DF/HCC Protocol #: 20-404

TITLE: A multicenter phase 2 study of belantamab mafodotin in relapsed or refractory plasmablastic lymphoma and ALK+ large B-cell lymphoma

Coordinating Center: Massachusetts General Hospital
Cancer Center Protocol Office – PCORP
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Other Agent(s): Belantamab mafodotin (GlaxoSmithKline PSC)

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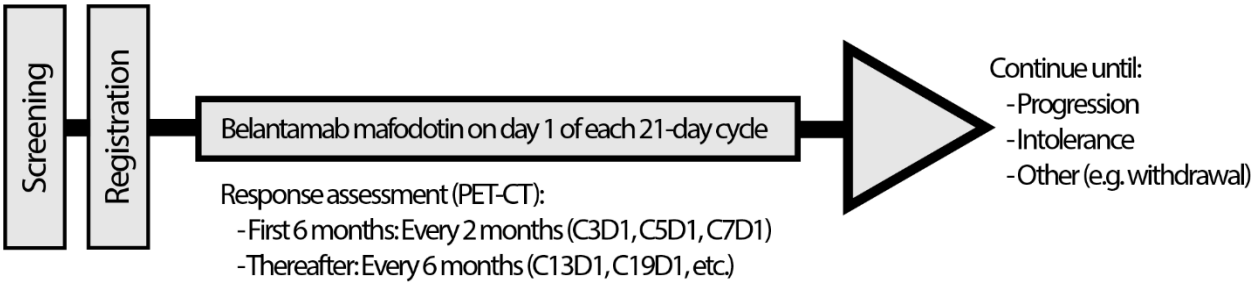
SCHEMA


Screening
Registration
Belantamab mafodotin on day 1 of each 21-day cycle
Response assessment (PET-CT):
- First 6 months: Every 2 months (C3D1, C5D1, C7D1)
- Thereafter: Every 6 months (C13D1, C19D1, etc.)
Continue until:
- Progression
- Intolerance
- Other (e.g. withdrawal)

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1. OBJECTIVES

1.1 Study Design

This is a multicenter phase 2 study of belantamab mafodotin in patients with plasmablastic lymphoma and ALK+ large B-cell lymphoma. The primary objective will be to determine the overall response rate of belantamab mafodotin in patients with these histologies. Patients will receive belantamab mafodotin at 2.5 mg/kg IV on day 1 of a 21-day cycle until progression or intolerance.

1.2 Primary Objectives

1. To determine the overall response rate of belantamab mafodotin in previously treated patients with plasmablastic lymphoma and ALK+ large B-cell lymphoma

1.3 Secondary Objectives

1. To assess safety and tolerability
2. To determine the complete response rate
3. To determine the durability of clinical benefit as measured by progression-free survival and overall survival
4. To determine the overall and complete response rates by subtype (i.e. plasmablastic lymphoma and ALK+ large B-cell lymphoma)

2. BACKGROUND

2.1 Plasmablastic lymphoma and ALK+ large B-cell lymphoma

Plasmablastic lymphoma (PBL) and ALK+ large B-cell lymphoma (ALK-LBL) are aggressive subtypes of diffuse large B-cell lymphoma with plasmablastic/immunoblastic morphology. They share three unique and important clinicopathologic characteristics:

1. Immunoblastic or plasmablastic morphology
2. Expression profile characteristic of plasma cells (with minimal expression of B cell markers)
3. Aggressive behavior with particularly poor prognosis and few long-term survivors.

The poor outcomes observed in patients with PBL and ALK-LBL may reflect that they are biologically distinct from B-cell lymphomas, and that they lack the targets for the approved targeted therapies in large cell lymphoma (e.g. CD20, CD79b, CD19). As a result, these patients have generally been excluded from clinical trials and there is no standard treatment approach. In the relapsed/refractory setting, PBL and ALK-LBL are uniformly fatal. The pathogenesis and biology of each of these uncommon lymphomas is poorly understood and there is a critical need to identify tractable therapies for these lymphomas.

2.2 Current therapies for relapsed or refractory plasmablastic lymphoma and ALK+ large B-cell lymphoma

2.2.1 Treatment of plasmablastic lymphoma

The prognosis of patients diagnosed with plasmablastic lymphoma are dismal, with a median OS of 3 months for HIV-positive plasmablastic lymphoma and 4 months for HIV-negative plasmablastic lymphoma.[1] The prognosis following initial CHOP-like therapy is dismal leading to the current NCCN guidelines recommending more intensive regimens e.g. infusional etoposide, vincristine and doxorubicin with bolus cyclophosphamide and prednisone (EPOCH),[2] or cyclophosphamide, vincristine, doxorubicin, methotrexate alternating with ifosfamide, etoposide, and cytarabine (CODOX-M/IVAC).[3–5] It is unclear treatment intensification has modified the natural history of this disease and the prognosis remains dismal.[6–9] Two prospective studies are evaluating the safety and efficacy of infusional EPOCH in patients with high-risk DLBCL and include plasmablastic lymphomas (NCT01092182 and CTSU-9177). A small case series of patients receiving EPOCH and bortezomib was also reported with limited efficacy.[10] Given the dismal prognosis, we contend that no established standard therapy exists for patients with plasmablastic lymphoma, nor is there an established standard therapy for patients with relapsed or refractory disease. Most patients receive salvage chemotherapies regimens used in other aggressive lymphomas e.g. ICE, DHAP in the relapsed/refractory setting, and there is an urgent need to identify novel therapies for these patients. The role of consolidation with high dose chemotherapy and autologous stem cell rescue (HDT/ASCR) or allogeneic stem cell transplant (ASCT) is unknown. However, HDT/ASCR or ASCT is considered given the dismal prognosis of this disease.

2.2.2 Treatment of ALK+ large B-cell lymphoma

The prognosis of patients with ALK+ large B-cell lymphoma is dismal, with a median OS of 20.3 months (95% CI, 12.2 to 42.6 months).[11] Among patients with advanced stage disease, the median survival is only 12.2 months (95% CI, 9.1 to 32.5 months) with no long-term survivors reported in the literature.[11] Given the rarity of this histology (100-200 patients reported throughout the literature), we have little-to-no data guiding management of these patients. For patients with limited stage disease, a combined modality approach with CHOP-like therapy and consolidative radiotherapy is often used and has been associated with durable remissions/cure in some patients. For patients with advanced stage disease, one series suggested a trend toward OS benefit with inclusion of etoposide (CHOP or da-EPOCH) over CHOP although this did not reach statistical significance in this small retrospective series ($p=0.185$).[12] Given the dismal prognosis, we contend that no established standard therapy exists for patients with ALK+ large B-cell lymphoma, nor is there an established standard therapy for patients with relapsed or refractory disease. Most patients receive salvage chemotherapies regimens used in other aggressive lymphomas e.g. ICE, DHAP in the relapsed/refractory setting, and there is an urgent need to identify novel therapies for these patients. There are case reports of transient response to the ALK inhibitor crizotinib +/- chemotherapy.[13,14] The role of consolidation with high dose chemotherapy and autologous stem cell rescue (HDT/ASCR) or allogeneic stem cell transplant (ASCT) is unknown. However, HDT/ASCR or ASCT is considered given the dismal prognosis of this disease.

2.3 Belantamab mafodotin

Belantamab mafodotin (GSK2857916) is a dual acting Antibody-Drug Conjugate (ADC), comprised of an anti-B-Cell Maturation Antigen (BCMA) afucosylated humanized immunoglobulin G1 (IgG1) conjugated with the tubulin polymerization disrupting agent monomethyl auristatin F (MMAF).

The normal function of BCMA is to promote cell survival by transduction of signals from two known ligands: B cell activating factor from the tumor necrosis factor (TNF) family (BAFF/BLys) and a proliferation inducing ligand (APRIL). BCMA expression is restricted to B cells at later stages of differentiation, with expression on germinal center B cells in tonsil, blood plasma blasts, and long-lived plasma cells. BCMA is expressed in various B cell malignancies, including multiple myeloma (MM), diffuse large B-cell lymphoma (DLBCL), large B-cell lymphoma (LBCL), chronic lymphocytic leukemia (CLL) and Waldenstrom's macroglobulinemia (WM) at varying frequencies.

Belantamab mafodotin binds to BCMA, is internalized, and releases free cys-mcMMAF, which disrupts the microtubule network, leading to cell cycle arrest and apoptosis. Belantamab mafodotin also mediates antibody-dependent cell-mediated cytotoxicity (ADCC) effector function directed towards BCMA-expressing cells. The mechanisms of action of belantamab mafodotin are designed to enable anti-tumor activity of cells by ADCC activity (non-dividing), as well as ADC activity (dividing cells). Moreover, ADC-induced apoptosis by belantamab mafodotin was recently shown to be potentially immunogenic as measured by cell surface externalization of calreticulin (CRT) and secretion of high mobility group box 1 (HMGB1) and adenosine triphosphate (ATP).

In the first-in-human study (BMA 117159) belantamab mafodotin was administered in a total of 80 patients, 74 subjects with relapsed/refractory multiple myeloma and 6 patients with non-Hodgkin lymphoma (NHL). In part 1, 38 patients were enrolled at dose levels ranging from 0.03 mg/kg to 4.6 mg/kg. Belantamab demonstrated a manageable safety profile, and the recommended dose of 3.4 mg/kg was identified. In part 2 (MM), the confirmed overall response rate for all patients was 60% (95% CI 0.42 – 0.76), the median duration of response (mDOR) for responders was 14.3 months (95% CI 10.6 – NR) and the estimated progression free survival (PFS) was 12.0 months (95% CI 3.1 – NR). Grade 3 or 4 AEs were reported in 29 (83%) patients, the most common of which were thrombocytopenia (grade 3, 9/35 [26%]; grade 4, 3/35 [9%]) and anemia (grade 3, 6/35 [17%]); no grade 5 AEs were reported. Serious AEs (SAEs) were reported in 17/35 (49%) patients, most commonly pneumonia (3/35; 9%), lung infection (2/35; 6%), and infusion-related reactions (2/35; 6%). Seven (20%) patients experienced SAEs related to study treatment, most commonly infusion-related reactions (2/35; 6%). Four patients died during the study, all due to progression of MM.

A subsequent pivotal phase II study is evaluating the efficacy and safety of two doses of belantamab mafodotin as monotherapy in relapsed or refractory multiple myeloma refractory to proteasome inhibitors (PI) and immune-modulating drugs (IMiD). This study treated 196 patients with belantamab mafodotin on day 1 of a 21-day cycle: 97 patients were treated with a dose of 2.5 mg/kg, 99 patients were treated with a dose of 3.4 mg/kg. As of June 21, 2019

(primary analysis data cut off date), 30 (31%, 97.5% CI 20.8 – 42.6) of the 97 patients in the 2.5 mg/kg cohort and 34 (34%, 97.5% CI 23.9 – 46.0) of the 99 patients in the 3.4 mg/kg cohort achieved an overall response. This study demonstrates single-agent belantamab mafodotin anti-myeloma activity with a manageable safety profile in patients with relapsed/refractory MM.

2.4 Rationale

2.4.1 Plasmablastic lymphoma and ALK+ large B-cell lymphoma are biologically similar to plasma cell neoplasms and express BCMA

Plasmablastic lymphoma and ALK+ large B-cell lymphoma are biologically more similar to plasma cell neoplasms than B-cell lymphomas:

- ***ALK+ large B-cell lymphoma:*** ALK-LBL lacks expression of B-cell markers CD20, CD79, and PAX5, but plasma cell related antigens CD138, BLIMP1 are diffusely expressed in virtually all cases, and MUM1, kappa or lambda light chain and IgA is expressed in most cases. All cases of ALK-LBL are EBV and HHV8 negative. On the basis of the striking plasma cell phenotype of ALK-LBL, our group utilized hierarchical DNA methylation profiling to find that ALK-LBL clustered more with plasma cells and plasma cell myeloma than with diffuse large B-cell lymphoma, which clusters closely with normal B cells, and away from plasma cell myeloma.

- ***Plasmablastic lymphoma:*** PBL expresses plasma cell markers, including CD38, CD138, MUM1, BLIMP1, and lacks expression of CD45 as well as markers of B-cell phenotype, including CD20, and PAX5. EBV is positive in 70% of cases, and HHV8 is always negative.

Given the striking plasma cell phenotype of both PBL and ALK-LBL, we hypothesized that BCMA would likely be expressed lymphomas, and may thus serve as viable therapeutic targets in these aggressive lymphomas that lack typical B cell markers. To this end, we stained a cohort of 11 cases of ALK-LBL with an antibody to BCMA and found that 9 of 11 cases of ALK-LBL were positive for BCMA. Similarly, BCMA has been shown to be uniformly and strongly expressed (3+) in PBL (7/7 cases; Khattar et al, ASH Proc 2017, Poster 622). Primary effusion lymphoma (PEL) is morphologically and immunophenotypically similar to plasmablastic and ALK+ B-cell lymphomas, with expression of the same plasma cell markers and without mature B cell markers. EBV and HHV8 are also often positive. Given its rarity, expression of BCMA has not been confirmed. However, given overlapping morphology and immunophenotype with plasmablastic and ALK+ B cell lymphomas, BCMA should be expressed in PEL. Therefore, we are conducting additional preclinical analysis of PEL cases to confirm BCMA expression, and would consider adding this histologic subtype if confirmed.

2.4.2 Belantamab mafodotin is active in ALK+ large B-cell lymphoma

We observed an objective response in a 44-year-old man with ALK-LBL refractory to 10 prior lines of therapy. Based on biopsy of an involved lymph node demonstrating refractory ALK+

large B-cell lymphoma with expression of BCMA, we were granted access to belantamab mafodotin through the GSK Compassionate Use program (IND #209233). The patient had high burden disease at initiation of therapy, i.e. with prolonged ICU stay for management of spontaneous tumor lysis syndrome, and achieved rapid disease response with marked reduction in LDH (from 18,000 to normal), resolution of tumor lysis syndrome after initial surge related to treatment effect, and restaging PET-CT demonstrated PR. He had localized progression with gastric involvement during cycle 3 for which he received RT. He continued to derive benefit from belantamab mafodotin until he developed systemic progression after 3.5 months on treatment. Given our observed outstanding response, Dr. Andrew Zelenetz (Memorial Sloan Kettering Cancer Center) treated a patient with ALK-LBL with belantamab mafodotin through the GSK Compassionate Use program (IND #145928); this patient achieved an objective response followed by consolidation with allogeneic transplant. Given the natural history of ALK-LBL characterized by a highly aggressive course and refractoriness to all available therapies, these observations warrant prospective study.

2.4.3 The current study

We hypothesize that the antibody drug conjugate belantamab mafodotin will be highly active in plasmablastic lymphoma and ALK+ large B-cell lymphoma. In the current study, we propose a multicenter phase 2 study of belantamab mafodotin in patients with plasmablastic lymphoma, and ALK+ large B-cell lymphoma. The primary objective will be to determine the overall response rate of belantamab mafodotin in patients with these histologies. Patients will receive belantamab mafodotin at 2.5 mg/kg IV on day 1 of a 21-day cycle until progression or intolerance.

2.5 Correlative Studies Background

Currently there are no available mouse models or reliable cell lines for most types of lymphoma, especially for uncommon types of lymphoma. As part of our research effort, our group has developed patient-derived xenograft (PDX) models of lymphoma for the study of lymphoma pathogenesis and to study mechanisms of drug response, refractoriness and resistance. Given our interest in belantamab mafodotin as potential therapy for ALK-LBL and PBL, we created a PDX model of ALK-LBL from a biopsy obtained from the index patient treated with belantamab mafodotin. The model was generated by surgical implantation of a 1mm x 1mm x 1mm portion of the patient's biopsy sample into the space between the renal capsule and kidney surface in an immunodeficient mouse. The resultant mouse developed a massive tumor, ultimately filling the abdominal cavity. The histology of and immunophenotype of the lymphoma was identical to the patient's original lymphoma. The lymphoma can be passaged over many generations, and the number of ALK+ LBCL PDX mice that can be created is scalable for need. As a point of reference, we are currently using this ALK+ LBCL PDX line to model therapeutic response to novel therapies in ALK+ LBCL.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Participants must have relapsed or refractory plasmablastic lymphoma or ALK+ large B-cell lymphoma by WHO criteria.

3.1.2 Participants must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter [LDi] to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥15 mm in LDi for nodal disease or ≥10 mm in LDi for extranodal lesions.[20]

3.1.3 Participants must have received prior systemic lymphoma therapy.

3.1.4 Age ≥18 years.

3.1.5 ECOG performance status ≤2 (Karnofsky ≥60%).

3.1.6 Participants must have adequate marrow function as defined below (unless abnormalities are considered related to marrow and/or splenic involvement by lymphoma). Transfusions are permitted for subjects to meet criteria for platelet and/or hemoglobin requirements:

– absolute neutrophil count	≥1,000/mcL
– platelets	≥50,000/mcL
– hemoglobin	≥ 8.0 g/dL

3.1.7 Participants must have adequate organ function as defined below (unless abnormalities are considered related to involvement by lymphoma; upon initiation of treatment, refer to the corresponding stopping criteria as applicable):

– total bilirubin	≤ 1.5 X institutional upper limit of normal (ULN); (Isolated bilirubin ≥1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional ULN
– Spot urine (albumin/creatinine)	<500 mg/g (56 mg/mmol)
OR	
Urine Dipstick	Negative/trace (if ≥1+ only eligible if confirmed ≤ 500 mg/g (56 mg/mmol) by albumin/creatinine ratio (spot urine from first void)

– Glomerular filtration rate (eGFR)≥30 mL/min/1.73 m^2 (MDRD Formula).

3.1.8 Participants with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible

for this trial, participants should be class 2B or better.

3.1.9 Belantamab mafodotin is potentially teratogenic. A female participant is eligible to participate if she is not pregnant or breastfeeding. Women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for at least 4 months after the last dose of study intervention. Please see Appendix E for contraception guidance. Women must also agree not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

Nonchildbearing potential is defined as follows (by other than medical reasons):

- ≥45 years of age and has not had menses for >1 year
- Patients who have been amenorrhoeic for <2 years without history of a hysterectomy and oophorectomy must have a follicle stimulating hormone value in the postmenopausal range upon screening evaluation
- Post-hysterectomy, post-bilateral oophorectomy, or post-tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure.

3.1.10 Women of childbearing potential must have a negative highly sensitive serum pregnancy test, and agree to repeat highly sensitive serum pregnancy testing within 72 hours before the first dose of study intervention (if screening pregnancy test was not within 72 hours of dosing).

3.1.11 Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 6 months after completion of administration. Men must also agree not to donate sperm during this period. Men may agree to remain abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) OR agree to use a male condom, even if they have undergone a successful vasectomy and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year when having sexual intercourse with a WOCBP (including pregnant females). Please see Appendix E for contraception guidance.

3.1.12 Participants with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the

investigational regimen are eligible for this trial at the discretion of the overall PI.

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

3.2 Exclusion Criteria

3.2.1 Participants must not have current corneal epithelial disease except mild changes in corneal epithelium.

3.2.2 Participant must not have current unstable liver or biliary disease defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. Note: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) or hepatobiliary involvement of malignancy is acceptable if otherwise meets entry criteria.

3.2.3 Participants who have not recovered from adverse events due to prior anti-cancer therapy (*i.e.*, have residual toxicities > Grade 1) with the exception of alopecia. At the discretion of the overall PI, participants with residual toxicities > Grade 1 may be considered eligible if in the opinion of the overall PI the residual toxicity is not likely to interfere with the safety or efficacy assessment of the investigational regimen.

3.2.4 Participants who are receiving any other investigational agents.

3.2.5 Participants must not have central nervous system involvement by lymphoma, as belantamab mafodotin is not known to penetrate the CNS.

3.2.6 Participant must not use contact lenses while participating in this study.

3.2.7 Participant must not be simultaneously enrolled in any interventional clinical trial.

3.2.8 Participant must not have used an investigational drug or approved systemic lymphoma therapy within 14 days or five half-lives, whichever is shorter, preceding the first dose of study drug. Steroids are permitted.

3.2.9 Participant must not have had major surgery within 4 weeks of initiating study treatment.

3.2.10 Participant must not have any evidence of active mucosal or internal bleeding.

3.2.11 Participants must not have known immediate or delayed hypersensitivity reaction or idiosyncratic reactions to belantamab mafodotin or drugs chemically related to belantamab mafodotin, or any of the components of the study treatment.

3.2.12 Participants must not have an uncontrolled intercurrent illness.

3.2.13 Participant must not have an uncontrolled active infection.

3.2.14 Participant must not have evidence of cardiovascular risk including any of the following:

- Evidence of current clinically significant uncontrolled arrhythmias, including clinically significant ECG abnormalities such as 2nd degree (Mobitz Type II) or 3rd degree atrioventricular (AV) block.
- History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting/bypass grafting within three (3) months of Screening.
- Class III or IV heart failure as defined by the New York Heart Association functional classification system [NYHA, 1994].
- Participant must not have uncontrolled hypertension defined as persistent systolic BP >160 mmHg or diastolic BP >100 mmHg.

3.2.15 Participant must not have psychiatric illness/social situations that would limit compliance with study requirements. Participants must not have any serious and/or pre-existing medical or other condition (including lab abnormalities) that could interfere with participant's safety in the opinion of the investigator.

3.2.16 Women who are pregnant or lactating are excluded from this study because belantamab mafodotin can cause embryo-fetal harm when administered to a pregnant woman. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with belantamab mafodotin, breastfeeding should be discontinued if the mother is treated with belantamab mafodotin.

3.2.17 Participant must not have presence of hepatitis B surface antigen (HBsAg), or hepatitis B core antibody (HBcAb) at screening or within 3 months prior to first dose of study treatment. Patients with presence of HBsAg, but demonstrate both HBSag and HBV PCR negativity will be eligible for the study.

3.2.18 Participant must not have positive hepatitis C antibody test result or positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment.
Note: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained.
Note: Hepatitis RNA testing is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.

3.2.19 Participant must not have uncontrolled HIV infection. HIV-infected patients on effective anti-retroviral therapy are eligible if they (1) have an undetectable viral load within the prior 6 months, or (2) have a detectable viral load with an absolute CD4 count of 200 cells per microliter or higher.

3.2.20 Participant must not have invasive malignancies other than disease under study, unless the second malignancy has been medically stable for at least 2 years and, in the opinion of the principal investigators, will not affect the evaluation of the effects of clinical trial treatments on the currently targeted malignancy. Participants with adequately treated basal, squamous cell carcinoma or non-melanomatous skin cancer, carcinoma in situ of the cervix, superficial bladder cancer not treated with intravesical chemotherapy or BCG within 6 months, localized prostate cancer and PSA <1.0 mg/dL on 2 consecutive measurements at least 3 months apart with the most recent one being within 4 weeks of study entry, may be enrolled without a 2-year restriction.

3.3 Inclusion of Women and Minorities

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

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 Principal Investigator (PI) of the registering site. 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 Massachusetts General Hospital by the Coordinating Center. All sites should call the Coordinating Center to verify slot availabilities.

Following registration, participants should begin protocol therapy within 5 days. Issues that would cause treatment delays should be discussed with the Sponsor-Investigator. 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. The Coordinating Center should be notified of cancellations as soon as possible.

4.4. Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the participating site and sent to the Coordinating Center:

- Copy of source documentation verifying all eligibility criteria and screening procedures, including but not limited to:
  - Pathology report
  - Radiology results/report
  - Medical history with details of prior treatments and therapies
  - Physical Exam
  - Laboratory report
  - Concomitant medication list
  - Study entry note confirming any eligibility criteria not directly addressed in source
- Demographic information
- Signed participant consent form
- HIPAA authorization form
- Eligibility Checklist

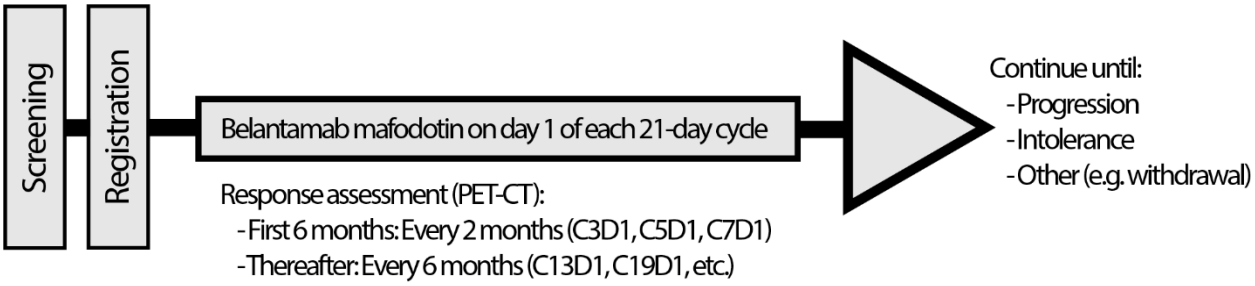
The Coordinating Center will review the above documentation to confirm eligibility and consent. To complete the registration process, the Coordinating Center will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (Policy#: REGIST-101) and register the participant on the protocol. Once registered a confirmation email with the participant study number, and if applicable the dose treatment level, will be sent to the participating site.

NOTE: Registrations can only be conducted by the Coordinating Center during the business hours of 8:30 AM and 5:00 PM Eastern Standard Time (or Eastern Daylight Time when applicable), Monday through Friday. A complete registration packet, including all documents listed above, must be received at least 24 hours *prior to* the anticipated registration to ensure adequate review. Same day treatment registrations will only be accepted with prior notice and discussion with the Coordinating Center.

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

5. TREATMENT PLAN

5.1 Treatment Regimen



A treatment cycle is defined as 21 consecutive days.

Belantamab mafodotin will be administered intravenously as a 2.5 mg/kg calculated dose on day 1 of each cycle. Treatment is intended to be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 8. Appropriate dose modifications are described in Section 6. 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 Pre-Treatment Criteria

5.1.1. Cycle 1, Day 1

Cycle 1 Day 1 (C1D1) laboratories need to be reviewed before treatment. Participants must have adequate organ and marrow function without clinically significant change to proceed with treatment.

5.1.2. Subsequent Cycles

Patients should be assessed clinically for toxicity at each visit using the NCI CTCAE v5.0 (http://evs.nci.nih.gov/ftp1/CTCAE) grading scale. Dosing should occur only if a patient's clinical assessment and laboratory test values are acceptable (See **Section 5.1.1**). The CBC with differential and chemistries must be reviewed prior to treatment administration.

5.3 Agent Administration

Belantamab mafodotin will be administered as a monotherapy intravenously as a 2.5 mg/kg calculated dose (see Section 9.1.8). Premedication is not required prior to infusion unless deemed medically necessary by the investigator. The dose of belantamab mafodotin must not exceed 2.5 mg/kg over a 21-day period.

For any participant experiencing an infusion-related reaction (IRR), immediately interrupt belantamab mafodotin infusion and manage symptoms. Once reaction symptoms resolve, resume infusion at a reduced rate as described in Section 6 Table 2. Premedication may be required with subsequent infusions as described in Section 6 Table 2. Participants that experience a Grade 4 IRR associated with belantamab mafodotin should be permanently withdrawn from the study.

Guidance on management of IRRs in provided in Section 6 Table 2.

5.4 Corneal Supportive Care Guidelines

Changes in visual acuity, which commonly manifest as changes in corneal epithelium, have been observed on ocular exams with antibody drug conjugates, including those conjugated to MMAF.

Sites are required to establish a close collaboration with an ophthalmologist or optometrist (if an ophthalmologist is not available) who will be responsible for assessing patients and managing those who develop changes in corneal epithelium on ocular examination:

- On-study ocular exams to be performed by an ophthalmologist or optometrist (if an ophthalmologist is not available) at baseline, prior to each dose of belantamab mafodotin in all cycles (should be within 5 days prior to dosing [supersedes window below in calendar] and all efforts should be made to schedule as close to belantamab mafodotin dosing as possible), and promptly for worsening symptoms.
    i. Additional exams may be performed by ophthalmologist as clinically indicated.
    ii. If vision changes or ocular symptoms develop, patient should be evaluated by an ophthalmologist.
    iii. In case of persistent or newly developed ocular symptoms or vision changes, the participants will have further ophthalmologic exams, at least every 3 months until resolution (to grade 1 or baseline) or more frequently as clinically indicated by the eye care specialist.

Patients will receive the following supportive care to reduce the risk of corneal epithelium changes:

- Prophylactic preservative-free artificial tears must be administered in each eye at least 4-8 times daily beginning on C1D1 until end of treatment. In the event of ocular symptoms (i.e. dry eyes), the use of artificial tears may be increased up to every 2 hours as needed.
- Corticosteroid eye drops are not required but can be used if clinically indicated per discretion of an eye-care specialist. Allow at least 5-10 minutes between administration of artificial tears and steroid eye drops (if administered).
- At the start of each infusion, participants may apply cooling eye masks to their eyes for approximately 1 hour or as long as tolerated.

Further information regarding changes in the corneal epithelium associated with belantamab mafodotin, including a grading scale and prophylactic measures are in Appendix C.

5.5 General Concomitant Medication and Supportive Care Guidelines

Participants should receive prophylactic allopurinol (or febuxostat if intolerant/allergy to allopurinol) and be encouraged to hydrate well on days 1-7 of cycle 1 for prevention of tumor lysis syndrome (may be started earlier or continued later at investigator discretion). For patients with elevated uric acid on C1D1, prophylactic rasburicase should be administered.

Participants should receive full supportive care during the study, including transfusions of blood

products, growth factors, and treatment with antibiotics, anti-emetics, antidiarrheal, and analgesics, as appropriate.

Elimination pathways for belantamab mafodotin and cys-mcMMAF have not been characterised in humans, however, cys-mcMMAF was shown to be a substrate of P-gp and OATP transporters in vitro. Caution should be exercised when belantamab mafodotin is combined with strong inhibitors of P-gp, and strong inhibitors of OATP should be avoided unless considered medically necessary.

The following medications and devices are prohibited while receiving study treatment:

- Concomitant administration of strong P-glycoprotein (P-gp) inhibitors and strong inhibitors of OATP with belantamab mafodotin should be avoided unless considered medically necessary.
- Any other anti-cancer therapy not specified in this protocol, and any investigational agents other than belantamab mafodotin.
- Contact lenses.
    - NOTE: Contact lens use may be restarted after the ophthalmologist (or an optometrist if an ophthalmologist is not available) confirms there are no other contraindications.

5.6 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 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 intravenous medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- Participant has met any of the protocol defined safety stopping criteria
- Pregnancy
- 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 participant's status must be updated in OnCore in accordance with REGIST-OP-1.

5.7 Duration of Follow Up

Participants will be followed for 2 years after removal from protocol therapy or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Participants with corneal signs or symptoms at the End of Treatment Visit will be followed once a month (± 7 days) until deemed clinically stable by an ophthalmologist (or an optometrist if an ophthalmologist is not available), or up to 1 year (whichever comes first).

5.8 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 the participant's status is updated in OnCore in accordance with REGIST-OP-1.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Adjustments due to body weight

The actual body weight in kg at baseline (assessed on C1D1 prior to dosing) will be used for dose calculation of belantamab mafodotin in all participants during the treatment period. However, if the change of body weight is greater than 5%, the dose must be recalculated based on the actual body weight at the time of dosing.

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

6.2 Dose reductions for toxicity

After Cycle 1, dose modifications may be made for individual participants, based on safety findings. Dose interruptions and reductions are permitted throughout the study per guidance in Table 1.

- Guidance for belantamab mafodotin dose reductions and delays - Table 2.
- Dose modification and management guidelines for drug-related adverse events not otherwise specified - Table 3.
- Dose Modification guidelines for belantamab mafodotin related corneal events – Table 4.

Table 1. Permitted Dose Reductions

Starting belantamab mafodotin dose	1st reduction	2nd reduction	3rd reduction
2.5 mg/kg	1.9 mg/kg	1.4 mg/kg	Discontinue

- The dose allowed for belantamab mafodotin may be reduced. If the participant is unable to tolerate at least belantamab mafodotin at 1.4 mg/kg, they will be withdrawn from the study due to unacceptable toxicity.
- In case of full resolution of symptoms which lead to dose reduction, further treatment at the previous dose may be considered by the investigator.

Dosing delays are permitted in the case of medical/surgical events or for logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, participant vacation and/or holidays) but not for participants' decision to delay treatment. If a dose is delayed, the participant should wait for the next scheduled dose to resume treatment. In individual cases, where in the judgement of an investigator waiting a full cycle to resume treatment after delay (skipping dose) related to toxicity which has resolved would be detrimental to patient's health, an earlier re-start may be considered at the discretion of the Sponsor-Investigator. The dosing with belantamab mafodotin cannot occur more frequently than every 21 days (± 3-day window).

Table 2. Dose Modification Guidelines for belantamab mafodotin-related Adverse Events

Toxicity	Grade/description of toxicity	Recommendations for belantamab mafodotin
Elevated serum creatinine which cannot be explained by concomitant sepsis, TLS, other severe condition with fever, or dehydration	If absolute serum creatinine increases from baseline by >0.5 mg/dL	• Repeat serum creatinine within 48 hours • If confirmed: withhold therapy, institute treatment and monitoring as clinically indicated, and follow for resolution
Serum creatinine >Grade 3	>3.0 mg/dL from baseline or 3.0-6.0x institutional ULN	• Provide appropriate medical treatment. • Permanently discontinue treatment with belantamab mafodotin

Toxicity	**Grade/description of toxicity**	**Recommendations for belantamab mafodotin**
Spot urine (albumin / creatinine ratios)	>2000 mg/g (or 224 mg/mmol)	• Re-test (at least 7 days apart). • If not confirmed, continue belantamab mafodotin at 100% dose • If confirmed on re-test and no clear evidence of disease progression o Interrupt treatment with belantamab mafodotin o Repeat testing within 4 weeks i. If spot urine ≤2000 mg/g (224 mg/mmol), may restart belantamab mafodotin with 1 dose level reduction ii. If spot urine remains >2000 mg/g (224 mg/mmol) after 4weeks, permanently discontinue belantamab mafodotin and withdraw participant from study; provide treatment as clinically indicated and follow for resolution
Urine Dipstick	Grade 2	• May continue belantamab mafodotin dosing. • Confirm by quantitative assessment using albumin/creatinine (spot urine from first void) • If albumin/creatinine ≥2000mg/g, at the next cycle follow guidance above for spot urine
	Grade ≥ 3	• Interrupt treatment and follow up for recovery. Implement quantification of albumin/creatinine ratio
Thrombocytopenia (on days of dosing)	Grade 3	• No bleeding: continue treatment with 1 dose level reduction. Consider reverting to previous dose once thrombocytopenia recovered to G2 or less. • With bleeding: withhold the dose, continue treatment after recovery to G2 or less with 1 dose level reduction • Consider additional supportive treatment (e.g. transfusion), as clinically indicated and per local guidance.

Toxicity	**Grade/description of toxicity**	**Recommendations for belantamab mafodotin**
Thrombocytopenia (On days of dosing)	Grade 4	• Withhold the dose. Consider restarting with 1 dose level reduction if recovered to ≤G3 only if there is no active bleeding at time of treatment re-start
		• If thrombocytopenia is considered disease related, is not accompanied by bleeding, and recovers with transfusion to >25x10^9/L continuing treatment with 1 dose level reduction may be considered
Afebrile neutropenia (graded according to NCI-CTCAE criteria)	Grade 3-4 (defined as ANC <1000/mm^3)	• If noted on Day 1 of any cycle, withhold belantamab mafodotin dose. • Resume belantamab mafodotin at pre-held dose once neutropenia recovers to Grade ≤ 2 (ANC ≥ 1000/mm^3) on Day 1 of a subsequent cycle. • Prophylactic antibiotics, per physician discretion and local institutional guidance. • Consider growth factors. • Local guidance must be followed for hematological monitoring, if more conservative than the protocol schedule of activities specifications. • In cases of frequent recurrent neutropenia (ANC <1000/mm^3), consider dose reduction of belantamab mafodotin by 1 dose level.
Febrile neutropenia (graded according to NCI-CTCAE criteria)	Grade 3-4 (defined as: single temp of 38.3°C, or sustained 38°C for >1 hr. AND ANC <1000/mm^3)	• Withhold the dose • Hospitalize participant and implement appropriate management, per institutional guidance • Consider additional supportive treatment per local practice (e.g. growth factors) • Continue treatment after resolution. Consider a dose reduction of belantamab mafodotin, if neutropenia was drug related
Infusion Reaction[a]	Grade 2	• Stop the infusion, provide medical treatment and continue at half the original infusion rate after resolution to Grade 0-1
	Grade 3	• Continuation only allowed after recovery to ≤G1 and with pre-medication, and extension of infusion time to 2-4 hours. Any future infusion needs to be pre-medicated

Toxicity	Grade/description of toxicity	Recommendations for belantamab mafodotin
	Grade 4	• Permanently discontinue
Pneumonitis	Grade 2	• Withhold the dose • When resolved, restart treatment with a 1 dose level reduction • If patient is already at the lowest dose level, then rechallenge with the same dose must be discussed with Medical Monitor
	Grade 3-4	• Permanently discontinue

a. If symptoms resolve within one hour of stopping infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant must be pre-medicated for the next scheduled dose.

Table 3. General Dose Modification and Management Guidelines for Drug-related Adverse Events Not Otherwise Specified[a]

Severity	Management	Follow-up
Grade 1	• Administer symptomatic treatment as appropriate • Continue study drug(s)[a]	Provide close follow-up to evaluate for increased severity, no dose modification necessary
Grade 2	• Administer symptomatic treatment • Investigate etiology • Consider consulting subspecialist, and/or diagnostic procedure	*Symptoms resolved in ≤7 days:* Continue after resolution at the current dose *Symptoms ongoing >7 days or worsening:* • Delay study drug, or consider 1 dose level reduction. If recovery takes >3 weeks, consult with study medical monitor • If symptoms continue or worsen to G3-4, see below
Grade 3	• Provide appropriate medical treatment • Consider Consulting subspecialist	• Delay treatment till recovery to G1 or less. • Consider dose reduction. • Exceptions: Participants who develop G3 toxicities which respond to standard treatment and resolve to ≤G1 within 48 hours may continue treatment at scheduled or reduced dose
Grade 4	• Provide appropriate medical treatment • Consider Consulting subspecialist	• Interrupt treatment. • Further treatment with belantamab mafodotin only allowed on individual basis it is agreed that benefits outweigh the risks for a given participant

a. Treatment-related decisions can be made based on local laboratory results if central results are not available or delayed.

Table 4. Dose Modification Guidelines for Corneal-Related Adverse Events Associated with belantamab mafodotin

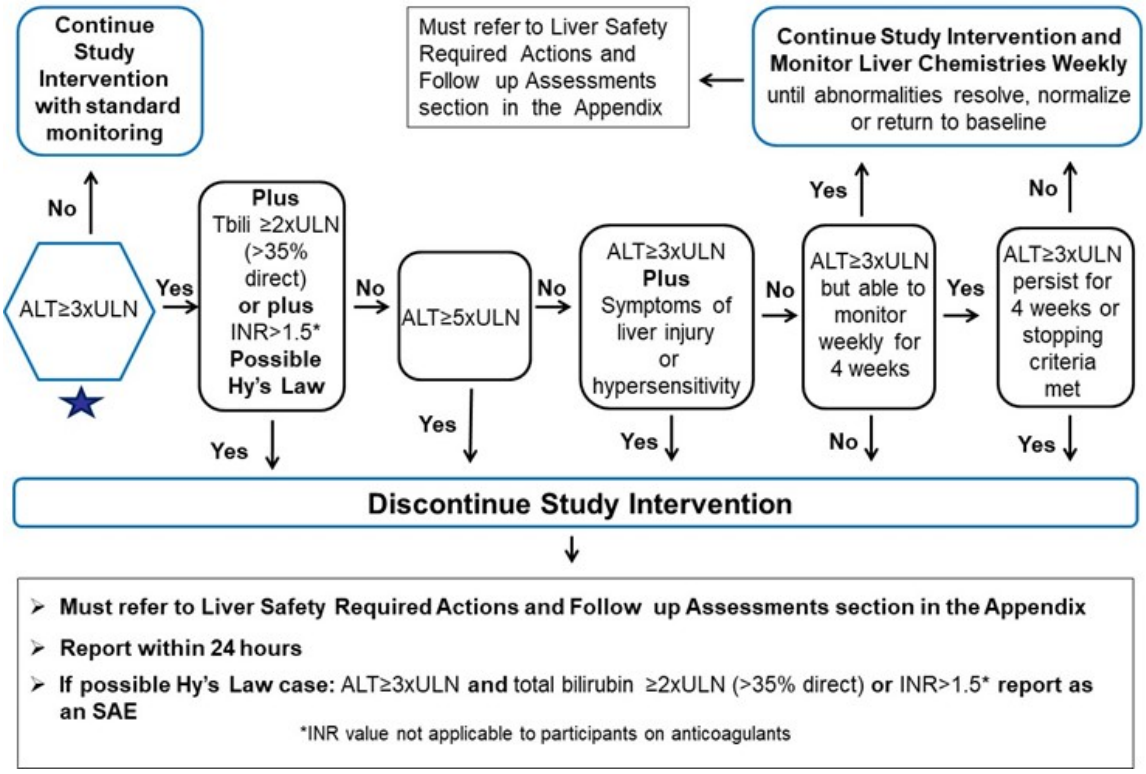
Grade/description of toxicity (as described in belantamab mafodotin Prescribing Information)	**Recommendations**
Grade 1: Based on worst finding in the worst affected eye, and should be based on either a corneal examination finding or a change in visual acuity per the Keratopathy and Visual Acuity Scale: *Corneal examination finding(s):* - Mild superficial keratopathy (documented worsening from baseline), with or without symptoms *Change in best-corrected visual acuity:* - Decline from baseline of 1 line on Snellen Visual Acuity due to treatment-related corneal findings	Continue treatment at current dose.
Grade 2: Based on worst finding in the worst affected eye, and should be based on either a corneal examination finding or a change in visual acuity per the Keratopathy and Visual Acuity Scale: *Corneal examination finding(s):* - Moderate superficial keratopathy with or without patchy microcyst-like deposits, subepithelial haze (peripheral), or a new peripheral stromal opacity. *Change in best-corrected visual acuity:* - Decline from baseline of 2 or 3 lines on Snellen Visual Acuity and not worse than 20/200	Hold treatment and allow to recover to ≤G1 (both corneal examination findings and change in best corrected visual acuity). Once recovered, resume therapy with 1 dose level reduction. • If already on 1.4 mg/kg, participant continues treatment at same dose. Upon resolution (e.g., G1), re-escalation to previous dose level may be considered with overall PI approval.
Grade 3: Based on worst finding in the worst affected eye, and should be based on either a corneal examination finding or a	Hold treatment and allow to recover to ≤G1 (both corneal examination findings

Grade/description of toxicity (as described in belantamab mafodotin Prescribing Information)	**Recommendations**
change in visual acuity per the Keratopathy and Visual Acuity Scale: *Corneal examination finding(s):* - Severe superficial keratopathy with or without diffuse microcyst-like deposits, subepithelial haze (central), or a new central stromal opacity. *Change in best-corrected visual acuity:* - Decline from baseline by more than 3 lines on Snellen Visual Acuity and not worse than 20/200	and change in best corrected visual acuity). Once recovered, resume therapy with 1 dose level reduction. • If already on 1.4 mg/kg, participant resumes at same dose. If after event resolution eye symptoms are considered stable for at least 3 cycles and if vision is ≤G1, consider re-escalation to dose prior to dose level reduction.
Grade 4: Based on worst finding in the worst affected eye, and should be based on either a corneal examination finding or a change in visual acuity per the Keratopathy and Visual Acuity Scale: *Corneal examination finding(s):* - Corneal epithelial defect such as corneal ulcers. *Change in best-corrected visual acuity:* - Snellen Visual Acuity worse than 20/200	Hold treatment, restart only after discussion with sponsor for patients whose vision improves to ≤G1 (both corneal examination findings and change in best corrected visual acuity). Resume treatment with 1 dose level reduction. If participant was already on 1.4 mg/kg, continue at the same dose.

7. STOPPING CRITERIA FOR BELANTAMAB MAFODOTIN

7.1 Liver Stopping Criteria

Liver chemistry stopping/increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology. Discontinuation of study treatment for abnormal liver tests related to belantamab mafodotin is required when the participant satisfies any of the stopping rules as shown below.



If a participant meets liver chemistry stopping criteria, do not restart/re-challenge participant with study treatment without overall approval by overall PI and Sponsor Medical Monitor.

7.2 QTc Stopping Criteria

ECGs are obtained at screening then only as clinically indicated (i.e. recommended if new QTc prolonging medications are initiated after treatment initiation). If a participant has corrected QT (QTc) interval duration criteria >530 msec, 2 additional ECGs will be obtained over a brief period (*e.g.*, within approximately 10 minutes of the abnormal ECG and approximately 2 minutes apart from each other, if possible).

- QTc is calculated by Fridericia's formula (QTcF)
- In the setting of a bundle branch block (BBB):
  QTc = calculated QTcF - (BBB duration – 120 msec)

If the averaged QTc values of the 3 ECGs is >530 msec, treatment will be withheld. Attempts should be made to correct the QTc (e.g. by reducing or stopping other QTc-prolonging medications and/or correcting electrolyte abnormalities), and study treatment may subsequently be resumed if the averaged QTc values of 3 ECGs is <500 msec.

7.3 Corneal Event Stopping Criteria

All belantamab mafodotin dose modifications and stopping criteria are to be based on the CTCAE v5. Corneal events will be graded according to Keratopathy and Visual Acuity (KVA) criteria for eye disorders.

Participants who develop Grade 4 corneal events must be discussed in detail with the treating ophthalmologist (or an optometrist if an ophthalmologist is not available), in order to determine whether the participant can be allowed to continue treatment with belantamab mafodotin, or permanently discontinue treatment. If a participant is allowed to continue treatment, the dose of belantamab mafodotin will be reduced by 1 dose level (Section 6). The decision will be documented in study files, together with individual assessment of risk-benefit.

7.4 Infusion Related Reaction Stopping Criteria

Premedication is not required prior to infusion unless deemed medically appropriate by the investigator following evaluation of infusion-related reactions (IRRs). Premedication should be considered in any participant who experienced an IRR at first or any subsequent infusion with belantamab mafodotin, and are administered per institutional policy. For infusion reactions of any grade/severity, immediately interrupt the belantamab mafodotin infusion and manage symptoms. Once reaction symptoms resolve, resume the infusion at a reduced rate. Premedication may be required with subsequent infusions.

A participant that experiences a Grade 4 IRR associated with belantamab mafodotin should be permanently withdrawn from the study without overall approval by overall PI and Sponsor Medical Monitor.

7.5 Allergic Reaction and Anaphylactic Reaction Stopping Criteria

All participants will be monitored carefully for evidence of allergic response to treatment. A participant who exhibits severe hypersensitivity or anaphylaxis will receive appropriate medical treatment and will permanently discontinue study treatment.

8. 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 (Section 8.1) and the characteristics of an observed AE (Section 8.3) will determine whether the event requires expedited reporting **in addition** to routine reporting.

8.1 Adverse Event List for belantamab mafodotin

Please refer to section 6 of the current investigator brochure for the comprehensive and updated list of adverse events.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Treatment belantamab mafodotin		
Changes on Ocular Examination	Changes to the corneal epithelium on ocular examination have been frequently observed with belantamab mafodotin. This was most commonly associated with: blurred vision, dry eyes, photophobia, and changes in vision.	Active monitoring for superficial corneal changes according to the study calendar (Section 8). Recommendations for dose delays/reductions are provided in Section 5.
Infusion-Related Reaction (IRR)	IRRs were reported in participants treated with belantamab mafodotin. Most IRRs observed to date were Grade 1 to 2 and manageable with medical treatment.	Participants will be closely monitored for signs of IRR. Premedication prior to first infusion of belantamab mafodotin is not mandatory but may be considered based on investigator judgment, and may be given per institution policy. If an IRR occurs during belantamab mafodotin administration, management will follow guidance in Section 5.
Thrombocytopenia	Thrombocytopenic events (Grades 1 to 4) are among the most common AEs associated with belantamab mafodotin.	Routine monitoring of haematologic panels as outlined in Section 8. Supportive therapy (including transfusions) per local medical practice Recommended dose reductions or treatment discontinuations are outlined in Section 5.
Neutropenia	Neutropenic events, including febrile neutropenia have been observed with treatment with belantamab mafodotin, In a study of belantamab mafodotin in combination with lenalidomide/ dexamethasone, two fatal cases of severe infections associated with neutropenia have been observed.	Routine monitoring of haematologic panels as outlined in Section 7. Prophylactic antibiotics, per institutional guidance, in participants with Grade 3-4 neutropenia (absolute neutrophil count [ANC] $<1.0x10^9/L$) Immediately hospitalize participants with febrile neutropenia Consider additional supportive

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		treatment(s) per local practice (e.g., transfusion, growth factors). Dose reductions or treatment discontinuations are outlined in Section 6.
Potential for Cardiotoxicity Related to an Inflammatory Response	Nonclinical studies, predominantly in monkey, increased activation of macrophages was noted in a number of organs at ≥3 mg/kg/week, reflective of a systemic inflammatory response. Minimal inflammatory changes (inflammatory cell infiltrate and/or haemorrhage) were also noted in hearts (atrial epicardium, ventricle endocardium) of single monkeys, which were nonadverse and reversible. Incidence of cardiac events reported to date with belantamab mafodotin was relatively low and mostly Grade 1-2.	Participants with significant cardiac risk factors will be excluded from study participation. Electrocardiogram and LVEF will be measured as clinically indicated.
Hepatotoxicity	In nonclinical studies liver is a target organ for toxicity, with increased liver weights and/or raised hepatobiliary enzymes and transaminases observed in both rat and monkey. These changes in the liver were without clinical consequence in the shorter duration studies and in the rat 13-week study. In the monkey 13-week study, progression of liver toxicity to include minimal multifocal hepatocellular necrosis was observed at all doses administered (≥3 mg/kg/week). Mild elevations of liver enzymes have been reported in some	Only participants with well-preserved liver function per the inclusion/exclusion criteria will be allowed on study. Participants with chronic HBV and HCV will be excluded. Liver function tests will be regularly monitored (Section 7) Liver stopping criteria outlined in Section 7.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	participants treated with belantamab mafodotin.	
Nephrotoxicity	Non-clinical safety studies have demonstrated dose dependent and reversible primary glomerular injury and tubular degeneration (in rat and monkey), accompanied by large molecular proteinuria (albuminuria) and enzymuria. Single cell necrosis of the kidney and bladder urothelium was also noted in the 13-week monkey study. Severe tubular degeneration/regeneration and marked glomerulonephritis exacerbated by immune complex disease, likely associated with ADA, led to the early euthanasia of one monkey following 5 weekly doses of 10 mg/kg. No significant renal findings were reported to date in clinical trials	Participants will be monitored for kidney function by assessing creatinine, eGFR, electrolytes, and albumin / creatinine ratios (spot urine). Participants will be educated about the need of maintaining adequate urinary output. Dose reductions and treatment stopping criteria will be applied according to Section 5 and Section 6.
Pulmonary toxicity (pneumonitis)	Nonclinical safety experiments have demonstrated the presence of progressive microscopic changes in the lungs (prominent alveolar macrophages associated with eosinophilic material; mixed perivascular/neutrophilic inflammation) in rats at all doses tested. To date no significant pulmonary toxicity has been reported in clinical trials.	Monitoring for clinical signs and symptoms potentially related to pulmonary toxicity. Further diagnostic tests and management will be implemented immediately according to recommendations provided in Section 6.
Immunosuppression	In nonclinical studies belantamab mafodotin has been associated with decreases in immunoglobulins in monkeys at all doses. An increase in immunoglobulins was seen in rats (rats are not an antigen	Participants who have active infection will be excluded. Patients with an active infection excluded. Monitoring for infections and immediate treatment according to standard practice.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	specific species for belantamab mafodotin). MM participants frequently are immunodeficient due to the underlying condition. Assessment of changes in immunoglobulin levels is challenging in participants with MM	
Potential for Other Laboratory Abnormalities	An increased magnitude of aspartate aminotransferase (AST) relative to alanine aminotransferase (ALT) consistent with increased skeletal troponin I was observed in the single dose monkey study. Increased skeletal troponin I and/or creatine kinase and aldolase were observed in the rat 3-week study. Cases of elevated AST, lactic dehydrogenase (LDH) and creatine kinase (CK), and gamma glutamyl transferase (GGT) alone or concomitant with no clear clinical correlate have been observed in clinical studies.	Laboratory parameters will be monitored as outlined in the study calendar (Section 11). Participants with significant laboratory elevations (≥3x institutional upper limit of normal [ULN]) should, where possible, have a sample sent for central testing of CK and LDH isoenzyme levels.
Embryo-Fetal Toxicity	Nonclinical reproductive studies with belantamab mafodotin have not been conducted. Embryo-fetal toxicity is expected due to the cytotoxic component, cys-mcMMAF via nonspecific uptake and/or BCMA-mediated toxicity (due to reports of BCMA expression in human placental cells). Use of belantamab mafodotin in pregnant women may cause fetal harm.	Pregnancy testing outlined in the study calendar (Section 11). See Contraception requirements in Appendix E.
Impaired Male and Female Fertility	In animal studies, belantamab mafodotin treatment has resulted in testicular toxicity and adverse	Men who may wish to father children in the future will be advised to have sperm samples

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	effects on spermatogenesis. Reversibility of testicular toxicity is unknown at this time. In addition, luteinized non-ovulatory follicles were observed in the ovaries of rats after 3 weekly doses. Ovarian toxicity not observed following 12 weeks off dose and only after weekly dosing.	frozen and stored prior to belantamab mafodotin treatment. Women of childbearing potential who may desire offspring in the future will be counselled about the option of having eggs frozen before treatment. See Contraception requirements in Appendix E.
Risks from Study Procedures		
Bone Marrow Aspiration/Biopsy	Pain, infection, bleeding may occur after the procedure.	Participants will be treated according to institution's practice
Incidental Findings During Imaging Data Acquisition	During the acquisition of imaging data (e.g., MRI, CT, PET, ECHO), non-MM disease or drug-related clinical abnormalities could be found by the radiographer or echocardiographer performing the exams.	All imaging scans will be reported to the site by an appropriate imaging clinician (non-anonymized) for non-MM disease- or drug-related and non-specific findings on clinical abnormalities.

8.2 Expected Toxicities

8.2.1. Adverse Events List

8.2.1.1. Adverse Event List for belantamab mafodotin

Single-agent belantamab mafodotin was demonstrated to have a manageable safety profile in heavily pre-treated participants with RRMM. Safety data for single-agent belantamab mafodotin was pooled (data as of 20Sep2019) for study 205678 (DREAMM-2) and supportive FTIH study BMA117159 (DREAMM-1) by treatment cohorts of 2.5 mg/kg and 3.4 mg/kg.

The most common AEs in both treatment cohorts were keratopathy (corneal epithelium changes observed on ophthalmic examination), thrombocytopenia and anaemia. The incidence of AEs, including Grade 3/4 AEs was comparable between belantamab mafodotin 2.5 mg/kg and 3.4 mg/kg cohorts. Adverse events leading to dose delays, and reductions were less frequent in 2.5 mg/kg cohort, 51% and 32% compared with the 3.4 mg/kg cohort, 67% and 52%, respectively. AEs leading to permanent treatment discontinuation occurred in 10% and 11% of participants in the 2.5 and 3.4 mg/kg cohorts, respectively. More participants in the 3.4 mg/kg cohort experienced SAEs (50%) and fatal SAEs (6%) compared with the 2.5 mg/kg cohort (41% and 3%, respectively).

Single agent belantamab mafodotin 2.5 mg/kg was selected as the recommended dose based on comparable efficacy with a more favourable safety profile (i.e. lower incidence of thrombocytopenia and neutropenia and less frequent dose delays or reductions) compared with the 3.4 mg/kg dose.

8.2.1.2. Description of key adverse event for belantamab mafodotin

Tumor lysis syndrome
On the basis of grade 4 tumor lysis syndrome (TLS) observed in the first patient enrolled on study, who exhibited very high pre-treatment disease burden, TLS was added to the informed consent form and investigators were advised to consider inpatient hospitalization / observation for close TLS monitoring during cycle 1 in patients with very high disease burden. This is at the discretion of the treating investigator per standard practice/care for patients with high-burden lymphoma initiating anti-lymphoma therapy.

Corneal Events
Corneal events, reported in most cases as keratopathy, blurred vision and dry eye events are the most frequently reported AEs with belantamab mafodotin.

In DREAMM-2 (data as of 31Jan2020), events in the Eye disorders SOC occurred in 78% of participants treated with belantamab mafodotin 2.5 mg/kg. The most common ocular AEs were keratopathy (71%, changes in corneal epithelium identified on eye exam, with or without symptoms), blurred vision (22%), and dry eye (13%). Decreased vision defined as Snellen score worse than 20/50 in the better seeing eye was reported in 18% of participants receiving belantamab mafodotin 2.5mg/kg. Severe vision loss defined as 20/200 or worse in the better

seeing eye was reported in 1% of participants receiving belantamab mafodotin 2.5 mg/kg.

The median time to onset of Grade 2 or above corneal findings (best corrected visual acuity or corneal examination) was 36 days (range: 19 to 143 days) in participants receiving belantamab mafodotin 2.5 mg/kg. The median time to resolution of these corneal findings was 91 days (range: 21 to 201 days).

Participants with history of dry eye were more prone to develop corneal examination findings. Therefore, active management of dry eye symptoms prior to and during treatment is recommended (i.e. administration of preservative-free artificial tears).

The ocular sub-study of DREAMM-2 provided no evidence that corticosteroid eye drops are beneficial in preventing or mitigating corneal events.

Infusion-Related Reactions
Infusion-related reactions (IRRs) are expected for biologic agents. In DREAMM-2 (data as of 31Jan2020), IRRs occurred in 21% of participants in the belantamab mafodotin 2.5 mg/kg, which were Grade 1 - 3 in severity. Most IRRs occurred with the first infusion and few participants experienced IRRs with subsequent infusions.

Although not protocol-mandated, pre-medications for IRR prophylaxis (including paracetamol, antihistamines, and steroids) were administered to 26%–27% of participants. One participant (2.5 mg/kg cohort) discontinued treatment due to IRRs (Grade 3 IRRs at first and second infusion).

Thrombocytopenia
In DREAMM-2 (data as of 31Jan2020), thrombocytopenic events (thrombocytopenia and platelet count decreased) occurred in 38% participants treated with belantamab mafodotin 2.5 mg/kg; severity ranging between Grade 1 and 4. The incidence of Grade 3 bleeding events was low (2%), with no Grade 4 or 5 events reported in participants treated with belantamab mafodotin 2.5 mg/kg.

Most participants had a decrease from baseline in their platelet counts during the study. In general, participants who initiated treatment with lower platelet numbers tended to continue to have thrombocytopenia while on treatment with belantamab mafodotin.

8.3 Adverse Event Characteristics

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

  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-

Specific Expedited Adverse Event Reporting Exclusions.

- **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.

8.4 Expedited Adverse Event Reporting

In the event of an unanticipated problem or life-threatening complications treating investigators must **immediately** notify the PI and the Coordinating Center.

Investigators **must** report to the PI/Coordinating Center any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 70 days of the last dose of treatment regardless of causality or expectedness. SAEs that occur after that must be reported if suspected as related to the study treatment. Reports should be submitted within 1 business day of event awareness using the FDA MedWatch 3500 form.

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.4.1. DF/HCC Expedited Reporting Guidelines

For Multi-Center Trials, each participating institution must abide by the reporting requirements set by the DF/HCC and DFCI IRB. The following events require expedited reporting:

- All life threatening and fatal Serious Adverse Events (grade 4 and 5) considered serious, unexpected, and related, must be submitted via a written adverse event report to the DFCI Office for Human Research Studies (OHRS) within 5 working days from notification of the event.
- For all other Serious Adverse Events considered serious, unexpected, and related, a full written adverse event report must be submitted to OHRS within 10 working days from notification of the event.

- Any unrelated adverse event does not require reporting to OHRS except grade 5 events which must be reported at the time of continuing review.

'Reasonable possibility' means there is evidence to suggest a causal relationship between the study intervention and the adverse event.

Unexpected means the adverse event is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan (e.g., protocol or consent form).
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 SAEs to the Coordinating Center and to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. The Coordinating Center will report external site events to OHRS per the requirements above.

	)				

8.4.2. Protocol-Specific Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the DF/HCC Sponsor-Investigator. However, they still must be recorded through the routine reporting mechanism (i.e. case report forms).

CTCAE SOC	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments
	N/A				

8.5 Reporting to the Food and Drug Administration (FDA)

The Sponsor-Investigator will be responsible for all communications with the FDA. The Coordinating Center, on behalf of the Sponsor-Investigator, 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. Initial and follow-up reports should be submitted to the Coordinating Center using the FDA MedWatch 3500 form.

8.7 Expedited Reporting to GSK

All SAEs and pregnancies, and follow up information must be reported to GSK on an SAE

Report Form or Pregnancy report form within 24 hours of Coordinating Center investigator becoming aware of the initial event or follow-up information. The Coordinating Center will submit all adverse events reports to GSK regardless of the site of occurrence. The Sponsor Institution must provide a causality assessment and must sign, and date all SAE Report Forms.

If supporting documentation is included in the submission to GSK (e.g., hospital reports, consultant reports, death certificates, autopsy reports, etc.), please redact any patient identifiers (including Medical Record number).

GSK SAE and Pregnancy Reporting Information
Email: OAX37649@gsk.com

On at least an annual basis, the Sponsor Institution will provide a copy of the safety reports submitted to applicable Regulatory Authorities or IECs. Annual reports should be provided to GSK within 3 business days of submission to the applicable regulatory body.

On a quarterly basis the Sponsor Institution will provide GSK with a line listing of all adverse events (serious and non-serious) received during a defined quarter. The line listing will include a subject ID, the AE term, onset date, outcome, causality assessment, severity, and study drug dosing information.

8.6.1. Relationship to Study Drug

The Investigator must provide a causality assessment regarding the relationship of the event with the study drug for all AEs. One of the following categories should be selected based on medical judgment, considering all contributing factors:

- **Related**: There is a reasonable possibility of a causal relationship between the medicinal product and AE, *i.e.* there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- **Not Related**: A causal relationship between the medicinal product and the AE cannot be established, based on consideration of factors described above.

The investigator may change their opinion of causality in light of follow-up information, and provide an updated causality assessment, in the originally completed SAE form, as applicable.

8.6.2. Adverse Events of Special Interest (AESI) for Belantamab mafodotin

An Adverse Event of Special Interest (AESI) is defined as any AE (serious or non-serious) that is of scientific and medical concern specific to the study treatment.

AESI's for belantamab mafodotin include the following:

- Thrombocytopenia
- Infusion related reactions

- Corneal events

Severity of corneal events will be graded according to the CTCAE v5.

8.6.3. Collection of Pregnancy Information

Male participants with partners who become pregnant:

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study and for 6 months following the last dose of belantamab mafodotin. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and send it to the Coordinating Center for submission to GSK within 24 hours of learning of the partner's pregnancy.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female participants who become pregnant:

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study and for 9 months following the last dose of belantamab mafodotin.
- Information will be recorded on the appropriate form and submitted to GSK by the Coordinating Center within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to GSK. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will discontinue study

treatment.

8.7 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.

8.8 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the 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.**

9. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 8.1.

9.1 Belantamab mafodotin

9.1.1. Description

Please refer to the current investigator brochure.

Belantamab mafodotin (GSK2857916) is a dual acting Antibody-Drug Conjugate (ADC), comprised of an anti-B-Cell Maturation Antigen (BCMA) afucosylated humanized immunoglobulin G1 (IgG1) conjugated with the tubulin polymerization disrupting agent monomethyl auristatin F (MMAF).

The normal function of BCMA is to promote cell survival by transduction of signals from two known ligands: B cell activating factor from the tumor necrosis factor (TNF) family (BAFF/BLys) and a proliferation inducing ligand (APRIL). BCMA expression is restricted to B cells at later stages of differentiation, with expression on germinal center B cells in tonsil, blood plasma blasts, and long-lived plasma cells. BCMA is expressed in various B cell malignancies, including multiple myeloma (MM), diffuse large B-cell lymphoma (DLBCL), large B-cell lymphoma (LBCL), chronic lymphocytic leukemia (CLL) and Waldenstrom's macroglobulinemia (WM) at varying frequencies.

Belantamab mafodotin binds to BCMA, is internalized, and releases free cys-mcMMAF, which disrupts the microtubule network, leading to cell cycle arrest and apoptosis. Belantamab mafodotin also mediates antibody-dependent cell-mediated cytotoxicity (ADCC) effector function directed towards BCMA-expressing cells. The mechanisms of action of belantamab mafodotin are designed to enable anti-tumor activity of cells by ADCC activity (non-dividing), as well as ADC activity (dividing cells). Moreover, ADC-induced apoptosis by belantamab mafodotin was recently shown to be potentially

immunogenic as measured by cell surface externalization of calreticulin (CRT) and secretion of high mobility group box 1 (HMGB1) and adenosine triphosphate (ATP).

Belantamab mafodotin (GSK2857916) is an afucosylated humanized IgG1κ monoclonal antibody conjugated with an average of four maleimidocaproyl monomethyl auristatin F (mcMMAF [SGD-1269]) that binds to BCMA.

The theoretical mass of protein containing carbohydrate conjugated with four drug linker molecules is 152.1 kDa (intact mass).

Plasma half-life is 12 days after the first dose and increases over time to be 14 days.

Following a single IV administration of 10 mg/kg 3H-cys-mcMMAF to rats, the majority of the radioactive dose was excreted in the faeces (approximately 83%). Urinary excretion (approximately 13%) was a minor route. Radioactivity was excreted rapidly, with 94% of the administered dose recovered in the first 48 hours after dosing. The total recovery of radioactivity over the 7-day collection period was 96%. Cys-mcMMAF was detected in human urine following IV administration. However it was not possible to make a quantitative assessment of renal excretion from the data.

No pharmacodynamic studies have been performed to evaluate possible interactions of belantamab mafodotin (GSK2857916) with other drugs that may be co-administered.

9.1.2. Form

Belantamab mafodotin (GSK2857916) is clear to opalescent; colorless to yellow to brown liquid and is administered intravenously (IV) via infusion.

	Belantamab mafodotin
Dosage form:	Lyophilized powder, 100 mg/vial in single-use vial for reconstitution
Unit dose strengths:	100 mg/vial (Lyophilized powder)
Route of Administration:	Delivered as IV solution over at least 30 minutes*.
Dosing instructions:	Reconstitute belantamab mafodotin lyophilized powder 100 mg/vial 2.0mL of water for injection (WFI); dilute with saline before use.
Manufacturer/ Source of Procurement:	GSK/Baxter

9.1.3. Storage and Stability

Belantamab mafodotin (GSK2857916) for Injection, 100 mg drug product is supplied as a lyophilized powder for solution for infusion. Prepared doses should be used as soon as possible because the product does not contain an antimicrobial preservative.

The recommended storage condition is 2-8 degrees C, protected from light. The expiry date, where required, is stated on the product label.

9.1.4. Compatibility

Belantamab mafodotin (GSK2857916) for Injection, 100 mg should not be administered concomitantly with other drugs in the same administration assembly.

9.1.5. Handling

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

9.1.6. Availability

Belantamab mafodotin (GSK2857916) is available from GlaxoSmithKline/Baxter.

9.1.7. Preparation

For IV administration, the drug product is reconstituted with 2.0 mL of WFI before use.

Please visually inspect the product solution to confirm it appears clear to opalescent; colorless to yellow to brown; free from visible particles. If the inspected solution does not match this description, do not use and alert GSK for further instructions. Once reconstituted, the solution should be used to prepare the dose as soon as possible. The dose is stable after dilution with 0.9% Sodium Chloride for Injection to 2 mg/mL – 0.2 mg/mL for up to 6 hours from initial vial reconstitution when stored at 15-25 degrees C and is compatible with the following contact materials: polyvinylchloride, polyolefin, polyurethane catheter and 0.2 μm polyethersulfone (PES) filters. It is recommended to prepare and administer the dosing solution in a 250 mL IV bag. If a closed system transfer device (CSTD) is used, instructions provided by the manufacturer must be followed to ensure intended dose is delivered.

9.1.8. Administration

Belantamab mafodotin (GSK2857916) is delivered as IV solution over at least 30 minutes.

9.1.9. Ordering

Belantamab mafodotin (GSK2857916) will be provided by GlaxoSmithKline/Baxter.

9.1.10. Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

9.1.11. Destruction and Return

Any expired supplies of the belantamab mafodotin will be destroyed. Belantamab mafodotin should be destroyed at the investigational site if permitted by local regulations.

10. CORRELATIVE STUDIES

Based on our preclinical data in ALK+ LBCL, we hypothesize that large cell lymphoma subtypes characterized by a plasma cell phenotype are more likely to respond to belantamab mafodotin. It will important to obtain a detailed understanding of both the biology underlying this response, as well as mechanisms that may lead to refractoriness in particular cases. In addition, there may be a need to understand mechanisms of possible resistance in particular cases after certain intervals of therapy. The generation of PDX lymphoma models can serve as a critical resource to achieve these goals. Note that we will collect research specimens for correlative studies with aim to perform these correlative studies for all subjects on study, although we recognize that in practice these correlative studies may not be completed in all enrolled patients.

To this end, we propose to establish a PDX line for each patient at the time of enrollment, in order to achieve the following specific aims:

1. **Generation of a PDX lymphoma line from a biopsy obtained from each patient enrolled:**
   We will obtain a biopsy sample from each patient at the time of biopsy both to confirm disease and to generate PDX mouse models. These models will be generated by direct implantation of biopsy samples into the renal subcapsular space of recipient NOD scid gamma (NSG) mice. The mouse lines can then be easily propagated indefinitely by the serial transfer of dissociated tumor cells into subsequent generations of mice by tail vein injection. Each PDX lymphoma line will be characterized by histology, immunohistochemical markers, and targeted sequencing and fusion analysis for disease confirmation.
2. **Model therapeutic response of ALK-LBL and PBL in PDX lymphoma models:**
   For each PDX line, we will generate a cohort of PDX lymphoma mice for treatment with belantamab mafodotin (n=6) or vehicle (n=6). We will examine the impact of therapy on tumor growth (in-vivo by ultrasound monitoring) and survival. We will deploy genetic, epigenetic, and transcriptomic profiling on PDX tumors treated with belatamab mafodotin and vehicle to (a) identify potential predictive biomarkers of response to belatamab mafodotin and (b) examine molecular changes that occur secondary to therapy. As part of this we will carefully examine the effects of therapy on BCMA expression on lymphoma cells, and the kinetics of this effect. We will be able to study the persistence of

remissions over time in mice to evaluate for relapse and then investigate mechanisms of resistance using the same molecular assays. Ultimately, we will correlate these potential predictive biomarkers as well as the histologic subtype to treatment outcomes in all enrolled patients and their respective PDX lines. The PDX mice may later be useful in studying any questions that may later be of interest, including the impact of drug combinations.

3. **Other investigations:**
   Tumor biopsies and PDX mouse models may be used be used for other correlative investigations aimed at better understanding the underlying biology of these rare histologies. Additionally, the PDX mice may later be useful in studying any questions that may later be of interest, including the impact of drug combinations.

Refer to the lab manual for details on sample collection and processing.

11. STUDY CALENDAR

Cycle = 21 days	**Screening**	**Cycle 1**		**Subsequent Treatment Cycles**	**EOT Visit 30d +/- 7d after discontinuation[10]**	**Survival/Follow-Up[6]**	**EDC Timepoints**
Window			**+/- 4 days**	**+/- 4 days**		**+/- 14 days**	
Study Day(s)	**-30 to 0**	**1**	**2**	**1**		**Every 3 Months**	
Belantamab mafodotin		X		X			D1 of Every Cycle
Cooling eye masks, preservative-free artificial tears[7]		X		X			D1 of Every Cycle
Informed consent	X						Screening
Medical history	X					X[6]	
Concurrent medications	X	X		X	X		Every study visit
Adverse Event Evaluation[9]	X	X	X	X	X[5]		C1D8 and every subsequent study visit
Vital signs	X	X	X	X	X		Every study visit
Physical exam	X	X	X	X	X		Every study visit
Ocular exam[7]	X[7]	X[7]		X[7]	X[7]		D1 of Every Cycle
Height	X						Screening
Weight	X	X		X			D1 of Every Cycle
ECOG performance status	X	X		X	X		D1 of Every Cycle
CBC with differential	X	X	X	X	X		Every study visit
Comprehensive metabolic panel, uric acid, phosphorus, CPK	X	X	X	X	X		Every study visit
Urinalysis (dipstick) or Spot Urine for albumin/creatinine ratio	X			X[8]			
LDH	X	X		X			Every study visit
B2-microglobulin	X	X					Screening
G6PD	X						
EKG	X						Screening
Serum pregnancy test (B-HCG)[1]	X[1]	X[1]		X	X	X	Screening and D1 of every cycle
HIV, Hepatitis B and C testing[2]	X[2]						Screening
PET-CT imaging[3]	X[3]			X[3]	X[3]		Screening, C3D1, C5D1, C7D1, every 6 months thereafter (C13D1, C19D1, etc.)
Fresh tumor biopsy for correlative studies[4]	X[4]			X[4]	X[4]		Screening
Saliva sample for correlative studies[4]	X[4]						

1- Not necessary if male or woman who is not of childbearing potential. If screening pregnancy test not within 72 hours prior to first dose, then this must be repeated to ensure negative highly sensitive serum pregnancy test within 72 hours prior to first dose of belantamab mafodotin.

For questionable cases, follicle-stimulating hormone (FSH) and estradiol (as needed in WOCBP) should be performed at local lab to determine childbearing potential. WOCBP must have a negative highly sensitive serum pregnancy test within 72 hours of dosing on C1D1. Subsequent pregnancy tests on dosing days may be either serum or urine. Final pregnancy test (serum or urine) must be performed in WOCBP at the EOT Visit. Follow up pregnancy assessment by telephone (for WOCBP only) should be performed 9 months after the last dose of belantamab mafodotin.

2- HIV, Hepatitis B and C testing may be performed within 30 days prior to date of protocol therapy start. See Exclusion Criteria for additional information.

3- CT neck/chest/abdomen/pelvis and FDG-PET scan are required during Screening; after 2 months (C3D1); after 4 months (C5D1); after 6 months (C7D1); then every 6 months on therapy (C13D1, C19D1, C25D1, et cetera), and at EOT.

4- Fresh tumor biopsy is required at Screening and per PI's discretion at subsequent progression. Saliva sample is required at Screening. See Lab Manual for details regarding collection, processing, and shipping of fresh tumor biopsy for correlative studies. In patients who do not have a site of disease amenable to biopsy, biopsy may be deferred with approval from the overall PI.

5- If clinically significant adverse event or abnormal result is observed that is not resolved by the end-of study visit, continue to monitor and record through 70 days after belantamab mafodotin discontinuation.

6- Survival/Follow-Up may be conducted in clinic or by telephone and is intended to document long term outcomes in patients who respond to protocol therapy and are no longer receiving active protocol therapy e.g. after undergoing consolidation with HDT/ASCR or ASCT.

7- For details on ophthalmic assessments, please see Section 5.4 and Appendix C.

a. If screening ocular exam occurs > 5 days prior to Belantamab mafodotin initiation, then this exam should be conducted again prior to first dose.
b. On-study ocular exams to be performed by an ophthalmologist or optometrist (if an ophthalmologist is not available) at baseline, prior to each dose of belantamab mafodotin in all cycles (should be within 5 days prior to dosing [supersedes window below in calendar] and all efforts should be made to schedule as close to belantamab mafodotin dosing as possible), and promptly for worsening symptoms.
    i. Additional exams may be performed by ophthalmologist as clinically indicated.
    ii. If vision changes or ocular symptoms develop, patient should be evaluated by an ophthalmologist.
    iii. In case of persistent or newly developed ocular symptoms or vision changes, the participants will have further ophthalmologic exams, at least every 3 months until resolution (to grade 1 or baseline) or more frequently as clinically indicated by the eye care specialist.
c. Corneal management information:
    i. Prophylactic preservative-free artificial tears must be administered in each eye at least 4-8 times daily beginning on Cycle 1 Day 1 until end of treatment. In the event of ocular symptoms (i.e. dry eyes), the use of artificial tears may be increased up to every 2 hours as needed.
    ii. Corticosteroid eye drops are not required but can be used if clinically indicated per discretion of an eye-care specialist. Allow at least 5-10 minutes between administration of artificial tears and steroid eye drops (if administered).
    iii. At the start of each infusion, participants may apply cooling eye masks to their eyes for approximately 1 hour or as long as tolerated.

8- Albumin/creatinine ratio (spot urine, preferably from first void) to be performed every 6 weeks from C1D1 OR Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be done in any participant with urine dipstick result of ≥2+, or with positive protein if urine dipstick protein quantification is not available.

9- AE/SAEs will be collected from the start of study treatment until at least 70 days following EOT, regardless of initiation of new cancer therapy. SAEs related to study participation or a GSK product are collected from time of consent up to and including any follow up.

10- EOT visits may be conducted by telephone and assessments may be omitted at the discretion of the investigator if determined infeasible for subject to come into clinic.

12. MEASUREMENT OF EFFECT

12.1 Antitumor Effect – 2014 Lugano Criteria

12.1.1 Selection of Target Lesions

Up to six of the largest dominant nodes or tumor masses selected according to all of the following:

1. Clearly measurable in two diameters (longest diameter [LDi] and shortest diameter) at baseline
    a. All nodal lesions must measure > 1.5 cm in longest diameter regardless of short axis measurement
    b. All measurable extranodal lesions should have a longest tumor diameter ≥ 1.0 cm
2. All other lesions (including nodal, extranodal, and assessable disease) should be followed as non-target lesions
3. If possible, the lesions should be from disparate regions of the body
4. Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved

12.1.2 Selection of Non-Target Lesions

Non-target lesions will be qualitatively assessed at each subsequent time point. All sites of disease present at baseline and not classified as target lesions will be classified as non-target lesions, including any measurable lesions that were not chosen as target lesions.

Examples of non-target lesions include:

1. All bone lesions, irrespective of the modality used to assess them
2. Lymphangitis of the skin or lung
3. Cystic lesions
4. Splenomegaly and hepatomegaly (all lymphomas)
    a. Cutoff for splenomegaly of more than 13 cm
    b. Diffusely increased or focal uptake, with or without focal or disseminated nodules, supports spleen or liver involvement
5. Irradiated lesions
6. Measurable lesions beyond the maximum number of six
7. Groups of lesions that are small and numerous
8. Pleural/pericardial effusions and/or ascites
    a. Effusions, ascites, or other fluid collections will be followed as non-target lesions

b. At each assessment point, radiologists will check for the presence or absence of effusions/ascites. If there is a significant volume increase in the absence of a benign etiology, progression can be assessed.

c. Significant new effusions, ascites or other fluid collections, which are radiographically suggestive of malignancy should be recorded as new lesions and should be assessed

Response should be determined on the basis of radiographic and clinical evidence of disease. Assessment by PET should follow the Lugano criteria described by Cheson et al[20] which is summarized in Appendix F.

13. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

13.1.1 Method

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

13.1.2 Responsibility for Data Submission

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

13.2 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 Sponsor-Investigator and study team.

The DSMC generally reviews 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 across all sites; 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.

13.2.1 Triggers for Safety review

The phase I study of belantamab mafodotin (BMA 117159) included patients with non-Hodgkin lymphoma. Belantamab mafodotin was deemed well tolerated in this population. Additionally, we have not observed unexpected rates/severity of toxicity in the first five patients enrolled, and all-cause AEs of interest included corneal toxicity (one patient, grade 3 keratitis), infusion related reaction (one patient, grade 3), platelet count decreased (one patient, grade 4), AST increase (one patient, grade 2), and no Safety Events (defined below). Therefore, formal stopping rules are not warranted in this phase II study of belantamab mafodotin in these NHL subtypes.

However, we designed predefined rules that trigger Safety Review led by by overall PI and site investigators. When ≤9 patients have been enrolled: If a Safety Event occurs in 3 or more of the first 9 patients enrolled in this protocol, overall PI and site investigators from all participating sites will convene to review safety data to monitor overall toxicity. When >9 patients have been enrolled: If a Safety Event occurs in one-third or more of the number patients enrolled in the study at any timepoint after >9 patients have been enrolled, overall PI and site investigators from all participating sites will convene to review safety data to monitor overall toxicity. Additionally, safety events must be reported to DSMC and indicated on the DSMC form at the next review.

A Safety Event is defined as an SAE meeting protocol-defined criteria for reporting to the DF/HCC IRB, which also meets at least one of the two following criteria (based on grading from CTCAE v5.0):

1. Grade 4 hematologic toxicity, deemed possibly, probably, or definitely related to protocol therapy, which does not improve to Grade 2 or better within 7 days despite adequate supportive care; OR
2. Grade 3 or higher non-hematologic toxicity deemed possibly, probably, or definitely related to protocol therapy, which does not improve to Grade 2 or better within 7 days despite adequate supportive care

If any death occurs on study and is considered possible, probably, or definitely related to study drug, we will pause enrollment to review and monitor toxicity from this study to provide guidance regarding whether to continue enrollment or terminate the study.

13.3 Multi-Center Guidelines

This protocol will adhere to DF/HCC Policy MULTI-100 and the requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Sponsor-Investigator, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in the Data and Safety Monitoring Plan (Appendix B).

13.4 Collaborative Agreements Language

N/A

14 STATISTICAL CONSIDERATIONS

This is a multicenter phase II study of belantamab mafodotin in patients with relapsed/refractory plasmablastic lymphoma and ALK+ large B-cell lymphoma. As described in Section 2, PBL and ALK LBCL is associated with a dismal prognosis which is typically measured in months from diagnosis. This is especially pronounced in the relapsed or refractory setting where these diseases are almost universally fatal. The primary objective will be to determine the overall response rate of belantamab mafodotin in patients with these histologies. Patients will receive belantamab mafodotin at 2.5 mg/kg IV on day 1 of a 21-day cycle until progression or intolerance.

14.1 Study Design/Endpoints

14.1.1 Primary efficacy endpoints

1. To describe the overall response rate

14.1.2 Secondary efficacy endpoints

1. To describe the complete response rate
2. To estimate the progression-free survival and overall survival
3. To determine the overall and complete response rates by subtype (i.e. plasmablastic lymphoma and ALK+ large B-cell lymphoma)

14.1.3 Primary safety endpoints

1. To describe the nature, frequency, severity, and timing of adverse events

14.2 Sample Size, Accrual Rate and Study Duration

The study will use a single-stage, exact binomial design. An objective response rate (ORR, PR or better) of at least 30% will be considered promising whereas an ORR of 10% or less will be considered non-promising. Twenty-five eligible patients will be enrolled. If at least 5 responses are observed in 25 patients, the study will be considered successful and the regimen worthy of further study. If the total number of responses observed is 4 or fewer, the regimen will be considered non-promising. This design has an overall power of 91% and a type I error of 0.098 and will use an exact binomial test. With a total sample size of 25 patients, the 90% exact binomial confidence interval for ORR will be no wider than 35%.

The study duration will be 4 years; 2 years of accrual and 2 years of follow-up on the last participant enrolled.

Accrual Targets								
Ethnic Category	**Sex/Gender**							
	Females			**Males**			**Total**	
Hispanic or Latino	5		+	5		=	10	
Not Hispanic or Latino	8		+	7		=	15	
Ethnic Category: Total of all subjects	13	(A1)	+	12	(B1)	=	25	(C1)

Racial Category						
American Indian or Alaskan Native	0	+	0	=	0	
Asian	1	+	1	=	2	
Black or African American	5	+	5	=	10	
Native Hawaiian or other Pacific Islander	0	+	0	=	0	
White	7	+	6	=	13	
Racial Category: Total of all subjects	13 (A2)	+	12 (B2)	=	25 (C2)	
	(A1 = A2)		(B1 = B2)		(C1 = C2)	

14.3 Stratification Factors

N/A

14.4 Interim Monitoring Plan

The DF/HCC DSMC will monitor safety and data quality across all participating institutions. Regular study teleconferences with all participating institutions will be held to discuss SAEs or other toxicities and study progress.

14.5 Analysis of Primary Endpoints

See Section 14.2 for description of the statistical methodology used to address the study's primary aim.

Patients will have their response classified per the 2014 Lugano criteria. The frequency of complete response will be tabulated and summarized descriptively.

14.6 Analysis of Secondary Endpoints

14.6.1 Complete response rate

Patients will have their response classified per the 2014 Lugano criteria (see Section 12). The frequency of complete response will be tabulated and summarized descriptively.

14.6.2 Progression-free and overall survival

Median Progression-free survival and overall survival will be summarized using Kaplan-Meier method with time of registration as time origin. Participants will be followed for 2 years after removal from protocol therapy or until death, whichever occurs first. Participants will be censored at the date of their last evaluation.

14.6.3 Nature, frequency, severity, and timing of adverse events

Patients will have their toxicities graded and reported at every visit according to criteria listed in

CTAE ver. 5.0. The nature, frequency, severity, and timing of adverse events will be tabulated and summarized descriptively.

14.7 Reporting and Exclusions

14.7.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

14.7.2 Evaluation of the Primary Efficacy Endpoint

All eligible participants included in the study must be assessed for response/outcome to therapy, unless they withdraw consent prior to first response evaluation. Participants who withdraw consent prior to first response evaluation will be replaced.

15 PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the 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

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

TABLE OF CONTENTS

1. INTRODUCTION

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

1.1 Purpose

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

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the following general responsibilities apply, in addition to those outlined in DF/HCC Policies for Sponsor-Investigators:

2.1 Coordinating Center

The Coordinating Center is the entity that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines).

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

- Assist in protocol development.
- Maintain CTEP, FDA or OBA correspondence, as applicable.
- Review registration materials for eligibility and register participants from External Sites in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to External Sites as needed.
- Review and approve External Site informed consent forms
- Oversee the data collection process from DF/HCC and External Sites.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by External Sites and provide to the DF/HCC Sponsor for timely review and submission to the IRB of record, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the reporting requirements for the IRB of record to all DF/HCC and External Sites.
- Provide External Sites with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out approved plan to monitor DF/HCC and External Sites either by on-site or remote monitoring.

- Maintain Regulatory documents of External Sites which includes but is not limited to the following: local IRB approvals/notifications from all External Sites, 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 Sites (conference calls, emails, etc) and maintain documentation all relevant communications.

2.2 External Site

An External Site is 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 External Site acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Each External Site is expected to comply with all applicable DF/HCC requirements stated within this Data and Safety Monitoring Plan and/or the protocol document.

The general responsibilities for each External Site 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 IRB of record. For studies under a single IRB, the Coordinating Center will facilitate any study-wide submissions.
- Maintain regulatory files as per ICH GCP and federal requirements.
- Provide the Coordinating Center with regulatory document, study logs (i.e. enrollment log, biospecimen log and violation log) or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required.
- 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 sponsor, Coordinating Center, and IRB of record as applicable, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to the Sponsor, Coordinating Center, and IRB of record as applicable, in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- 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.
- Notify the sponsor immediately of any regulatory authority inspection of this protocol at the External Site.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

Certain DF/HCC Policy requirements apply to External Sites participating in DF/HCC research. 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 Revisions and Closures

The External Sites will receive notification of protocol revisions and closures from the Coordinating Center. When under a separate IRB, it is the individual External Site's responsibility to notify its IRB of these revisions.

- **Protocol revisions:** External Sites will receive written notification of protocol revisions from the Coordinating Center. All protocol revisions should be IRB approved and implemented within a timely manner from receipt of the notification.

- **Protocol closures and temporary holds:** External Sites 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 External Sites on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.2 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for External Sites. The External Site 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 Investigator-Sponsored Multi-Center Trials. This document will be provided separately to each External Site upon request.

External Sites must send their version of the informed consent document to the Coordinating Center for sponsor review and approval **prior to local submission**. If the HIPAA authorization is a separate document, please submit to the sponsor for the study record. Once sponsor approval is obtained, the External site may submit to their IRB of record, as applicable. In these cases, 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 External Site will identify the appropriate members of the study team who will be obtaining consent and signing the consent form for protocols. External Sites must follow the DF/HCC requirement that 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.

3.3 IRB Re-Approval

Verification of IRB re-approval for the External Sites 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 for the External Site on or before the anniversary of the previous approval date.

3.4 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 participant registration number be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.5 Participant Registration and Randomization

Please refer to protocol [**Section 4.0: Registration Procedures]**

3.5.1 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 confirmation of the participant's registration has been received. The DF/HCC Sponsor and IRB of record must be notified of any violations to this policy.

3.5.2 Eligibility Exceptions

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

3.6 Data Management

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

Data should be entered promptly and completely after each assessment, but no later than 2 weeks after the completion of a study visit/timepoint.

3.6.1 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.

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

3.7 Protocol Reporting Requirements

3.7.1 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 and to the IRB of record.

3.7.2 Reporting Procedures

Requests to deviate from the protocol require approval from the IRB of record and the sponsor.

All protocol violations must be sent to the Coordinating Center in a timely manner. Major violations should be reported within 1 business day of identification; minor violations are reported cumulative on a monthly basis. The Coordinating Center will provide training for the requirements for the reporting of violations.

3.7.3 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports per DF/HCC requirements, and ensure that all IND Safety Reports are distributed to the External Sites as required by DF/HCC Policy. External Sites will review/submit to the IRB according to their institutional policies and procedures.

4. MONITORING: QUALITY CONTROL

The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

4.1 Ongoing Monitoring of Protocol Compliance

DF/HCC and External Sites will be subject to on-site and remote monitoring conducted by the Coordinating Center and may be required to submit participant source documents to the Coordinating Center for monitoring.

The Coordinating Center will implement ongoing monitoring activities to ensure that all Sites are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the protocol begins, continue

during protocol performance and through study completion. Monitoring practices include but are not limited to; source data verification and review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol departures, pharmacy records, tissue and biospecimen sample logs, response assessments, and data management.

All DF/HCC and External Sites will undergo on-site monitoring by the Coordinating Center within 3 months of completion of the first patient accrual; Combination on-site and remote monitoring will occur every 4-6 months thereafter with at least 1 on-site visit every 12 months. Remote monitoring may be done in lieu of on-site monitoring if no active patients are on trial. Once all site participants are off treatment and have completed the post-treatment assessment, remote monitoring will be conducted annually for confirmation of long term follow-up data and regulatory documentation.

For remote monitoring visits, External Sites will be asked to provide remote electronic medical record access to the monitor or will be required to forward redacted copies of participants' medical record and source documents to the Coordinating Center to aid in source data verification. The participants and CRFs to be reviewed at the visit will be communicated at least 2 weeks in advance of the scheduled monitoring visit. Source documentation can be provided to the Coordinating Center via an encrypted memory stick or via a secure file transfer system. During remote monitoring visits, the Site Specific File will be reviewed in lieu of the site regulatory binder.

On-Site Monitoring will be scheduled several weeks in advance and will be conducted over a 2-3 day period. During an on-site monitoring visit 2-4 participants will be monitored. Source documentation verification (SDV) will be conducted by having access to participants' complete medical record and source documents. DF/HCC and External Sites will be expected to coordinate the necessary resources for the monitor, including a desk, access to all participant medical and research records (electronic and hard copy), the regulatory binders and access to a photocopier. The Site research team will also be asked to assist in scheduling a pharmacy visit and a brief exit interview on the final day of the visit with the Study Coordinator and the Site investigator.

All Sites will be required to participate in monthly Coordinating Center initiated teleconferences. Once all participants have completed treatment, teleconferences will be scheduled as needed.

4.2 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 External Sites that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

4.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each External Site. Accrual will be monitored for each External Site by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination. For this study, the minimum accrual requirement is 3 participants per site/annually. However, given the additional regulatory burden and cost of overseeing each site, a consideration of 5 per site/annually should be a minimum target for each site.

5. AUDITING: QUALITY ASSURANCE

5.1 DF/HCC Internal Audits

All External Sites 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.

5.2 Audit Notifications

It is the External Site'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.

5.3 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 IRB as applicable.

5.4 External Site Performance

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

External Sites 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 put on hold or closed

APPENDIX C OCULAR MONITORING AND MITIGATION STRATEGY

Ocular Examinations:

Patients will be assessed by ophthalmologist or optometrist (if an ophthalmologist is not available). A full screening/baseline ophthalmic examination for all participants must include for both eyes (OU), but is not limited to:

1- Best corrected visual acuity
2- Documentation of manifest refraction and the method used to obtain best corrected visual acuity
3- Current glasses prescription (if applicable)
4- Intraocular pressure measurement & time checked.
5- Selected anterior segment (slit lamp) examination with focus on the cornea and lens, including fluorescein staining of the cornea.
6- Dilated fundoscopic exam.

The on treatment ophthalmic exam should match the baseline (screening) exam should be performed for both eyes (OU) as described below:

1- Best corrected visual acuity.
2- Documentation of manifest refraction and the method used to obtain best corrected visual acuity.

The end of study treatment and last follow-up ophthalmic exam should match the screening/baseline exam.

Additional examinations should be performed at the discretion of the treating eye specialist.

Changes in Corneal Epithelium: Severity Grading and Mitigation Strategy
AEs including corneal, will be graded by the investigator according to the NCI-CTCAE v5.
In order to minimize the changes in corneal epithelium associated with belantamab mafodotin, patients must receive prophylactic preservative-free artificial tears. The recommended administration is to use one drop in each eye at least 4 to 8 times daily, beginning on Cycle 1 Day 1 until the subject discontinues treatment. In the event of ocular symptoms (e.g., dry eyes), the use of artificial tears may be increased up to every 2 hours as needed.

Corticosteroid eye drops are not required but can be used if clinically indicated per discretion of an eye-care specialist. Allow at least 5-10 minutes between administration of artificial tears and steroid eye drops (if administered together). If steroid eye drops are deemed medically necessary and prescribed, intraocular pressure must be monitored if used for >7 days.

While not yet clinically demonstrated, it is theoretically possible that the application of a cooling eye mask during belantamab mafodotin administration, and in the first few hours after infusion may subsequently decrease ocular side effects.

On the day of infusion at the discretion of the patient and the physician, the following may be considered: Beginning with the start of each belantamab mafodotin infusion, patients may apply cooling eye masks to their eyes for approximately 1 hour or as much as tolerated. Patients may continue using the cooling eye mask beyond the first hour for up to 4 hours. Further use beyond 4 hours is at the patient's discretion.

Contact lenses are prohibited while the participant is on study treatment. Contact lens use may be restarted after a qualified eye care specialist confirms there are no other contraindications.

Use of bandage contact lenses is permitted during study treatment as directed by the treating qualified eye care specialist.

An ophthalmology or optometry (if ophthalmology is not available) consult is required for all patients who develop signs or symptoms of changes in corneal epithelium.

A summary of prophylactic interventions for changes in corneal epithelium associated with belantamab mafodotin is provided in

Table . Changes in corneal epithelium must be graded according to the NCI-CTCAE scale.

Table 5 Prophylactic measures for changes in corneal epithelium associated with belantamab mafodotin

Prophylactic Measure	**Dose and Administration**	**Timing**
Preservative-free artificial tears	Administer in each eye at least 4 to 8 times daily	Administer daily beginning on Cycle 1 Day 1 until EOT.
Cooling eye mask	May apply cooling eye mask to both eyes for approximately 1 hour or as much as tolerated	During belantamab mafodotin infusion administration in the first hour for up to 4 hours, as tolerated

APPENDIX D LIVER SAFETY REQUIRED ACTIONS AND FOLLOW UP ASSESSMENT

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT - absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** total bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5
Cannot Monitor	ALT ≥ 3xULN **and** cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions, Monitoring and Follow up Assessments	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study intervention • Report the event to GSK **within 24 hours** • Complete the liver event form and complete SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments as described in the Follow Up Assessment column • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING**) *For the purpose of these guidelines "baseline" refers to laboratory assessments performed closest and prior to first dose of study intervention* **MONITORING:**	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH), gamma glutamyl transferase [GGT], and serum albumin. • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity • Record use of concomitant medications including acetaminophen, herbal remedies, recreational drugs and other over the counter medications

If ALT≥3xULN AND total bilirubin ≥ 2xULN or INR >1.5:

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within **24 hours**
- Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline
- A specialist or hepatology consultation is recommended

For All other criteria (bilirubin <2xULN and INR ≤1.5):

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within **24-72 hours**
- Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline

RESTART/RECHALLENGE

- **Restart/rechallenge is allowed per protocol but do not resume study intervention unless Sponsor approval is granted;** If restart/rechallenge is **not granted**, permanently discontinue study intervention and continue participant in the study for any protocol specified follow up assessments.

- Record alcohol use

If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5 obtain the following in addition to the assessments listed above:

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins)
- Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week. (e.g., where the participant has been resident in the clinical unit throughout)
- Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease;
- Liver biopsy may be considered and discussed with local specialist if available, for instance:
  - In patients when serology raises the possibility of autoimmune hepatitis (AIH)
  - In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention
  - In patients with acute or chronic atypical presentation:

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥ 3xULN **and** total bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** total bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; the INR threshold value stated will not apply to participants receiving anticoagulants

3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody. In those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody. *Only include for studies with clearly non-immunosuppressive agents. For studies with potent immunosuppressive agents these participants are to be excluded; see additional guidance regarding eligibility criteria.* If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].

5.4.1.1.1 Phase I/II liver chemistry increased monitoring criteria with continued study intervention

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN **but** <5xULN **and** total bilirubin <2xULN or INR ≤1.5, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks	• Notify the Sponsor medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, total bilirubin and INR) until they resolve, stabilise or return to within baseline *For the purpose of these guidelines "baseline" refers to laboratory assessments performed closest and prior to first dose of study intervention* • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and total bilirubin <2xULN and INR ≤1.5, monitor participants twice

	monthly until liver chemistries resolve or return to within baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

APPENDIX E CONTRACEPTION

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods[b] That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)[c]
- Bilateral tubal occlusion
- Vasectomized partner
  - *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*

Highly Effective Methods[b] That Are User Dependent

- Combined (estrogen-/progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - oral
  - intravaginal
  - transdermal
  - injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation
  - oral
  - injectable
- Sexual abstinence. *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

APPENDIX F LUGANO RESPONSE CRITERIA (2014)

Response and Site	PET-CT–Based Response	CT-Based Response
Complete Response	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 [a] with or without a residual mass on 5PS [b] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC-negative
Partial Response	Partial metabolic response	Partial remission (all of the following):
Lymph nodes and extralymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size. At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease.	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal; use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable

Response and Site	PET-CT–Based Response	CT-Based Response
No Response or Stable Disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive Disease	Progressive metabolic disease	Progressive disease requires at least one of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	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 (e.g., 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
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

Response and Site	PET-CT–Based Response	CT-Based Response
New Lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis 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
Bone Marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS =5-point scale; CT =computed tomography; FDG =fluorodeoxyglucose; GI =gastrointestinal; IHC =immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI =magnetic resonance imaging; PET =positron emission tomography; PPD =cross product of the LDi and perpendicular diameter; SDi =shortest axis perpendicular to the LDi; SPD =sum of the product of the perpendicular diameters for multiple lesions.

[a] *Measured dominant lesions: up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).*

[b] *PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.*

APPENDIX G PROHIBITED MEDICATIONS

The following table provides a list of clinically relevant inhibitors and inducers of P-gp. Drugs that are listed as P-gp inhibitors have been shown in a clinical study to increase the AUC of a sensitive substrate more than 25% or decrease the clearance of a sensitive substrate more than 20%. Drugs listed as P-gp inducers have been shown in a clinical study to decrease the AUC of a sensitive substrate more than 20% or increase the clearance of a sensitive substrate more than 25%.

It is important to note that information related to P-gp inhibitors and inducers abd OATP interactions changes rapidly and thus the contents of this table should only be considered to represent a snapshot of the information available at the time that this document was generated.

P-glycoprotein Inhibitors	P-glycoprotein Inducers
Amiodarone	Apalutamide
Azithromycin (Systemic)	CarBAMazepine
Capmatinib	Fosphenytoin
Carvedilol	Lorlatinib
Clarithromycin	Phenytoin
Cobicistat	RifAMPin
CycloSPORINE (Systemic)	St John's Wort
Daclatasvir	
Dronedarone	
Elagolix	
Elagolix, Estradiol, Norethindrone	
Elexacaftor, Tezacaftor, and Ivacaftor	
Eliglustat	
Erythromycin (Systemic)	
Flibanserin	
Fostamatinib	
Glecaprevir and Pibrentasvir	
Itraconazole	
Ivacaftor	
Ketoconazole (Systemic)	

P-glycoprotein Inhibitors	P-glycoprotein Inducers
Lapatinib	
Ledipasvir	
Neratinib	
Ombitasvir, Paritaprevir, and Ritonavir	
Osimertinib	
Propafenone	
QuiNIDine	
QuiNINE	
Ranolazine	
Ritonavir	
Rolapitant	
Simeprevir	
Tezacaftor and Ivacaftor	
Tucatinib	
Velpatasvir	
Vemurafenib	
Verapamil	
Voclosporin	

Examples of clinical inhibitors for transporters (for use in clinical DDI studies and drug labeling) (9/26/2016)

Transporter	Gene	Inhibitor
P-gp[(a)]	*ABCB1*	amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil
BCRP	*ABCG2*	curcumin, cyclosporine A, eltrombopag
OATP1B1, OATP1B3	*SLCO1B1, SLCO1B3*	atazanavir and ritonavir, clarithromycin, cyclosporine, erythromycin, gemfibrozil, lopinavir and ritonavir, rifampin (single dose), simeprevir

OAT1, OAT3	*SLC22A6, SLC22A8*	p-aminohippuric acid (PAH)(b), probenecid, teriflunomide
MATE1, MATE2-K	*SLC47A1, SLC47A2*	cimetidine, dolutegravir, isavuconazole, ranolazine, trimethoprim, vandetanib

Note:
Criteria for selecting in vivo inhibitors are as follows:

- P-gp: (1) AUC fold-increase of digoxin ≥2 with co-administration and (2) in vitro inhibitor.
- BCRP: (1) AUC fold-increase of sulfasalazine ≥1.5 with co-administration and (2) in vitro inhibitor. Cyclosporine A and eltrombopag were also included, although the available DDI information was with rosuvastatin, where inhibition of both BCRP and OATPs may have contributed to the observed interaction.
- OATP1B1/OATP1B3: (1) AUC fold-increase ≥2 for at least one of clinical substrates in Table 2-3 with co-administration and (2) in vitro inhibitor.
- OAT1/OAT3: (1) AUC fold-increase ≥1.5 for at least one of clinical substrates in Table 2-3 with co-administration and (2) in vitro inhibitor.<. i="">
- OCT2/MATE: (1) AUC fold-increase of metformin ≥ 1.5 with co-administration and (2) in vitro inhibitor.

This table is prepared to provide examples of clinical inhibitors for various transporters and not intended to be an exhaustive list. DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database [Hachad et al. (2010), Hum Genomics, 5(1):61].
(a)Most of P-gp inhibitors also inhibit CYP3A. (b)In vivo data suggested specific inhibition of OAT1.
Abbreviations:
AUC: area under the plasma concentration-time curve.