NCI Protocol #: N/A

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TITLE: A Multi-Cohort Phase 1b Clinical Trial of Rituximab in Combination with Immunotherapy in Untreated and Previously Treated Follicular Lymphoma

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Agents: Rituximab (commercial supply); Utomilumab (investigational, supplied by Pfizer); PF-04518600 (investigational, supplied by Pfizer); Avelumab (investigational, supplied by Pfizer)

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IND Sponsor: Caron Jacobson, MD

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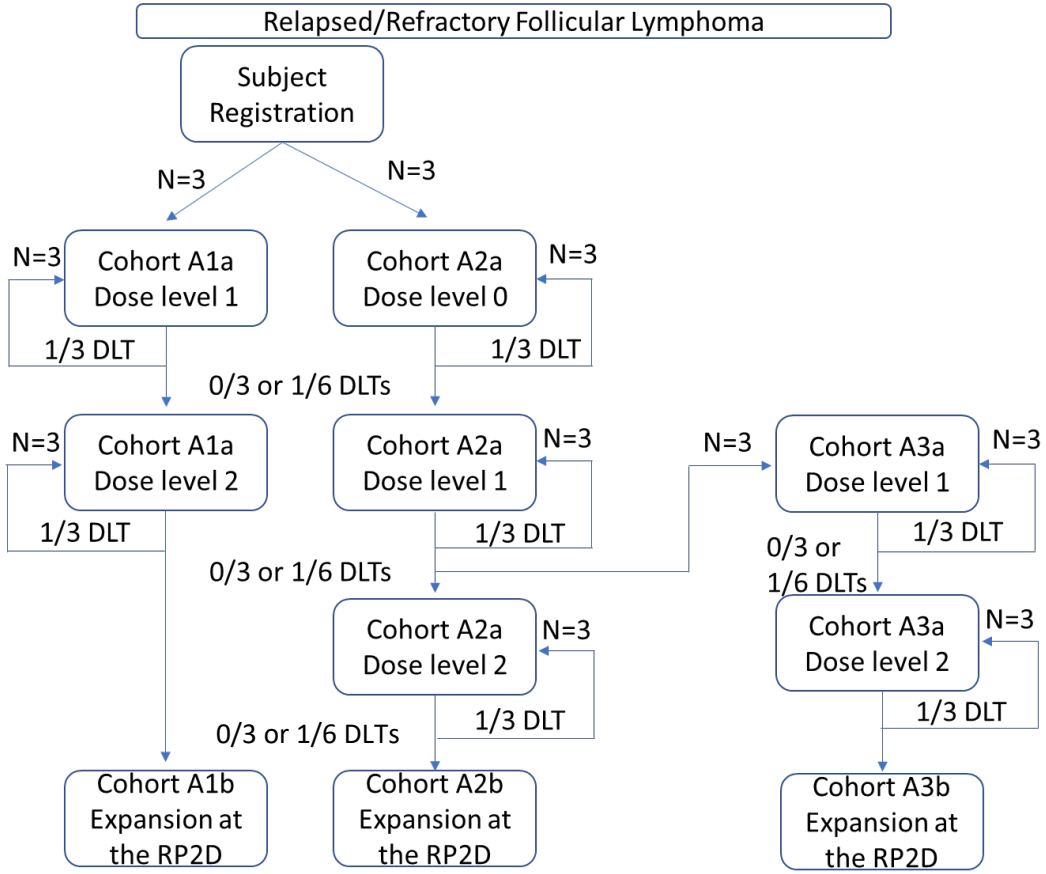
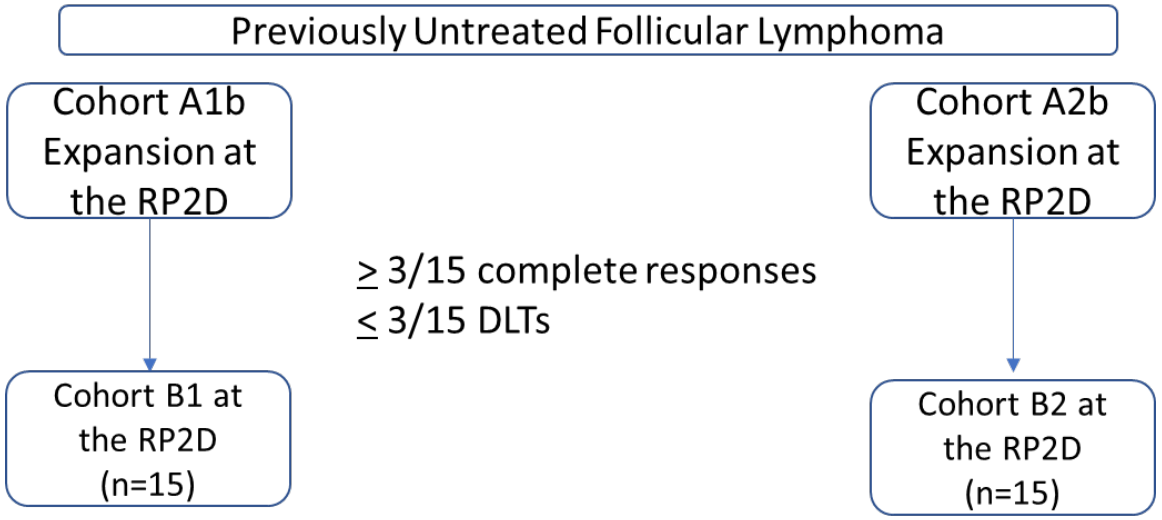
SCHEMA 1: RELAPSED/REFRACTORY DOSE ESCALATION AND EXPANSION DESIGN



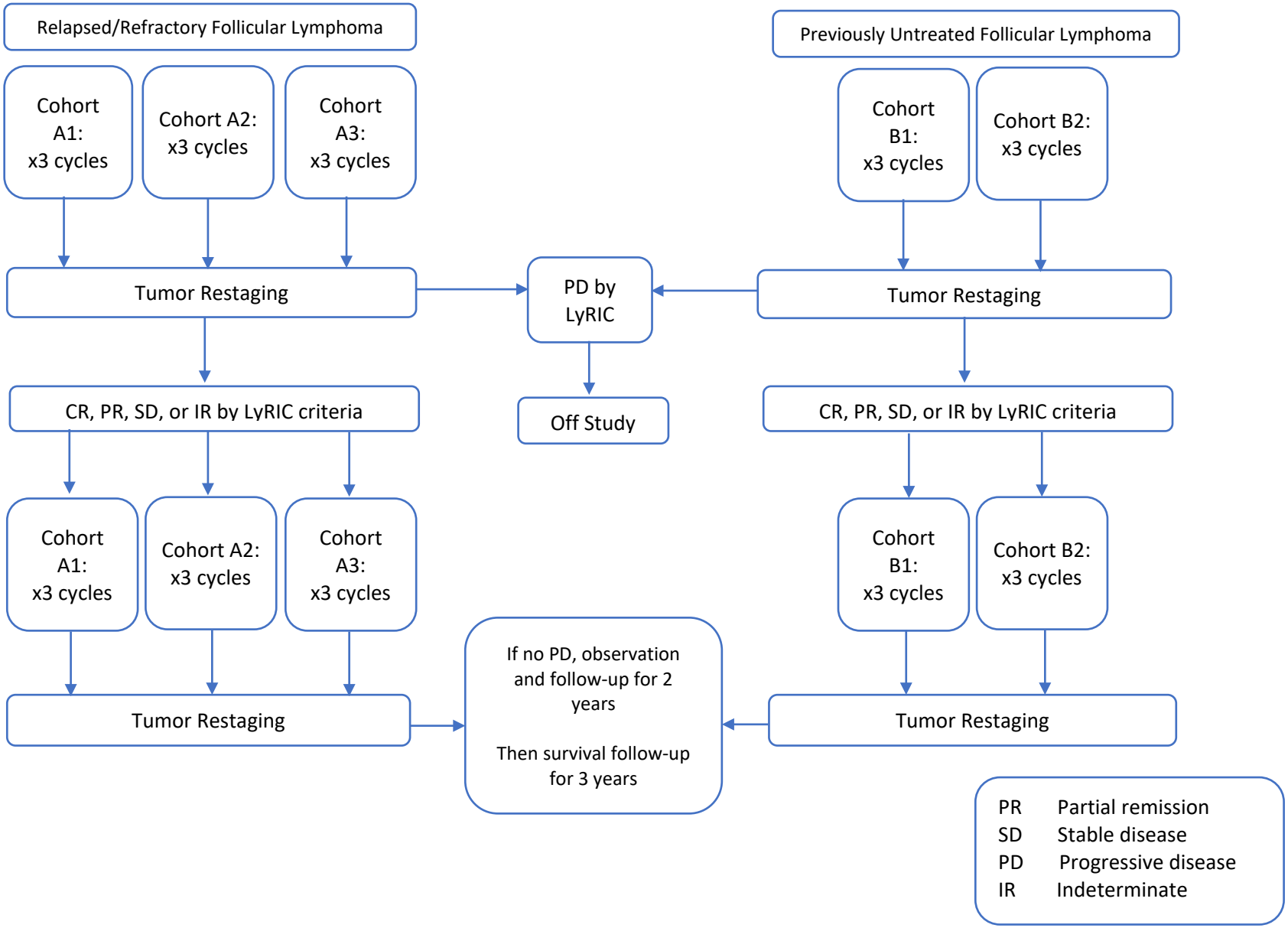
A1a, dose level 1: Rituximab (or rituximab biosimilar) 375mg/m2 IV q7 days x 4 doses, utomilumab 100mg IV q28d, avelumab 3mg/kg IV q14 days;
A1a, dose level 2: Rituximab (or rituximab biosimilar) 375mg/mg2 IV q7 days x 4 doses, utomilumab 100mg IV q28d, avelumab 10mg/kg IV q14 days;
A2a, dose level 0: PF-04518600 0.3mg/kg IV q14 days;
A2a, dose level 1: Rituximab (or rituximab biosimilar) 375mg/m2 IV q7 days x 4 doses, PF-04518600 0.3mg/kg IV q14 days;
A2a, dose level 2: Rituximab (or rituximab biosimilar) 375mg/m2 IV q7 days x 4 doses, PF-04518600 0.3mg/kg IV q14 days, utomilumab 100mg IV q28 days;
A3a, dose level 1: Rituximab (or rituximab biosimilar) 375mg/m2 IV q7 days x 4 doses, PF-04518600 0.3mg/kg IV q14 days, avelumab 3mg/kg IV q14 days;
A3a, dose level 2: Rituximab (or rituximab biosimilar) 375mg/m2 IV q7 days x 4 doses, PF-04518600 0.3mg/kg IV q14 days, avelumab 10mg/kg IV q14 days;
RP2D: recommended phase 2 dose (if 0/3 or 1/6 DLTs at dose level 2 for a given cohort, this will be dose level 2; if 2+/6 DLTs at dose level 2 for a given cohort, this will be dose level 1; n=15 patients in total at a given dose)

SCHEMA 2: CRITERIA TO OPEN, AND EARLY STOPPING RULES FOR, PREVIOUSLY UNTREATED COHORTS



B1: Rituximab (or rituximab biosimilar) 375mg/mg2 IV q7 days x 4 doses, utomilumab 100mg IV q28d, avelumab at the RP2D IV q14 days;
B2: Rituximab (or rituximab biosimilar) 375mg/m2 IV q7 days x 4 doses, PF-04518600 0.3mg/kg IV q14 days, utomilumab 1.2mg/kg IV q28 days;
Early stopping rule: a cohort will be closed if >2 patients at any point meet the criterion for DLT.

SCHEMA 3: TREATMENT CYCLES AND RESPONSE ASSESSMENTS ON STUDY



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1. OBJECTIVES

1.1 Study Design

This is a multi-cohort Phase 1b open label study to assess efficacy and safety of immunotherapy in combination with rituximab in relapsed/refractory (R/R) and untreated follicular lymphoma (FL). This study is designed to rapidly test various combinations of immunotherapeutic or immunomodulatory agents in both R/R and untreated FL. For a given combination, pre-defined safety and efficacy benchmarks must be met in the R/R cohort before the combination can be tested in untreated disease. The goals of this study are:

1. to determine whether any of the combinations are promising enough to justify further testing in subsequent phase 2 studies;
2. to explore the efficacy in untreated patients of combinations that are promising in R/R patients;
3. through correlative studies, to further our understanding of the immunobiology of FL and the determinants of response/resistance to checkpoint blockade.

Immunotherapy will consist of a combination of drugs, including utomilumab, avelumab, and PF-04518600. All combinations will be administered for ~6 months. Response will be assessed with PET/CT scans following the completion of treatment. Minimal residual disease (MRD) and progression-free survival (PFS) will be monitored as a key secondary endpoint.

1.2 Primary Objectives

- To determine the recommended phase 2 dosing (RP2D) of immunotherapy combinations with rituximab for the treatment of relapsed/refractory or untreated follicular lymphoma
- To evaluate clinical efficacy of immunotherapy in combination with rituximab in relapsed/refractory or untreated FL as measured by the complete response (CR) rate using the 2014 Lugano criteria[1]

1.3 Secondary Objectives

- To evaluate clinical efficacy of immunotherapy in combination with rituximab in relapsed/refractory or untreated FL as measured by:
    - Objective response rate (2014 Lugano[1])
    - Overall and complete response rate (LyRIC[2])
    - PFS, overall survival (OS), and time to next treatment (TTNT)
        - PFS will be analyzed by both 2014 Lugano[1] and LyRIC[2] criteria
    - Objective response rate, complete response rate, and MRD negativity will be stratified by grade (1-2 versus 3A) and by FL International Prognostic Index (FLIPI)[3]
- Evaluate safety of these combinations in relapsed/refractory FL and previously untreated FL.
    - Rate of grade 3 or higher toxicity regardless of attribution
    - Rate of grade 3 or higher toxicity at least possibly related to study treatment

- Rate of grade 2 or higher toxicity at least probably related to study treatment

1.4 Exploratory Objectives

- To perform correlative laboratory studies using pre-treatment and on-treatment peripheral blood and tumor samples to evaluate for biomarkers of response and resistance
- To analyze pre-treatment fecal microbiome to investigate relationship with response or resistance to immunotherapy
- Rate of MRD negativity at 6 and 12 months

2. BACKGROUND

2.1 Follicular Lymphoma (FL)

There will be approximately 70,000 new cases of non-Hodgkin lymphoma (NHL) this year in the United States, and 20,000 deaths. Follicular lymphoma is the second most common B cell NHL, with approximately 25,000 new cases diagnosed each year in the United States. It is the most common indolent B cell NHL and generally presents at advanced stage and is incurable with conventional therapies. Though incurable, it does tend to be chemotherapy responsive with high rates of initial response, but it exhibits progressively lower rates of response and remission duration with subsequent lines of therapy, and always with invariable relapse.

Of the many effective treatment modalities for FL, overall survival benefits have not been demonstrated favoring one treatment approach over another, with the exception of rituximab-containing chemotherapy versus chemotherapy alone.[4,5] Increased intensity regimens have been shown to improve CR rates and PFS without improvement in OS. Choice of therapy has thus been based upon balancing efficacy and tolerability. Available treatment approaches currently employed in chemotherapy naïve patients include rituximab monotherapy, R-bendamustine, R-CVP (rituximab, cyclophosphamide, vincristine, prednisone), and R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, prednisone). For the relapsed/refractory setting, these options remain but additional options include fludarabine-based regimens, radioimmunotherapy, and targeted therapies with the immunomodulatory drug lenalidomide and the PI3 kinase inhibitor idelalisib.[6,7] Furthermore, lenalidomide has been used in combination with rituximab in the upfront setting and has excellent response rates, including a CR rate of 87%.[8]

Both autologous and allogeneic stem cell transplantation have been used for the treatment relapsed FL.[9,10] The former may consolidate a second or third line chemotherapy remission and results in a median progression free survival (PFS) of 4-5 years. The latter is currently the only potentially curative therapy for advanced stage FL, with a long term PFS of 60-80%, but with a considerable risk of morbidity and mortality. It is thus reserved for multiply relapsed disease with suboptimal depth and/or duration of response. Its efficacy, however, supports the use of immune strategies for the treatment of this disease.

2.2 General Rationale for Study

The success of allogeneic transplantation in FL mentioned above, as well as the preliminary successes of checkpoint blockade and co-stimulatory agonism mentioned below, strongly support the hypothesis that FL is an inherently immunosensitive malignancy. Despite this, most existing therapies are cytotoxic or targeted therapies, leaving a wide opening for immunotherapy studies in this disease. Fortunately, there are now a number of available therapeutic agents that target specific agonist and checkpoint pathways and that so far have shown very good tolerability in patients with cancer. The experience to date in FL (and more broadly in non-Hodgkin lymphoma) suggests that while these drugs can lead to meaningful responses, any of these drugs given alone will be unlikely to provide effective and durable responses in FL in the majority of patients.[11] One of the likely reasons for this is that tumor cells can use alternative checkpoint or agonist pathways as escape mechanism for single pathway inhibition. This understanding has paved the way for combination studies of immunotherapeutic drugs, which have already shown success (for example the combination of CTLA-4 and PD-1 blockade in melanoma).[12] At the present time, we do not understand the immunobiology of FL enough to rationally predict which particular combination is most likely to be effective.

Based on the above, we have therefore designed the present study to allow the rapid testing of multiple attractive combinations of co-stimulatory agonists/checkpoint blockade/immunomodulatory drugs, all administered in combination with CD20 blockade. This will allow the empiric selection of the most promising combination(s) for further testing. Importantly, the extensive correlative studies that are planned may allow us to build the scientific understanding of FL immunobiology that should help to optimize immunotherapy combinations in future trials.

In the following sections, we describe the various agents used in this study, and then expand on the rationale for their use in combination in R/R and untreated FL.

2.2.1 Rationale for rituximab combined with immunotherapy in relapsed/refractory and previously untreated follicular lymphoma

Follicular lymphoma is sensitive to immunotherapy as evidenced by the ability of allogeneic stem cell transplantation (alloSCT) to cure a majority of patients with advanced disease.[13] AlloSCT, however, is often prohibitively toxic. Similarly, anti-CD19 directed CAR T cell therapy has yielded long term remissions in this disease but is complicated by cytokine release syndrome and neurotoxicity.[14] This supports the investigation into novel forms of immunotherapy to successfully engage the patient's own immune system to deliver long-lasting disease control with improved morbidity and mortality.

Both inhibitory antibodies against the T cell inhibitory receptor PD1, and activating antibodies against the T cell costimulatory molecule 4-1BB have shown some promise in the clinic in this disease, but as single agents their efficacy appears to be limited to undefined subsets. The anti-PD1 antibody, nivolumab, was tested in a phase 1 study in refractory lymphoma and myeloma.[11] Ten patients had follicular lymphoma and four patients achieved a response (CR rate 10%); the median duration of response was not yet reached at nearly 2 years of follow-up. Combining rituximab and pidilizumab, a putative anti-PD1 antibody, in patients with relapsed, rituximab

sensitive, follicular lymphoma yielded complete responses in just over half of patients (52%); the median duration of response was 20 months and the combination was well tolerated.[15] However, these patients had disease that was sensitive to rituximab and so it is unclear the degree to which this response was due to pidilizumab. Additionally, we have since learned that the mechanism of action of pidilizumab does not appear to work through inhibition of PD1 but is instead unknown.

As previously mentioned, the combination of utomilumab and rituximab has been tested in rituximab-refractory follicular lymphoma. This is based on preclinical data demonstrating an enhancement of the anti-lymphoma NK cell ADCC activity of rituximab by anti-4-1BB agonist mAbs.[16] Using CD20+ lymphoma cell lines, it was shown that recognition of rituximab-coated tumor B cells induces CD137 up-regulation on human NK cells, and that subsequent stimulation of these NK cells with anti-CD137 mAb enhances anti-lymphoma ADCC.[16] These results were confirmed *in vivo* using a syngeneic immunocompetent mouse model, and a human xenotransplant model of lymphoma. The combination of utomilumab with rituximab, then, may restore rituximab sensitivity in patients with refractory disease. In a phase 1/1b clinical trial, the combination of utomilumab and rituximab has yielded deep and durable responses in a subset of patients but the objective response rate has been disappointing.

The follicular lymphoma microenvironment may hold the key to the lack of generalizable efficacy of immunotherapy agents when used alone or in combination with rituximab. It is rich in immune cells, including PD1+ T cells and PD-L1 positive macrophages, as well as regulatory T (Treg) cells, all of which may result in a net inhibitory signal on tumor-directed T cells.[17] We hypothesize that combining immunotherapy agents to shift this net inhibitory signal to an activation signal will improve response rates while preserving a tolerable safety profile.

PD1 blockade and 4-1BB agonism work synergistically

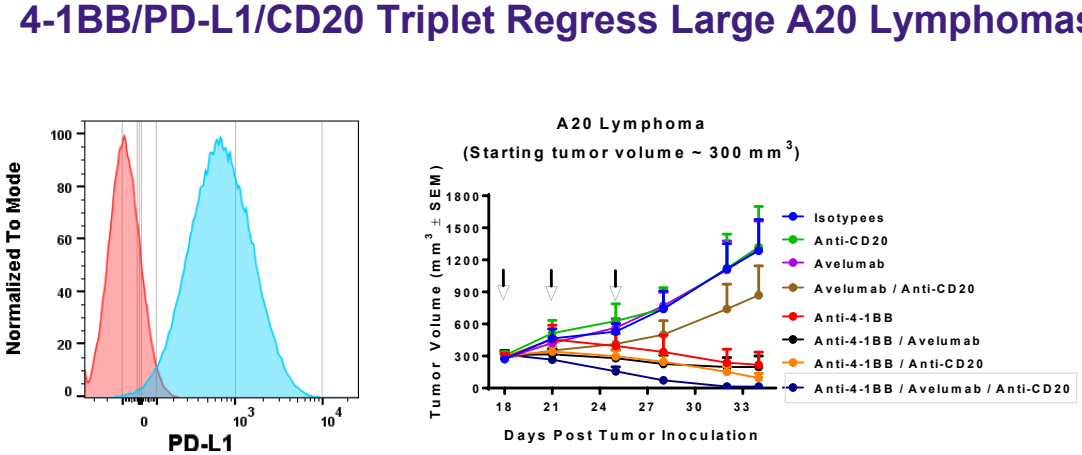
There is preclinical data to support the combination of anti-PD1 therapy with agonist antibodies against 4-1BB, although this data is in animal models that have not been validated as surrogates for clinical disease. A 4-1BB agonist antibody resistant mouse MC38 colon cancer tumor model expressing PD-L1 was used to examine anti-tumor activity using the combination of a 4-1BB agonist antibody with PD-1 antagonist antibody compared with either agent alone. Combination treatment of animals with 4-1BB agonist in combination with a PD-1 antagonist resulted in 63.2% reduction in tumor growth as compared with vehicle controls (unpaired t test *p = 0.0125). Significant tumor growth inhibition by either agent dosed individually was not observed. Consistent with the proposed mechanism for the combination, significant increases in $CD8^+$ effector memory cells and tumor responsive IFN-γ producing cells were found in the spleens of mice treated with the combination. In addition, preliminary toxicology data in mice suggest that the toxicity of an anti-4-1BB agonist is not increased by the addition of an anti-PD-1 antagonist.

Other pre-clinical studies indicate that PD-L1 expression confers resistance to therapeutic anti-4-1BB antibody in mice with established tumors. The resistance is accompanied by failure of antigen specific $CD8^+$ cytotoxic TLs to destroy tumor cells without impairment of cytotoxic TL function. Blockade of PD-L1 or PD-1 using mAbs could reverse this resistance and enhance therapeutic efficacy.[18] A mastocytoma cell line negative for PD-L1, was either mock transfected or transfected with a PD-L1 construct. The cells were then injected into the strain of mouse

where the tumor cells were derived (DBA/2). Anti-PD-L1 mAbs were shown to abrogate the response to anti-4-1BB mAbs, suggesting that PD-L1 blockade might enhance the response to anti-4-1BB.

The hypothesis that a triplet comprising avelumab, rituximab and utomilumab might provide enhanced clinical activity in B cell lymphoma has been tested in an A20 lymphoma model (Unpublished Pfizer data on file). In this model the triplet combination of avelumab, anti-4-1BB, and rituximab resulted in a higher frequency of tumor-free mice than either of the corresponding doublets or monotherapy (Figure 1).

Figure 1. A20 Lymphoma Model Data Showing Synergy of Simultaneous PD-L1, Anti-4-1BB, and Rituximab Blockade



Treatments	# Tumor-Free Mice
Isotypes	0 / 8
Anti-CD20	0 / 8
Avelumab	0 / 8
Avelumab / Anti-CD20	0 / 8
Anti-4-1BB	3 / 8
Anti-4-1BB / Avelumab	4 / 8
Anti-4-1BB / Anti-CD20	4 / 8
Anti-4-1BB / Avelumab / Anti-CD20	7 / 8

Doublet and triplet combinations of agonist antibodies to OX40 and 4-1BB with or without anti-PD1 therapy, respectively, improve efficacy preclinically

Similarly, OX40 is expressed in the FL microenvironment, including on PD1+ T cells, and preclinical studies suggest that OX40 targeting therapy may enhance the effect of immune checkpoint blockade therapy.[19] Specifically, high circulating and intratumoral regulatory T (Treg) cell levels pre-treatment has been associated with decreased PFS following chemotherapy and immunotherapy (rituximab and pidilizumab). These intratumoral Tregs are activated and suppress the function of anti-tumoral T cells, but this suppression could be overcome *in vitro* through the addition of toll-like receptor ligands, including OX40.[19] Similarly, while OX40 and

4-1BB are from the same TNFR superfamily of costimulatory molecules, they have complementary mechanisms that elicit distinct immune functions. Indeed, dual targeting of OX40 and 4-1BB has been shown to synergistically induce CD8 and cytotoxic CD4 T cell clonal expansion.[20-22] In studies by Lee et al.[20], a combination of OX40 and 4 1BB agonists induced tumor growth inhibition in an immunologically resistant fibrosarcoma model. In preclinical studies conducted by Pfizer, a combination of anti-OX40 (OX86 mIgG1) and anti-4-1BB IgG1 mouse surrogate antibodies inhibited tumor growth by 96.4%, compared with 63.3% (4-1BB) and 35.3% (OX86) inhibition following single antibody treatment. In a less immunogenic B16-F10 murine melanoma model, a combination of OX40 and 4-1BB agonists significantly enhanced tumor T-cell infiltration and T-cell proliferation. PF-04518600 is currently being tested alone and in combination with avelumab and utomilumab in advanced solid tumor malignancies.

Preclinical studies of triplet therapy with anti-PDL1 antibodies combined with agonist antibodies against OX40 and 4-1BB demonstrated antitumor synergy over single or double antibody treatments in the MC38 colon cancer model and the B16F10 melanoma model. The increase in activity seen with the triplet therapy was associated with an increased CD8 T -cell infiltration as well as increased T cell activation and proliferation in the peripheral blood. In these models, there was no increased toxicity observed in the triplet therapy group compared to animals treated with any of the antibodies alone.

2.2.2 Rationale for Study Design

We hypothesize that although follicular lymphoma is highly sensitive to immunotherapy in the form of allogeneic stem cell transplant and CAR T cell therapy, the tumor microenvironment is sufficiently immune suppressive such that immunotherapeutic agents, including immune checkpoint inhibitors, as single agents have had limited success. The long natural history of this disease, along with the morbidity and mortality risk of allogeneic stem cell transplant and CAR T cell therapy, however, make finding effective yet tolerable therapies a high priority and an unmet need. Combining therapy targeting several different checkpoint pathways, in association with standard immunotherapy targeting CD20 (rituximab) has the potential to overcome the FL immunosuppressant microenvironment and could provide significant therapeutic benefit while retaining the relatively high tolerability characteristic of rituximab and checkpoint targeting monoclonal antibodies. In addition, the incurable nature of this disease with a long natural history makes finding a non-chemotherapy regimen that is well tolerated a goal both in the upfront and relapsed setting, but it also makes accrual to clinical trials more difficult, and leads to a delay in moving experimental regimens into the clinic.

In this study we will rapidly test a variety of immunotherapy combinations with rituximab in small cohorts of patients with untreated and relapsed follicular lymphoma in order to identify regimens with a promising efficacy and safety profile to explore further in a larger clinical trial. By enrolling patients sequentially into cohorts testing different immunotherapy combinations in the relapsed setting, and quickly moving combinations that meet a pre-specified safety and efficacy benchmark into testing in the upfront setting we will be able to identify combinations that are worth further exploration, either in cohort expansion within the current study, or in a larger clinical trial. The parallel testing in both the relapsed/refractory and upfront testing will

substantially shorten the duration of the study so that the results will be clinically useful and meaningful in a disease with a long natural history with many available treatment options.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Patients must have histologically determined follicular lymphoma, grade 1-3A, with pathologic review at the participating institutions, that has either:

- Relapsed or primary refractory after at least one line of therapy including anti-CD-20 monoclonal antibody treatment (part A) or;
- Has had no previous anti-lymphoma therapy other than corticosteroids or radiotherapy (part B).

3.1.2 Patients with active histologic transformation are excluded. Relapsed/refractory patients with prior transformation may be included as long as there is no evidence of transformation at the time of study entry by pathology, imaging, or clinical status

3.1.3 Patients in part B, without prior anti-lymphoma therapy, must be in need of treatment as defined by any of the following criteria:

- Symptomatic adenopathy
- Organ function impairment due to disease involvement, including cytopenias due to marrow involvement (WBC $<1.5x10^9$/L; absolute neutrophil count [ANC] $<1.0x10^9$/L, Hgb <10g/dL; platelets $<100x10^9$/L)
- Constitutional symptoms
- Maximum diameter of disease $\geq$ 7cm
- $\geq$3 nodal sites of involvement
- Risk of local compressive symptoms
- Splenomegaly (craniocaudal diameter $\geq$ 16cm on CT imaging)
- Clinically significant pleural or peritoneal effusion
- Leukemic phase ($>5x10^9$/L circulating malignant cells)
- Rapid generalized disease progression
- Renal infiltration
- Bone lesions

3.1.4 Patients may have had a prior autologous stem cell transplant and may have been treated with autologous chimeric antigen receptor T-cells (CAR T-cells).

3.1.5 Not in need of urgent cytoreductive therapy in the opinion of the investigator

3.1.6 Measurable disease that has not been previously irradiated on CT scans of at least 1.5 cm, OR if the patient has had previous radiation to the marker lesion(s), there must be evidence of progression since the radiation. Imaging must be completed no greater than 6 weeks prior to study enrollment.

3.1.7 Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (see Appendix A)

3.1.8 Adequate hematologic and organ function:

- Absolute neutrophil count $\geq$ $1.0x10^9$/L unless due to marrow involvement by lymphoma in which case ANC must be $>0.5x10^9$/L
- Platelets > 75 $x10^9$/L, unless due to marrow involvement by lymphoma, in which case platelets must be >50 $x10^9$/L
- Creatinine < 1.5 x ULN (upper limit of normal) or estimated GFR > 40ml/min
- Total bilirubin < 1.5 X ULN, unless Gilbert syndrome, in which case direct bilirubin must be < 3 x ULN

3.1.9 AST/ALT < 2.5 X ULN, unless documented liver involvement by lymphoma, in which case AST/ALT must be <5 x ULN

3.1.10 Age $\geq$18 years

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

3.1.12 Willingness to provide pre-treatment (or recent archival w/o intervening therapy), and on-treatment tumor samples by core needle or excisional surgical biopsy

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not eligible for admission into the study:

3.2.1 Patients currently receiving anticancer therapies or who have received anticancer therapies within 28 days of the start of study drug (including chemotherapy, radiation therapy, antibody based therapy, etc.), or 56 days for radioimmunotherapy. Steroids for symptom palliation are allowed, but must be either discontinued or on stable doses of $\leq$ 10mg daily of prednisone (or the equivalent) at the time of initiation of protocol therapy.

3.2.2 Patients may not be receiving any other investigational agents, or have received investigational agents within 4 weeks (or 3 half-lives, whichever is longer) of beginning treatment.

3.2.3 History of severe allergic or anaphylactic reactions to monoclonal antibody therapy unless in consultation with an allergy specialist they are deemed eligible for retreatment with desensitization.

3.2.4 Patients who have previously received therapy with any drug that works by a similar mechanism of action as any drug being tested in a given cohort will be excluded from that cohort but will be allowed to enroll in other open cohorts.

3.2.5 Patients who have undergone prior allogeneic stem cell transplantation

3.2.6 Patients with a history of or active autoimmune disease (except controlled asthma, Hashimoto thyroiditis, atopic dermatitis, and/or vitiligo), or requiring systemic corticosteroids at a dose of 10mg prednisone equivalent daily. Patients with a history of autoimmune disease who never required corticosteroids and with no evidence of disease activity, and in whom the risk of reactivation is felt not to be serious, may be enrolled after discussion with the overall study chair. Exceptions to this are patients with a history of inflammatory bowel disease (ulcerative colitis and Crohn's disease). These patients are excluded regardless of whether their disease is active or inactive.

3.2.7 Patients with active pneumonitis or colitis, or patients with chronic liver disease and/or cirrhosis

3.2.8 Patients, who have had a major surgery or significant traumatic injury within 4 weeks of start of study drug, patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia) or patients that may require major surgery during the course of the study.

3.2.9 Patients with known leptomeningeal or brain metastases. Imaging or spinal fluid analysis to exclude CNS involvement is not required, unless there is clinical suspicion by the treating investigator.

3.2.10 Patients with known HIV infection or hepatitis B or C infection. Testing for HIV is optional. Testing for hepatitis B and C is mandatory. Patients with hepatitis B core Ab positivity but negative surface antigen and negative viral load may be enrolled if they can be treated with a prophylactic agent (eg, entecavir); patients with hepatitis C seropositivity who have undergone successful treatment with negative viral load can also be enrolled.

3.2.11 Patients with a systemic fungal, bacterial, viral, or other infection not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).

3.2.12 Prior history of another malignancy (except for non-melanoma skin cancer or *in situ* cervical or breast cancer) unless disease free for at least three years. Patients with prostate cancer are allowed if PSA is less than 1.

3.2.13 Patients should not have received immunization with attenuated live vaccine within one week of study entry or during study period.

3.2.14 Female patients who are pregnant or breast feeding, or adults of reproductive potential who are not using effective birth control methods. Women of child bearing potential (WOCBP) or male study participants of reproductive potential must agree to use double barrier birth control method of contraception during the course of the study treatment period and for 3 months after completing study treatment. WOCBP are defined as sexually mature women who have not undergone a hysterectomy or who are not postmenopausal (no menses) for at least 12 consecutive months. WOCBP must have a negative urine or serum pregnancy test within 14 days prior to administration of treatment.

3.2.15 History of noncompliance to medical regimens.

3.2.16 Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:

- New York Heart Association Class III or IV cardiac disease, including pre-existing clinically significant arrhythmia, congestive heart failure, or cardiomyopathy
- Patients with a history of previous anthracycline treatment and are at risk of cardiac failure (New York Heart Association Class II or above) are excluded from cohorts A2, A3, and B2 (cohorts that include PF-04518600)
- Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction within 6 months of start of study drug, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease

3.2.17 Patients with any one of the following currently on or in the previous 6 months will be excluded from cohorts A2, A3, and B2 (any cohort that includes treatment with PF-04518600) myocardial infarction, congenital long QT syndrome, torsade's de points, left anterior hemiblock (bifascicular block), unstable angina, coronary/peripheral artery bypass graft, cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism or other clinically significant episode of thrombo-embolic disease*. Ongoing cardiac dysrhythmias of NCI CTCAE grade $\geq$ 2, atrial fibrillation of any grade, or QTcF interval >470msec at screening (except in case of right bundle branch block, these cases must be discussed with the principal investigator). *Cases must be discussed in detail with the principal investigator to judge eligibility. Anticoagulation (heparin only, no vitamin K antagonists or factor Xa inhibitors will be allowed if indicated.

3.2.18 Other uncontrolled intercurrent illness that would limit adherence to study requirements.

3.3 Inclusion of Women and Minorities

Women, minorities and underrepresented populations should be eligible for this trial at a similar rate to men and patients not from underrepresented populations. The inclusion and exclusion criteria should not be affected by gender or ethnicity, except for the exclusion of pregnant or lactating women.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention 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 may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

4.3 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 the Project Manager at Samantha_Pazienza@dfci.harvard.edu to verify dose level availabilities.

Following registration, participants should begin protocol therapy within 72 hours or as soon as possible. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. The Project Manager should be notified of participant status changes as soon as possible. Except in very unusual circumstances, each Participating Institution will order the study agent(s) directly from the supplier. A Participating Institution may order the agent(s) only after the initial IRB approval for the site has been forwarded by Coordinating Center to the supplier.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the participating site and or e-mailed to Samantha_Pazienza@dfci.harvard.edu:

- Copy of required laboratory tests required at screening (see study calendar)
- Signed informed consent document
- HIPAA authorization form (if separate from the informed consent document)

- Completed Eligibility Checklist

The participating site will then e-mail Samantha_Pazienza@dfci.harvard.edu to verify eligibility. The Project Manager will follow DF/HCC policy (REGIST-101) and register the participant on the protocol. The Project Manager will e-mail the participant study number, and if applicable the dose treatment level, to the participating site. The Project Manager will also contact the participating site and verbally confirm registration

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

5. TREATMENT PLAN

5.1 Study Design

This study will consist of 3 cohorts (A1-A3) in the relapsed/refractory setting tested in two stages: 1) dose escalation and 2) dose expansion. If a combination meets prespecified safety and efficacy endpoints in the expansion stage, and after discussion with regulatory authorities, 2 additional cohorts (B1, B2) will open testing these combinations in the upfront setting in previously untreated FL patients.

The cohorts for this study will be as follows:

- Dose escalation stage:

		Rituximab (or rituximab biosimilar)	**Utomilumab**	**Avelumab**	**PF-04518600**
Cohort A1a	*Dose Level 1*	375mg/m2 IV q7d for 4 doses (cycle 1 only)	100mg IV q28d cycle 1-6	3mg/kg IV q14d cycle 1-6	n/a
	Dose Level 2	375mg/m2 IV q7d for 4 doses (cycle 1 only)	100mg IV q28d cycle 1-6	10mg/kg IV q14d cycle 1-6	n/a
Cohort A2a	*Dose Level 0*	n/a	n/a	n/a	0.3mg/kg IV q14d cycle 1-6
	Dose Level 1	375mg/m2 IV q7d for 4 doses (cycle 1 only)	n/a	n/a	0.3mg/kg IV q14d cycle 1-6
	Dose Level 2	375mg/m2 IV q7d for 4 doses (cycle 1 only)	100mg IV q28d cycle 1-6	n/a	0.3mg/kg IV q14d cycle 1-6
Cohort A3a	*Dose Level 1*	375mg/m2 IV q7d for 4 doses (cycle 1 only)	n/a	3mg/kg IV q14d cycle 1-6	0.3mg/kg IV q14d cycle 1-6
	Dose Level 2	375mg/m2 IV q7d for 4 doses (cycle 1 only)	n/a	10mg/kg IV q14d cycle 1-6	0.3mg/kg IV q14d cycle 1-6

- Dose Expansion Cohorts
    - Cohort A1b: Rituximab (or rituximab biosimilar), utomilumab, avelumab at the recommended phase 2 dose
    - Cohort A2b: Rituximab (or rituximab biosimilar), utomilumab, PF-04518600 at the recommended phase 2 dose
    - Cohort A3b: Rituximab (or rituximab biosimilar), avelumab, PF04516800 at the recommended phase 2 dose
- Upfront Cohorts (B1, B2) (n=up to 15)
    - Cohort B1: Rituximab (or rituximab biosimilar), utomilumab, avelumab at the recommended phase 2 dose
    - Cohort B2: Rituximab (or rituximab biosimilar), utomilumab, PF-04518600 at the recommended phase 2 dose

Enrollment will begin with the phase 1 dose escalation stage to test the safety of these combinations in relapsed/refractory FL and to determine the recommended phase 2 dose (RP2D) to use for the phase 1b dose expansion cohorts as well as for the potential upfront cohorts. The cohorts in the phase 1 dose escalation stage will follow a 3+3 dose escalation schema, such that there will be a safety pause and evaluation after the first 3 patients at any given dose level have completed 6 weeks of therapy. If there are no dose limiting toxicities (DLTs) seen, the next dose level will open. If there is 1 DLT, an additional 3 patients will be enrolled at that dose level with a safety pause and evaluation after all 3 have completed 6 weeks of treatment. If there are 2 or more DLTs at any time in a given dose level, no further testing of that dose level will be done. If, however, there are no additional DLTs at that dose level, the next dose level will open. The next dose levels will follow the same 3+3 dose escalation schema (**Schema 1**). Once a recommended phase 2 dose is determined, this dose will be used in both the dose expansion cohorts as well as in the potential upfront dosing cohorts.

Enrollment will begin with cohorts A1a, dose level 1, and A2a, dose level 0 in an alternating fashion. Each subsequent cohort will be filled sequentially beginning with cohort A1a dose level 2, followed by cohort A2a dose level 1, then A2a dose level 2, then A3a dose level 1, and finally A3a dose level 2. If a patient is not eligible for the cohort that is being filled preferentially at the time of enrollment due to prior treatment history, they may be enrolled in the next cohort for which they are eligible. Note, if a patient in cohort A2a, dose level 0, has not had a response by the midtreatment response assessment following cycle 3, they will be allowed to received rituximab 375mg/m2 q7d for 4 weeks during cycle 4 (C4D1, C4D8, C4D15, C4D22).

Dose limiting toxicities (DLTs) are defined as any grade 3 or greater toxicity unless directly, and incontrovertibly, related to progressive disease with the exception of the following:

- Grade 3 hematologic abnormalities
- Grade 4 hematologic abnormalities that recover to grade 2 or lower with supportive treatment (including transfusion, IVIg, or growth factor) within 7 days
- Non-hematologic abnormalities:
    - Transient (≤24 hours) Grade 3 fatigue, local reactions, or headache that resolves to Grade ≤1;
    - Grade 3-4 nausea and vomiting controlled by optimal medical therapy within 72 hours;

  - Grade 3 hypertension controlled by medical therapy;
  - Grade 3 diarrhea that improves to Grade ≤2 within 72 hrs after medical management has been initiated;
  - Grade 3 skin toxicity that resolves to Grade ≤1 in less than 7 days after medical management (eg, immunosuppressant treatment) has been initiated;
  - Any Grade ≥3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis;
  - Grade 3 endocrinopathies controlled with medical therapy;
  - Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
- Non-hematologic Grade ≥3 laboratory abnormality if medical intervention is required to treat the patient or the abnormality leads to hospitalization.
  - Single laboratory values out of normal range that are unlikely related to trial treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤1 within 7 days with adequate medical management are not to be considered DLTs;
- ALT or AST >3 x upper limit of normal (ULN) (if normal at baseline) or >3 x ULN and doubling the baseline (if > ULN at baseline) associated with bilirubin >2 x ULN

For part B (untreated disease cohorts), enrollment will open following the completion of the corresponding dose expansion cohort in part A (cohorts A1b and A2b), assuming that the corresponding cohort in part A meets its efficacy and safety criteria for success ($\geq$ 3 complete responses and $\leq$ 3 DLTs).

All cohorts in part B will have an early stopping rule if >2 patients at any point meet the criterion for a DLT.

Toxicity will be continuously monitored and recorded using CTCAE 4 criteria, up to 30 days following the last dose of the study treatment or until resolution of toxicity to grade 1 or baseline, whichever occurs last. Response will be assessed 4-6 weeks after the completion of therapy (either after cycle 6 of therapy for patients who complete the planned cycles of therapy, or after their last dose of treatment for patients who discontinue treatment before cycle 6) by PET and CT scans of the neck (if involved at baseline), chest, abdomen, and pelvis, as well as at 6, 12, and 18 months from the end of treatment (+/- 2 weeks) in the absence of disease recurrence or progression (PET may be omitted once patient is in CR). In addition, CT scans of the chest, abdomen, and pelvis +/- neck will be obtained 4 weeks (+/- 1 week) after the completion of cycle 3 while on therapy. If patients experience evidence of progressive disease confirmed by imaging while on treatment, they will be allowed to complete treatment if they meet the definition of an indeterminate response according to LyRIC criteria.[2]

Expected toxicities and potential risks for all drugs are described in Section 6 (Dosing Delays/Dose Modifications). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.2 Treatment Regimen

It is expected that treatment will be administered on an outpatient basis. A cycle will be 28 days and there will be a planned 6 cycles of therapy. Therapy will consist of the following, with each cohort consisting of 15 patients each:

5.2.1 Cycle 1

Cohort A1a:

(i) Rituximab (or rituximab biosimilar) 375 mg/m^2/dose intravenously per institutional standards for four weekly treatments for cycle 1 only, starting on day -6.
(ii) Utomilumab 100mg intravenously over 1 hour on day 2.
(iii) Avelumab 3mg/kg (dose level 1) or 10mg/kg (dose level 2) intravenously over 1 hour on day 16.

Cohort A1b and B1:

(i) Rituximab (or rituximab biosimilar) 375 mg/m^2/dose intravenously per institutional standards for four weekly treatments for cycle 1 only, starting on day -6.
(ii) Utomilumab 100mg intravenously over 1 hour on day 2.
(iii) Avelumab at the recommended phase 2 dose intravenously over 1 hour on day 16.

Cohort A2a, Dose Level 0:

(i) PF-04518600 0.3mg/kg intravenously over 1 hour on day 1 and day 15.

Cohort A2a, Dose Level 1:

(i) Rituximab (or rituximab biosimilar) 375 mg/m^2/dose intravenously per institutional standards for four weekly treatments for cycle 1 only, starting on day -6.
(ii) PF-04518600 0.3mg/kg intravenously over 1 hour on day 2 and day 16.

Cohort A2a, Dose Level 2:

(i) Rituximab (or rituximab biosimilar) 375 mg/m^2/dose intravenously per institutional standards for four weekly treatments for cycle 1 only, starting on day -6.
(ii) Utomilumab 100mg intravenously over 1 hour on day 2.
(iii) PF-04518600 0.3mg/kg intravenously over 1 hour on day 16.

Cohort A2b and B2:

(i) Rituximab (or rituximab biosimilar) 375 mg/m^2/dose intravenously per institutional standards for four weekly treatments for cycle 1 only, starting on day -6.
(ii) Utomilumab 100mg intravenously over 1 hour on day 2.
(iii) PF-04518600 0.3mg/kg intravenously over 1 hour on day 16.

Cohort A3a:

(i) Rituximab (or rituximab biosimilar) 375 mg/m^2/dose intravenously per institutional standards for four weekly treatments for cycle 1 only, starting on day -6.

(ii) PF-04518600 0.3mg/kg intravenously over 1 hour on day 2 and day 15. PF-04518600 will be given first and must have completed administration at least 30 minutes (but a maximum of 28 hours) prior to rituximab (day 15)
(iii) Avelumab 3mg/kg (dose level 1) or 10mg/kg IV (dose level 2) over 1 hour on day 16.

Cohort A3b:
(i) Rituximab (or rituximab biosimilar) 375 mg/m^2/dose intravenously per institutional standards for four weekly treatments for cycle 1 only, starting on day -6.
(ii) PF-04518600 0.3mg/kg intravenously over 1 hour on day 2 and day 15. PF-04518600 will be given first and must have completed administration at least 30 minutes (but a maximum of 28 hours) prior to rituximab (day 15)
(iii) Avelumab at the recommended phase 2 dose intravenously over 1 hour on day 16.

5.2.2 Cycle 2-6

Cohort A1a:
(i) Utomilumab 100mg intravenously over 1 hour once every 4 weeks x 5 (up to 5 additional doses) on day 1 of each cycle. Utomilumab must have completed administration at least 30 minutes (but a maximum of 28 hours) prior to avelumab.
(ii) Avelumab 3mg/kg (dose level 1) or 10mg/kg (dose level 2) intravenously over 1 hour once every 2 weeks x 10 (up to 10 additional doses), on day 1 and day 15 of each cycle. On days when avelumab will be given in combination with utomilumab it must be given at least 30 minutes (maximum 24+/-4 hours) following the completion of utomilumab.

Cohort A1b and B1:
(i) Utomilumab 100mg intravenously over 1 hour once every 4 weeks x 5 (up to 5 additional doses) on day 1 of each cycle. Utomilumab must have completed administration at least 30 minutes (but a maximum of 28 hours) prior to avelumab.
(ii) Avelumab at the recommended phase 2 dose intravenously over 1 hour once every 2 weeks x 10 (up to 10 additional doses), on day 1 and day 15 of each cycle. On days when avelumab will be given in combination with utomilumab it must be given at least 30 minutes (maximum 24+/-4 hours) following the completion of utomilumab.

Cohort A2a, Dose level 0:
(i) PF-04518600 0.3mg/kg intravenously over 1 hour on day 1 and day 15.
***If there is no response on midtreatment scans following cycle 3, patients may get Rituximab (or rituximab biosimilar) 375mg/m2 intravenously on day 1, 8, 15, and 22 of cycle 4, with PF-04518600 0.3mg/kg intravenously over 1 hour on day 1 and day 15 of this cycle. On days when rituximab will be given in combination with PF-04518600 it must be given at least 30 minutes (maximum 28 hours) following the completion of PF-04518600.*

Cohort A2a, Dose level 1:
(i) PF-04518600 0.3mg/kg intravenously over 1 hour on day 1 and day 15.

Cohort A2a, Dose level 2:

(i) Utomilumab 100mg intravenously over 1 hour once every 4 weeks x 5 (up to 5 additional doses), on day 1 of each cycle. Utomilumab must have completed administration at least 30 minutes (but a maximum of 28 hours) prior to PF-04518600.

(ii) PF-04518600 0.3mg/kg intravenously over 1 hour once every 2 weeks x 10 (up to 10 additional doses), on day 1 and day 15 of each cycle. On days when PF-04518600 will be given in combination with utomilumab it must be given at least 30 minutes (maximum 28 hours) following the completion of utomilumab.

Cohort A2b and B2:

(i) Utomilumab 100mg intravenously over 1 hour once every 4 weeks x 5 (up to 5 additional doses), on day 1 of each cycle. Utomilumab must have completed administration at least 30 minutes (but a maximum of 28 hours) prior to PF-04518600.

(ii) PF-04518600 0.3mg/kg intravenously over 1 hour once every 2 weeks x 10 (up to 10 additional doses), on day 1 and day 15 of each cycle. On days when PF-04518600 will be given in combination with utomilumab it must be given at least 30 minutes (maximum 28 hours) following the completion of utomilumab.

Cohort A3a:

(i) PF-04518600 0.3mg/kg intravenously over 1 hour once every 2 weeks x 10 (up to 10 additional doses), on day 1 and day 15 of each cycle. PF-04518600 will be given first and must have completed administration at least 30 minutes (but a maximum of 28 hours) prior to avelumab

(ii) Avelumab 3mg/kg (dose level 1) or 10mg/kg (dose level 2) intravenously over 1 hour once every 2 weeks x 10 (up to 10 additional doses), on day 1 and day 15 of each cycle. Avelumab will be given at least 30 minutes (maximum 28 hours) following the completion of PF-04518600.

Cohort A3b:

(ii) PF-04518600 0.3mg/kg intravenously over 1 hour once every 2 weeks x 10 (up to 10 additional doses), on day 1 and day 15 of each cycle. PF-04518600 will be given first and must have completed administration at least 30 minutes (but a maximum of 28 hours) prior to avelumab

(iii) Avelumab at the recommended phase 2 dose intravenously over 1 hour once every 2 weeks x 10 (up to 10 additional doses), on day 1 and day 15 of each cycle. Avelumab will be given at least 30 minutes (maximum 28 hours) following the completion of PF-04518600.

5.3 General Concomitant Medication and Supportive Care Guidelines

Medications or vaccinations specifically prohibited in the exclusion criteria are also not allowed during the active treatment period, except for administration of inactivated vaccines (for example, inactivated influenza vaccine). If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, permanent discontinuation from study therapy may be required. The Investigator should consult with the Principal investigator about individual cases. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician. However, the decision to continue the patient on study therapy or medication/vaccination schedule requires the mutual agreement of the Investigator, the Principal investigator, and the patient. Prior/concomitant treatment considered necessary for the patient's well-being may be given at discretion of the treating physician.

Concomitant medications and treatments, including herbal supplements, will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment (at Days 30, 60, and 90 post-treatment +3 days). Non-Drug Supportive Interventions should be recorded in the CRF including supportive care drugs (eg, antiemetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).

Medications intended solely for supportive care (ie, antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

5.3.1 Pre-medications

Participants will be premedicated as outlined in Section 8.1.2.8 prior to each dose of avelumab and by institutional standards prior to each dose of rituximab, or as needed for utomilumab and/or PF-04518600. On days when patients are receiving multiple infusions, premedications do not need to be redosed prior to subsequent infusions unless it has been > 4 hours since their previous administration or since administration of medications to treat a hypersensitivity reaction.

5.3.2 Antibiotics

Prophylactic antibiotics or anti-virals are not required on this trial.

5.3.3 Hydration

No pre-hydration or hydration is required with this regimen.

5.3.4 Tumor lysis prevention and management

Participants with bulky disease (>10cm in maximal tumor diameter) and/or circulating disease ≥ 25,000 circulating malignant cells/ mm^3 will receive allopurinol 300mg orally daily for 14 days starting with the first dose of rituximab. All participants will have a complete metabolic panel, phosphorus, LDH and uric acid checked pre-treatment and at each study visit in cycle 1. For

patients deemed at risk for tumor lysis syndrome (TLS) these labs will also be monitored more closely according to institutional practices. The management of established tumor lysis (see appendix B for definition and grading of tumor lysis) should follow standard institutional practice.

5.3.5 Other supportive treatments

Growth factors, blood product transfusions, and the use of bisphosphonates are permitted at the discretion of the treating physician.

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to any available American Society of Clinical Oncology (ASCO) guidelines.

Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator including but not limited to the items outlined below:

- Diarrhea: All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion;
- Nausea/Vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.
- Anti-infectives: Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice. Prophylactic administration should be considered for the cases outlined in Table 2, Management of Immune Related Adverse Events;
- Anti-inflammatory or narcotic analgesics may be offered as needed.

Patients who need to be on anticoagulant therapy during treatment should be treated with low molecular weight heparin. If low molecular weight heparin cannot be administered, coumadin or other coumadin derivatives or other anticoagulants (including direct Xa inhibitors) may be allowed; however, appropriate monitoring of prothrombin time/international normalized ratio (PT/INR) should be performed.

5.3.6 Other Prohibited Concomitant Medications and Treatments

Patients are prohibited from receiving the following therapies during the treatment phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Investigational agents other than avelumab and utomilumab.
- Radiation therapy.

- Immunosuppressive drugs, unless otherwise indicated for the treatment of irAEs and for premedication (see Table 2 and Clarification About Steroid Use below), or for treatment of issues unrelated to study drug after consultation with study chair.
- Medications or vaccinations specifically prohibited in the exclusion criteria are also not allowed during the active treatment period; however, the administration of inactivated vaccines (eg, influenza vaccine) is allowed during the study.
- Herbal remedies or vitamins used as anticancer treatments.
- Herbal remedies with immunostimulating properties (eg, mistle toe extract) or known to potentially interfere with major organ function (eg, hypericin).
- Daily intake over 2 grams acetaminophen/paracetamol.

Clarifications About Steroid Use with Utomilumab, Avelumab and/or PF-04518600: Data have indicated that corticosteroids have an adverse effect on T-cell function and that they inhibit and damage lymphocytes.[23] Furthermore, as with all immunotherapies intended to augment cell mediated immunity, there is a risk that concomitant immunosuppressives such as steroids will counteract the intended benefit of the proposed study treatment. However, studies with anti-CTLA-4 compounds have indicated that short-term use of steroids may be employed without compromising clinical outcomes.[24] Therefore, the use of steroids during this trial is restricted as follows:

- Therapeutic use: for the treatment of infusion related reactions, premedication for the prevention of an infusion reaction, and short-term treatment of irAEs, steroids are permitted according to the modalities indicated in Table 2: Management of Immune-Related Adverse Events.
- Physiologic use: steroid replacement for adrenal insufficiency at doses equivalent to ≤10 mg prednisone daily is acceptable.

5.4 Criteria for Taking a Participant Off Protocol Therapy

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 for 25 weeks or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation 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 case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

5.5 Duration of Follow Up

Patients who complete treatment or come off treatment for reasons other than progressive disease (PD) will have active follow up through 24 months or until death, PD, or next treatment, whichever comes first. After 24 months, PD, or next treatment, patients will enter survival follow up. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.6 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 for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

6. DOSING DELAYS/DOSE MODIFICATIONS

Every effort should be made to administer investigational products using the planned dose and schedule.

Dose modifications may occur in one of two ways during study conduct:

- Within a cycle, dosing may be interrupted until adequate recovery from toxicities;
- Next cycle administration may be delayed due to persisting toxicity when a new cycle is due to commence.

Patients whose treatment is delayed due to adverse events should be evaluated at intervals of one week or less until adequate recovery has been documented or no further improvement is expected. No dose reductions are allowed for avelumab, utomilumab, PF-04518600, or rituximab. Intra-patient dose escalation is not allowed for any of the study drugs at any time.

Any suspected immune-related adverse event should be managed according to the Management of Immune Related Adverse Events (irAEs) guidance (see Table 2).

The same irAEs management guidelines will apply to utomilumab, avelumab and PF-04518600. In addition, in the event of an irAE, dosing with rituximab should continue per protocol if

applicable for the current cycle, but may be interrupted for the same duration as utomilumab, avelumab, and/or PF-04518600, or for longer at the discretion of the Investigator, following prior discussion with the Principal investigator.

In the event of significant toxicity; dosing may be delayed and/or reduced as outlined below. In the event of multiple toxicities, dose modifications should be based on the worst observed toxicity. Patients must be instructed to notify Investigators at the first occurrence of any adverse symptom/s.

All treatment modification recommendations must be followed unless previously discussed with and agreed by the Principal investigator. All dose modifications/adjustments must be clearly documented in the patient's notes and in the CRF.

6.1 Special Precautions for Avelumab Administration

As with all monoclonal antibody therapies, there is a risk of allergic reaction including anaphylactic shock.

In order to mitigate the risk of avelumab related infusion-related reactions, a pre-medication regimen comprising 25 to 50 mg IV (or oral equivalent) diphenhydramine, and 650 mg IV (or oral equivalent) acetaminophen/paracetamol (per local practice) is mandatory and should be administered approximately 30 to 60 minutes prior to each dose of avelumab. This may be modified, as appropriate, according to local treatment practice and guidelines.

If the avelumab is administered more than 1 hour after the preceding drug and/or if no premedication has already been administered, then the premedication must be repeated and/or initiated. The line should be flushed, according to local practice, between infusions, and a new administration set should be used for avelumab.

Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and 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. Infusion of avelumab will be stopped in case of Grade ≥2 infusion-related, allergic, or anaphylactic reactions. Following avelumab infusion, patients must be observed for 2 hours for potential infusion-related reactions. If an allergic reaction occurs, the patient should be treated according to the best available medical practice. Patients should be instructed to report any delayed reactions to the Investigator immediately. Monitoring may be reduced to 30 minutes after cycle 1 at the investigator's discretion.

Investigators should additionally monitor patients closely for potential irAEs, which may only become apparent following several weeks of treatment. Immune-related adverse events described with this class of drugs include pneumonitis, colitis, hepatitis, endocrinopathies including thyroid disorders (hyperthyroidism, hypothyroidism, thyroiditis), adrenal insufficiency, hypophysitis, and diabetes mellitus, renal dysfunction, encephalitis, eye disorders (uveitis, iritis), myositis and myocarditis. Treatment recommendations for the management of irAEs are

outlined in Section 6.3 and Table 2.

6.2 Management of Avelumab Infusion-Related Reactions

Symptoms may include one or more of the following: fever, chills, rigors, diaphoresis, and headache.

Once the avelumab infusion rate has been decreased by 50% due to an infusion-related reaction, the same decreased infusion rate must be used for all subsequent infusions.

Table 1. Avelumab Treatment Modifications 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 ≤ 24h	• Temporarily discontinue 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 have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment

IV: intravenous; NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs: nonsteroidal anti-inflammatory drugs.

6.2.1 Additional Avelumab Treatment Modifications for Patients with Grade 2 Infusion-Related Reactions

In the event of a Grade 2 infusion-related reaction that does not improve or that worsens following implementation of the modifications indicated in Table 1 (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids per local guidelines, and the infusion should be stopped for that day. At the time of the next cycle, the Investigator may consider adding H2-blocker antihistamines (eg, famotidine or ranitidine) and/or hydrocortisone 100mg IV, or the steroid equivalent, to the mandatory pre-medication.

If the patient has a second infusion-related reaction of Grade ≥2 on the reduced infusion rate, with or without the addition of further medication/s to the mandatory pre-medication, the infusion should be stopped, and the patient discontinued from avelumab treatment.

6.2.2 Management of Avelumab Severe Hypersensitivity Reactions and Flu-Like Symptoms

Symptoms of hypersensitivity may include impaired airway, decreased oxygen saturation (<92%), confusion, lethargy, hypotension, pale or clammy skin, and cyanosis. These symptoms may, if necessary, be managed with epinephrine and dexamethasone. Oxygen therapy should be administered as appropriate. Patients should be immediately placed on a cardiac monitor, and the intensive care unit (ICU) alerted for possible transfer if required. In extreme cases, intubation may be necessary.

For prophylaxis of flu-like symptoms, 25 mg of indomethacin or a comparable nonsteroidal anti-inflammatory drug (NSAID) dose (for example, ibuprofen 600 mg, naproxen sodium 500 mg) may be administered 2 hours prior to and 8 hours after the start of each avelumab IV infusion. Alternative treatments for fever (eg, paracetamol) may be given to patients at the discretion of the Investigator.

6.3 Immune-Related Adverse Events

NOTE: The same irAE management guidelines apply to utomilumab, avelumab and PF-04518600.

As these drugs stimulate the immune system, irAEs may occur. Treatment of irAEs is dependent upon their severity (NCI-CTCAE grade):

- **Grade 1 to 2:** treat symptomatically or with moderate dose steroids, and more frequent monitoring;
- **Grade 1 to 2 (persistent):** manage as per high-grade (ie, Grade 3 to 4) AEs;
- **Grade 3 to 4:** treat with high-dose corticosteroids.

Any event suspected to be immune-related should be managed according to the guidance for management of immune-related adverse events in this section and in Table 2. There are no dose modifications on this protocol of any of the agents. However, treatment may be temporarily or permanently discontinued following the recommendations in Table 2. Also note that the recommendations may be superseded by the judgement of the treating clinician, although this should be discussed with the Study Chair.

Immune-related adverse events described with this class of drugs include: pneumonitis, colitis, hepatitis, endocrinopathies including thyroid disorders (hyperthyroidism, hypothyroidism, thyroiditis), adrenal insufficiency, hypophysitis, and diabetes mellitus or hyperglycemia, rash, nephritis and renal dysfunction, encephalitis, eye disorders (including uveitis, iritis), and other immune-mediated reactions including myositis and myocarditis.

Any adverse event which may have an underlying immune-mediated mechanism including those described above, and without other confirmed etiologies, should be considered immune-related and managed according to guidelines described in this section.

Table 2. Management of Immune Related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue immunotherapy agent Symptomatic treatment (e.g. loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2, 3 or 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	Withhold all immunotherapy agents Symptomatic treatment	If improves to Grade ≤ 1: Resume immunotherapy agents If persists > 5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold all immunotherapy agents for Grade 3. Permanently discontinue immunotherapy agents for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone 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 immunotherapy agents following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue immunotherapy agents Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: Withhold all immunotherapy agents Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume immunotherapy agents 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	Withhold all immunotherapy agents for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤ 1: Taper steroids over at least 1 month; resume immunotherapy agents following steroids taper (for initial Grade 3).
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	Consider withholding all immunotherapy agents Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Withhold all immunotherapy agents Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume all immunotherapy agents following steroids 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 all immunotherapy agents. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1: Taper steroids over at least 1 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 v4)	**Initial Management**	**Follow-up Management**
Grade 1	Continue immunotherapy agents	Continue liver function monitoring If worsens:

Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN		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	Withhold all immunotherapy agents Increase frequency of monitoring to every 3 days.	If returns to Grade ≤ 1: Resume routine monitoring; resume immunotherapy agents. If elevation persists > 5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Permanently discontinue all immunotherapy agents Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or 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 ≤ 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.
Renal irAEs†		
Grade of Creatinine Increased (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue immunotherapy agents	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	Withhold all immunotherapy agents 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	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume immunotherapy agents following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue all immunotherapy agents 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.

ǂFor pts with a baseline Cr 1-1.5x ULN, management of specific changes in Cr are at the discretion of the treating physician

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.	Withhold all immunotherapy agents. 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 per cardiology consult. * Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start immunotherapy agents. 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 all immunotherapy agents. Guideline based supportive treatment as appropriate as per cardiology consult. * 1.0 to 2.0 mg/kg/day prednisone 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. ESC or AHA guidelines
ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines
AHA guidelines website:
http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

Endocrine irAEs

Endocrine Disorder	Initial Management	Follow-up Management
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue immunotherapy agents 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)	Withhold all immunotherapy agents Consider hospitalization Endocrinology consult 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)	Resume all immunotherapy agents 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 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 all immunotherapy agents if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold all immunotherapy agents 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 all immunotherapy agents 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.
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**

Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold all immunotherapy agents pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting all immunotherapy agents If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold all immunotherapy agents 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume all immunotherapy agents following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue all immunotherapy agents 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue all immunotherapy agents 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade ≤ 1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	Permanently discontinue all immunotherapy agents Specialty consult	

6.4 Recommended Treatment Modifications

Dose delays for drug-related non-immune related toxicities related to utomilumab, avelumab, PF-04518600, and rituximab are detailed in Table 3 and Table 4. If a toxicity can be attributed just to one of the drugs in the combination, dose delays can be implemented independently for each drug. In instances where it is not possible to attribute the toxicity to only one of the three drugs, the treatment modifications detailed in Table 3 and Table 4 should be followed for all drugs.

Table 3. Treatment Modifications for Treatment-Related Hematologic Toxicities*

Hematologic Toxicity (NCI CTCAE version 4.03)	Utomilumab	Avelumab	PF-04518600	Rituximab
Grade 1	Continue per schedule	Continue per schedule	Continue per schedule	Continue per schedule
Grade 2	Continue per schedule	Continue per schedule	Continue per schedule	Continue per schedule
Grade 3	Hold treatment up to 4 weeks until Grade ≤1, or baseline then rechallenge. Permanent discontinuation if recurrence to Grade 3 (Unless resolve to Grade ≤1 or baseline within 7 days following appropriate medical management).	Hold treatment up to 4 weeks until Grade ≤1, or baseline, then rechallenge. Permanent discontinuation if recurrence to Grade 3. (Unless resolve to Grade ≤1 or baseline within 7 days following appropriate medical management	Hold treatment up to 4 weeks until Grade ≤1, or baseline, then rechallenge. Permanent discontinuation if recurrence to Grade 3. (Unless resolve to Grade ≤1 or baseline within 7 days following appropriate medical management	Hold treatment up to 4 weeks until Grade ≤1, or baseline, then rechallenge. Permanent discontinuation if recurrence to Grade 3. (Unless resolve to Grade ≤1 or baseline within 7 days following appropriate medical management
Grade 4	Permanent discontinuation (Unless resolve to Grade ≤1, or baseline within 7 days following appropriate medical management).	Permanent discontinuation (Unless resolve to Grade ≤1, or baseline within 7 days following appropriate medical management).	Permanent discontinuation (Unless resolve to Grade ≤1, or baseline within 7 days following appropriate medical management).	Permanent discontinuation (Unless resolve to Grade ≤1, or baseline within 7 days following appropriate medical management).
* Patients with baseline hematologic abnormalities due to lymphoma involvement of the bone marrow or spleen need not follow these guidelines if the ongoing cytopenias are felt to be due to lymphoma. Management of cytopenias in these cases are at the discretion of the treating physician.				

Table 4. Treatment Modifications for Treatment-Related Non-Hematologic Toxicities

Non-Hematologic Toxicity (NCI CTCAE v. 4.03)	Utomilumab	Avelumab	PF-04518600	Rituximab
Progressive multi-focal leuco-encephalopathy (PML) – any grade	Permanently discontinue	Permanently discontinue	Permanently discontinue	Permanently discontinue
Viral Hepatitis B – any grade	Permanently discontinue	Permanently discontinue	Permanently discontinue	Permanently discontinue
Grade ≥3 infection	Permanently discontinue	Permanently discontinue	Permanently discontinue	Permanently discontinue
Grade ≥3 cardiac arrhythmia	Permanently discontinue	Permanently discontinue	Permanently discontinue	Permanently discontinue
Grade ≥3 renal toxicity (eg, acute kidney injury, urine output decreased)	Permanently discontinue	Permanently discontinue	Permanently discontinue	Permanently discontinue

Grade ≥3 muco cutaneous reactions including paraneoplastic pemphigus, Steven Johnson syndrome, lichenoid dermatitis, vesciculobullous dermatitis, and toxic epidermal necrolysis	Permanently discontinue	Permanently discontinue	Permanently discontinue	Permanently discontinue
Any Grade ≥3 liver function test abnormality	Permanently discontinue	Permanently discontinue	Permanently discontinue	Permanently discontinue
Other - Grade 1 or 2	Continue per schedule	Continue per schedule	Continue per schedule	Continue per schedule
Other- Grade 3	Hold until resolved to grade 1 or baseline	Hold until resolved to grade 1 or baseline	Hold until resolved to grade 1 or baseline	Hold until resolved to grade 1 or baseline
Other-Grade 4	Permanently discontinue*	Permanently discontinue*	Permanently discontinue*	Permanently discontinue*
irAEs	See Table 2	See Table 2	See Table 2	
Infusion-related reactions	See section 6.2	See section 6.2	See section 6.2	

*For asymptomatic grade 4 laboratory abnormalities including lipase, amylase, CK elevations, the subject may be restarted on treatment if the abnormality resolves to grade 1 or baseline, in cases where the investigator judges that the benefit of resuming treatment outweighs the risk, and after discussion with the Study Chair.

6.5 Treatment Delays

A new treatment cannot start unless the ANC is ≥1.0 $x10^9$/L, the platelet count is ≥75 $x10^9$/L (or an ANC > 0.5$x10^9$/L and platelets >50$x10^9$/L if due to marrow involvement by the lymphoma), and non-hematologic toxicities have returned to baseline or Grade ≤1 severity.

A new treatment may be delayed for a maximum duration of 4 weeks to allow for ANC and platelet count recovery. In the event that recovery does not occur within 4 weeks, all study drugs must be permanently discontinued. The 4-week recovery window commences on the day of the planned treatment.

If avelumab, utomilumab, and/or PF-04518600 treatment is delayed due to toxicities attributable to avelumab and/or utomilumab or PF-04518600 (eg, pneumonitis or hypothyroidism), rituximab administration does not need to be delayed. If the start of rituximab administration is delayed due to toxicities attributable to rituximab, administration of other drugs does not need to be delayed.

6.6 Dose Reductions

No dose reductions are permitted for utomilumab, avelumab, PF-04518600, or rituximab.

6.7 Management of Immune-Related Adverse Events

The irAE management guidelines outlined in Section 6.3 apply to utomilumab, avelumab and PF-04518600. Any event suspected to be immune related should be managed according to the guidance for management of immune related adverse event in Table 2.

In case of a potential irAE, besides the management related to utomilumab, avelumab and PF-04518600 therapy, rituximab doses may also be modified or interrupted based on the guidance provided for combination toxicity management in Table 3 and Table 4, product labeling and institutional guidelines according to Investigator's best medical judgment.

6.8 Management of Infusion-Related Reactions

For utomilumab and/or PF-04518600, the rates of infusion reactions are rare and no empiric premedication is recommended. If an infusion related reaction occurs following these infusions, the same management guidelines outlined in Section 6.2 for avelumab are applicable.

Rituximab may cause severe, including fatal, infusion reactions. Severe reactions typically occur during the first infusion, with time to onset typically being 30-120 minutes. Patients with pre-existing cardiac or pulmonary conditions, those who have experienced prior cardio-pulmonary adverse reactions, and those with high numbers of circulating malignant cells ($\geq$25,000/mm^3) should be closely monitored. In order to mitigate infusion related reactions, a premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of rituximab (if more than 60 minutes have passed since the completion of the prior infusion and/or if no prior premedication has been given) is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent). This may be modified based on local treatment standards and guidelines, as appropriate.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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 (Section 9) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Events List(s)

7.1.1.1 *Utomilumab*

Frequent (reported in at least 10% of patients):

- Fatigue

Occasional (Between a 1-10% chance that this will happen). These cases were generally mild to moderate:

- Dizziness
- Gastrointestinal symptoms: abdominal pain, decreased appetite, diarrhea, nausea, and/or vomiting

- Anemia
- Thrombocytopenia.
- Back pain
- Chills/Flu-like illness
- Shortness of breath
- Ear discomfort
- Inflammation of the intestines (enterocolitis)
- Eye irritation
- Swelling and pain in the joints
- Headache
- Hypertension
- Hyponatremia
- Insomnia
- Muscle spasm and/or pain
- Sore throat
- Neuropathy
- Pneumonitis
- Fever
- Maculo-papular rash
- Vaginal infection
- Weight loss
- Abnormal liver tests

7.1.1.2 *Avelumab*

Very common (Observed in greater than or equal to 10% of patients)

- Infusion reactions
- Fatigue
- Gastrointestinal side effects including diarrhea, constipation, decreased appetite, nausea, belly pain
- Weight loss
- Anemia
- Fever
- Respiratory side effects including cough, shortness of breath
- Swelling of the feet and legs
- Back pain
- Joint pain

Common (Observed in 2-9% of patients)

- Chills and/or fever with or without flu-like symptoms of body aches and weakness
- Hypothyroidism.
- Skin symptoms including itchy skin, rash
- Abnormal liver function tests
- Muscle pain

- Weakness
- Headache

Side effects resulting from an increased activity of the immune system following treatment with avelumab have also been observed. Most of these side effects are reversible, which means they will stop once treatment with avelumab is discontinued, however in some cases these reactions may be severe (approximately 2% of patients) and could lead to death in rare cases. The reactions that are more severe may require treatment with drugs that decrease the immune system function, also called immunosuppressant drugs (like corticosteroids or more potent drugs, such as infliximab). The side effects resulting from an increased activity of the immune system that were observed in patients receiving avelumab include the following:

Immune side effects observed in less than 1% of patients:

- Inflammation of the liver
- Adrenal insufficiency
- Uveitis
- Myositis
- Myocarditis or pericarditis
- Nephritis
- Diabetes
- Guillain-Barre syndrome

Immune side effects observed in 1% to less than 5% of patients:

- Pneumonitis
- Colitis

Immune side effects observed in 5% to less than 10% of patients:

- Inflammation of the skin (could include skin rash, itchy skin, redness or blisters in the skin)
- Autoimmune thyroid dysfunction

7.1.1.3 *PF-04518600*

<u>Common (10-50%)</u>

- Fatigue
- Fever
- Gastrointestinal symptoms: Nausea, vomiting, constipation, diarrhea, abdominal pain
- Anorexia
- Abnormalities in liver function tests
- Respiratory symptoms: shortness of breath, cough
- Itching of the skin
- Headache
- Insomnia
- Anemia

Rare (<1%-10%)

- Chills
- Congestive heart failure
- Dry mouth
- Hypophosphataemia
- Muscle pain (myalgia)
- Pain (whole body)
- Proteinuria
- Rash

7.1.1.4 *Rituximab*

Common (>20%)

- Nausea
- Infusion reactions. This risk is greatest with the first infusion.
- Fatigue

Occasional (4-20%)

- Anemia
- Bruising or bleeding
- Leukopenia
- Diarrhea
- Vomiting
- Body and/or joint pain
- Cough
- Stuffy nose
- Rash, itching or hives
- Increased blood sugar
- Dizziness

Rare (<4%)

- Stevens-Johnson syndrome
- Pneumonitis
- Viral infections including hepatitis in participants who are carriers of the hepatitis virus
- Progressive multifocal leukoencephalopathy (PML)
- Tumor lysis syndrome
- Abnormal heartbeat

7.1.2 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 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 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 Package Insert, the Investigator Brochure or is included in the informed consent document as a potential risk.
  - **Unexpected** adverse events are those not listed in the Package Insert (P.I.) or 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

7.2 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 adverse event (AE) 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.

The study period, during which AEs and SAEs must be reported, begins after starting the first dose of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to study treatment. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be assessed and reported, when appropriate. Abnormal laboratory values will not be reported unless deemed to be clinically significant. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to study therapy, expectedness, and actions taken.

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events. These requirements are delineated for 3 types of events: (1) SAEs;

(2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

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.

7.2.1 DF/HCC Adverse Event Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

Table 5. DF/HCC Reportable Adverse Events(AEs)

Attribution	Gr. 2 & 3 AE Expected	Gr. 2 & 3 AE Unexpected	Gr. 4 AE Expected	Gr. 4 AE Unexpected	Gr. 5 AE Expected or Unexpected
Unrelated Unlikely	Not required	Not required	10 working days#	10 working days	24 hours*
Possible Probable Definite	Not required	10 working days	10 working days#	10 working days	24 hours*

If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.

* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.

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

7.3 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.

7.4 Expedited Reporting to Pfizer

Within 24 hours of first awareness of the event (immediately if the event is fatal or life-threatening), the study team will report to Pfizer by facsimile any Serious Adverse Event

("SAE," as defined below) for which reporting is required under this provision (as described below). Such SAEs are to be reported for study subjects or individuals otherwise exposed to the Pfizer Product as described below. The study teams should report SAEs as soon as they are determined to meet the definition, even if complete information is not yet available.

Study teams will report SAEs using Form FDA 3500A (MedWatch). The *Reportable Event Fax Cover Sheet* provided by Pfizer must also be included with each SAE submitted.

7.4.1 SAE Definition for Reporting to Pfizer

An SAE is any adverse event, without regard to causality, that is life-threatening (ie, causes an immediate risk of death) or that results in any of the following outcomes: death; in-patient hospitalization or prolongation of existing hospitalization; persistent or significant disability or incapacity (i.e., substantial disruption of the ability to conduct normal life functions); or a congenital anomaly or birth defect. Any other medical event that, in the medical judgment of the Principal Investigator, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above is also considered an SAE. A planned medical or surgical procedure is not, in itself, an SAE.

7.4.2 Exposure During Pregnancy, Exposure During Lactation, Occupational Exposure

Even though there may not be an associated SAE, exposure to Utomilumab, Avelumab, and/or PF-04518600 during pregnancy, exposure to Utomilumab, Avelumab, and/or PF-04518600 during lactation, and occupational exposure to Utomilumab, Avelumab and/or PF-04518600 are reportable to Pfizer.

7.4.3 Hy's Law Cases

Cases of potential drug-induced liver injury as assessed by laboratory test values ("Hy's Law Cases") are also reportable to Pfizer. If a participant develops abnormal values in aspartate transaminase (AST) or alanine transaminase or both, concurrent with abnormal elevations in total bilirubin and no other known cause of liver injury, that event would be classified as a Hy's Law Case.

7.4.4 Exclusions from SAE Reporting Requirements

Specifically excluded from the reporting requirements for SAEs under this provision is any SAE identified in the Protocol as anticipated to occur in the Study population at some frequency independent of drug exposure, unless the Principal Investigator assesses such an event as related to study medication. Also, specifically excluded from the reporting requirements is any SAE judged by the Overall Investigator to represent progression of the malignancy under study, unless it results in death within the SAE Reporting Period.

7.4.5 SAE Reporting Period

The SAEs that are subject to this reporting provision are those that occur from after the first dose

of study medication(s) through 30 calendar days after the last administration of the study medication(s). In addition, if a Principal Investigator becomes aware of an SAE occurring within 30 days of last dose of study medication in Utomilumab and PF-0451600 and within 90 days of avelumab the Principal Investigator should report that SAE to Pfizer if the Principal Investigator suspects a causal relationship between the study drug and the SAE. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents.

7.5 Reporting to Hospital Risk Management

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

7.6 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. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational other agent(s) administered in this study can be found in Section 7.1.

8.1 Investigational Product

Administration of investigational products should be performed by an appropriately qualified, Good Clinical Practice (GCP) trained, and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance. All trial treatments will be administered at the Investigational site.

Investigational product administration details will be recorded on the CRF.

8.1.1 <u>Utomilumab</u>

Utomilumab is an intravenous (IV) fully human IgG2 monoclonal antibody (mAb) that binds to the extracellular domain of human 4-1BB with high affinity and specificity and is capable of 4-1BB agonism. 4-1BB (CD137, TNFRSF9), is a membrane spanning glycoprotein of the Tumor Necrosis Factor (TNF) receptor superfamily. It is 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[25], and activated B cells[26]. 4-1BB expression has also been demonstrated on tumor vasculature[27,28] and atherosclerotic

endothelium.[29] 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.[26] 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.[30] The addition of 4-1BB agonists to in vitro cultures of B lymphoma cells with rituximab and NK cells resulted in increased lymphoma killing.[16] 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.[31] Some members of the TNFRSF can cleave the extracellular domain from the cell surface and exist in a soluble form. Soluble 4-1BB and soluble 4-1BBL have been demonstrated in the serum of some patients with autoimmune diseases and cancers (Michel et al. 1998; Furtner et al. 2005; Hentschel et al. 2006).[32-34]

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.[35]

Numerous studies of murine and human T cells indicate that 4-1BB promotes enhanced cellular proliferation, survival, and cytokine production.[36] 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.[37] 4-1BB agonists also inhibit autoimmune reactions in a variety of autoimmunity models.[38] 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.

Pre-clinical studies have demonstrated activity of utomilumab alone and in combination with mAbs in lymphoma models. Injection with utomilumab has been shown to correlate with tumor cell line growth inhibition in xenogenic tumor models as a single agent. In addition, 4-1BB agonist mAbs demonstrate significant combinatorial efficacy with ADCC antibodies in lymphoma 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.

As a single agent, utomilumab has exhibited the ability to increase lymphocyte proliferation. In

small animal models developed to test the *in vivo* function of utomilumab, utomilumab was able to enhance expansion of human leukocytes in a dose dependent manner as evidenced by an increase in the proportion of human CD45+ cells in the peripheral blood of engrafted mice. Similarly, a dose dependent increase in the proportion of human leukocytes expressing the proliferation marker Ki-67 was noted. In addition, utomilumab treatment of cynomolgus monkeys in single or multiple dose studies increased proliferation among cytotoxic central memory T cells (CD8 TCM) in PBMC samples. Taken together, these data demonstrate evidence of utomilumab's ability to enhance lymphocyte response *in vivo*.

Utomilumab alone has also demonstrated anti-tumor activity in pre-clinical studies. Tumor cell lines representing melanoma, colon, and prostate tumor types were tested in a xenogenic tumor model. None of the tumor lines expressed 4-1BB; therefore, tumor cells were mixed with primary human PBMC from a healthy volunteer donor prior to injection in all cases. Once tumors were established, animals were treated with utomilumab. Utomilumab was found to be efficacious against all 3 tumor types.

Utomilumab has been tested in combination with mAbs in animal models with resultant additive effects on cancer growth and survival. Antibody dependent cellular cytotoxicity (ADCC) has been hypothesized as a mechanism of tumor destruction resulting in direct antigen presentation and in the induction of tumor antigen specific T cell responses ('cross-priming").[39] This is supported by preclinical experiments demonstrating that the therapeutic efficacy of an anti-HER2/neu antibody depends on both innate and adaptive immunity.[40]

The combinatorial anti-tumor activity of ADCC inducing mAb with 4-1BB agonist mAbs was assessed. A mouse anti-mouse CD20 antibody with ADCC inducing activity was selected as a surrogate mAb for rituximab.[41] MAB9371 was selected as a surrogate for utomilumab, as utomilumab does not cross react with murine 4-1BB. MAB9371 is a commercially available rat anti mouse 4-1BB agonist mAb (R & D Systems, Minneapolis MN). The binding affinity of MAB9371 for murine 4-1BB is similar to the affinity of utomilumab for human 4-1BB. In both models, treatment with a combination of surrogate mAbs at concentrations with limited single agent efficacy, showed significant tumor growth inhibition (A20 model) and/or enhanced survival (Eμ-myc model).

8.1.1.1 *Clinical Experience*

The clinical experience with utomilumab has included five phase 1 or phase 1b/2 studies of utomilumab alone or in combination with pembrolizumab, mogamulizumab, avelumab, PF-04518600, or rituximab in advanced solid tumors and B cell non-Hodgkin lymphoma. The first of these studies is the phase 1 study of utomilumab alone in solid tumors, and utomilumab in combination with rituximab in relapsed or refractory CD20 positive NHL.

8.1.1.2 *Pharmacokinetics*

Preliminary PK data following single dose of treatments are available from 81 patients (46 in Portion A (utomilumab monotherapy) and 35 in Portion B (utomilumab + rituximab) from the first in human Phase 1 study B1641001. Following attainment of C_{max}, PF-05082566 serum

concentrations showed a bi-exponential decline with a mean terminal elimination half-life of 208-349 hrs, a low systemic clearance (CL = 0.271-0.372 mL/hr/kg) and a small volume of distribution (Vss = 83.3-231 mL/kg) in Cycle 1 of Portion A. In Portion B, PF-05082566 also showed a bi-exponential decline with a mean terminal elimination half-life of 274-550 hrs, a low systemic clearance (CL = 0.175-0.335 mL/hr/kg) and a small volume of distribution (Vss = 88.4-164 mL/kg). A dose proportional increase in exposure was observed.

Preliminary population PK analysis has been conducted using data from 68 patients (n=41 in Portion A and n=27 from Portion B) receiving utomilumab doses from 0.006 to 5 mg/kg Q4W using serial and sparse PK samples in Study B1641001. A two-compartment model with linear elimination best described these data. Among the covariates tested, both baseline body weight and treatment portion had statistically significant effect on clearance (CL). Baseline body surface area and gender were found to significantly correlate with central volume of distribution (Vc). No other covariates had a statistically significant effect on either CL or Vc. Simulations were performed at various dosing schedules which indicated that the exposure at dose levels higher than 0.12 mg/kg was above the assumed efficacious concentration (Ceff, 1730 ng/mL) with both once every 3 weeks (Q3W) and once Q4W schedule. Although body weight was identified as a significant covariate on CL, it accounted for only a small percentage (~<7%) of the inter-individual variability in serum PF-05082566 exposure. In addition, simulations indicated that utomilumab exposure is similar between body weight based and fixed dosing regimens. Based on these data, and in accordance with emerging data for monoclonal antibodies which reveal that body weight-based dosing regimens do not result in less variability in measures of exposure over fixed dosing regimens, a fixed dosing regimen was proposed for future utomilumab clinical studies.

The flat dose levels chosen for further exploration were based on the following data from Study B1641001. The highest planned dose of 10 mg/kg utomilumab was tested with no DLTs reported in Portion A or in Portion B and no further dose escalation was performed. At utomilumab dose levels of 0.24 mg/kg and above, adequate exposure was achieved based on the simulation and biomarker data [circulating T and natural killer (NK) cells, and soluble 4-1BB] that indicated target modulation can be detected at utomilumab dose levels from 0.24 to 1.2 mg/kg. In addition, early signs of clinical activity were reported with single-agent utomilumab dose levels between 0.24 mg/kg to 0.6 mg/kg in patients with Merkel cell carcinoma (MCC) and melanoma and responses were also observed with the combination of utomilumab and rituximab in NHL at dose levels as low as 0.03 mg/kg with the majority of responses observed at dose levels ≤1.2 mg/kg. Finally, exploratory exposure (dose) response analyses indicated that better efficacy is expected at utomilumab dose levels ≤1.2 mg/kg. Taken these data together, a few dose levels can be further evaluated based on emerging data: 0.24 mg/kg (20 mg) and 1.2 mg/kg (100 mg).

Doses of 20mg and 100mg were tested in single agent and combination studies and based on PK and safety data, a dose of 100mg is being evaluated in all ongoing studies, both single agent and in combination with avelumab and PF-04518600 (see discussions of combinations below).

8.1.1.3 *Immunogenicity*

Levels of anti-drug antibodies (ADA) to utomilumab in human serum were determined using a validated, quasi-quantitative bridging electro chemi-luminescence method. Preliminary analyses

based on quality-controlled, non-quality-assured data are presented. In Portion A, 8 out of 48 (16.7%) patients exhibited positive ADA prior to treatment with utomilumab. Thirty out of 48 patients (63%) were positive for ADA for at least one time point regardless of baseline ADA status. For patients with positive ADA at any time, the maximum fold increase in titer at post-treatment compared to baseline ranged from 1 to 3.1 fold.

In Portion B, 2 out of 39 (5%) patients exhibited positive ADA against utomilumab prior to treatment with utomilumab plus rituximab. Three out of 39 patients (8%) were positive for ADA for at least one time point regardless of baseline ADA status when administered in combination with rituximab. For patients with positive ADA at any time, the maximum fold increase in titer at post-treatment versus baseline ranged from 1 to 1.5 fold.

The impact of ADA on PK of utomilumab was characterized. ADA negative patients were defined as those with negative antibody status for all samples collected during the study including baseline (pre-treatment). ADA positive patients were defined as those with at least positive ADA sample anytime during the study including baseline (pre-treatment). The CL was similar in ADA negative and ADA positive patients suggesting that ADA status had minimal impact on the PK of utomilumab.

8.1.1.4 *Safety*

In Study B1641001, utomilumab was given as a single agent in patients with solid tumors or R/R B-cell lymphoma (Portion A), and was given in combination with rituximab in patients with R/R $CD20^+$ NHL (Portion B). The administered dose levels were 0.006 mg/kg to 10 mg/kg once every 4 weeks (Q4W) for Portion A, and 0.03 mg/kg to 10 mg/kg Q4W for Portion B. The maximum tolerated dose (MTD) for utomilumab was not reached as a single agent or in combination with rituximab. Rituximab was administered only in Cycle 1 at a fixed dose of 375 mg/m^2, once per week for a total of 4 weeks. The first dose of rituximab was administered on Cycle 1 Day (-7) followed by the second dose a week later on Day (0) followed by utomilumab on C1D1. No DLT or Grade 4 or 5 treatment-related AEs were observed in either study portion.

Based on a data cutoff date of 05-May-2015, 47 patients in Portion A (29 male, 18 female, mean age of 59.7) and 40 patients in Portion B (24 male, 16 female, mean age of 60.8) were treated.

A total of 19 (40.4%) patients out of 47 experienced treatment-related AEs in Portion A. The most frequently reported treatment-related AE was pyrexia (5 patients, 10.6%), which was generally mild, followed by fatigue (4 patients, 8.5%), which was mild except for one patient treated at 10 mg/kg, the highest utomilumab dose studied. This case was considered as a Grade 3, non-serious AE.

For Portion B of this study, a total of 18 out of 40 treated patients (45%) experienced treatment-related AEs, with the most common AE being fatigue (22.5% of patients). AEs were mild to moderate, with the exception of one case of Grade 3 thrombocytopenia (platelet count decreased), which lasted less than 7 days, and was not considered as a serious adverse event (SAE).

Additional information for utomilumab may be found in the SRSD, which for this study is the PF-05082566 (utomilumab) Investigator's Brochure (IB).

8.1.1.5 *Efficacy*

The anti-tumor activity of single agent utomilumab in patients with advanced malignancies and utomilumab in combination with rituximab in patients with B-cell NHL is being assessed in Study B1641001. This study does not have a control arm, and tumor responses are reported by Investigators per Response Evaluation Criteria in Solid Tumors (RECIST 1.1)[42] for Portion A patients or International Working Group (IWG) criteria[43] for Portion B. Forty-seven patients in Portion A and 40 patients in Portion B (24 male, 16 female, mean age 60.8 years) have been treated.

In the single-agent portion (Portion A) of the study, best objective responses observed have been 1 CR and 1 PR in Merkel cell carcinoma (MCC) patients who were treated at 0.24 mg/kg and 0.6 mg/kg, respectively.

In patients treated with the combination of utomilumab and rituximab (Portion B), 8 patients with follicular lymphoma (7 patients were refractory to prior rituximab-containing regimen) achieved an objective response: 4 patients achieved a CR (2 treated at 1.2 mg/kg, 1 at 0.12 mg/kg, and 1 at 0.03 mg/kg) and 4 patients achieved a PR (2 treated at treated at 0.18 mg/kg, 1 treated at 1.2 mg/kg, and 1 treated at 5.0 mg/kg). One (1) patient with CD20 + Hodgkin's lymphoma treated at 1.2 mg/kg achieved a PR and 1 patient with Mantle Cell Lymphoma (MCL) treated at 2.4 mg/kg achieved a PR.

8.1.1.6 *Ordering*

Utomilumab will be supplied by Pfizer. No patients or third-party payers will be charged. Use the Drug Supply Request Form provided to order utomilumab. For all inquiries regarding utomilumab supplies, please contact:

Donna Stocker
100 Rt. 206 North
SOM-PPK3-020323
Peapack, NJ 07977
Phone 908-901-7356

Utomilumab is a sterile, colorless solution intended for IV administration. The drug product provided will contain 100mg of utomilumab in a 10mL solution in single-use glass vials, stoppered with a rubber septum and sealed with an aluminum polypropylene flip-off seal.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines.

Utomilumab will be packed in cartons each containing one vial. The information on the labels will be in accordance with approved submission documents. Utomilumab will be shipped in transport cool containers (2°C to 8°C) that are monitored with temperature monitoring devices.

8.1.1.7 *Preparing and Dispensing*

The contents of the utomilumab vials are sterile and nonpyrogenic, and do not contain bacteriostatic preservatives. Any spills that occur should be cleaned up using the facility's standard cleanup procedures for biologic products.

For administration in this trial, utomilumab must be diluted with 0.9% sodium chloride (normal saline solution). 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 Investigational Product Manual (IP Manual). Tubing with in line, low protein binding 0.2 micron filter made of polyether sulfone (PES) must be used during administration of utomilumab. A fixed dose of utomilumab at 100mg will be used for all cohorts in this study.

Utomilumab must not be used for any purpose other than for the trial. The administration of trial drug to patients who have not been enrolled into the trial is prohibited. Vials are for single use only. Any unused portion of the solution must be discarded in a biohazard waste disposal container with final disposal according to accepted local and national standards of incineration.

8.1.1.8 *Administration*

All study treatments will be administered at the investigational site on an outpatient basis as described in the IP Manual.

Utomilumab is administered in this study as a 1 hour IV infusion at a dose of 100mg each 28-day cycle and must have completed administration at least 30 minutes prior to subsequent drug administration.

Site staff should make every effort to target the timing of utomilumab infusion to be as close to 1 hour as possible. However, given the variability of infusion pumps from site to site, time windows of minus 10 minutes and plus 20 minutes is permitted (ie, infusion time is 50-80 minutes). The exact duration of infusion should be recorded in both source documents and CRFs.

8.1.2 Avelumab

Avelumab is a fully human monoclonal antibody of the immunoglobulin (Ig) G1 isotype against PD-L1. Avelumab selectively binds to PD-L1 and competitively blocks its interaction with PD 1. Unlike anti-PD-1 antibodies that target T cells, avelumab targets tumor cells, and therefore is expected to have fewer side effects, including a lower risk of autoimmune-related safety issues, as blockade of PD-L1 leaves the PD L2/PD 1 pathway intact to promote peripheral self-tolerance.[44] Avelumab is being developed jointly by Pfizer and Merck KGaA.

8.1.2.1 *Clinical Experience*

The clinical development program for avelumab currently includes multiple ongoing studies in

patients with various solid tumors (Phase 1 studies in patients with solid tumors, as well as studies in Merkel cell carcinoma, non-small cell lung cancer (NSCLC), breast cancer, ovarian and endometrial cancer, urothelial cancer, renal cell cancer, glioblastoma multiforme, head and neck cancer, GI adenocarcinoma, classical Hodgkin lymphoma, diffuse large B cell lymphoma, and acute myeloid leukemia). The recommended phase 2 dose from the early phase studies is 10mg/kg administered intravenously every 2 weeks.

8.1.2.2 *Pharmacokinetics*

Pharmacokinetics following the first 1-hour infusion and dose proportionality of avelumab have been characterized in 77 Caucasian patients treated in the dose escalation and expansion cohort of Study EMR 100070-001 by standard non-compartmental analysis. This analysis showed that the exposure parameters of C_{max} and AUC_{τ} increased in a dose proportionate fashion across the 1, 3, 10, and 20 mg/kg doses. Apparent half-life tended to increase with dose, likely due to target-mediated disposition at lower doses, but terminal half-life of 10 and 20 mg/kg doses were similar (102-120 hours). This suggested that target-mediated elimination does not increase at these two doses, and that target occupancy is very high.

Target occupancy on peripheral blood $CD3^+$ T cells was investigated in human blood in vitro using flow cytometry after spiking of whole blood samples from eight healthy volunteers with avelumab over a concentration of 0.003-10 μg/mL. Fifty percent (50%) receptor occupancy was observed at a drug concentration of 0.122 μg/mL ±0.042 μg/mL with a plateau indicating at least a (95% receptor occupancy reached in all blood samples at 1 μg/mL. PK profiles obtained from the dose escalation phase of Trial EMR 100070-00 found all patients at 10 mg/kg dose reached or exceeded the serum level (mean Ctrough 22±12 μg /mL at Day 15) of avelumab required for >95% target occupancy. For patients treated with 3 mg/kg of avelumab, 10 of 13 patients reached the required serum level (3.7-8.3 ug/mL).

8.1.2.3 *Immunogenicity*

Based on the Phase 1/1b Trial EMR 100070-001, the incidence of anti-drug antibodies (ADA) was relatively low, observed in 1 out of 39 patients (2.6%) in the dose escalation cohorts and 10 out of 338 patients (2.9%) in a non-small cell lung cancer (NSCLC) expansion cohort. In 8 of these 10 patients, a positive signal was observed at a single time point and a decrease in avelumab plasma exposure was observed in the 2 patients with multiple positive samples.

From these 11 positive patients, 2 patients had symptoms on the day of the infusion compatible with an immune reaction (chills and fever, nausea and vomiting) and, therefore, these AEs could be ADA-related. For the other 9 ADA-positive patients, no such AEs were reported.

Additional information for avelumab may be found in the SRSD, which for this study is the avelumab Investigator's Brochure.

8.1.2.4 *Safety*

As of April 11, 2017, 1738 patients have been treated with avelumab on clinical trials. The most common AEs, observed in 10% or more of patients, include the following: Tiredness; Nausea;

Loose or watery stools (diarrhea); Constipation; Reduced appetite; Decrease in weight; Vomiting; Low number of red blood cells (anemia); Belly pain; Cough; Fever; Shortness of breath; Swelling of feet and legs; Back pain; Joint pain.

In addition, over 10% of patients experienced at least 1 episode of infusion-related reaction. Most of the events were of Grade 1 or Grade 2 severity. Fewer than 1% had severe reactions (Grade 3 or 4) and no Grade 5 events were reported. Most of the infusion-related reactions occurred after the first or second infusion. These reactions included chills or shaking, fever, flushing, back pain, belly pain, shortness of breath or wheezing, decrease in blood pressure, hives.

Potential Immune-Related Adverse Events (irAEs): Potential irAEs (based on a list of pre-defined Preferred Terms without further clinical evaluation of individual cases), which were considered treatment-related occurred in <10% of patients based on investigator's causality assessment. The most frequent treatment-related potential irAEs were: hypothyroidism and skin inflammation/rash (occurring in 5-10% of patients). Additionally, 1-5% of patients experienced the following: colitis, pneumonitis. Fewer than 1% of patients experienced autoimmune hepatitis, nephritis, adrenal insufficiency, diabetes, uveitis, myositis, myocarditis, Guillain-Barre syndrome. The majority of potential irAEs were Grade 1 or Grade 2 in severity; approximately 2% were severe.

Additional information for avelumab may be found in the single reference safety document (SRSD), which for this study is detailed in the avelumab Investigator's Brochure.

Guidelines for the Management of Infusion-Related Reactions and Severe Hypersensitivity Reaction are found in Section 6.2.1 and Section 6.2.2.

8.1.2.5 *Efficacy*

Avelumab itself has not been tested as a single agent in B cell non-Hodgkin lymphomas, but other checkpoint inhibitors, including the anti-PD1 antibody nivolumab, have.[11] Ten patients had follicular lymphoma and four patients achieved a response (CR rate 10%); the median duration of response was not yet reached at nearly 2 years of follow-up.

8.1.2.6 *Ordering*

Avelumab will be supplied for the study by the manufacturer. No patients or third-party payers will be charged. Use the Drug Supply Request Form provided to order avelumab. For all inquiries regarding avelumab supplies, please contact:

Donna Stocker
100 Rt. 206 North
SOM-PPK3-020323
Peapack, NJ 07977
Phone 908-901-7356

Avelumab is a sterile, clear, and colorless solution intended for IV administration. Avelumab is formulated as a 20 mg/mL solution and will be supplied by Pfizer in single-use glass vials, stoppered with a rubber septum and sealed with an aluminum polypropylene flip-off seal.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines. Avelumab will be packed in cartons each containing one vial. The information on the labels will be in accordance with approved submission documents.

Avelumab will be shipped in transport cool containers (2°C to 8°C) that are monitored with temperature monitoring devices.

8.1.2.7 *Preparing and Dispensing*

The contents of the avelumab vials are sterile and nonpyrogenic, and do not contain bacteriostatic preservatives. Any spills that occur should be cleaned up using the facility's standard cleanup procedures for biologic products.

For administration in this trial, avelumab must be diluted with 0.9% sodium chloride (normal saline solution). 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 Investigational Product Manual (IP Manual). Tubing with in line, low protein binding 0.2 micron filter made of polyether sulfone (PES) must be used during administration of avelumab.

The dose amount required to prepare the avelumab infusion solution will be based on the patient's weight in kilograms (kgs). All patients should be weighed within 3 days prior to dosing for every cycle to ensure they did not experience either a weight loss or gain >10% from the weight used for the last dose calculation. For weight change less than 10% the decision to recalculate the avelumab dose can be in accordance with institutional practice. If the patient experienced either a weight loss or gain >10% compared to the weight used for the last dose calculation, the amount of study drug must be recalculated.

Avelumab must not be used for any purpose other than for the trial. The administration of trial drug to patients who have not been enrolled into the trial is prohibited. Vials are for single use only. Any unused portion of the solution must be discarded in a biohazard waste disposal container with final disposal according to accepted local and national standards of incineration.

8.1.2.8 *Administration*

All study treatments will be administered at the investigational site on an outpatient basis as described in the IP Manual.

Avelumab will be administered as a 1 hour IV infusion once every 2 weeks of each 28-day cycle. In order to mitigate infusion related reactions, a premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent. This may be modified based on local treatment standards

and guidelines, as appropriate.

If the avelumab is administered more than 4 hours after premedication is administered for the preceding drug and/or if no premedication has been given, then the premedication must be repeated or dosed. The line should be flushed, according to local practice, between infusions, and a new administration set should be used for avelumab.

Site staff should make every effort to target the timing of avelumab infusion to be as close to 1 hour as possible. However, given the variability of infusion pumps from site to site, time windows of minus 10 minutes and plus 20 minutes is permitted (ie, infusion time is 50-80 minutes). The exact duration of infusion should be recorded in both source documents and CRFs. Possible modifications of the infusion rate for the management of infusion related reactions are described in Section 6.2.

8.1.3 Utomilumab and Avelumab Combination Therapy

B9991004 is an ongoing Phase 1b/2 open-label, multi-center, multiple-dose study to evaluate the safety, pharmacokinetic (PK), pharmacodynamics, and preliminary antitumor activity of avelumab (anti-PD-L-1) at 10 mg/kg Q2W in combination with other cancer immunotherapies in patients with locally advanced or metastatic solid tumors.

As of the 17 December 2016 cutoff date, the study has enrolled and treated 153 patients with the combination of utomilumab and avelumab. There were 8 cases with 12 SAEs assessed as related to avelumab by the Investigator (PTs included 2 SAEs of infusion related reaction and 1 SAE each of pneumonitis, abdominal pain, chills/hyperthermia/hypertension/tachycardia, diarrhea, diabetic ketoacidosis/pancreatic disorder, vomiting). There was no SAE with fatal outcome assessed as related to avelumab.

The most common treatment-emergent, all-causality Grade 3, 4 AEs were dyspnea (16.7%), hypoxia (16.7%) and, nausea (5.6%). There were no treatment-emergent, treatment-related Grade 3, 4 or 5 AEs reported. There were 3 cases of fatal outcome (Grade 5) attributed to disease progression.

8.1.4 PF-04518600

PF-04518600 is a fully human IgG2 (immunoglobulin g2) agonistic monoclonal antibody (mAb) specific for human OX40. OX40 (CD134, TNFRSF4 [tumor necrosis factor receptor superfamily, member 4]), a member of the tumor-necrosis factor receptor (TNFR) superfamily like 4-1BB, is a co-stimulatory receptors that are expressed by antigen stimulated T cells but not native T cells.[37,45,46] Following OX40 binding to OX40 ligand (also known as OX40L, CD252 or TNFSF4), OX40 signaling activates both the canonical and noncanonical NF-κB (nuclear factor kappa-light-chain enhancer of activated B cells) survival pathways, leading to an upregulation of anti-apoptotic molecules including Bcl-2 (B-cell lymphoma-2), Bcl-xL, and survivin.[47] A number of studies support the potential for agonistic OX40 antibodies to reverse T cell's anergic state, and enhance tumor immunity. This includes a number of published preclinical studies demonstrating eradication of tumor growth in syngeneic models of melanoma, sarcoma, glioma, colon, breast, prostate, and renal cancers.[46,48-50] Preclinical studies completed at Pfizer support these published

findings; using OX86 (a murine IgG1 surrogate anti-OX40 agonistic antibody), growth inhibition of colon tumors was demonstrated in a syngeneic mouse model.

In vitro mechanism of action studies with PF-04518600 have been completed. PF-04518600 showed minimal binding to resting human T cells compared with activated cells. Consistent with the binding data, PF 04518600 demonstrated dose-dependent induction of cell proliferation and pro-inflammatory cytokine release (TNF, IFNγ [interferon gamma] and IL-10 [interleukin-10]) in CD3 activated T cells but not in non-activated whole blood or peripheral blood mononuclear cells (PBMCs). Biacore experiments also confirmed PF-04518600 to be highly selective and specific for human OX40. PF-04518600 showed no significant binding to other members of the TNFR super-family, such as CD40, 4-1BB, and GITR (glucocorticoid-induced tumor necrosis factor receptor), and no binding crossreactivity for murine, rat, rabbit, or dog OX40.

8.1.4.1 *Clinical Experience*

PF-04518600 has been tested in a first-in-human study in advanced solid tumor malignancies, with or without utomilumab. There have been 2 confirmed partial responses (PRs); 1 PR was reported in a melanoma patient treated at 0.1 mg/kg dose level, and a second PR was reported in a hepatocellular carcinoma (HCC) patient treated at 0.3 mg/kg dose level. A total of 52% of patients, of the 49 evaluable patients treated in experienced a best overall response of stable disease (SD). There is also an ongoing phase 1b/2 study of avelumab in combination with various immune modulators, including PF-04518600 alone or in combination with utomilumab, in locally advanced of metastatic solid tumors.

8.1.4.2 *Pharmacokinetics*

Preliminary PK data are available for 52 patients at the 0.01, 0.1, 0.3, 1.5, 3.0, or 10 mg/kg dose levels of the ongoing FIP study. The preliminary PK results suggest that exposure increased with increasing dose in an approximately dose-proportional manner between the doses of 0.3 and 10 mg/kg. The mean half-life ($t_{1/2}$) ranged from 4.0 to 10.1 days at the dose range of 0.1 to 10 mg/kg. Following multiple IV infusions of PF-04518600 once every 14 days, the mean (±SD) accumulation ratio was 1.4 ±0.5, 1.7 ±0.4, 1.8 ±0.2, 2.0±0.2 and 2.0 ±03. at the dose levels of 0.1, 0.3, 1.5, 3, and 10 mg/kg, respectively, based on a total of 28 patients with full PK profiles from both Cycle 1 and Cycle 3.

The flat dose that is equivalent to 0.3 mg/kg was determined to be 25 mg in terms of matching the center of the distributions based on the population PK/PD analysis. However, 30 mg was chosen as the low dose to ensure the 5th percentile of trough concentrations (C_{trough}) to be at or above which the full receptor occupancy was observed. The flat dose that is equivalent to 3 mg/kg was determined to be 250 mg.

8.1.4.3 *Immunogenicity*

Anti-drug antibody (ADA) against PF-04518600 was determined using a validated electrochemiluminescence assay based on a tiered approach with screening, confirmation and titer assays. As of 17 November, 2016, preliminary data were available for 46 patients who had the baseline and at least one post-dose ADA sample analyzed from the monotherapy portion of

B0601002 study. A total of 3 patients (6.5%) tested positive for ADA at baseline. A total of 16 patients (35%) were ADA positive at a minimum of one post-dose time point. The majority of ADA responses were transient with no noticeable effect on the PK of PF-04518600, except for 3 patients at the 0.1 mg/kg dose level; these 3 patients had the highest titers in that group and the C_{trough} of PF-04518600 appeared to be lower compared to the expected profiles.

8.1.4.4 *Safety*

PF-04518600 as monotherapy has been well-tolerated in doses from 0.01 to 10 mg/kg. Fifty-two patients (43 male and 9 female, mean ages of 60.0 years) were treated with PF-04518600 across 6 dose levels (0.01, 0.1, 0.3, 1.5, 3 and 10 mg/kg) in the FIP study.

The most frequent treatment-emergent adverse events (TEAEs) regardless of causality that occurred in ≥10% of patients were: fatigue (46.2%), nausea (28.8%), decreased appetite (23.1%), pruritus (23.1%), anemia (21.2%), aspartate aminotransferase increase (21.2%), abdominal pain (19.2%), constipation (19.2%), dyspnea (19.2%), headache (17.3%), alanine aminotransferase increase (15.4%), chills (15.4%), cough (15.4%), diarrhea (15.4%), pyrexia (15.4%), vomiting (15.4%), back pain (13.5%), blood bilirubin increase (11.5%), and insomnia (11.5%).

A total of 30 (57.7%) patients out of 52 experienced treatment-related AEs. The most frequent treatment-related AE experienced by ≥10% of patients was fatigue (25.0%). Most treatment-related events reported were Grade 2 or below. There was 1 Grade 3 treatment-related event of gamma-glutamyltransferase increased reported. There did not appear to be a dose-dependent increase in any treatment-related AEs. No dose-limiting toxicities (DLTs) were observed.

The only treatment-related Serious Adverse Event (SAE) reported to date was Grade 2 congestive heart failure (CHF) in an HCC patient receiving the 0.1 mg/kg dose. This patient had a prior history of anthracycline exposure. There were no treatment-related deaths in the FIP study.

8.1.4.5 *Efficacy*

There have been 4 confirmed PRs; 1 PR was reported in a melanoma patient treated at 0.1 mg/kg dose level, and three PRs were reported in patients treated at 0.3 mg/kg dose level. A total of 57% of patients, of the 49 evaluable patients treated experienced a best overall response of SD.

8.1.4.6 *Ordering*

PF-04518600 will be supplied by Pfizer. No patients or third-party payers will be charged. Use the Drug Supply Request Form provided to order PF-04518600. For all inquiries regarding PF-04518600 supplies, please contact:

Donna Stocker
100 Rt. 206 North
SOM-PPK3-020323
Peapack, NJ 07977

Phone 908-901-7356

PF-04518600 drug product, 10 mg/mL injection is presented as a sterile solution for IV administration, compounded in histidine buffer with excipients at pH 5.5. Each vial contains 108 mg of PF-04518600 in 10.8 mL of aqueous buffered solution, with a nominal volume of 10 mL, is sealed with a coated stopper and an overseal, and labeled according to local regulatory requirements. The vial is intended for single use only. The drug product should be stored refrigerated (2-8ºC) and protected from light.

8.1.4.7 *Preparing and Dispensing*

Detailed information on the preparation of PF-04518600 will be provided in the IP Manual. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance. Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of biologic agents.

The dose amount required to prepare the PF-04518600 infusion solution will be based on the patient's weight in kilograms (kgs). All patients should be weighed within 3 days prior to dosing for every cycle to ensure they did not experience either a weight loss or gain >10% from the weight used for the last dose calculation. For weight change less than 10% the decision to recalculate the PF-04518600 dose can be in accordance with institutional practice. If the patient experienced either a weight loss or gain >10% compared to the weight used for the last dose calculation, the amount of study drug must be recalculated.

PF-04518600 must not be used for any purpose other than for the trial. The administration of trial drug to patients who have not been enrolled into the trial is prohibited. Vials are for single use only. Any unused portion of the solution must be discarded in a biohazard waste disposal container with final disposal according to accepted local and national standards of incineration.

8.1.4.8 *Administration*

PF-04518600 will be administered per the IP Manual as an IV infusion over 60 minutes on an outpatient basis. On days whereby both PF-04518600 and utomilumab are to be administered on the same day, PF-04518600 will be administered after, but no sooner than 30 minutes after completion of the utomilumab infusion in absence of infusion reaction. On days whereby both PF-04518600 and avelumab are to be administered on the same day, avelumab will be administered after, but no sooner than 30 minutes after completion of the PF-04518600 infusion in absence of infusion reaction.

Site staff should make every effort to target the timing of PF-04518600 infusion to be as close to 1 hour as possible. However, given the variability of infusion pumps from site to site, time windows of minus 10 minutes and plus 20 minutes is permitted (ie, infusion time is 50-80 minutes). The exact duration of infusion should be recorded in both source documents and CRFs.

8.1.5 PF-04518600 and Utomilumab Combination Therapy

PF-04518600 is currently being tested in a phase 1 clinical trial in combination with utomilumab in selected locally advanced or metastatic carcinoma. Forty-two patients (23 male and 19 females, mean ages of 58.6 years) were treated with PF-04518600 across 5 dose levels of PF-04518600 (0.1, 0.3, 1 or 3 mg/kg) in combination with 20 or 100 mg of utomilumab.

The most frequent all-causality TEAEs that occurred in ≥10% of patients include: decreased appetite (23.8%), nausea (21.4%), fatigue (19.0%), anemia (16.7%), pyrexia (16.7%), abdominal pain (14.3%), constipation (14.3%), diarrhea (14.3%), and pain (11.9%).

A total of 15 (32.1%) patients out of 42 experienced treatment-related TEAEs. The most frequent treatment-related TEAE experienced in ≥5% of patients include fatigue (9.5%) and nausea (7.1%). All treatment-related events reported were Grade 1 or 2, with the exception of a Grade 3 amylase and a Grade 4 lipase elevation in a single subject receiving 0.3 mg/kg PF-04518600 and 100 mg utomilumab. No DLTs have been reported.

The only treatment-related SAE, which occurred on 19June2017, was a Grade 3 infusion reaction attributed to PF-04518600 but not utomilumab in a 67-year-old patient with bladder cancer who was receiving 1 mg/kg PF-04518600 and 100 mg utomilumab.

8.1.6 IP Storage

The Investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products, including any comparators and/or marketed products, are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label. See the IP Manual, package insert, or equivalent for storage conditions of the product once reconstituted and/or diluted.

Storage conditions stated in the SRSD (eg, investigator's brochure [IB], core data sheet [CDS], United States package insert [USPI], summary of product characteristics [SPC], or local product document [LPD]) will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study.

Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations.

The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported to the Overall Principal Investigator upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer. Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation.

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of the temperature range described in the labeling are not considered excursions. Specific details regarding information the site should report for each excursion will be provided to the site.

Site staff will instruct patients on the proper storage requirements for take home investigational products.

8.1.7 IP Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record. For all drugs from a commercial supply, sites should keep records per their institutional policies.

8.1.8 IP Destruction

The Principal Investigator or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the Investigator site, the Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

8.2 Other Agent(s)

8.2.1 Rituximab

Single agent monoclonal antibodies are an attractive treatment option given excellent tolerability. Rituximab is approved as a single agent in relapsed or refractory FL and in combination with chemotherapy for first line therapy of FL.[51]

Rituximab is a genetically engineered, chimeric, murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant pre-B and mature B cells. The antibody is an $IgG_1 \kappa$ immunoglobulin containing murine light and heavy-chain

variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular mass of 145 kD. Rituximab has a binding affinity for the CD20 antigen of ~8.0 nM. Several mechanisms of action have been proposed in various models including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytoxicity (ADCC), induction of apoptosis, and a "vaccinal" effect.[52] It is likely that rituximab works through a combination of these mechanisms.

The objective response rate for rituximab monotherapy in relapsed low-grade B-cell lymphoma is approximately 24-36% with complete response rates of approximately 7%.[53] Several mechanisms for rituximab resistance have been proposed including variable CD20 expression by lymphoma subtype, variability in complement activation, and polymorphisms in Fc receptors.[54-56] Novel agents that overcome these resistance mechanisms might offer similar complete response rates to combined chemotherapy and immunotherapy with improved tolerability.

Rituximab monotherapy has been evaluated in the upfront therapy as well. When given as 4 weekly infusions to patients who would otherwise have undergone observation, the objective response rate was 72% and the median time to progression was 2.2 years.[51] The addition of maintenance rituximab, given once every 8 weeks for 4 treatments, to patients with at least stable disease following induction therapy with rituximab monotherapy is associated with an improvement in event free survival (24 versus 13 months, <0.001).[57]

8.2.2 *Ordering*

Rituximab and rituximab biosimilars are commercially available from various manufacturers. All supplies will be provided locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements. Detailed information regarding rituximab formulation can be found in the Package Insert (PI) or Summary of Product Characteristics (SPC).

8.2.3 *Preparing and Dispensing*

Refer to specific preparation and dispensing instructions provided in the Package Insert.

8.2.4 *Administration*

Rituximab is administered in this study at the dose of 375 mg/m^2 weekly for four treatments starting on Day -6. On days when rituximab is to be given with other intravenous agents, it will be given last, at a minimum of 30 minutes (but up to 28 hours) after the last infusion has completed.

Rituximab should not be administered as an IV push or bolus. Premedication with acetaminophen and an antihistamine should be administered 30 minutes before each IV infusion.

Premedication with acetaminophen and an antihistamine is mandatory. If rituximab is administered more than 4 hours after premedication for avelumab, then the premedication must

be repeated. The line should be flushed, according to local practice, between infusions.

Infusions will follow institutional guidelines.

The infusion should be interrupted or slowed for infusion reactions. Upon improvement of symptoms, continue the infusion at one-half the previous rate. Medical management should be instituted (glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion reactions as needed. Depending on the severity of the infusion reaction and the required interventions, temporarily or permanently discontinue rituximab.

If the infusion cannot be completed within 1 day, the patient is allowed to receive the remainder of the infusion the following day as long as the dose is administered within 2 consecutive days. This will only be allowed if the reason for dose interruption does not include a Grade ≥3 toxicity attributed to rituximab. Any patient requiring two dose interruptions, each of which prevent administration of the full rituximab dose within 24 hours will be withdrawn from the study.

9. BIOMARKER STUDIES

The biomarkers for the trial include measurements from tumor tissues and analyses of blood samples to explore molecular, cellular, and soluble markers that may be relevant to the mechanism of action of the drug(s) or response/resistance to the drug(s). We will also collect stool samples to explore the relationship between the microbiome and immune response.

Peripheral blood samples will be collected before treatment on C1D-6 (for all cohorts except cohort A2a, dose level 0), C1D1, C1D2, C1D8, C1D15, C1D16, on day 1 of C2-6, and the end of treatment visit, and every 6 months from 6-24 months following the end of treatment. Analyses may include flow cytometry and CyTOF for immune cell subsets and their cell surface markers (including PD1, 4-1BB, and OX-40) as well as intracellular markers of immune cell activation; Luminex technology for measurement of soluble receptors and cytokines; and/or tumor free DNA sequencing and TCR sequencing for minimal residual disease (at baseline, at the end of treatment, and at 6 months +/- 2weeks from the end of treatment) and T cell repertoire studies, respectively.

Fresh tumor biopsies will be collected during screening, between C1D22 and C2D1, and at the time of progression. An archival sample within 90 days and without intervening treatment is acceptable as the pre-treatment biopsy assuming that the following provisions are met: 1.) Priority: tumor containing formalin-fixed, paraffin-embedded (FFPE) tissue block; 2). Priority: if the tumor containing FFPE tissue block cannot be provided in total, sections from this block should be provided that are freshly cut and mounted on positively-charged glass slides (SuperFrost Plus are recommended). Preferably, 25 slides should be provided; if not possible, a minimum of 15 slides is required.

These may be obtained by excisional or core needle biopsy. Biopsies may be analyzed for tumor and microenvironmental expression of checkpoint markers and for immune architecture by a combination of immunohistochemistry and multiparameter spectral imaging. Ideally, 4-6 core needle biopsies will be collected. Baseline patient samples from all sites will be used from the

following studies (in order of priority): 1) immunohistochemistry and multiparameter spectral imaging; 2) whole exome sequencing and RNAseq; 3) sequencing for clonotype determination (for minimal residual disease analysis) and TCR repertoire analysis; 4) banked biospecimens for future research pertaining to the drugs and/or disease being studied on this study. On treatment patient samples from sites will be analyzed, in the following order of priority, by: 1) immunohistochemistry and multiparameter spectral imaging; 2) RNAseq; 3) sequencing for TCR repertoire analysis. In addition, freshly obtained baseline and on-treatment samples from Dana-Farber Cancer Institute (DFCI) will be used for single-cell RNA sequencing testing. DFCI specimens will be allocated for this testing after 1) immunohistochemistry/multiparameter spectral imaging and prior to 2) whole exome sequencing/RNAseq.

Tissue processing: The cancer tissues should be fixed in 10% neutral buffered formalin, paraffin embedded, and routinely processed for histological evaluation. Formalin substitutes are not suitable as fixatives. Sample and tissue repository: Biomarker samples may be stored beyond the end of the trial and utilized at a later time jointly with samples from other studies in order to investigate actions of the investigational drug(s) or aspects of the disease under study.

Banked biospecimens will be handled in a manner that protects each subject's privacy and confidentiality. Banked biospecimens will be assigned the subject's study identification code (ID) at the site. The data generated from these banked biospecimens will also be indexed by this ID. Biospecimens will be kept until destruction in facilities with access limited to authorized personnel, and biospecimen-derived data will be stored on password-protected computer systems. The key between the subject's ID and the subject's direct personally identifying information (eg, name, address) will be held at the study site. Biospecimens will be used only for the purposes described in the protocol and informed consent document; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored for many years (no time limit) to allow for research in the future, including research conducted during the lengthy drug-development process and also postmarketing research. Subjects may withdraw their consent for the use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining biospecimens will be destroyed, but data already generated from the biospecimens will continue to be available to protect the integrity of existing analyses. Unless prohibited by local regulations or ethics committee decision, a 4-mL blood genomic banked biospecimen Prep D1 (dipotassium edetic acid [ethylenediaminetetraacetic acid] [K_2EDTA] whole-blood collection optimized for DNA analysis) will be collected at the time specified in the Study Calendar section of the protocol to be retained for potential pharmacogenomic/genomic/biomarker analyses related to drug response and disease/condition under study. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined. The primary purpose is to examine DNA; however, the biospecimen may also be used to study other molecules (eg, RNA, proteins, and metabolites).

Stool samples will be collected at screening, during cycle 1, and at the end of treatment, for analysis of gut microbial composition in fecal samples using 16S ribosomal RNA gene sequencing or equivalent phylogenetic method.

Details of time points and sampling are provided in the Study Calendar. Reference the laboratory manual for specimen collection, processing, and shipment instructions.

In order to complete all the assessments on tumor materials and blood and fecal samples, the Principal investigator will provide instructions and necessary supplies to the site, including shipping materials and prepaid mailers. The panel of biomarkers might be adjusted based on results from ongoing research related to anti-PD-1/PD-L1 therapies and/or safety; therefore, each patient will also be asked whether any remaining tumor tissue and/or blood-derived samples can be stored at a central repository (until such time as these samples cannot support any further analysis) and can be used for future exploratory research on the drug(s) and / or disease-related aspects. Biomarker analyses may be conducted after the conclusion of this study and may be based on samples derived from multiple studies.

10. STUDY CALENDAR

All patients must sign an informed consent document prior to undergoing any study-specific procedures; informed consent must be obtained within 28 days to start of protocol therapy.

Baseline evaluations are to be conducted within 4 weeks prior to the start of protocol therapy. Recent scans may be used but must be done $\leq$ 6 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

All assessments must be performed prior to administration of any study medication. All study assessments and medications should be administered within $\pm$ 2 days of the protocol-specified date, unless otherwise noted.

Study Calendar Cohorts A1a (all dose levels), A1b and B1

			Cycle 1							**Cycles 2-6**		**EOT[8]**	**Follow-up**
Study Assessment		**Baseline**	**Week -1**	**Week 1**		**Week 2**	**Week 3**		**Week 4**			**Week 4 from last treatment**	**Every 3 months +/- 2 weeks)**
Study Days		-28 to -1	-6	1	2	8	15	16	22	1	15		
Visit window +/- days		0	0	2	N/A	2	2	N/A	2	2	2	N3	14
Study Drug	*Utomilumab*				x					x			
	Avelumab							x		x	x		
	Rituximab (or rituximab biosimilar)		x	x		x	x						
Medical History, Medication Review, Physical Exam, Weight		x	x	x		x	x			x	x	x	x
Toxicity Assessment		x	x	x		x	x			x	x	x	x
ECOG Performance Status (Appendix A)		x		x						x		x	x
CBC, Differential, and Blood chemistries[1]		x	x	x	x	x	x	x		x	x	x	x
TSH, creatinine kinase, lipase, triglycerides, urine dipstick for blood and protein		x		x						x		x	
Hepatitis B and C testing[2]		x											
Pregnancy testing		x	x		x		x			x			
Tumor restaging[3]		x[3]								x[3]		x[3]	x[3]
Peripheral blood collection for biomarker studies[4]			x	x	x	x	x	x		x[4]		x[4]	x[4]

		Cycle 1							**Cycles 2-6**		**EOT[8]**	**Follow-up**
Study Assessment	**Baseline**	**Week -1**	**Week 1**		**Week 2**	**Week 3**		**Week 4**			**Week 4 from last treatment**	**Every 3 months +/- 2 weeks)**
Study Days	-28 to -1	-6	1	2	8	15	16	22	1	15		
Visit window +/- days	0	0	2	N/A	2	2	N/A	2	2	2	N3	14
Bone marrow biopsy[5]											x[5]	
Tumor biopsies for biomarker studies	x							x[6]				
Stool studies for biomarker/microbiome studies[7]	x							x			x	
TTE or MUGA scan	x											

[1] See Sections 10.1 and 10.2. All tests will be required at screening and tumor lysis labs (CMP, uric acid, LDH, phosphorus) will be repeated at each study visit in cycle 1. Patients do need to meet laboratory eligibility criteria on C1D-6.
[2] Consisting at a minimum of hepatitis C antibody, hepatitis B surface antigen and hepatitis B core antibody.
[3] See Sections 10.1, 10.2, and 10.3.
[4] One pretreatment peripheral blood sample(s) will be collected for correlative studies (Section 9) before rituximab on C1D-6, and then before treatment on C1D1, C1D2, C1D8, C1D15, C1D16 and on day 1 of cycles 2-6, at the end of treatment visit and at every other follow-up visit beginning 6 months (+/- 2 weeks) from the end of treatment and then every 6 months (+/- 2 weeks) until 24 months from the end of treatment.
[5] A bone marrow biopsy done will be required at the end of treatment if a PET/CT scan shows a complete metabolic response to confirm a complete response.
[6] On treatment tumor biopsy will be done between C1D22 and C2D1. A tumor biopsy will also be done at the time of disease progression.
[7] Stool studies will be collected during Screening, between C1D22 and C2D1, and at the completion of therapy by patient at home using kit provided by the research staff.
[8]EOT = end of treatment, to take place 4-6 weeks from the last dose of study treatment.

Study Calendar Cohort A2a, Dose Level 0

		Cycle 1						**Cycles 2-6**		**EOT[10]**	**Follow-up**
Study Assessment	**Baseline**	**Week 1**		**Week 2**	**Week 3**		**Week 4**			**Week 4 from last treatment**	**Every 3 months +/- 2 weeks)**
Study Days	-28 to -1	1	2	8	15	16	22	1	15		
Visit window +/- days	0	2	N/A	2	2	N/A	2	2	2	N3	14
Study Drug *PF-04518600*		x			x			x	x		
Medical History, Medication Review, Physical Exam, Weight	x	x		x	x			x	x	x	x
Toxicity Assessment	x	x		x	x			x	x	x	x
ECOG Performance Status (Appendix A)	x	x						x		x	x
CBC, Differential, and Blood chemistries[1]	x	x	x	x	x	x		x	x	x	x
TSH, creatinine kinase, lipase, triglycerides, urine dipstick for blood and protein	x	x						x		x	
Troponin, NTproBNP	x							x[11]			
Hepatitis B and C testing[2]	x										
Pregnancy testing	x				x			x			
Tumor restaging[3]	x[3]							x[3]		x[3]	x[3]

		Cycle 1						**Cycles 2-6**		**EOT[10]**	**Follow-up**
Study Assessment	**Baseline**	**Week 1**		**Week 2**	**Week 3**		**Week 4**			**Week 4 from last treatment**	**Every 3 months +/- 2 weeks)**
Study Days	-28 to -1	1	2	8	15	16	22	1	15		
Visit window +/- days	0	2	N/A	2	2	N/A	2	2	2	N3	14
Peripheral blood collection for biomarker studies[4]	x	x	x	x	x	x		x[4]		x[4]	x[4]
Bone marrow biopsy[5]										x[5]	
Tumor biopsies for biomarker studies	x						x[6]				
Stool studies for biomarker/microbiome studies[7]	x						x			x	
EKG[8]	x[8]	x[8]			x[8]			x[8]	x[8]	x[8]	
TTE or MUGA scan[9]	x							x[9]			

[1] See Sections 10.1 and 10.2. All tests will be required at screening and tumor lysis labs (CMP, uric acid, LDH, phosphorus) will be repeated at each study visit in cycle 1. Patients do need to meet laboratory eligibility criteria on C1D-6
[2]Consisting at a minimum of hepatitis C antibody, hepatitis B surface antigen and hepatitis B core antibody.
[3] See Sections 10.1, 10.2, and 10.3. *Note, patients with SD or PD at midtreatment CT scans restaging after cycle 3 will have the option to stay on study and received 4 weekly infusions of rituximab 375mg/m2 during cycle 4 (days 1, 8, 15, and 22) while continuing PF-04518600 at the same dose and schedule.*
[4] One pretreatment peripheral blood sample(s) will be collected for correlative studies (Section 9) before treatment on C1D1, and then before treatment C1D2, C1D8, C1D15, C1D16 and on day 1 of cycles 2-6, at the end of treatment visit and at every other follow-up visit beginning 6 months (+/- 2 weeks) from the end of treatment and then every 6 months (+/- 2 weeks) until 24 months from the end of treatment.
[5] A bone marrow biopsy done will be required at the end of treatment if a PET/CT scan shows a complete metabolic response to confirm a complete response.
[6] On treatment tumor biopsy will be done between C1D22 and C2D1. A tumor biopsy will also be done at the time of disease progression.
[7] Stool studies will be collected during Screening, between C1D22 and C2D1, and at the completion of therapy by patient at home using kit provided by the research staff.
[8] EKGs (single EKG at screening and then triplicate EKGs for all subsequent EKGs) will be performed for patients in cohorts A2, A3, and B2 at screening, on each day of administration of PF-04518600 and at the EOT visit.
[9] TTE/MUGA will be performed at screening and every 3 months on treatment and when clinically indicated.
[10] EOT = end of treatment, to take place 4-6 weeks from the last dose of study treatment.
[11]For patients with a previous history of anthracycline treatment and who are at high risk of cardiac failure (ie those that have New York Heart Association Class I heart failure), troponin I (troponin T is allowed if the assay utilized can be verified to have cardiac specificity) and N-terminal of the prohormone brain natriuretic peptide (Nt-proBNP) levels will be evaluated at baseline in screening and every other cycle starting with cycle 2 and when clinically indicated. Any elevation in troponin or Nt-proBNP should be discussed with the study principal investigator prior to enrollment or treatment.

Study Calendar Cohort A2a Dose Level 1

			Cycle 1							**Cycles 2-6**		**EOT[10]**	**Follow-up**
Study Assessment		**Baseline**	**Week -1**	**Week 1**		**Week 2**	**Week 3**		**Week 4**			**Week 4 from last treatment**	**Every 3 months +/- 2 weeks)**
Study Days		-28 to -1	-6	1	2	8	15	16	22	1	15		
Visit window +/- days		0	0	2	N/A	2	2	N/A	2	2	2	N3	14
Study Drug	*PF-04518600*				x			x		x	x		
	Rituximab (or rituximab biosimiar		x	x		x	x						
Medical History, Medication Review, Physical Exam, Weight		x	x	x		x	x			x	x	x	x
Toxicity Assessment		x	x	x		x	x			x	x	x	x
ECOG Performance Status (Appendix A)		x		x						x		x	x
CBC, Differential, and Blood chemistries[1]		x	x	x	x	x	x	x		x	x	x	x
TSH, creatinine kinase, lipase, triglycerides, urine dipstick for blood and protein		x		x						x		x	
Troponin, NTproBNP		x								x[11]			
Hepatitis B and C testing[2]		x											
Pregnancy testing		x	x				x			x			
Tumor restaging[3]		x[3]								x[3]		x[3]	x[3]

		Cycle 1							**Cycles 2-6**		**EOT[10]**	**Follow-up**
Study Assessment	**Baseline**	**Week -1**	**Week 1**		**Week 2**	**Week 3**		**Week 4**			**Week 4 from last treatment**	**Every 3 months +/- 2 weeks)**
Study Days	-28 to -1	-6	1	2	8	15	16	22	1	15		
Visit window +/- days	0	0	2	N/A	2	2	N/A	2	2	2	N3	14
Peripheral blood collection for biomarker studies[4]		x	x	x	x	x	x		x[4]		x[4]	x[4]
Bone marrow biopsy[5]											x[5]	
Tumor biopsies for biomarker studies	x							x[6]				
Stool studies for biomarker/microbiome studies[7]	x							x			x	
EKG[8]	x[8]			x[8]			x[8]		x[8]	x[8]	x[8]	
TTE or MUGA scan[9]	x								x[9]			

[1] See Sections 10.1 and 10.2. All tests will be required at screening and tumor lysis labs (CMP, uric acid, LDH, phosphorus) will be repeated at each study visit in cycle 1. Patients do need to meet laboratory eligibility criteria on C1D-6
[2]Consisting at a minimum of hepatitis C antibody, hepatitis B surface antigen and hepatitis B core antibody.
[3] See Sections 10.1, 10.2, and 10.3.
[4] One pretreatment peripheral blood sample(s) will be collected for correlative studies (Section 9) before rituximab on C1D-6, and then before treatment on C1D1, C1D2, C1D8, C1D15, C1D16 and on day 1 of cycles 2-6, at the end of treatment visit and at every other follow-up visit beginning 6 months (+/- 2 weeks) from the end of treatment and then every 6 months (+/- 2 weeks) until 24 months from the end of treatment.
[5] A bone marrow biopsy done will be required at the end of treatment if a PET/CT scan shows a complete metabolic response to confirm a complete response.
[6] On treatment tumor biopsy will be done between C1D22 and C2D1. A tumor biopsy will also be done at the time of disease progression.
[7] Stool studies will be collected during Screening, between C1D22 and C2D1, and at the completion of therapy by patient at home using kit provided by the research staff.
[8] EKGs (single EKG at screening and then triplicate EKGs for all subsequent EKGs) will be performed for patients in cohorts A2, A3, and B2 at screening, on each day of administration of PF-04518600 and at the EOT visit.
[9] TTE/MUGA will be performed at screening and every 3 months on treatment and when clinically indicated.
[10] EOT = end of treatment, to take place 4-6 weeks from the last dose of study treatment.
[11]For patients with a previous history of anthracycline treatment and who are at high risk of cardiac failure (ie those that have New York Heart Association Class I heart failure), troponin I (troponin T is allowed if the assay utilized can be verified to have cardiac specificity) and N-terminal of the prohormone brain natriuretic peptide (Nt-proBNP) levels will be evaluated at baseline in screening and every other cycle starting with cycle 2 and when clinically indicated. Any elevation in troponin or Nt-proBNP should be discussed with the study principal investigator prior to enrollment or treatment.

Study Calendar Cohorts A2a dose level 2, A2b, and B2

			Cycle 1							**Cycles 2-6**		**EOT[10]**	**Follow-up**
Study Assessment		**Baseline**	**Week -1**	**Week 1**		**Week 2**	**Week 3**		**Week 4**			**Week 4 from last treatment**	**Every 3 months +/- 2 weeks)**
Study Days		-28 to -1	-6	1	2	8	15	16	22	1	15		
Visit window +/- days		0	0	2	N/A	2	2	N/A	2	2	2	N3	14
Study Drug	*Utomilumab*				x					x			
	PF-04518600							x		x	x		
	Rituximab (or rituximab biosimilar)		x	x		x	x						
Medical History, Medication Review, Physical Exam, Weight		x	x	x		x	x			x	x	x	x
Toxicity Assessment		x	x	x		x	x			x	x	x	x
ECOG Performance Status (Appendix A)		x		x						x		x	x
CBC, Differential, and Blood chemistries[1]		x	x	x	x	x	x	x		x	x	x	x
TSH, creatinine kinase, lipase, triglycerides, urine dipstick for blood and protein		x		x						x		x	
Troponin, NTproBNP		x								x[11]			
Hepatitis B and C testing[2]		x											
Pregnancy testing		x	x				x			x			
Tumor restaging[3]		x[3]								x[3]		x[3]	x[3]

		Cycle 1							**Cycles 2-6**		**EOT[10]**	**Follow-up**
Study Assessment	**Baseline**	**Week -1**	**Week 1**		**Week 2**	**Week 3**		**Week 4**			**Week 4 from last treatment**	**Every 3 months +/- 2 weeks)**
Study Days	-28 to -1	-6	1	2	8	15	16	22	1	15		
Visit window +/- days	0	0	2	N/A	2	2	N/A	2	2	2	N3	14
Peripheral blood collection for biomarker studies[4]		x	x	x	x	x	x		x[4]		x[4]	x[4]
Bone marrow biopsy[5]											x[5]	
Tumor biopsies for biomarker studies	x							x[6]				
Stool studies for biomarker/microbiome studies[7]	x							x			x	
EKG[8]	x[8]						x[8]		x[8]	x[8]	x[8]	
TTE or MUGA scan[9]	x								x[9]			

[1] See Sections 10.1 and 10.2. All tests will be required at screening and tumor lysis labs (CMP, uric acid, LDH, phosphorus) will be repeated at each study visit in cycle 1. Patients do need to meet laboratory eligibility criteria on C1D-6

[2]Consisting at a minimum of hepatitis C antibody, hepatitis B surface antigen and hepatitis B core antibody.

[3] See Sections 10.1, 10.2, and 10.3.

[4] One pretreatment peripheral blood sample(s) will be collected for correlative studies (Section 9) before rituximab on C1D-6, and then before treatment on C1D1, C1D2, C1D8, C1D15, C1D16 and on day 1 of cycles 2-6, at the end of treatment visit and at every other follow-up visit beginning 6 months (+/- 2 weeks) from the end of treatment and then every 6 months (+/- 2 weeks) until 24 months from the end of treatment.

[5] A bone marrow biopsy done will be required at the end of treatment if a PET/CT scan shows a complete metabolic response to confirm a complete response.

[6] On treatment tumor biopsy will be done between C1D22 and C2D1. A tumor biopsy will also be done at the time of disease progression.

[7] Stool studies will be collected during Screening, between C1D22 and C2D1, and at the completion of therapy by patient at home using kit provided by the research staff.

[8] EKGs (single EKG at screening and then triplicate EKGs for all subsequent EKGs) will be performed for patients in cohorts A2, A3, and B2 at screening, on each day of administration of PF-04518600 and at the EOT visit.

[9] TTE/MUGA will be performed at screening and every 3 months on treatment and when clinically indicated.

[10] EOT = end of treatment, to take place 4-6 weeks from the last dose of study treatment.

[11]For patients with a previous history of anthracycline treatment and who are at high risk of cardiac failure (ie those that have New York Heart Association Class I heart failure), troponin I (troponin T is allowed if the assay utilized can be verified to have cardiac specificity) and N-terminal of the prohormone brain natriuretic peptide (Nt-proBNP) levels will be evaluated at baseline in screening and every other cycle starting with cycle 2 and when clinically indicated. Any elevation in troponin or Nt-proBNP should be discussed with the study principal investigator prior to enrollment or treatment.

Study Calendar Cohorts A3a, all dose levels, and A3b

			Cycle 1							**Cycles 2-6**		**EOT[10]**	**Follow-up**
Study Assessment		**Baseline**	**Week -1**	**Week 1**		**Week 2**	**Week 3**		**Week 4**			**Week 4 from last treatment**	**Every 3 months +/- 2 weeks)**
Study Days		-28 to -1	-6	1	2	8	15	16	22	1	15		
Visit window +/- days		0	0	2	N/A	2	2	N/A	2	2	2	N3	14
Study Drug	*Avelumab*							x		x	x		
	PF-04518600				x		x			x	x		
	Rituximab (or rituximab biosimilar)		x	x		x	x						
Medical History, Medication Review, Physical Exam, Weight		x	x	x		x	x			x	x	x	x
Toxicity Assessment		x	x	x		x	x			x	x	x	x
ECOG Performance Status (Appendix A)		x		x						x		x	x
CBC, Differential, and Blood chemistries[1]		x	x	x	x	x	x	x		x	x	x	x
TSH, creatinine kinase, lipase, triglycerides, urine dipstick for blood and protein		x		x						x		x	
Troponin, NTproBNP		x								x[11]			
Hepatitis B and C testing[2]		x											
Pregnancy testing		x	x				x			x			
Tumor restaging[3]		x[3]								x[3]		x[3]	x[3]

		Cycle 1							**Cycles 2-6**		**EOT[10]**	**Follow-up**
Study Assessment	**Baseline**	**Week -1**	**Week 1**		**Week 2**	**Week 3**		**Week 4**			**Week 4 from last treatment**	**Every 3 months +/- 2 weeks)**
Study Days	-28 to -1	-6	1	2	8	15	16	22	1	15		
Visit window +/- days	0	0	2	N/A	2	2	N/A	2	2	2	N3	14
Peripheral blood collection for biomarker studies[4]		x	x	x	x	x	x		x[4]			x[4]
Bone marrow biopsy[5]											x[5]	
Tumor biopsies for biomarker studies	x							x[6]				
Stool studies for biomarker/microbiome studies[7]	x							x			x	
EKG[8]	x[8]			x[8]		x[8]			x[8]	x[8]	x[8]	
TTE or MUGA scan[9]	x								x[9]			

[1]See Sections 10.1 and 10.2. All tests will be required at screening and tumor lysis labs (CMP, uric acid, LDH, phosphorus) will be repeated at each study visit in cycle 1. Patients do need to meet laboratory eligibility criteria on C1D-6. .
[2] Consisting at a minimum of hepatitis C antibody, hepatitis B surface antigen and hepatitis B core antibody.
[3] See Sections 10.1, 10.2, and 10.3.
[4] One pretreatment peripheral blood sample(s) will be collected for correlative studies (Section 9) before rituximab on C1D-6, and then before treatment on C1D1, C1D2, C1D8, C1D15, C1D16 and on day 1 of cycles 2-6, at the end of treatment visit and at every other follow-up visit beginning 6 months (+/- 2 weeks) from the end of treatment and then every 6 months (+/- 2 weeks) until 24 months from the end of treatment.
[5] A bone marrow biopsy done will be required at the end of treatment if a PET/CT scan shows a complete metabolic response to confirm a complete response.
[6] On treatment tumor biopsy will be done between C1D22 and C2D1. A tumor biopsy will also be done at the time of disease progression.
[7]Stool studies will be collected during Screening, between C1D22 and C2D1, and at the completion of therapy by patient at home using kit provided by the research staff.
[8] EKGs (single EKG at screening and then triplicate EKGs for all subsequent EKGs) will be performed for patients in cohorts A2, A3, and B2 at screening, on each day of administration of PF-04518600 and at the EOT visit.
[9]TTE/MUGA will be performed in all patients at screening and every 3 months on treatment and when clinically indicated.
[10] EOT = end of treatment, to take place 4-6 weeks from the last dose of study treatment.
[11]For patients with a previous history of anthracycline treatment and who are at high risk of cardiac failure (ie those that have New York Heart Association Class I heart failure), troponin I (troponin T is allowed if the assay utilized can be verified to have cardiac specificity) and N-terminal of the prohormone brain natriuretic peptide (Nt-proBNP) levels will be evaluated at baseline in screening and every other cycle starting with cycle 2 and when clinically indicated. Any elevation in troponin or Nt-proBNP should be discussed with the study principal investigator prior to enrollment or treatment.

10.1 Required Data for Study Screening

The following must be obtained within 28 days prior to the 1st day of treatment:

- Medical history, medication review, physical exam, height and weight, ECOG performance status (see Appendix A)
- CBC with differential, blood chemistries including complete metabolic panel, phosphorus, magnesium, uric acid, LDH, TSH, creatinine kinase, lipase, triglycerides. Urine studies to include a urine dipstick for blood and protein and if positive (2+ or greater for protein) a microscopic urinalysis and 24 hour urine collection (for protein).
    - For patients assigned to cohorts A2, A3, and B2 with a previous history of anthracycline treatment and who are at high risk of cardiac failure (ie those that have New York Heart Association Class I heart failure), troponin I (troponin T is allowed if the assay utilized can be verified to have cardiac specificity) and N-terminal of the prohormone brain natriuretic peptide (Nt-proBNP) levels will be evaluated at baseline in screening and every other cycle starting with cycle 2 and when clinically indicated. Any elevation in troponin or Nt-proBNP should be discussed with the study principal investigator prior to enrollment or treatment.
- Serum or urine β-HCG for females of childbearing potential
- Tumor restaging (within 6 weeks). This will consist of PET and CT scans (including neck, chest, abdomen/pelvis), which can be a combined study. MRIs may be used for patients in whom CT imaging is contraindicated.
- Tumor biopsy for biomarker studies (Section 9). An archival sample within 90 days and without intervening treatment is acceptable as the pre-treatment biopsy assuming that at least 15 unstained slides are available for evaluation.
- Stool sample for microbiome biomarker studies (Section 9)
- 12-Lead Electrocardiogram (EKG). A single 12-lead EKG will be done at screening in patients in cohorts A2, A3, and B2.
- Echocardiogram (TTE) or multigated acquisition (MUGA) scan: TTE or MUGA scan should be performed at screening for patients. All patients with an EF<50% must be discussed with the principal investigator prior to enrollment.

10.2 Required Data During Study

The following must be obtained during the study:

- Medical history, medication review, physical exam, and weight, ECOG performance status (see Appendix A)
- Toxicity assessment
- CBC with differential, blood chemistries including complete metabolic panel, phosphorus, magnesium, uric acid, LDH. These are required at each planned study visit during cycle 1 (C1D-6, C1D1, C1D2, C1D8, C1D15, C1D16) and on day 1 and day 15 of cycles 2-6. Patients do need to meet laboratory eligibility criteria on C1D-6.

- TSH, creatinine kinase, lipase, and triglycerides, as well as urine studies to include a urine dipstick for blood and protein and if positive a microscopic urinalysis and 24 hour urine collection (for protein) will be checked on day 1 of each cycle 1-6.
    - For patients assigned to cohorts A2, A3, and B2 with a previous history of anthracycline treatment and who are at high risk of cardiac failure (ie those that have New York Heart Association Class I heart failure), troponin I (troponin T is allowed if the assay utilized can be verified to have cardiac specificity) and N-terminal of the prohormone brain natriuretic peptide (Nt-proBNP) levels will be evaluated at every other cycle starting with cycle 2 and when clinically indicated. Any elevation in troponin or Nt-proBNP should be discussed with the study principal investigator prior to treatment.
- Pregnancy test at screening, C1D-6 (except for cohort A2a dose level 0), C1D2 (only for cohorts A1a, A1b, and B1), C1D15, and C2-6D1.
- Peripheral blood sample for biomarker studies before treatment on C1D-6 (for all cohorts except cohort A2a, dose level 0), C1D1, C1D2, C1D8, C1D15, C1D16, and on day 1 of C2-6 (Section 9).
- Tumor biopsy between C1D22 and C2D1.
- Tumor restaging: CT scans with PO and IV contrast of the chest, abdomen and pelvis (+/- neck if involved at screening baseline) between C3D22 and C4D1. MRIs may be used for patients in whom CT scans are contraindicated.
    - Patients enrolled in cohort A2a, dose level 0, who have SD or PD on this scan have the option to remain on study and receive 4 weekly doses of rituximab during cycle 4 (days 1, 8, 15, and 22) while remaining the same dose and schedule of PF-04518600.
- Stool sample for biomarker studies between C1D22 and C2D1 using a home kit
- EKGs: Triplicate 12-lead EKGs will be done in cycle 1 in patients in cohorts A2, A3, and B2 on days when PF-04518600 is administered prior to administration. Triplicate 12-lead EKGs will be done on day 1 and 15 of cycles 2-6 in cohorts A2, A3, and B2 prior to therapy on those days. If the mean QTcF is prolonged (>501msec) immediate correction for reversible causes should be performed. If the QTc reverts to <501msec, and in the judgment of the investigator(s) and principal investigator is determined to be due to cause(s) other than investigational product, treatment may be continued with regular EKG monitoring. If in that timeframe the QTcF intervals rise above 501msec the investigational product will be held until the QTcF interval decreases to $\leq$ 480msec. Patients will then restart the investigational product. If the QTcF has not decreased to 480msec of less after 2 weeks, or if at any time a patient has a QTcF interval >515msec or becomes symptomatic, the patient will be removed from the study. Additional triplicate EKGs should be performed as clinically indicated (ie at the time of any cardiac or neurologic AE)
- Echocardiogram (TTE) or multigated acquisition (MUGA) scan: TTE or MUGA scan should be performed every 3 months while on therapy for patients in cohorts A2, A3, and

B2. All patients with an EF<50%, or a decrease from baseline EF of >10%, must be discussed with the principal investigator prior to treatment.

10.3 Required at End of Treatment (4-6 weeks from last study treatment)

The following must be obtained at post-treatment visit (4-6 weeks from the last day of treatment).

- Medical history, medication review, physical exam, height and weight, ECOG performance status (see Appendix A)

- Toxicity assessment

- CBC with differential, blood chemistries including complete metabolic panel, phosphorus, magnesium, uric acid, LDH, TSH, creatinine kinase, lipase, triglycerides. Urine studies to include a urine dipstick for blood and protein and if positive (2+ or greater for protein) a microscopic urinalysis and 24 hour urine collection (for protein).
    - For patients assigned to cohorts A2, A3 and B2 with a previous history of anthracycline treatment and who are at high risk of cardiac failure (ie those that have New York Heart Association Class I heart failure), troponin I (troponin T is allowed if the assay utilized can be verified to have cardiac specificity) and N-terminal of the prohormone brain natriuretic peptide (Nt-proBNP) levels will be evaluated at the end of treatment visit

- Peripheral blood sample for biomarker studies

- Tumor restaging, which will consist of PET and CT scans, which may be a combined study; in the event of a complete response by imaging, a bone marrow biopsy will be necessary to confirm a complete response. MRIs may be used for patients in whom CT scans are contraindicated. Restaging will occur 4-6 weeks after the last dose of study therapy, then at 6, 12, and 18 months from the end of treatment (+/-2 weeks). CT scans (neck if involved at baseline, chest, abdomen, pelvis) may be done in place of PET scans for surveillance at the above timepoints following a complete response. For all complete responses by imaging, a bone marrow biopsy will be necessary as part of their restaging to confirm complete remission.

- Stool sample for biomarker testing

- EKG: Triplicate 12-lead EKGs will be done in patients in cohorts A2, A3, and B2 at the end of treatment visit.

- Echocardiogram (TTE) or multigated acquisition (MUGA) scan: TTE or MUGA scan should be performed at the end of treatment visit (if not performed within the preceding 3 months) for patients in cohorts A2, A3, and B2

10.4 Required during Follow-Up (every 3 months +/- 2 weeks from the end of treatment)

- Medical history, medication review, physical exam, height and weight, ECOG performance status (see Appendix A)
- Toxicity assessment
- CBC with differential, blood chemistries including complete metabolic panel, phosphorus, magnesium, uric acid, and LDH.
- Peripheral blood sample for biomarker studies at every other follow-up visit starting at 6 months (+/- 2 weeks) from the end of treatment until 24 months (+/- 2 weeks) from the end of treatment.
- Tumor restaging, which will consist of PET and CT scans, which can be a combined study, at month 6, 12, and 18 months from the end of therapy; in the event of a complete response by imaging, a bone marrow biopsy will be necessary to confirm a complete response. Also in the event of a complete response, PET scans need not be repeated and patients may be followed with CT scans of the chest, abdomen and pelvis (+/- neck if the neck was previously involved) with PO and IV contrast alone. MRIs may be used for patients in whom CT scans are contraindicated.
- Tumor biopsy at the time of progression
- After 2 years of follow up, patients will be followed only for relapse and survival with follow up in person or by phone call with the patient or the local physician every 6 months.

11. MEASUREMENT OF EFFECT

11.1 Disease Response Assessments

18F-fluorodeoxyglucose (18F-FDG) Positron Emission Tomography (PET) imaging will be used in conjunction with Computerized Tomography (CT) imaging to confirm a disease assessment of CR at the end of treatment. The screening 18F-FDG PET-CT imaging will be used to determine evaluable index lesions for each patient. For 18F-FDG PET-CT, tumor background ratios and development of new sites of abnormality will be recorded.

Results of the 18F-FDG PET studies will be scored according to methods developed by the American College of Radiology Imaging Network. All centers participating in the study will use the same 18F-FDG PET methodologies and measures, to the extent possible, and one center will be designated as the central lab to be used for final interpretation of 18F-FDG PET data.

Anti-cancer activity will be assessed at baseline, during treatment as specified in the Study Calendar, whenever disease progression is suspected (eg, symptomatic deterioration), at the time of withdrawal from treatment (if not performed in the previous 6 weeks) or at the end of treatment (4-6 weeks from the last dose of study therapy) and at follow-up visits 6, 12, and 18 months (+/- 2weeks) from the end of therapy or until disease progression.

If imaging is used in disease assessment, the same imaging technique (CT) used to characterize each identified and reported lesion at baseline will be employed in post-baseline disease assessments.

Assessment of response will be made using the Lugano 2014 criteria and LyRIC (Appendix D).

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

For all patients who achieve a complete response (CR) by imaging, a bone marrow biopsy is necessary to confirm a complete remission.

11.1.1 Duration of Response

Duration of overall response: The duration of overall 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, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: 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, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.2 Progression-Free and Overall Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

11.1.3 Response Review

For purposes of data analysis and reporting, responses on this trial will be centrally assessed through the Tumor Imaging Metrics Core at DF/HCC.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

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

12.1.2 Responsibility for Data Submission

Investigative sites are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 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. STATISTICAL CONSIDERATIONS

This is an open-label, phase 1b clinical trial of immunotherapy in combination with rituximab in patients with both relapsed/refractory or previously untreated follicular lymphoma.

13.1 Study Design/Endpoints

Primary endpoints:

- Determine the RP2D of these immunotherapy combinations for further testing
- Complete response rate using 2014 Lugano criteria

Secondary endpoints:

- Efficacy as measured by the objective, complete and partial response, stable disease and progressive disease rates by 2014 Lugano and LyRIC criteria, rate of MRD negativity at 6 and 12 months, 2-year progression free survival (by 2014 Lugano and LyRIC), overall survival and time to next treatment response duration
- Safety categorized by the rate of:
    - Grade 3 and higher toxicities, both regardless of attribution, and at least possibly attributed to the study treatment
    - Grade 2 or higher toxicity at least probably related to study treatment.
    - Adverse events leading to discontinuation due to toxicity.

Correlative or exploratory endpoints (when possible):

- Correlation between overall and complete response rates and MRD negativity and histologic grade (1-2 versus 3A) and FLIPI
- Calculation of the m7-FLIPI and correlation with overall and complete response rate and MRD negativity
- Comparisons of the tumor microenvironment composition and gene expression pre- and on-treatment
- Comparisons of the composition of the circulating immune environment, including the T cell repertoire, in the peripheral blood pre- and on-treatment
- Exploration of genetic markers of tumor response or resistance to therapy through whole exome sequencing
- Correlation between fecal microbiome and response or resistance to therapy

All exploratory or correlative endpoints will be analyzed descriptively.

13.2 Sample Size, Accrual Rate and Study Duration

13.2.1 Determining RP2D

The Dose Escalation phase of this study follows a 3+3 design with 2 or 3 dose levels for each cohort to determine the RP2D for each drug combination being tested. The RP2D will be defined as the highest dose level for which there are no more than 1/6 DLTs observed.

The following table shows the probability of escalation under various true DLT rates. With this design there is 91% probability of dose escalation if the true rate of DLT is 10% and 8% probability of escalation if the true DLT rate is 60%.

True Rate of DLT	Probability of escalation
10%	0.91
20%	0.71
30%	0.49
40%	0.31
50%	0.17
60%	0.08

Dose Expansion
Once the RP2D is established for a given cohort/drug combination in the relapsed/refractory setting (part A), an additional 9 or 12 eligible patients will be treated at the RP2D, for a total of 15 patients treated at that dose level. Whether it is 9 or 12 is dependent on whether 6 or 3 patients were treated at that dose level to determine the RP2D, respectively. With 15 patients, the 90% confidence interval for DLT will be no wider than +/- 23%.

A combination will be judged promising in terms of efficacy **in part A (relapsed/refractory setting)** if in addition to being tolerable 3 or more patients out of 15 obtain a CR (based on a null hypothesis of CRR 5% and alternative hypothesis of CRR 30% with 87% power and a 4% one sided type I error).

True but unknown CR rate	**0.05**	0.1	0.15	0.2	0.25	**0.3**
Prob of observing ≥ 3 CRs	**0.04**	0.18	0.40	0.60	0.76	**0.87**

In the **relapsed/refractory setting (part A)**, a particular combination (A1b, A2b, A3b) will be judged tolerably safe if 3 or fewer patients out of 15 experience a DLT (based on a null hypothesis for DLT rate of 40% and an alternative hypothesis of 10% with 94% power and a 9% one-sided type I error).

True but unknown prob. of excessive toxicity	0.05	**0.1**	0.15	0.2	0.25	0.3	0.35	**0.4**
Prob of observing ≤3 pts with excessive tox	0.99	**0.94**	0.82	0.65	0.46	0.30	0.15	**0.09**

If a cohort in part A meets these efficacy and toxicity endpoints, it will open in cohort B in previously untreated FL patients. These cohorts will treat up to 15 patients each. A combination will be judged promising in terms of efficacy **in part B (previously untreated setting)** if in addition to being tolerable based on above criteria) if 6 or more patients out of 15 obtain a CR (based on a null hypothesis of CRR 20% and alternative hypothesis of CRR 50% with 85% power and a 6% one sided type I error).

True but unknown CR rate	**0.2**	0.25	0.3	0.35	0.4	**0.5**
Prob of observing ≥ 6 CRs	**0.06**	0.15	0.28	0.44	0.60	**0.85**

In the **upfront setting** (**part B**), a particular combination (B1, B2) will be judged safe if 2 or fewer patients out of 15 experience excessive toxicity as defined above (based on a null hypothesis for excessive toxicity rate of 35% and an alternative hypothesis of 10% with 82% power and a 6% one-sided type I error).

True but unknown prob. of excessive toxicity	0.05	**0.1**	0.15	0.2	0.25	0.3	**0.35**
Prob of observing ≤2 pts with excessive tox	0.96	**0.82**	0.60	0.40	0.24	0.13	**0.06**

Based on historical rates, anticipated accrual will be 24 months. The anticipated time to primary endpoint is 30 months, and to study completion 48 months.

13.3 Reporting and Exclusions

The primary analysis will be performed on all evaluable patients.

13.4 Disclosures and Confidentiality

The investigator requests strict confidentiality from his/her staff and the IRB. Study documents provided by Pfizer (protocols, investigators' brochures, case report forms, and other material) will be stored appropriately to ensure their confidentiality. The information provided by Pfizer to the investigator may not be disclosed to others without direct written authorization from Pfizer, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

14. PUBLICATION PLAN

The results of this study will be submitted for presentation at national meetings and for publication in appropriate journals within 24 months of the completion of the study. The first analysis and submission will be conducted when all patients have reached the End of Study visit (or been taken off study).

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B CAIRO-BISHOP CLINICAL TUMOR LYSIS SYNDROME DEFINITION AND GRADING

Complication	0	1	2	3	4	5
Creatinine	≤ 1.5xULN	1.5xULN	>1.5-3.0xULN	>3.0-6.0xULN	>6.0xULN	Death
Cardiac arrhythmia	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device	Life-threatening (eg arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Seizure	None	----	One brief, generalized seizure well controlled by anticonvulsant or infrequent focal motor seizures not interfering with ADLs	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive, or difficult to control (eg status eplipecticus, intractable epilepsy)	Death

Note: Tumor lysis syndrome is defined by laboratory tumor lysis syndrome (uric acid ≥ 476µmol/L or 8mg/dL or a 25% increase from baseline; potassium ≥ 6.0mmol/L or 6mg/L or a 25% increase from baseline; phosphorus ≥ 1.45mmol/L or a 25% increase from baseline; calcium ≤ 1.75mmol/L or a 25% decrease from baseline) and at least one clinical complication.
Increases in creatinine and seizures are considered a clinical complication if they are not deemed attributable to the therapeutic agent

APPENDIX C DF/HCC MULTI-CENTER DATA AND SAFETY MONITORING PLAN

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 (CTEP, 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. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (i.e. the FDA). 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 (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) 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 (i.e. CTEP Multi-Center 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 Clinical Trials Research Informatics Office (CTRIO): 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, **Caron Jacobson, MD,** 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 (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with the FDA (investigator-held IND trials) 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, only attending physicians may obtain initial informed consent and any re-consent that requires a full revised consent form.

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 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.

3.6.1 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.

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration and Randomization

To register a participant, the following documents should be completed by the Participating Institution and e-mailed to Samantha_Pazienza@dfci.harvard.edu the Coordinating Center

- Copy of required laboratory tests including: see section 10.1
- Signed informed consent document
- HIPAA authorization form (if separate from the informed consent document)
- Completed Eligibility Checklist

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).
- Upon receiving confirmation of registration, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number, and, if applicable, assigned treatment and/or dose level.

Treatment or other protocol-specific interventions may not begin without confirmation from the Coordinating Center that the participant has been registered.

3.7.2 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.

3.7.3 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.

3.8 DF/HCC Protocol Case Number

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.

3.8.1 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.

3.8.2 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.

3.8.3 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.

3.9 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.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 7.

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

3.9.2 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. Participating Institutions will review/submit to their IRB according to their institutional policies and procedures.

3.10 Data Management

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

3.10.1 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 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.

Participating institutions will be required to participate in regular Coordinating Center initiated teleconferences.

Participating institutions will be required to participate in monitoring every 6 months. At this time, source documentation verification (SDV) will be conducted by having access to participants' complete medical record and source documents.

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. Minimum site accrual expectations have been set to 3 subjects per year.

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.

APPENDIX D RESPONSE CRITERIA FOR LYMPHOMA: LUGANO 2014 AND LYRIC

Criteria	Complete Response (CR)	Partial Response (PR)	Stable Disease (SD)	Progressive disease (PD)
Lugano	PET-CT, score 1, 2, or 3* with or without a residual mass on 5PS† *Or* on CT, target nodes/nodal masses must regress to ≤ 1.5 cm in LDi, and no extralymphatic sites of disease	PET-CT Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size. *Or* On CT ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites; no increase in non-measured lesions; spleen if enlarged must have regressed by >50% in length beyond normal	Neither CR, PR, nor PD	PET-CT score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment. *Or* On CT, an individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly. New or clear progression of preexisiting nonmeasured lesions. Regrowth of previously resolved lesions. A new node > 1.5 cm in any axis or a new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma *And/Or* New or recurrent involvement of the bone marrow

Criteria	Complete Response (CR)	Partial Response (PR)	Stable Disease (SD)	Progressive Disease (PD)
LYRIC	Same as Lugano	Same as Lugano	Neither CR, PR, PD, nor IR	As with Lugano with the following exceptions: Indeterminate response (IR) IR1: ≥50% increase in SPD in first 12 wks IR2: <50% increase in SPD with a. New lesion(s), or b. ≥50% increase in PPD of a lesion or set of lesions at any time during treatment IR(3): Increase in FDG uptake without a concomitant increase in lesion size meeting criteria for PD

SPD – sum of the product of the diameters; PPD – product of the perpendicular diameters; LDi – longest diameter; SDi – short diameter; 5PS – 5-point scale; IR – immune response

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).