N is less than or equal to Nx then enrollment will pause in order to more fully review the nature, frequency, severity and timing of the events. The Table gives the criteria for pausing enrollment to more fully evaluate safety.

Criteria for pausing enrollment because of DLTs to more fully review safety, for sample size up to 40 patients, with probability of pausing of 0.05 when the true toxicity rate is 15%.

Number of patients for whom DLT is reported	X	1	2	3	4	5	6	7	8	9	10	11	12
Pause enrollment if safety-evaluable patients N is ≤Nx	Nx	-	-	≤4	≤7	≤10	≤14	≤18	≤23	≤27	≤31	≤36	≤40
Continue enrollment if safety-evaluable patients N is ≥ Nx	Nx	≥1	≥2	≥5	≥8	≥11	≥15	≥19	≥24	≥28	≥32	≥37	-

13.3.2 Assessment of first 6 patients per investigational treatment group

Once 6 patients assigned to each investigational treatment group (Arms B, C) have received at least one cycle of assigned treatment, a safety review will be conducted before additional patients are enrolled. Based on the monitoring criteria, if ≥4 of 6 patients (or before 6, if 3/3, ≥3/4, ≥4/5 patients) experience DLT within the first cycle of treatment, then the treatment regimen will be modified or discontinued. The review will include a per-patient listing of all reported AEs to date, including actions required for dosing, to more fully review the nature, frequency, severity and timing of the events. This information combined with fewer DLTs may also result in modification of a treatment regimen.

13.4 Multi-Center Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix C.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.
- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.
- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

13.5 Collaborative Research and Future Use of Data and Biospecimens

Tissue, blood, bodily fluids, and other materials derived from these will be collected in this study to analyze genes, DNA, RNA, proteins and cells for the study's correlative endpoints and potential future research, utilizing new types of biomarker testing as it becomes available.

These samples and any data generated as a part of these clinical trials may be used for future research studies and may be provided to collaborating investigators both within and outside of the DF/HCC for either correlative endpoints or secondary use. Samples and data may be shared with outside non-profit academic investigators, as well as with for-profit pharmaceutical investigators or commercial entities, with whom we collaborate. When samples or data are sent to collaborators and when any research is performed on them, all information will be identified with a code, and will not contain any PHI, such as name, birthday, or MRNs.

In order to allow the greatest amount of research to be performed on the specimens and information generated as a part of this trial, researchers in this study may share results of genetic sequencing with other scientists. De-identified specimen or genetic data may be placed into one of more publicly-accessible scientific databases, such as the National Institutes of Health's Database for Genotypes and Phenotypes (dbGaP). The results from the correlative research on this study will be shared with these public databases. Through such databases, researchers from anywhere will have access to de-identified samples or data for future research. More detailed information, beyond the public database, may only be accessed by scientists at other research centers who have received special permission to review de-identified data.

13.6 Reorting to the NCI

As a provision of funding from the NCI under the Dana-Farber Cancer Institute Breast Cancer SPORE, the NCI will be notified should there be any temporary or permanent suspension of the trial. This notification will be inclusive of any actions taken by the FDA, institutional IRB, institutional PI, or commercial sponsor. Additionally, any major changes in the scope or aims of the study that would affect the objectives of the funding grant will be communicated to the NCI.

14. PUBLICATION PLAN

14.1 Publication

It is understood that any manuscript or releases resulting from the collaborative research must be approved by the Protocol Chair and will be circulated to applicable participating sites/investigators prior to submission for publication or presentation.

Additionally, any publication of study data and results must conform to the publications policy as stated the Translational Breast Cancer Research Consortium's (TBCRC) "Policies and Procedures".

15. STATISTICAL CONSIDERATIONS

15.1 Study Design/ Endpoints

This is a proof-of-concept, randomized, three-arm, phase II open-label study to evaluate the efficacy and safety of trastuzumab/vinorelbine alone, or in combination with avelumab OR avelumab and utomilumab (doublet immunotherapy) in patients with HER2-positive, locally advanced of metastatic breast cancer who have received prior trastuzumab and pertuzumab.

The primary endpoint is progression-free survival (PFS; defined in Section 11.4.6). Secondary efficacy endpoints include objective response and duration of response, and overall survival (defined in Section 12).

The study will include additional monitoring of safety (see Section 13.3), implementing a continuous monitoring for toxicity using Pocock-type boundary.

15.2 Sample Size/ Accrual Rate

One hundred (100) patients will be enrolled and randomized in a 1:2:2 ratio. An enrollment period of 30 months (3.3 patients per month) is anticipated.

The TH3RESA study (Krop et al. 2014) included patients with progressive HER2-positive advanced breast cancer who had received two or more HER2-directed regimens in the advanced setting, including trastuzumab and lapatinib, and previous taxane therapy in any setting. In that study, the median investigator-assessed PFS for patients randomized to T-DM1 was 6.2 months (95% CI 5.59-6.87) and was 3.3 months (95% CI 2.89-4.14) in the physician's choice control group. Patients entering this study will be more heavily pre-treated with pertuzumab as standard first-line therapy, so achieving a similar PFS as for T-DM1 is a reasonable goal of therapy. Studies evaluating vinorelbine with trastuzumab in 2nd line and beyond patients have shown a PFS of around 5 months, without prior pertuzumab treatment [LUX1, BOLERO-3], hence today's advanced HER2-population are likely to have a much shorter PFS in the 2nd line setting and beyond.

One primary objective is to determine whether the addition of Utomilumab to the combination of avelumab and trastuzumab/vinorelbine will improve PFS compared to the avelumab, trastuzumab/vinorelbine combination alone (Arm C vs Arm B). With 80 patients randomized to the investigational treatments, (40 per group) there is 80% power for a log-rank test to detect a difference in median PFS of 6.67 months with avelumab and Utomilumab vs. 4 months with avelumab (HR=0.60) with one-sided α=0.10, assuming analysis with a total of 70 PFS events.

A second primary objective is to determine whether the addition of avelumab to the combination of trastuzumab/vinorelbine will improve PFS compared to the trastuzumab/ vinorelbine combination alone (Arm B vs Arm A). With 60 patients randomized (40 Arm B; 20 Arm A) there is 88% power for a log-rank test to detect a difference in median PFS of 4 months with avelumab/ trastuzumab/vinorelbine vs. 2.0 months with trastuzumab/vinorelbine (HR=0.50) with one-sided α=0.10, assuming analysis with a total of 57 PFS events; power is 65% if median PFS is 2.5 months with trastuzumab/vinorelbine (HR=0.625).

The calculations assumed 30 months of uniform accrual and 6 months' additional follow-up after the last patient enrolled and no dropout (i.e., no withdrawn consent or loss to follow-up prior to a PFS event). No interim efficacy analysis is planned. As a proof-of-concept phase II trial, two one-sided α=0.10 level tests will be conducted without α-level adjustment.

15.3 Modification of study design due to ad hoc futility analysis

As noted in Section 2.3.8, Pfizer's discontinuation of utomilumab led to an ad hoc futility analysis of the comparison of Arm C vs Arm B on 2 February 2021, in consultation with the DSMB. This interim analysis met the criteria for utomilumab inefficacy (see below). Based on this result, further randomization to Arm C is discontinued and the trial will continue with randomization to Arms A and B only, maintaining the 1:2 randomization. At the time of this change in design, a total of 87 patients had been enrolled, (ARM A: 17, ARM B: 36,ARM C: 34). To account for missed C3D1 tissue biopsies in approximately 40 patients (predominately due to inaccessible tissue), this study will continue to enroll to the original goal of 100 patients in order to provide a small number of additional biopsy samples in Arms A and B to facilitate the planned correlative analyses.

15.4 Stratification Factors

Randomization will be stratified, as described in Section 6. Details for incorporating stratification factors in the analyses will be described in the statistical analysis plan.

15.5 Analysis of Primary Endpoint

For the primary and secondary efficacy endpoints, the analysis population is intention-to-treat of all randomized patients who initiate treatment.

The hazard ratio for PFS will be estimated using a stratified Cox proportional hazard model. Consistent with the design (1-sided α=0.10), a two-sided 80% CI will be reported, and may be

accompanied by a two-sided 90% CI. The distributions of PFS according to treatment assignment will be compared using a stratified logrank test (one-sided α=0.10) and will be estimated by Kaplan-Meier method, with reporting of median PFS and 12-month PFS with two-sided 90% CIs.

Sensitivity analyses for the censoring rules, considering for example new anti-cancer treatment initiated before PD or missed disease assessments, will be described in the statistical analysis plan.

15.6 Analysis of Secondary Efficacy Endpoints

The objective response rate will be reported as N (%) with two-sided 90% CIs, according to treatment assignment. Among patients having objective response, the distribution of duration of response will be estimated by Kaplan-Meier method, according to treatment assignment.
The distribution of overall survival will be estimated by Kaplan-Meier method, including estimation of 2-year OS with two-sided 90% CIs, according to treatment assignment.

These endpoints, as well as PFS, will also be summarized for the subset of patients randomized to Arm A who crossover to receive the combination of trastuzumab, Avelumab and Utomilumab after progression on vinorelbine/trastuzumab. The endpoints will be defined from the time that crossover treatment begins.

15.7 Analysis of Safety and Tolerability

The safety population is randomized patients who initiate treatment as defined in Section 15.8, to be summarized according to treatment received. Safety and tolerability will be assessed based on adverse events reported according to NCI-CTCAE version 4.0. Of particular emphasis for safety reporting are cardiac, hepatic and pulmonary events. Details of the safety monitoring plan are described in Sections 13.3.1 and 13.3.3.

For each patient within the safety analysis population, recorded AE data over time will summarized as maximum grade observed of each AE. All reported AEs will be tabulated by maximum grade, according to treatment, as N and percentage of patients. For AEs, including cardiac, hepatic and pulmonary events, more detailed summaries of timing of onset, duration and severity (grade) over time may be reported, for example by swimmers plot.

As well, clinical laboratory results during and following administration of study therapy will be summarized over time according to treatment, specifically hemoglobin, absolute neutrophil count and platelet count to assess anemia, neutropenia and thrombocytopenia.

15.8 Exploratory and Biomarker Objectives

15.8.1 Overview of Analyses

PFS measures as defined by immune modified RECIST will be analyzed similarly as for the primary analysis of PFS.

Considering the number of biomarker and exploratory analyses, the emphasis will be on descriptive and graphical summaries of data, and the interpretation based on the cumulative evidence of the analyses rather than on any one analysis in isolation.

Analyses investigating pre-treatment markers (e.g., tumor PD-L1 and TILs) with efficacy endpoints (PFS and objective response) will use modeling (Cox or logistic, respectively) to investigate the association overall, as well as the interaction with treatment assignment, by reporting of HRs/ORs (and two-sided 90% CI). Test of marker-by-treatment interaction will be performed but emphasis will be on the HR (and CI) estimates of treatment effect according to marker status. As for the primary objective, the key treatment comparisons continue to be Arms B vs C and Arms B vs A. The PFS distributions and summary measures will be estimated using the Kaplan-Meier method as described for the primary analysis.

It is also of interest to understand immune status (defined by PD-L1 expression, TILs and other markers by mRNA and IHC), ER status and HER2 measures (copy number, FISH ratio, mRNA levels) prior to treatment in relation to efficacy, and interactions of these markers would be investigated with the same approach, as feasible in consideration of subgroup sizes.

Tissue samples will be collected at multiple timepoints. The association of change in TILs after 2 cycles of treatment with PFS will be assessed using a conditional landmark approach, redefining PFS from start of C3D1. Its association with response assessment after 2 cycles of treatment will also be investigated. Other markers measured in the samples following 2 cycles of therapy samples would be similarly analyzed. Analyses incorporating the tissue biopsy at progression would be descriptive and graphical, for example with spider plots to show marker levels at baseline, after 2 cycles and at the actual timepoint of progression. Serial plasma samples are also collected and markers would be analyzed in the same framework.

Markers in relation with safety signals would be explored with the same approaches as for efficacy endpoints; the safety endpoints could be defined as binary or time-to-event.

15.8.2 Sample Size Considerations

For the association of pre-treatment biomarkers with PFS among the 3 treatment groups combined, assuming 80% success rate with any biomarker, the analysis population would be expected to be about 80 patients and 65-70 PFS events. This sample size would provide 80% power (two-sided α=0.10) to detect HR=0.55 if marker-positive prevalence is 50% and HR=0.50 if marker-positive prevalence is 25%.

For the association of pre-treatment baseline biomarkers with OR among the treatment groups combined, assuming 80% success rate with any biomarker, the analysis population would be expected to be about 80 patients and 16-20 objective responses if the ORR is 20-25% across all 3 treatment groups. This sample size would provide 75-80% power (one-sided α=0.10) to detect odds ratios of at least 3.7 (approx. 30-40% vs 10-15% ORR) if marker-positive prevalence is 50% and odds ratio of at least 3.9 (approx. 40-45% vs 13-18% ORR) if marker-positive prevalence is 25%.

For the association of 2-cycle biomarker change with PFS status after 2 cycles among the treatment groups combined, the detectable odds ratio would be similar, as the 2-month progression rate would be expected to be about 24% in the treatment groups combined, under the same assumption that 80% of patients have successfully established change in marker status from pre-treatment to post 2 cycles of treatment.

15.9 Reporting and Exclusions

The primary and secondary efficacy analysis population will be defined according to an intention-to-treat approach, of all randomized patients, and reported according to CONSORT guidelines.

The safety analysis population is all patients who initiate avelumab +/- utomilumab treatment; any toxicity among a patient who receives trastuzumab and/or vinorelbine after randomization but without avelumab +/- utomilumab will be described separately.

15.10 Interim analysis for inefficacy, Arm C vs B

An ad hoc interim analysis was added, in consultation with the DSMB. Based on the linear inefficacy boundary (LIB20) approach[46], a single interim analysis for inefficacy for the primary objective (arm C vs B) was conducted to ensure some signal of benefit of the addition of utomilumab. With the design one-sided α=0.10 and power 80%, the LIB20 would suggest interim analysis after 60% events, at which point an estimated HR>1 would imply that the 2-sided 90% CI for log HR would exclude the design alternative of 0.60. At the analysis, the observed information fraction was 53% events and the critical value was HR>1.02 indicating inefficacy.

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Appendices

Appendix A: ECOG Performance Status Scale
Appendix B: Strong CYP3A Inducers/Inhibitors and Information on Possible Drug Interactions
Apprendix C: DF/HCC Multi-Center Data Safety Monitoring Plan

APPENDIX A: ECOG Performance Status Scale

Score	Definition	Karnofsky Equivalent
0	Asymptomatic	100
1	Symptomatic, fully ambulatory	80 – 90
2	Symptomatic, in bed less than 50% of day	60 – 70
3	Symptomatic, in bed more than 50% of day, but not bedridden	40 – 50
4	Bedridden	20 – 30

APPENDIX B: Strong CYP3A Inducers/Inhibitors and Information on Possible Drug Interactions

Medications that strongly inhibit CYP3A:
Amprenavir
Atazanavir
Boceprevir
Clarithromycin
Conivaptan
Delavirdine
Diltiazem
Erythromycin
Fosamprenavir
Indinavir
Itraconazole
Ketoconazole
Lopinavir
Mibefradil
Miconazole
Nefazodone
Nelfinavir
Posaconazole
Ritonavir
Saquinavir
Telaprevir
Telithromycin
Verapamil
Voriconazole
Grapefruit, grapefruit juice, or any product containing grapefruit

Medications that strongly induce CYP3A:
Carbamazepine
Felbamate
Nevirapine
Phenobarbital
Phenytoin
Primidone
Rifabutin
Rifampin
Rifapentin
St. John's wort

APPENDIX C: Data Safety Monitoring Plan

DFCI Protocol #: 17-455

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

TABLE OF CONTENTS

1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol who takes responsibility for initiation, management and conduct of the protocol at all research locations. The DF/HCC Sponsor will serve as the single liaison with any regulatory agencies. The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines. In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Research Informatics Office (RIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Dr. Adrienne Gropper Waks will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training (and/or a Site Initiation Visit prior to enrolling participants) and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable FDA reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with the FDA, as applicable.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.

- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.

- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions

required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution upon request.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent for all interventional drug, biologic, or device research.

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution’s IRB.
- Participating Institution’s IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB and will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.7 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.8 DF/HCC Multi-Center Protocol Registration Policy

Participant Registration and Randomization

Please refer to Protocol Section 4 for participant registration information. Treatment cannot begin until site has received confirmation that participant has been registered with DF/HCC CTMS.

Randomization can only occur during normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Standard Time.

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case

number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.9 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.10 Deviations, Violations, and Exceptions

3.10.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.10.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.10.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.10.4 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

3.10.5 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated therapy will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.
Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.10.6 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 12.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

3.10.7 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions, if applicable. Participating Institutions will review/submit to their IRB according to their institutional policies and procedures.

3.10.8 Data Management

DF/HCC RIO develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC RIO provides a web based training for all eCRF users.

3.10.9 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol section 8.

Participating Institutions should order their own agent regardless of the supplier.
If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB.

If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent (i.e., NCI or a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

Additionally, a plan will be formulated to provide regular and ongoing communication to Participating Institutions about study related information which will include participation in regular Lead Institution initiated teleconferences. Teleconferences will occur every 2 weeks and will continue regularly until completion of accrual. Upon completion of accrual, teleconferences will occur monthly until all patients complete protocol therapy. Upon completion of protocol therapy, teleconferences will occur every 3 months until study completion. Additional communication may be distributed via “Newsletter” or email as deemed appropriate by DF/HCC Sponsor.

On-Site Monitoring: On-site monitoring will occur on an as-needed basis. Participating Institutions will be required to provide access to participants’ complete medical record and source documents for source documentation verification during the visit. In addition, Participating Institutions should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the Participating Site. On-site monitoring visits can be substituted with remote (virtual) monitoring visits at the discretion of the Principal Investigator.

Remote Monitoring: Remote monitoring will be performed on an as-needed basis by the Clinical Trial Monitor. Sites will be asked to provide source documentation via fax, email, or mail as specified by the Clinical Trial Monitor for virtual monitoring.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

A minimum of 3 participants per site annually is recommended for Phase II trials. However, given the additional regulatory burden and cost of overseeing each site, a consideration of 5 per site/annually should be a minimum target for each site.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, applicable Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2-day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.2 Audit Notifications

It is the Participating Institution's responsibility to notify the Coordinating Center of all external audits or inspections (e.g., FDA, EMA, NCI) that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the

DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Participating Institution Performance

The DF/HCC Sponsor and the DFCI IRB are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.