CLINICAL PROTOCOL

A Multicenter Phase II Study of Maintenance Belantamab Mafodotin (Blenrep®) After BCMA-Directed Chimeric Antigen Receptor T-cell Therapy in Patients With Relapsed and/or Refractory Multiple Myeloma

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A Multicenter Phase II Study of Maintenance *Belantamab Mafodotin (Blenrep®)* after BCMA-Directed Chimeric Antigen Receptor T-Cell Therapy in Patients with Relapsed and/or Refractory Multiple Myeloma (RRMM)

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PROTOCOL SUMMARY

Title	A Multicenter Phase II Study of Maintenance Belantamab Mafodotin (Blenrep®) after BCMA-Directed Chimeric Antigen Receptor T-cell Therapy in Patients with Relapsed and/or Refractory Multiple Myeloma (RRMM)
IND Sponsor	Sponsor-investigator
Principal Investigator	Meera Mohan, MD
Anticipated Study Sites	Three (including MCW)
Clinical Trial Phase	Phase II
Study Disease	Relapsed and/or refractory multiple myeloma
Main Inclusion Criteria	1. Diagnosis of multiple myeloma with measurable disease (at the time of diagnosis: serum M-protein ≥ 0.5 g/dL or urine M-protein ≥200 mg/24 hours or involved serum-free light chain ≥10 mg/dL provided that the ratio of involved/uninvolved light chain is abnormal) prior to receiving anti-BCMA CAR-T. Patients with no biochemically measurable disease prior to CAR-T may be enrolled if bidirectionally measurable plasmacytomas or bone marrow plasmacytosis ≥10% are present prior to CAR-T infusion. 2. Received at least four prior lines of therapy (including a PI, IMiD, and anti-CD38 monoclonal antibody – note radiation therapy is considered a line of therapy) before BCMA-targeted CAR-T,and has not progressed/relapsed after receiving CAR-T therapy. 3. Achieved at least SD as a response to CAR-T therapy and remained progression-free after anti-BCMA CAR-T administration until enrollment (this requirement is also necessary prior to administration of first study drug).
Main Exclusion Criteria	1. Prior exposure to belantamab mafodotin before enrollment on the trial, including before administration of anti-BCMA CAR-T. 2. Evidence of progression/relapse after BCMA CAR-T before enrollment (this requirement is also necessary prior administration of first study drug). 3. Subject has achieved CR/sCR at the time of enrollment (this requirement is also necessary prior to administration of first study drug). 4. Subject was given BCMA CAR-T under EAP (expanded access protocol) for non-conforming product. 5. Subject progressed on a prior anti-BCMA therapy before receiving commercial anti-BCMA CAR-T. 6. Any previous treatment-related adverse events higher than grade 1 at enrollment (except for alopecia and grade 2 neuropathy). 7. Acute active infection requiring treatment within 14 days of enrollment (this requirement is necessary also prior to administration of first study drug). 8. Current or prior involvement of the central nervous system by multiple myeloma. 9. Smoldering multiple myeloma or POEMS.
Primary Objectives	To describe 12-month progression-free survival (PFS) of patients receiving belantamab mafodotin as maintenance therapy (every eight weeks) after anti-BCMA CAR-T administration for relapsed/refractory myeloma.
Primary Endpoints	12-month conditional PFS, defined as the probability of being alive without progression/relapse or death at 12 months from the time of CAR-T administration conditional on being alive without progression/relapse at 3 months from the time of CAR-T.

Secondary Objectives	1. To describe the toxicity profile of belantamab mafodotin given as maintenance after CAR-T. 2. To describe progression-free survival. 3. To describe changes in International Myeloma Working Group (IMWG) response category for patients not in CR when initiating therapy with belantamab mafodotin as post-CAR-T maintenance. 4. To identify the rate of elimination of minimal residual disease (MRD) (≤10–5) in patients with myeloma at baseline and after starting belantamab mafodotin as post-CAR-T maintenance (at screening/baseline, after two, six, and 12 cycles). 5. Patient-reported quality of life studies (QoL). 6. To describe the overall survival (OS) for the entire cohort from the time of CAR-T administration.
Secondary Endpoints	1. Best objective response on the trial (by IMWG criteria). 2. Progression-free survival. 3. Negative MRD ($\leq 10^{-5}$, by clonoSEQ®), including imaging plus MRD-negativity ($\leq 10^{-5}$ in bone marrow and no area of PET-CT FDG uptake greater than mediastinal blood pool or surrounding normal tissue). 4. Duration of response on maintenance. 5. Time to progression/relapse after CAR-T. 6. Overall survival for the entire study population. 7. Adverse events on the trial. 8. QoL parameters.
Exploratory Objectives	1. Exploratory: BCMA expression by flow cytometry and soluble BCMA/BAFF/APRIL levels will be monitored at screening/baseline, and after two, six, and 12 cycles.
Exploratory Endpoints	1. Baseline and on-treatment sBCMA/BAFF/APRIL and BCMA expression on myeloma cells.
Study Design	This is a multicenter phase II, open-label study evaluating the efficacy and safety of belantamab mafodotin maintenance in participants with RRMM who have received commercially available anti-BCMA CAR-T-cell therapy. Subjects will be enrolled 60–120 days after CAR-T and receive belantamab mafodotin as maintenance therapy. Although screening can occur as early as day 60 post CAR-T therapy, study treatment cannot be started prior to day 90 post CAR-T therapy. Each maintenance cycle will have a duration of 56 days (+/- three days) and belantamab mafodotin will be administered at a dose of 1.9 mg/kg IV on day 1 of each cycle. The study will enroll up to 45 subjects with an interim analysis performed when 23 patients have been treated and followed to the 12th month after CAR-T.
Study Intervention Description	Subjects will receive belantamab mafodotin as maintenance therapy. Belantamab mafodotin will be administered IV over approximately 30 minutes at the recommended dose of 1.9 mg/kg IV on day 1 of every eight-week (+/- three days) cycle. Maintenance therapy with belantamab mafodotin will continue until progressive disease (PD), death, unacceptable toxicity, withdrawal of consent or end of study, whichever occurs first. Dose interruptions or reductions may be required to address potential drug-associated toxicities. The dose to be administered will be based on actual body weight calculated at baseline. However, if the change in body weight is greater than 10%, the dose will be recalculated based on the actual body weight at the time of dosing. The dose may be reduced to address toxicity, as described in Section 5.3.
Number of Subjects	Total sample size for this phase II study will be 45 patients. The sample size was computed to achieve 80% power at a one-sided 5% significance level to detect an increase in 12-month conditional PFS to 74% from the historical value of 54%. This corresponds to raising the 12-month unconditional PFS from 40% to 55%.

Estimated Time to Complete Enrollment:	Approximately three years.
Estimated Time to Study Completion:	Ten years (~3 years enrollment, ~2 years for completion of treatment for all patients, and ~5 years of long-term survival follow-up)

STUDY SCHEMA

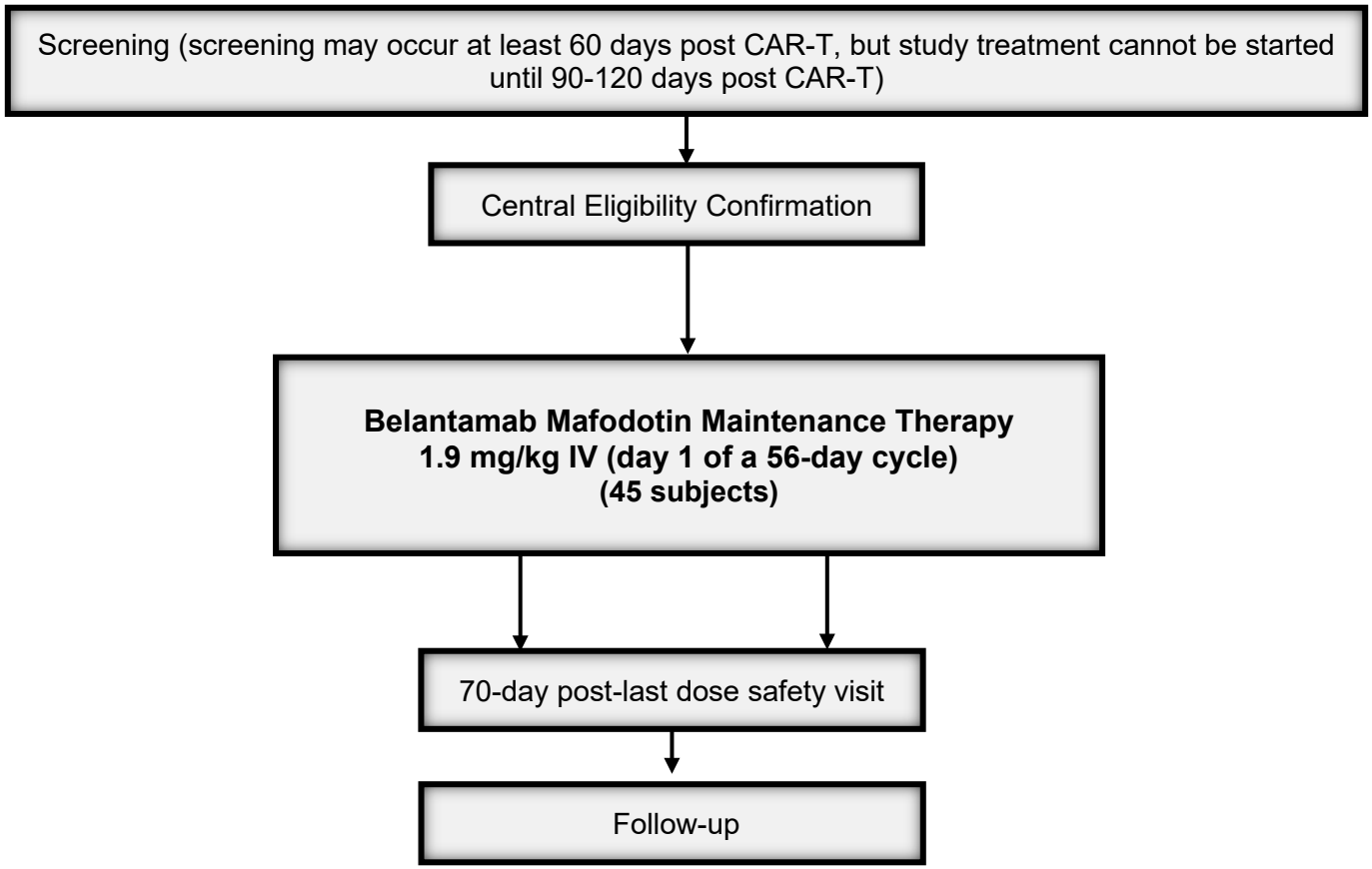


Table 1. STUDY CALENDAR (SCHEDULE OF ACTIVITIES)

Study Assessments	**Screening[1]**	**C1D1 (56 days)[9]**	**C2D1 (56 days)[9]**	**C3D1 (56 days)[9]**	**C4D1 (56 days)[9]**	**C5D1 (56 days)[9]**	**C6D1 (56 days)[9]**	**C7D1 (56 days)[9]**	**C8D1 (56 days)[9]**	**C9D1 (56 days)[9]**	**C10D1 (56 days)[9]**	**C11D1 (56 days)[9]**	**C12D1 (56 days)[9]**	**70-day post-last dose Safety Visit[10]**	**Pre - Progression Q3 mo[18]**	**LTFU (Q6 mo)[19]**
Visit window	**Day -30 to enrollment**		**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 30 days**	**+/- 30 days**
Informed consent	x															
H&P	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Ocular exam[2]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x[2]
ECOG Performance Status	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events/SAEs collection/reporting[3]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Concomitant medications[4]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Vital signs (BP, HR, body temperature)	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Height	x															
Body weight	x	x	x	x	x	x	x	x	x	x	x	x	x		x	
Hematology[5]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Chemistry[6]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
eGFR by MDRD	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
HbsAg, HbcAb, and hepatitis C antibody. hepatitis C RNA[7]	x															
Pregnancy test for WOCBP[8]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
12-lead ECG	x															

Echocardiogram or MUGA for LVEF	x															
24-hour urine protein electrophoresis[11]	x		x		x		x		x		x		x	x	x	
Urine immunofixation[11]	x		x		x		x		x		x		x	x	x	
Serum immunofixation	x		x	x	x	x	x	x	x	x	x	x	x	x	x	
SPEP	x		x	x	x	x	x	x	x	x	x	x	x	x	x	
Quantitative IgG, IgM, IgA	x		x	x	x	x	x	x	x	x	x	x	x	x	x	
β2-microglobulin	x															
Serum kappa, lambda free LC, FLC ratio	x		x	x	x	x	x	x	x	x	x	x	x	x	x	
Imaging for bone (lytic) lesions: skeletal survey, CT or PET-CT[12]	x							x						x		
Imaging (whole-body PET-CT or CT or MRI) if history of extramedullary disease[13]	x							x						x		
Whole-body PET-CT[14]	X[14]															
BM aspirate/biopsy for disease assessment[15 and 14]	x[14]			x[14]				x[14]						x[14]		
BM for FISH testing[15]	x													x		
NGS for MRD (ClonoSEQ®)[16]	x^			x^				x^						x^		
Correlatives: BM aspirate sample flow cytometry and cytotoxicity assays	x			x				x						x		
Correlatives: Soluble	x			x				x						x		

BCMA/BAFF/APRIL (serum)																
Premedication if needed		x	x	x	x	x	x	x	x	x	x	x	x			
Belantamab mafodotin IV administration		x	x	x	x	x	x	x	x	x	x	x	x			
Preservative-free artificial tears		x	x	x	x	x	x	x	x	x	x	x	x			
PRO questionaires[17]		x	x	x	x	x	x	x	x	x	x	x	x	x		
Spot urine (creatinine/albumin ratio) or urine dipstick for protein[20]	x		x	x	x	x	x	x	x	x	x	x	x	x		
LTFU data															x	x
Obtain archived Diagnostic samples		x														

1. Screening: May start 60 days post-CAR-T, but must be completed within 30 days prior to enrollment. Consent may occur at any time prior to screening period and does not count within the 30-day time window requirement. Subjects will be enrolled in the trial within 30 days of screening procedures (consent not included) and start treatment within the 90–120 days window after anti-BCMA CAR-T.
2. Screening ocular examination to be performed by an ophthalmologist (or an optometrist, if an ophthalmologist is not available) within 30 days prior to enrollment. See Sections 5.2.4 and 5.3 for lists of ophthalmic exam procedures. On treatment, ocular exams are to be performed prior to each dosing of belantamab mafodotin until the 70-day safety visit. In case of persistent or newly developed ocular symptoms or vision changes, participants will have further ophthalmologic exams, at least every three months until resolution (to grade 1 or baseline) or more frequently as clinically indicated by the eye care specialist or up to one year (whichever comes first). Ocular exam may be performed up to five days prior to second dose onwards for belantamab mafodotin.
3. Continuously, adverse event (AE) assessments: AEs should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. SAEs and AEs will be collected and reported after first treatment dose, through 70 days post last dose of belantamab mafodotin..
4. Concomitant treatments: All concomitant treatments, blood products, as well as nondrug interventions received by subjects will be recorded on the eCRF from screening through end of study.
5. Hematology includes complete blood count (CBC) with differential.
6. Chemistry: alanine aminotransferase (ALT), albumin, alkaline phosphatase, aspartate aminotransferase (AST), bicarbonate, total bilirubin, blood urea nitrogen (BUN), chloride, serum calcium, creatinine, glucose, lactate dehydrogenase, magnesium, sodium, phosphorus or phosphate, and potassium.
7. For subjects with serologic evidence of resolved HBV infection (i.e., positive anti-HBs or positive anti-HBc) at screening, HBV DNA testing by PCR must be performed locally Q12W during treatment, at the end-of-treatment visit, and Q12W for up to six months after the last dose of study treatment. HBV DNA is not necessary for patients positive for anti-HBs, but negative for anti-HBc and with a history of hepatitis B vaccination.
8. Perform only in women of childbearing potential (WOCBP). Two serum pregnancy tests should be performed prior to treatment: at screening prior to enrollment and within 72 hours prior to C1D1. Other pregnancy tests may be either serum or urine. For questionable cases, follicle-stimulating hormone (FSH) and estradiol (as needed in women of non-childbearing potential only) should be performed at local lab. Final pregnancy test (serum or urine) must be performed in WOCBP at least 70 days after the last dose of belantamab mafodotin, preferably at a visit, or via a urine pregnancy test kit mailed to the participant's home with results reported by telephone. Follow-up pregnancy assessment by telephone (for WOCBP only) should be performed four months after the last dose of belantamab mafodotin.
9. Subjects will be enrolled in the trial within 30 days of screening procedures (consent not included) and start treatment within the 90–120 days window after anti-BCMA CAR-T. Each cycle is eight weeks +/- three days. If treatment cycle cannot be resumed within 16 weeks of the previous cycle (from day 1), the patient may permanently discontinue belantamab mafodotin treatment on the trial.
10. 70-day post-last dose safety visit due to half-life of belantamab mafodotin side effect profile: within 70 days +/- three days of last dose. Treatment may continue until discontinuation due to AEs, completion of 12 cycles, progression of myeloma, or beginning of a subsequent anti-myeloma therapy.
11. UPEP with urine immunofixation: Necessary only when M-spike in urine is main parameter for response assessment (based on screening assessment), and will be completed on day 1 of cycles two, four, six, eight, 10, 12, and at end of study. After day 0, if urine M-protein is 200 mg/24 hour, 24-hour urine collections can be stopped, except to determine/confirm M-protein is <100 mg/24 hours for VGPR or undetectable for CR.
12. Imaging of bones for lytic lesions by method aligned with institutional guidance (skeletal survey, CT, or MRI).
13. For patients with extramedullary disease, imaging is only required by either CT, MRI, or PET/CT per local guidance. Needs to be performed by the same method throughout the study as was done at baseline. Selected target lesion needs to be measured and followed over time. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans. Skin lesions, if present, should be measured with a ruler. Measurement of tumor size will be determined by the sum of the products of the maximal perpendicular diameters of measured lesions (SPD).

14. Whole-body PET-CT must performed at screening. Whole-body PET-CT should be repeated if positive for disease at the time of screening, and repeated at the next BM timepoints (e.g., Cycle 3 Day 1, and Cycle 7 Day 1 if not negative at the Cycle 3 Day 1 timepoint). Whole-body PET-CT will be performed during/after treatment to confirm MRD-negativity if MRD-positive at screening/prestudy (if FDG-avid extramedullary lesions are seen at screening).
15. This assessment will include morphology, flow cytometry, FISH for myeloma-associated abnormalities and sample to be sent to Adaptive Biotechnologies for identification of myeloma-specific sequences. Fluorescence *in situ* hybridization (FISH) testing to be performed locally at least for t(4;14), t(14;16), amp(1q), del(1p) and del(17p13). If participant is known to have tested positive for t(4;14) or t(14;16) on previous tests regardless of timeframe, FISH for these translocations does not need to be repeated. FISH results from samples taken within 90 days prior to first dose are acceptable. Samples are also to be obtained/sent for correlative studies (refer to Appendix 5).
16. NGS for MRD assessment (clonoSEQ®) will be performed on bone marrow aspirate sample. Bone marrow aspiration with MRD assay (first pull, in subjects found to be MRD-informative based on clone identification sample) and flow cytometry/cytotoxicity assays will be performed within seven days before cycle 3 day 1, and cycle 7 day 1 and within seven days before or after cycle 12 day 56. Samples are also to be obtained/sent for correlative studies (refer to Appendix 5).
17. Patient-reported outcomes (refer to Appendix) PRO assessments should be completed before any other study procedures are performed (except for blood draws).:
    a. EORTC-QLQ-MY20 and EORTC QLQ-C30
        i. Collect at cycle 1 day 1 (prior to treatment), cycle 3 day 1, cycle 7 day 1, cycle 9 day 1, and 70-day safety visit.
    b. OCULAR SURFACE DISEASE INDEX (OSDI)
        i. Collect at cycle 1 day 1 (prior to treatment), every cycle day 1, and 70-day safety visit.
18. For patients who discontinue treatment prior to progression, continue standard-of-care follow-up every three months until progression or start of another treatment (whichever comes first), then continue to long-term follow-up.
19. Long-term survival data collected/reported approximately every six months (+/- 30 days).
20. 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 ≥1+ at screening, or with positive protein if urine dipstick protein quantification is not available.

LIST OF ABBREVIATIONS

ADPR	adenosine diphosphate-ribose
AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASCT	autologous stem-cell transplantation
AST	aspartate aminotransferase
BM	bone marrow
BMA	bone marrow aspiration
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CFR	Code of Federal Regulations
CL	clearance, IV dosing
CLL	chronic lymphocytic leukemia
CR	complete response
CRC	clinical research coordinator
CRF	case report form
CRi	complete remission with incomplete blood count recovery
CRM	continual reassessment method
CRP	C-reactive protein
CSF	cerebral spinal fluid
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P_{450}
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DSMC	Data and Safety Monitoring Committee
DSMP	data and safety monitoring plan
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

EDC	electronic data capture
EOS	end of study (visit)
EOT	end of treatment (visit)
FDA	United States Food and Drug Administration
GCP	good clinical practice
G-CSF	granulocyte colony stimulating factor
GI	gastrointestinal
GLP	good laboratory practices
GMP	good manufacturing practice
Hb	hemoglobin
HCT	hematocrit
HDT	high-dose therapy
HGB	hemoglobin
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IMWG	International Myeloma Working Group
IEC	independent ethics committee
IP	investigational product
IRB	Institutional Review Board
IRR	infusion-related reaction
ITT	intent to treat
IV	intravenous; intravenously
kDa	kilodalton
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LFT	liver function test(s)
MCWCC	Medical College of Wisconsin Cancer Center
MedDRA	Medical Dictionary for Regulatory Activities
MIDD	monoclonal immunoglobulin deposition disease
MM	multiple myeloma
MMBD	multiple myeloma bone disease
MRI	magnetic resonance imaging
MRD	minimal residual disease
MRU	medical resource utilization

MTD	maximum-tolerated dose
NDMM	newly diagnosed multiple myeloma
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
ORR	overall response rate
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	disease progression
PFS	progression-free survival
Pgp	P-glycoprotein
PK	pharmacokinetics
PO	per os; by mouth (orally)
PR	partial response
PRO	subject-reported outcome
PIM	proto-oncogene serine/threonine-protein kinase
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RBC	red blood cell (count)
RI	renal impairment
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
SC	subcutaneous
sCR	stringent complete response
SD	stable disease
SD	standard deviation
sFLC	serum-free light chains
sIRB	single Institutional Review Board
SmPC	summary of product characteristics
SPEP	serum M-protein immunoelectrophoresis
SRC	Scientific Review Committee
SQ	subcutaneous
$t_{1/2}$	terminal disposition half-life
TEAE	treatment emergent adverse events
T_{max}	single-dose time to reach maximum (peak) concentration
TTP	time to progression
ULN	upper limit of the normal range
UP	unanticipated problem

UPEP	urine M-protein immune-electrophoresis
UPIRSO	unanticipated problems involving risks to subjects or others
US	United States
VGPR	very good partial response
WBC	white blood cell (count)
WBLD	whole-body low dose
WHO	World Health Organization

1 BACKGROUND

1.1 Multiple Myeloma

Multiple myeloma (MM) is a malignant plasma cell disease that is characterized by clonal proliferation of plasma cells in the bone marrow and the production of excessive amounts of a monoclonal immunoglobulin (usually of the IgG or IgA type or free urinary light chain [paraprotein, M-protein or M-component]).(1) It is a disease predominantly associated with advancing age with more than 80% of patients aged 60 years or older.(2) Patients with MM may experience bone pain, bone fractures, fatigue, anemia, infections, hypercalcemia, and kidney problems.(3) The disease course for MM varies with the aggressiveness of the disease and related prognostic factors. Median survival is approximately three years; however, some patients can live longer than 10 years.(4) Treatment options and survival are based on the patient's age, fitness, and disease status.

Patients under the age of approximately 65, presenting with symptomatic active disease in good physical health will generally receive initial therapy with autologous stem cell transplantation (ASCT). To achieve cytoreduction of the disease before collecting stem cells, induction chemotherapy is administered. Induction treatment regimens include alkylating agents, dexamethasone alone, thalidomide plus dexamethasone, and vincristine, Adriamycin® (doxorubicin), and dexamethasone (VAD; or modifications to this regimen); however, the latter two regimens are associated with higher toxicity.(3, 4) Newer treatments with Velcade® (bortezomib) alone, bortezomib combinations, and Revlimid® (lenalidomide) plus dexamethasone show some promise as induction therapy, and these agents demonstrate higher response rates and lower toxicity.(3, 4)

The current aim of MM therapy is to control disease as effectively as possible, to maximize quality of life and to prolong survival. Treatments for relapsed and/or refractory disease are often referred to as salvage therapy. The initial chemotherapy regimen (e.g., melphalan plus prednisone or VAD) can be reinstituted for relapsed/refractory disease if the disease relapsed more than six months after the last therapy ended. The patients for whom stem cells were cryopreserved early in the disease course, and who are transplant candidates, can benefit from ASCT as salvage therapy.(3, 4) Subsequent treatment decisions are based on whether the patient experiences an indolent or aggressive relapse. Patients with relapsed disease may continue taking one drug or treatment regimen as maintenance therapy until relapse or toxicity. In general, MM patients will receive an average of four to eight different regimens during their lifespan utilizing agents such as proteasome inhibitors (e.g., bortezomib and carfilzomib) and immune modulatory agents (e.g., lenalidomide and pomalidomide). However, once a patient becomes refractory to those agents, survival is limited, and newer treatment options are needed to treat patients after they have failed stem cell transplant, chemotherapy, proteasome inhibitors, and immunomodulatory imide agents (IMiDs®). Despite the dramatic improvement in patient outcomes with newer therapies, MM remains an incurable disease. Thus, the treatment of patients who have received at least three different lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who are double refractory to a proteasome inhibitor and an IMiD® remains an unmet medical need.

1.2 BCMA-directed CAR-T Cells

B-cell maturation antigen (BCMA) is expressed on clonal and polyclonal plasma cells, although the intensity of expression can vary with time(5, 6). Highly prevalent expression on plasma cells and exclusivity to the B-cell lineage has made BCMA an attractive target for multiple myeloma (MM) therapeutics, including chimeric antigen receptor (CAR)-T-cell technology. In a phase 1 study of bb2121, a BCMA-targeting CAR T-cell construct with 4-1BB costimulatory molecule, 33 of the 36 enrolled patients received CAR-T cells after lymphodepleting chemotherapy.(7) ORR was 85%, including a CR rate of 45%. Of the

16 patients with a response who were evaluated for MRD, 15 were MRD negative at 10^{-5}. Cytokine release syndrome occurred in 76% patients and was grade 3 in 6%. Neurotoxicity occurred in 42% patients, with grade 3 or 4 in 3%. Based on phase II KarMMa study data, Bristol Myers Squibb and bluebird bio, Inc. submitted a biologics license application to the U.S. Food and Drug Administration (FDA) for bb2121 (idecabtagene vicleucel [ide-cel]) on March 31, 2020 for treatment of myeloma patients who have received at least four prior lines of therapy, including immunomodulatory agent (IMiD), proteasome inhibitor (PI) and anti-CD38 antibody.

Available data from clinical studies demonstrate that peak expansion of BCMA-directed CAR-T cells generally correlates with response, whereas the extent of baseline BCMA expression does not, although most MM cells express BCMA.(8-10) BCMA expression on residual MM cells generally decreases after CAR T-cell therapy, more so in responders than in non-responders. At the time of progression, an increase in BCMA expression has been observed, potentially suggesting that additional BCMA-targeted therapies may be a future treatment option. Another postulated mechanism of disease progression is the lack of long-term persistence of CAR-T cells. Persistence of CAR-T cells has ranged from a few days in most patients to a few months in some patients, with some variability across studies. In a phase I study of bb2121, 96%, 86%, 57%, and 20% patients had detectable CAR-T cells at one, three, six, and 12 months, respectively. (7)

In the heavily relapsed/refractory setting, BCMA CAR-T cells, despite their high response rates, do not lead to long-term durable remissions in the majority of cases. (7, 9, 11, 12) Relapses are systematically observed after BCMA-targeting CAR-T cell therapy, even in patients who achieved minimal residual disease negativity, with a median progression-free survival (PFS) of 12.1 months at the target dose of 450 x 10^6 CAR-T cells in the KarMMa(12) trial and with a PFS rate of 86% at 9 months in the CARTITUDE-1 study(13). Although transient downregulation or loss of BCMA expression has been described following BCMA CAR-T cell therapy, in most cases BCMA expression is maintained at progression(9, 11), suggesting patients may be able to respond to a subsequent BCMA-targeted modality.

1.3 Belantamab Mafodotin

Belantamab mafodotin (GSK2857916) is a first-in-class, 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 toward 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, phase 1 DREAMM-1 study, belantamab mafodotin showed promising anti-myeloma activity, inducing responses in heavily pre-treated patients with relapsed or refractory multiple myeloma(14). DREAMM-2 built on the results from DREAMM-1, showing that the responses observed with single-agent belantamab mafodotin at both the 2.5 mg/kg and 3.4 mg/kg doses (every 3 weeks) compare favorably with the responses described with other approved treatments in patients who were heavily pretreated and refractory to immunomodulatory drugs and proteasome inhibitors and refractory or intolerant to anti-CD38 monoclonal antibodies (either alone or in combination).(15) Results from DREAMM-2 also showed that the safety profile of belantamab mafodotin was manageable, with no new safety concerns compared to DREAMM-1. Belantamab mafodotin was originally an approved treatment option for patients with relapsed or refractory multiple myeloma as a single-agent treatment, who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor (PI), and an immunomodulatory agent (IMiD).

Additional studies of belantamab mafodotin in combination with standard of care or novel agents are ongoing. There is, however, currently no safety and efficacy data available from prospective trials of belantamab mafodotin in patients who previously received BCMA-directed CAR-T. Most recent trials of BCMA-targeted therapies excluded patients previously treated with other BCMA-targeted agents. The absence of clinical trial data on patients sequentially exposed to these agents poses a challenge, even though at least two BCMA-directed therapies (idecabtagene vicleucel (12) and belantamab mafodotin (15)) are commercially available. Conducting a clinical trial using belantamab mafodotin in patients who received BMCA-targeting CAR-T therapy will fulfill an unmet clinical need.

The differing mechanisms of action between ADCs and CAR-T cells also support consideration of sequential use. CAR T-cell therapy by definition is dependent on patient T-cell function; in fact, premanufacturing T-cell phenotype and other parameters of "fitness" may be predictive of in vivo CAR-T cell expansion and clinical response.(9, 16) In contrast, ADCs work primarily through T cell-independent mechanisms. For belantamab mafodotin, these mechanisms include direct multiple myeloma cell apoptosis via internalization and release of the MMAF toxin, antibody-dependent cellular cytotoxicity, via binding to Fc receptors on natural killer cells and monocytes, and inhibition of prosurvival and proliferation signals to multiple myeloma cells through blockade of the BCMA receptor.(17, 18) While most recently published trials excluded patients with prior BCMA-directed therapy exposure, there are case reports of sequential use of these agents (19, 20) all demonstrating clinical activity of BCMA-targeted therapies in patients previously treated with other BCMA-targeted agents. The long-term response durability of all anti-BCMA agents remains unknown currently and the optimal sequencing of these therapies remains unclear.(21)

There is anecdotal data in the published medical literature that demonstrates that patients receiving belantamab mafodotin after failing BCMA-targeting CAR-T therapy may experience response, without having increased or unanticipated toxicity. Cohen et al. described 2 patients who progressed after 1 BCMA-targeted therapy and then responded to a subsequent BCMA-targeted therapy, including one patient who progressed 1 month after receiving BCMA CAR-T therapy (CD3z/4-1BB domains, lentiviral vector, University of Pennsylvania/Novartis study(9)) but responded with minimal response after two doses of belantamab mafodotin at 3.4 mg/kg IV every three weeks. Belantamab mafodotin was held for 6 weeks because of corneal toxicity, and then restarted at 2.5 mg/kg for two additional doses before she had myeloma progression. Gazeau et al. described two clinical cases of patients receiving sequential anti-BCMA therapies, illustrating the feasibility of this approach. One patient with RRMM received three sequential anti-BCMA therapies: 2 BCMA-targeting CAR T-cell infusions (ide-cel; stringent CR to first CAR-T infusion, but no response to second CAR-T infusion) followed by belantamab mafodotin. The patient achieved a very good partial response after three doses of belantamab mafodotin and was still in response five months later. A second RRMM patient remained in CR after ide-cel infusion, but then progressed with plasma cell leukemia. He was subsequently treated with belantamab mafodotin and had a rapid response, with a rapid clearance of circulating plasma cells and had stable disease, but progressed after two doses.

Vaxman *et al.* reported the "real world" efficacy and safety of belantamab in 36 RRMM patients treated at Mayo Clinic between Sep 2020 and June 2021. (21) Twenty-seven patients (75%) underwent prior autologous transplantation. All patients were refractory to daratumumab, PIs, and IMiDs. Seven patients (19%) had received prior CAR-T therapy. This cohort of 36 patients was a heavily pretreated group of patients with a median of eight prior lines of therapy and a median time from diagnosis to first belantamab dose of seven years. Reasons for treatment discontinuation of belantamab mafodotin were progressive disease in 28 patients (77%) and keratopathy in three patients (8%). None of the patients that were treated with CAR-T before belantamab responded to therapy (two had stable disease, and five had progressive disease). These data emphasize the possibility of using sequential belantamab mafodotin in BCMA+ relapses after CAR-T therapy, which remain a functional target even after prior therapeutic pressure on this axis and suggest that this population should be included in future trials.

The ALGONQUIN study is a phase I/II trial designed to evaluate the recommended phase II dose (RP2D), safety, and preliminary efficacy of belantamab mafodotin in combination with pomalidomide and dexamethasone (B-Pd) in patients with RRMM.(22) The initial data from the dose-escalation phase of the study identified 2.5 mg/kg in combination with standard dosing of pomalidomide/dexamethasone as the maximum tolerated dose (MTD)(23). Pomalidomide was administered at 4 mg days 1-21 Q28 days, dexamethasone weekly in conjunction with belantamab mafodotin single (1.92 or 2.5 mg/kg) Q4W, 2.5 mg/kg loading dose followed by 1.92 mg/kg Q4W from cycle ≥2, 2.5 mg/kg dosed Q8W or Q12W or belantamab mafodotin split (2.5 or 3.4 mg/kg) equally on days 1 and 8 Q4W.

As of Oct 2021, 56 patients were enrolled in dose cohorts receiving either 1.92 or 2.5 mg/kg belantamab mafodotin with pomalidomide/dexamethasone. Median age was 64 years and median prior lines of treatment was 2.5. All patients were PI and lenalidomide-exposed, 75% lenalidomide- and PI-refractory and 48% were daratumumab, lenalidomide, and PI-refractory. 54 patients were evaluable for response with median follow-up of 11.0 months. Across all dosing cohorts, overall response rate was 89%. The safety profile of B-Pd is consistent with that observed for pomalidomide/dexamethasone and belantamab mafodotin individually. Both dose cohorts (1.92 and 2.5 mg/kg Q4W) demonstrated deep and durable responses; however, the 2.5 mg/kg dose appeared to have better efficacy with PFS of 25.3 months vs. 16.2 months. The 2.5 mg/kg Q8W dosing schedule has been selected for the part 2 cohort expansion based on optimized safety and efficacy: lower rate of Grade ≥3 blurred vision and neutropenia and superior PFS with 2.5 mg/kg (vs. 1.92 mg/kg).

BelaRd is an open-label, single-center, phase I/II study, aiming to enroll 66 newly diagnosed, transplant-ineligible MM patients.(24) The study comprises two parts. Part 1 will evaluate three doses of belantamab mafodotin (2.5, 1.9, and 1.4 mg/kg) in combination with lenalidomide and dexamethasone (Rd), each given in an individual cohort of patients, and will determine the recommended phase 2 dose (RP2D). In this part, belantamab mafodotin will be administered Q8W and, depending on toxicity, dosing may be rescheduled to Q4W or Q12W. In Part 2, a single cohort of patients will be treated with belantamab mafodotin in the RP2D in combination with Rd to further evaluate the safety and clinical activity of this regimen. An initial safety analysis of Part 1 was presented at the 63rd ASH Annual Meeting in Dec 2021 and included 18 patients who received ≥1 belantamab mafodotin dose and were followed up for ≥8 weeks. The median age of the patients was 72 years (range, 65–82). By the cut-off date (July 2021), patients had received a median of four treatment cycles, with 17 (94%) patients still being on treatment; one (6%) pt died due to pneumonia, unrelated to the study treatment. Sixteen (89%) patients experienced ≥1 treatment emergent adverse event (TEAE). In total, 11 (61%) patients had ≥1 TEAE grade 3/4, of which one was related to belantamab mafodotin; one (6%) patient experienced a serious adverse event (SAE). There were two cases of dose reduction and one case of dose delay. Regarding belantamab mafodotin-related ocular AEs, there were two cases of superficial punctuate keratopathy (grade 1 and 2 each, both in the 2.5 mg/kg cohort), 10 cases of decreased visual acuity (grade 1 [eight patients, 44%]: four in the 1.9 mg/kg cohort and four in the 1.4 mg/kg cohort.

With 13-month follow-up in the DREAMM-2 trial, responses (achieved by 32% of patients) with single-agent belantamab mafodotin 2.5 mg/kg were sustained(15, 25). The median overall survival was 13.7 months, and the median duration of response in the 2.5 mg/kg group was 11 months. In the overall population, the median PFS was 2.8 months. In the belantamab mafodotin 2.5 mg/kg dose group, dose delays because of adverse events (AEs) occurred in 51 (54%) of 95 patients. Keratopathy was the most frequent reason for dose delays (45 of 95 patients; 47%). However, few (nine of 95 patients; 9%) permanently discontinued study treatment because of AEs; one patient discontinued for keratopathy and 2 additional patients for blurred vision and reduced visual acuity. A post hoc analysis to evaluate the outcomes of responding patients in DREAMM2 who had prolonged dose delays (in which ≥3 treatment cycles were missed) was performed.(25) Of the patients who had a response in the 2.5 mg/kg group, 16 of 31 patients (52%) had ≥1 prolonged dose delay (>63 days, or three treatment cycles). Twelve of 16 patients (75%) either had deepening of response (38%) during delay or maintained their response (38%). These data provide indirect evidence that Q8W dosing (instead of Q3W dosing as is approved based on DREAMM-2) will likely still provide disease control and in addition, will likely reduce the incidence of ocular toxicity.

Based on ongoing prospective ALGONQUIN and BelaRd clinical trials(22, 24), Q8W dosing will be selected for maintenance therapy using belantamab mafodotin in this trial. The incidence of ocular toxicity is evidently lower with Q8W dosing than more frequent dosing (Q3W-Q4W), based on preliminary clinical trials data. DREAMM-2 long-term follow-up data from 16 patients(25) who withheld belantamab mafodotin for >3 treatment cycles while waiting for resolution of ocular toxicity demonstrated no progression of multiple myeloma in 88% of patients, indicating that less frequent administration of belantamab mafodotin, such as Q8W, may be acceptable in maintaining disease control. With regards to starting dose of belantamab mafodotin for maintenance, since the objective of the study is to maintain response achieved with anti-BCMA CAR-T cell therapy, improve durability of response and prolong progression-free survival, a starting dose of 1.9 mg/kg will be selected, based on the limited efficacy data from ALGONQUIN and BelaRd trials. Traditionally, maintenance therapies using standard-of-care treatment options for multiple myeloma are used at reduced doses, in an effort to lower the incidence of toxicity. As these patients are already at lower risk of progression than patients with actively relapsed/refractory multiple myeloma, it is critical to use maintenance therapy at a dose and schedule that not only maintains response but also does not subject the patients at higher risk of toxicity. Therefore, belantamab mafodotin 1.9 mg/kg Q8W will be the starting dose level.

1.4 Study Rationale

While CAR T-cell therapy is dependent on patient T-cell function, (9, 16, 20) belantamab mafodotin works primarily through T-cell-independent mechanisms, including direct multiple myeloma cell apoptosis via internalization and release of the MMAF toxin, antibody-dependent cellular cytotoxicity, via binding to Fc receptors on natural killer cells and monocytes, and inhibition of prosurvival and proliferation signals to MM cells through blockade of the BCMA receptor. (26, 27) Belantamab mafodotin has also been postulated to induce immunogenic cell death, (27) potentially priming an endogenous anti-MM immune response.

BCMA expression does not appear to correlate with clinical response with CAR-T. (7, 10) Baseline soluble BCMA (sBCMA) levels have been suggested to be inversely correlated with future response to treatment, (5, 28) though this correlation has not been observed in all studies. (29) Changes in sBCMA levels tend to correlate with the clinical status of MM patients during treatment. Patients who have responded to therapy have reduced sBCMA levels compared with patients with progressive disease. (5, 28)

The loss of CAR-T persistence over time, and the complementary but distinct MOA of belantamab mafodotin compared with BCMA CAR-T support the sequential use of CAR-T and belantamab. Indeed,

early anecdotal reports suggest the benefit of belantamab mafodotin in patients progressing after BCMA CAR-T. (20, 30) It is therefore reasonable to consider that the use of belantamab mafodotin as maintenance will prolong remission status after BCMA CAR-T.

This trial is investigating belantamab mafodotin maintenance therapy after anti-BCMA CAR-T, and it will be started three to four months (day 90–120 days) after CAR-T administration so as to allow recovery of blood counts, improvement in performance status, and resolution of non-hematologic toxicity (due to lymphodepleting chemotherapy and CAR-T). Statistically, it is prudent to have as narrow a time period as possible to start maintenance therapy, as the data used to arrive at the sample size is based on responses to the previous treatment (CAR-T therapy in this case) at a fixed time interval, such as day 90. For that reason, we have selected a narrow window after CAR-T therapy to start maintenance belantamab mafodotin (30 days). Extending the time period to initiate maintenance therapy to say 90–180 days will be problematic given patients were seen to be progressing in the three to six months post-CAR-T period in pivotal CAR-T trial,(7, 12). Therefore, we require a time window to start maintenance belantamab mafodotin 90 to 120 days after anti-BCMA CAR-T, ensuring adequate patient status and permitting operational flexibility in the setting of a research protocol.

Keratopathy was the most common adverse event in DREAMM-2 trial (67 of 95 patients [71%] receiving belamaf 2.5 mg/kg).(15) These events were also the most common reason for dose reductions (22 of 95 patients; 23%) and dose delays (45 of 95 patients; 47%) but rarely led to permanent discontinuation of treatment (one of 95 patients; 1%). The median time to the onset of the first keratopathy examination finding was 37. days (range, 19–143 days), with 66 of 68 patients who had keratopathy experiencing their first finding by treatment cycle 4. Seventy-seven percent patients recovered (resolution or return to baseline) from their first keratopathy examination finding of grade ≥2. The median time to recovery of the first examination finding was 86.5 days (range, 8-358 days). A post hoc analysis to evaluate the outcomes of patients with a response who had prolonged dose delays (in which ≥3 treatment cycles were missed) was performed. Of the patients who had a response according to IMWG criteria in the 2.5-mg/kg group, 16 of 31 patients (52%) had ≥1 prolonged dose delay(25). Fourteen of 16 patients (88%) continued to experience a clinical benefit during the first prolonged delay. Taking into account these data on development of keratopathy at the approved administration schedule of q3weeks and the fact that myeloma control was maintained in patients having dose delays, and the goal of any maintenance therapy to continue treatment without dose interruptions and delays, patients will be receiving belantamab mafodotin q56 days. In addition, these patients do not have progressive disease and therefore, do not require use of belantamab mafodotin at the approved dosing schedule of q3weeks.

Despite improvements in the outcome of myeloma with the use of BCMA-directed CAR-T, the treatment is not curative, and most patients will have progression of disease within a year. There is no standard approach to treatment after the CAR-T cell therapy. New treatment strategies must be developed for maintaining remissions in patients with myeloma following CAR-T and therefore, this trial is important because it has the potential to define a new approach to remission extension following BCMA CAR-T cell therapy for multiple myeloma. The risks associated with the use of belantamab mafodotin in the study are familiar, belantamab mafodotin is approved for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent..(15, 25) There is substantial data available on adverse events associated with belantamab mafodotin. Overall, 93 of 95 patients (98%) receiving belamaf 2.5 mg/kg experienced at least 1 AE. (31) with treatment-related AEs occurring in 84 of 95 patients (88%). Fatal serious AEs occurred in three of 95 patients (3%). One of these events (sepsis) was considered treatment related. Grade 3 and 4 AEs were reported in 79 of 95 patients (83%) and were treatment-related in 54 of 95 patients (57%). The most common any grade and grade ≥3 AEs were keratopathy, thrombocytopenia, and anemia.

1.5 Supplemental Studies

Durable responses to antibody-drug conjugates (ADCs) are limited by acquired mechanisms of resistance. As part of the proposed clinical study, we aim to prospectively investigate mechanisms of resistance to belantamab mafodotin maintenance therapy following anti-BCMA CAR T-cell therapy. Understanding the mechanisms of resistance are critically important as we combine emerging immunotherapies.

Preclinical studies of belantamab mafodotin demonstrated mechanisms of action including induction of apoptosis through caspase-3/7 pathways, antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis of myeloma cells.(27) As reviewed in Collins et al., resistance mechanisms directly affecting mechanisms of action include antibody-antigen interactions and also the delivery and response to the cytotoxic drug payload. (32) We anticipate that some patients will relapse despite belantamab mafodotin maintenance therapy. We hypothesize that acquired resistance to belantamab mafodotin will be found in these patients.

To determine the resistance mechanisms acquired during belantamab mafodotin maintenance therapy following anti-BCMA CAR T-cell therapy, we propose to specifically investigate several possible mechanisms.

1. To evaluate for antigen downregulation, we will perform flow cytometry on samples from each patient to document surface expression of BCMA on myeloma and plasma cells. (33) In addition to belantamab mafodotin, persistence of anti-BCMA CAR-T cells will also put selective pressure on BCMA expression by myeloma cells. CAR-T cells will be identified by protein L or recombinant BCMA staining during flow cytometry. Serum concentrations of soluble BCMA and its ligands, BAFF and APRIL, will be determined by ELISA. These studies will be performed on bone marrow aspirate samples obtained prior to the start of belantamab mafodotin maintenance therapy, and at approximately six-month intervals during the duration of the study. We will compare each patient's samples over time using the screening as a baseline. The samples from each timepoint will be analyzed together allowing for mean fluorescent intensity measurements from flow cytometric analysis to be directly compared. The percentage of relapse of non-relapsed patients with antigen downregulation and the magnitude of the downregulation will be compared.

   Biallelic loss of BCMA was recently described as a mechanism of resistance to BCMA-directed immunotherapy(34). Samur et al. reported a patient with MM who suffered biallelic loss of BCMA and relapse following anti-BCMA CAR T-cell therapy. Sequencing analysis demonstrated a one copy deletion of 16p (which includes the *BCMA* locus on 16p13.13) and a second copy mutation which created an early stop codon in the gene. It is unknown how frequent BCMA loss/mutation is following BCMA-directed therapy. We propose to investigate this possibility in relapsed patients with no detectable membrane-bound or soluble BCMA. For these samples, we will work with the MCW Genomic Sciences and Precision Medicine Center to conduct sequencing analysis to detect allelic deletions and mutations. To determine when the genetic lesions were acquired, we will compare the relapse sample to prior samples from the patient (including diagnostic slides when available) and to $CD138^-$ cells (germline control).

2. Acquired resistance to drug-mediated apoptosis and ADCC will be investigated in samples from patients who relapse following belantamab mafodotin maintenance. CD138+ cells (largely containing the myeloma population) will be isolated from patient bone marrow samples for these studies. Two to 4 ml of bone marrow aspirate will provide adequate numbers of CD138+ cells. We anticipate using the sample numbers depicted in the table below as these studies are labor intensive

and it is not feasible to perform them on samples from all the patients in the study. Bone marrow samples obtained prior to belantamab mafodotin therapy will serve as a baseline for determining resistance in relapsed patients. Samples from non-relapsed patients will serve as controls for differences that preceded BCMA-directed therapy. Samples will be selected as they accrue and up to the limits proposed in the following table.

	N=	BM samples obtained prior to belantamab therapy	BM samples obtained at relapse following belantamab therapy	Total samples
Relapsed	12	12	12	24
Non-relapsed	12	12	0	12
				36

a) CD138+ cells will be cultured with belantamab mafodotin *in vitro*. After two to three days, apoptosis will be assessed by flow cytometry for annexin V and propidium iodide staining and by bioluminescent detection of caspase-3/7 activity as described by Tai et al. (27)
b) ADCC against patient CD138+ cells will be assayed using xCELLigence Real-Time Cell Analysis system. CD138+ cells (targets) will be tethered by using anti-CD9 antibodies. After addition of belantamab mafodotin and autologous CD138- cells or donor NK cells (effectors), cytotoxicity will be measured in real time.

These studies will be performed by the MCW Cell Therapy Laboratory under Drs. Johnson and Kearl (refer to Appendix for logistical details).

2 HYPOTHESIS AND OBJECTIVES

We hypothesize that belantamab mafodotin as maintenance therapy post-CAR-T until progression will be safe, and will prolong progression-free survival (PFS) regardless of the degree of best response after CAR-T.

2.1 Primary Objectives

To describe PFS of patients receiving belantamab mafodotin as maintenance (eight weekly) after anti-BCMA CAR-T administration for relapsed/refractory myeloma.

2.2 Primary Endpoint

1. Twelve-month conditional progression-free survival (PFS), defined as the probability of being alive without progression/relapse or death at 12 months from the time of CAR-T administration conditional on being alive without progression/relapse at 3 months from the time of CAR-T. Follow-up time will be counted from the date of CAR-T cell infusion, left-truncated at the start of study treatment, to the date of first documentation of progression or death due to any cause. Patients last known to be alive and progression-free are censored at date of last contact.

2.3 Secondary Objectives

1. To describe the toxicity profile of belantamab mafodotin given as maintenance after CAR-T.
2. To describe progression-free survival.
3. To describe changes in IMWG response for patients not in CR when initiating therapy with

belantamab mafodotin as post-CAR-T maintenance.

4. To identify the rate of elimination of MRD ($<10^{-5}$) in patients with myeloma at baseline and after starting belantamab mafodotin as post-CART maintenance (at screening/baseline, and after two, six, and 12 cycles).
5. Patient-reported quality of life studies (QoL).
6. To describe the overall survival for the entire cohort from the time of CAR-T administration.

2.4 Secondary Endpoints

1. Best objective response on the trial (by IMWG criteria).
2. Progression-free survival.
3. Negative MRD ($\leq 10^{-5}$, by clonoSEQ®), including imaging plus MRD-negativity ($\leq 10^{-5}$ in bone marrow and no area of PET-CT FDG uptake greater than mediastinal blood pool or surrounding normal tissue.
4. Duration of response on maintenance.
5. Time to progression/relapse after CAR-T.
6. Overall survival for the entire study population.
7. Adverse events on the trial.
8. QoL parameters.

2.5 Exploratory Objectives

1. Exploratory: myeloma cell BCMA expression by flow cytometry and soluble BCMA/BAFF/APRIL levels will be monitored (at baseline, two, six, and 12 cycles).

2.6 Exploratory Endpoints

1. Baseline and on-treatment sBCMA/BAFF/APRIL and BCMA expression on myeloma cells.

3 STUDY DESIGN

3.1 General Description

This is a multicenter phase II, open-label study evaluating the efficacy and safety of belantamab mafodotin maintenance in participants with RRMM who have received commercially available anti-BCMA CAR-T cell therapy.

Subjects will be screened and enrolled 60–120 days after anti-BCMA CAR-T and receive belantamab mafodotin as maintenance therapy. Each maintenance cycle will have a duration of 56 days (+/- three days) and belantamab mafodotin will be administered at a dose of 1.9 mg/kg IV on day 1 of each cycle.

The study will include a screening period, central eligibility confirmation, a treatment period, and a follow-up period. During the 30-day screening period, participants will be evaluated for study eligibility per protocol as defined in the inclusion/exclusion criteria. Eligible participants must have a confirmed diagnosis of MM, been previously treated with anti-BCMA CAR-T cell therapy and have achieved at least SD, and not achieved CR/sCR. Following screening, central eligibility confirmation occurs and participants will be started on maintenance therapy within 90–120 days after receiving CAR-T cell therapy. Subjects will be enrolled in the trial within 30 days of screening procedures (consent not included) and start treatment within the 90–120 days window after anti-BCMA CAR-T.

During the treatment period, subjects will receive belantamab mafodotin as maintenance therapy. Each treatment cycle will have a duration of 56 days (i.e., eight weeks +/- three days). Safety and disease assessments will be performed regularly according to the Schedule of Activities.

For all subjects, disease evaluations will continue to be performed at least every 56 days (± seven days) until confirmed PD, death, start of a new anti-cancer treatment, withdrawal of consent, or loss to follow-up, whichever occurs first. Traditional efficacy assessment will be performed every cycle by serum protein electrophoresis and immunofixation and serum-free light chains, and after every two cycles by 24-hour urine protein electrophoresis and immunofixation. Minimal residual disease (MRD) assessment by next generation sequencing (clonoSEQ®), BCMA expression on bone marrow plasma cells and soluble BCMA/BAFF/APRIL will occur at screening and after two, six, and 12 cycles of belantamab mafodotin maintenance (refer to correlative schedule). In case of PD, subjects will be followed to ascertain subsequent anti-cancer therapy, if any, and survival status every six months (± 30 days) until withdrawal of consent, lost to follow-up, death, or the end of the study. Patients who discontinue treatment prior to progression will continue standard-of-care follow-up every three months until progression or start of another treatment (whichever comes first), then they will continue to long-term follow-up.

3.2 Study Population

Adult patients with myeloma who are within 90–120 days after receiving BCMA-directed CAR-T as standard of care for relapsed/refractory myeloma and having received at least four prior lines of therapy (including a PI, IMiD and anti-CD38 monoclonal antibody) before CAR-T.

3.3 Estimated Time for Completion of Study Enrollment

The study will reach primary enrollment completion in approximately 24 months from the time the study opens to accrual.

3.4 Estimated Time for Study Completion

The study will reach study completion in approximately nine years (four years for completion of treatment for all patients, and five years of long-term survival follow-up) from the time the study opens to accrual.

4 SUBJECT PARTICIPATION, DISCONTINUATION AND WITHDRAWAL

The MCW sIRB is the IRB of record for all participating sites. All sites must follow MCW sIRB requirements and policies regarding subject participation, found here:

https://www.mcw.edu/HRPP/Policies-Procedures.htm

4.1 Subject Status

Subject statuses throughout the trial are defined as follows:

- Prescreening: preconsent (subject considering trial or study staff considering patient for the trial per institutional recruitment methods).
- Screening: period after consent, but prior to eligibility confirmation.

- Consented: consented, prior to eligibility confirmation.
- Eligible: the local investigator confirms all eligibly criteria apply.
- On study/enrolled: date eligibility is confirmed.
- On arm: date of enrollment.
- On treatment: first day treatment was given to the last day treatment was given.
- Off treatment: the last day treatment was given.
- Off arm: the last day treatment was given.
- On follow up: from last day of treatment to the end of follow-up period.
- Off study: follow-up period completed, with no additional data gathered.
- Withdrawn: subject fully withdraws consent (i.e., refuses ALL follow-up, even survival) or is taken off study by the local PI.

4.2 Prescreening and Screening Log

The MCW study PI regularly reviews screen failure reasons to understand barriers to accrual and consider amending eligibility criteria. Screen failures are defined as participants who were considered for the trial to participate in the clinical trial with or without consent but are not subsequently assigned to the study intervention or enrolled in the study.

Prescreening/screening logs are maintained at each site and provided deidentified to MCW upon request.

4.3 Consent

Investigators or their designees will identify potentially eligible subjects from their clinics, subject self-referrals, referrals from other clinicians, and/or other sIRB-approved recruitment methods. No study conduct, including subject screening, can occur until after sIRB initial study approval and an official activation letter.

A written, signed informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization (as applicable) must be obtained before any study-specific assessments are initiated.

After consent, the following occur:
- The site should email the MCW Multisite Team email as soon as possible.
- An OnCore® new subject entry must occur within 24 hours of consent.
- A case/subject/sequence number is assigned in OnCore® from the site in sequence (i.e., inputted from the site staff, not generated by OnCore®).
- Sites enter the case number according to the following template "Site-EMBRACE-001" (unless otherwise specified by the MCW Multisite Team), where "site" is an abbreviation of the site name (e.g., MCW), EMBRACE indicates the trial, and "001" is the sequential subject who consented to the trial at the site (e.g., the first consented subject at MCW would MCW-EMBRACE-001).

4.4 Screening Procedures

Refer to the study calendar of events.

Visit procedures that were performed as standard of care prior to consent (without the specific intent to make the subject eligible for the trial), may count toward screening tests and eligibility if they are within the screening window.

4.5 Central Eligibility Confirmation

Central eligibility confirmation occurs in the following manner:

Participating sites prepare eligibility documents.

- The local PI or designated sub-investigator must review and sign/date (or confirm via email) the eligibility criteria section.
- It is highly recommended that participating sites include written dates and/or values of procedures next to all criteria on the right margin of the page (e.g., 'ECOG score is 0 on date 01/01/1900).
- Subject initials and study case/sequence number should be written on each page of the eligibility pages and supporting source documents — all of which must be deidentified.
- Supporting source documents are required for all item's eligibility criteria (i.e., pathology report, prior therapy history, age, consent, etc.), consent, and documentation of consent process (with key information highlighted or circled if possible, to aid in auditing and quick central eligibility confirmation).

Central Eligibility Confirmation

- The eligibility documents required above should be uploaded into the shared study folder (site folder access shared by the MCW Multisite Team) or emailed, and sites should notify the MCW Multisite Team email and MCW PI via email of completion. Participating site staff must inform the MCW PI if the MCW Multisite Team email returns an out-of-office email reply. If sites have an issue uploading into Box, emailed documents will suffice until the issue is resolved. MCW eligibility confirmation may occur via email if a physical signature would significantly delay enrollment.
- The MCW PI or MCW sub-investigator, with the assistance from the MCW Multisite Team, will review, request additional information, and confirm subject eligibility within approximately one business day of receipt of documents via email (Monday through Friday, excluding holidays. Sites must email the MCW Multisite Team prior to a Friday enrollment or holiday.)
- **Eligibility criteria within a timeframe of "enrollment" means central eligibility confirmation from MCW (not the local investigator).** Sites must ensure the one business day window for central confirmation does not put an eligibility procedure outside of the required time window. If this is potentially an issue, sites should notify the MCW Multisite Team email and MCW PI with supporting documents prior to intended enrollment date.

*Note (for MCW only): After signoff from the MCW enrolling investigator, MCW staff should provide the MCW Multisite Team central eligibility documents for their review and clarification/documentation requests. The MCW study PI (or Study Chair) will then sign off (or confirm via email) for central eligibility confirmation (if they are unavailable, another MCW designee who is not the local enrolling investigator may sign off). If the enrolling investigator is the MCW study PI, MCW staff should provide the MCW Multisite Team signed central eligibility documents for their review and clarification/documentation requests, then the Study Chair (or vice versa study PI) will sign off (or confirm via email) for central eligibility confirmation (if they are unavailable, another MCW investigator may sign off, unless that is not possible).

Subject Initials: _____ Subject Study ID: _____

Enrolling physician signature: _____ Date: _____

4.6 Eligibility Criteria

Study staff must adhere to MCWCC CTO SOPs regarding eligibility review/confirmation.

No waivers of protocol eligibility will be granted. When clinical factors relating to an eligibility item are unclear or questionable, the study PI (Meera Mohan, *memohan@mcw.edu*) can only provide guidance or clarification on eligibility.

Inclusion Criteria

Each subject must meet all the following inclusion criteria to be enrolled in the study:

1. Diagnosis of multiple myeloma with measurable disease (at the time of diagnosis: serum M-protein ≥ 0.5 g/dL or urine M-protein ≥200 mg/24 hour or involved serum-free light chain ≥10 mg/dL provided that the ratio of involved/uninvolved light chain is abnormal). Patients with no biochemically measurable disease may be enrolled if bidirectionally measurable plasmacytomas or bone marrow plasmacytomas >10% are present prior to CAR-T infusion (sites must explicitly identify these patients to the MCW Multisite Team upon enrollment, as only four of these patients will be permitted on study, after which no future patients will be permitted to be enrolled).
2. Received at least four prior lines of therapy (including a PI, IMiD, **and** anti-CD38 monoclonal antibody – note radiation therapy is considered a line of therapy) given before anti-BCMA CAR-T cell therapy, and has not progressed/relapsed after receiving CAR-T therapy.
3. Achieved at least SD to CAR-T therapy and remained progression-free after anti-BCMA CAR-T administration until enrollment (this requirement is also necessary prior administration of first study drug).
4. Voluntary consent (per sIRB requirements) must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.
5. Age ≥ 18 years.
6. Life expectancy ≥ six months.
7. Eastern Cooperative Oncology Group (ECOG) performance status 0–2.
8. Creatinine clearance (CrCl) ≥ 30 mL/min/1.73 m^2 (using formula MDRD).
9. Adequate hepatic function evidenced by AST and ALT ≤ 2.5 x ULN, bilirubin ≤ 1.5 x ULN (isolated bilirubin ≥1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
10. Adequate bone marrow function evidenced by hemoglobin ≥8 g/dL, platelets ≥75,000/mm^3 (without transfusion of platelets in the prior seven days) and absolute neutrophil count ≥1,500/mm^3 (growth factors are allowed during screening, but not within seven days prior to obtaining this result).
11. Spot urine (albumin/creatinine ratio) < 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).
12. Female participants:
    Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

Is not a woman of childbearing potential (WOCBP).
OR
Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency during the intervention period and for four months after the last dose of belantamab mafodotin and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- WOCBP must have a negative highly sensitive serum pregnancy test within 72 hours of dosing on C1D1 and agree to use a highly effective method of contraception during the study and for four months after the last dose of belantamab mafodotin.
- Additional requirements for pregnancy testing during and after study intervention are provided in Appendix 4 and the study calendar (schedule of activities).

13. Male participants:
Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Male participants are eligible to participate if they agree to the following from the time of first dose of study until six months after the last dose of belantamab mafodotin to allow for clearance of any altered sperm:

Refrain from donating sperm.

AND either:

Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

Must agree to use contraception/barrier as detailed below:

- 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 as described in when having sexual intercourse with a WOCBP (including pregnant females).

Subject Initials: _____ Subject Study ID: _____

Enrolling physician signature: _____ Date: _____

Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Prior exposure to belantamab mafodotin before enrollment on the trial, including before administration of commercial anti-BCMA CAR-T.
2. Evidence of progression/relapse after BCMA CAR-T before enrollment (this requirement is also necessary prior to administration of first study drug).
3. Subject has achieved CR/sCR at the time of enrollment (this requirement is also necessary prior to administration of first study drug).
4. Patient was given BCMA CAR-T under EAP (expanded access protocol) for non-conforming product.
5. Subject progressed on a prior anti-BCMA therapy before receiving commercial anti-BCMA CAR-T.
6. Any previous treatment-related adverse events higher than grade 1 at enrollment (except for alopecia and grade 2 neuropathy).
7. Acute active infection requiring treatment within 14 days of enrollment (this requirement is necessary also prior administration of first study drug).
8. Current or prior involvement of central nervous system by multiple myeloma.
9. Smoldering multiple myeloma or POEMS.
10. Pregnant or lactating females.
11. Major surgery or prior treatment with a monoclonal antibody within 30 days prior to enrollment (this requirement is necessary also prior administration of first study drug).
12. Evidence of cardiovascular risk including any of the following:
    a. Evidence of current clinically significant untreated arrhythmias, including clinically significant ECG abnormalities including second-degree (Mobitz Type II) or third-degree atrioventricular (AV) block.
    b. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within three months of enrollment.
    c. Class III or IV heart failure as defined by the New York Heart Association functional classification system (NYHA, 1994)
    d. Uncontrolled hypertension.
13. Nonhematologic malignancy within the past three years with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) carcinoma *in situ* of the cervix or breast; c) prostate cancer of Gleason score 6 or less with stable prostate-specific antigen levels; or d) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder or benign tumors of the adrenal or pancreas.
14. Participant must not have current corneal epithelial disease except mild changes in corneal epithelium.
15. 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.
16. Participant must not have presence of active renal condition (infection, requirement for dialysis or any other condition that could affect participant's

safety). Participants with isolated proteinuria resulting from MM are eligible, provided they fulfil inclusion criteria.

17. Participant must not use contact lenses while participating in this study, unless directed by an ophthalmologist.
18. Participant must not have used an investigational drug or approved systemic anti-myeloma therapy (including systemic steroids) within 14 days or five half-lives, whichever is shorter, preceding enrollment (this requirement is also necessary prior administration of first study drug). Participant must not have received radiation therapy within 14 days of enrollment.
19. Participant must not have had plasmapheresis within seven days prior to enrollment (this requirement is also necessary prior administration of first study drug).
20. Participant must not have had major surgery ≤ four weeks prior to enrollment (this requirement is also necessary prior administration of first study drug).
21. Participant must not have any evidence of active mucosal or internal bleeding.
22. Participant 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.
23. Participant must not have known HIV infection (screening test not required), unless the participant can meet all of the following criteria:
    a. Established anti-retroviral therapy (ART) for at least 4 weeks and HIV viral load <400 copies/mL
    b. CD4+ T-cell (CD4+) counts ≥350 cells/uL
    c. No history of AIDS-defining opportunistic infections within the last 12 months
24. Participant must not have presence of hepatitis B surface antigen (HBsAg), or hepatitis B core antibody (HBcAb) at screening or within three months prior to first dose of study treatment. Note: presence of hepatitis B surface antibody (HBsAb) indicating previous vaccination will not exclude a participant.
25. Participant must not have positive hepatitis C antibody test result or positive hepatitis C RNA test result at screening or within three 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.
26. Prior allogenic stem cell transplant within one year before enrollment, or current evidence of GvHD, or on systemic immunosuppressive therapy for GvHD at least six weeks before enrollment. NOTE – Participants who have undergone syngeneic transplant will be allowed, only if no history of GvHD
27. Symptomatic amyloidosis, active POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma proliferative disorder, skin changes) or active plasma cell leukemia at the time of screening.
28. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions (including lab abnormalities) that could interfere with participant's safety, obtaining informed consent or compliance to the study procedures.
29. Administration of live or live-attenuated vaccines are contraindicated 30 days

prior to the first dose of study treatment. Killed or inactivated vaccines may be administered; however, the response to such vaccines cannot be predicted.

"I have reviewed all inclusion/exclusion criteria and confirm the subject is eligible."	
Enrolling Investigator Name (print)	
Enrolling Investigator Signature	**Date**

"This subject is eligible for the study and considered on study/enrolled."	
MCW Study PI or Study Chair (print) *or designee name	
MCW Study PI or Study Chair Signature (or email confirmation) *or designee	**Date**

4.7 Discontinuation of Study Treatment, Withdrawal, and Compliance

Discontinuation from the study treatment does not mean discontinuation from the study. Subject will be considered in follow-up, study procedures should still be completed as indicated by the study protocol, and AEs/SAEs will continue to be reported according to this protocol.

It is preferred that in cases of intended discontinuation from study intervention that are not due to adverse events or of immediate subject safety concern participating sites email the MCW Multisite Team prior to the discontinuation to determine if any efforts/actions might be safely taken to continue subject participation.

The MCW Multisite Team should be notified via the MCW Multisite Team email within 24 hours of discontinuation of study intervention, describing the nature of the discontinuation. OnCore® subject status (treatment and follow-up tabs) and discontinuation eCRF should be completed within 24 hours of discontinuation.

In the absence of treatment delays due to adverse events (refer to dose modification section and holds in Section 5), study treatment/intervention may continue until:

- Disease progression.
- General or specific changes in the subject's condition renders the subject unacceptable for further treatment in the investigator's judgment.
- Inter-current illness that prevents further treatment administration.
- Subject decides to withdraw from the study.
- The subject has significant noncompliance with the protocol (see below).
- Unacceptable adverse event(s).
- Study discontinuation or closure.

Subjects who sign the informed consent form and are enrolled but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, enroll and receive the study intervention, but subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced.

Consent Withdrawal

A subject may decide to withdraw from the study at any time. Sites must follow the sIRB SOPs regarding consent withdrawal.

If a subject intends on withdrawing consent, sites should confirm which of the following options the subject chooses, document the discussion, upload the documentation to shared site study folder and update OnCore®, and email the MCW team email:

a. Full consent withdrawal, with no study follow-up.
b. Selective consent withdrawal from interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information.

Investigator-initiated Withdrawal

The investigator will withdraw a subject whenever continued participation is no longer in the subject's best interests. Reasons for withdrawing a subject include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a subject's request to end participation, a subject's noncompliance (see below) or simply significant uncertainty on the part of the investigator that continued

participation is prudent. Sites should notify the MCW Multisite Team (via the MCW Multisite Team email) within 24 hours in such cases. The reason for study withdrawal and the date the subject was removed from the study must be documented in OnCore®.

Subject Compliance

The study team should re-educate the subject on the importance of compliance as necessary and document noncompliance. If this is an ongoing issue, then, the MCW PI should be contacted to determine whether the subject should continue on trial.

4.8 Lost to Follow-up

The following actions should be taken if a participant fails to return to the clinic for a required study visit and/or is unable to be reached for follow-up:

- The investigator or designee should make every effort to regain contact and/or reschedule a missed visit with the participant.
- A participant is deemed lost to follow-up if his/her status cannot be obtained after all of the following occurs at two consecutive scheduled protocol calendar time points:
  - Three telephone calls (at least one day apart) from the study team are unanswered.
    AND
  - A letter to the participant's last known mailing address goes unanswered (refer to Appendix 2). Sites may use their own letter but must follow sIRB policies regarding approval.
    AND
  - These contact attempts should be documented in the participant's medical record or study file.

- Update OnCore® (follow-up tab and eCRF) when a participant is officially considered lost to follow-up.
- If a subject is considered lost to follow-up, but subsequently contacts the participating site study team, the subject should be considered in follow-up again, with subject approval, and the study team must notify the MCW Multisite Team via the MCW Multisite Team email.

4.9 Accrual Suspension and Closure

The MCW Multisite Team facilitates the suspension and closing of accrual in the following manner:

- The MCW Multisite Team sends accrual reports periodically and notifies sites when nearing suspension requirements.
- Sites must inform the MCW Multisite Team (via the MCW Multisite Team email) of any new or potential consents by the end of the business day.
- The MCW Multisite Team will inform participating sites when the actual or potential number of consents equals the number of available enrollment slots, at which time new consenting is suspended.
- If one of the consented subjects (in screening) is ineligible, accrual reopens until a subject is consented to fill that accrual spot.
- If all the consented subjects end up being eligible, the MCW Multisite Team emails an accrual closure notice.

4.10 End of Study Definition

A participant is considered to have completed the study if he or she completed all phases of the study, including the last visit or the last scheduled procedure shown in the calendar of events or has been discontinued.

4.11 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause (as determined by the MCW Multisite Team, DSMC, drug manufacturers, FDA, and/or sIRB). Written notification documenting the reason for study suspension or termination will be provided by the suspending or terminating party to study participants, investigator, funding agency, the investigational new drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the MCW Principal Investigator (PI) and MCW Multisite Team will promptly inform study sites, the MCW Institutional Review Board (sIRB), and sponsor, and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes. Participating sites will adhere to the sIRB policies.

5 TREATMENT PLAN

5.1 Treatment

Subjects will receive belantamab mafodotin as maintenance therapy. Belantamab mafodotin will be administered IV over approximately 30 minutes at the recommended dose of 1.9 mg/kg IV day 1 of every 56-day cycle (+/- 3 days).

Maintenance therapy with belantamab mafodotin will continue until progressive disease (PD), death, unacceptable toxicity, withdrawal of consent or end of study, whichever occurs first. Dose interruptions or reductions may be required to address potential drug-associated toxicities.

The dose to be administered will be based on actual body weight calculated at baseline (cycle 1 day 1). However, if the change in body weight is greater than 10%, the dose will be recalculated based on the actual body weight at the time of dosing. The dose may be reduced to address toxicity as described in Section 5.2.

Arm	Belantamab mafodotin (Day 1 of every 56-day cycle)
A	1.9 mg/kg IV over at least 30 minutes

5.2 Dose Modifications

5.2.1 Adjustments Due to Body Weight

The actual body weight in kg at baseline (on cycle 1 day 1) will be used for dose calculation of belantamab mafodotin in all subjects during the treatment period. As noted above, if the change of body weight is greater than 10%, the dose should be recalculated based on the actual body weight at the time of dosing.

5.2.2 Dose Reductions for Toxicity

Permitted dose reductions for belantamab mafodotin are shown in **Table 2**. Belantamab mafodotin-related AEs are summarized in **Table 3**. General dose modification and management guidelines for drug-related AEs not otherwise specified are summarized in **Table 3**. Dose modification guidelines for cornea-related AEs associated with belantamab mafodotin are summarized in **Table 4**.

Table 2. Permitted dose reduction for belantamab mafodotin

Starting dose	First reduction	Additional reduction
1.9 mg/kg	1.4 mg/kg	If dose delays/modifications detailed below do not satisfy the conditions needed to avoid another dose reduction, the subject must be discontinued. Recommend emailing study PI (cc: MCW Multisite Team) prior to this occurring whenever possible.

Only one dose reduction (to 1.4 mg/kg) is permitted from the starting dose of 1.9 mg/kg. If the participant cannot tolerate the drug after the allowed dose reduction of belantamab mafodotin, the participant will permanently discontinue treatment for lack of tolerability. Any dose level below 1.4 mg/kg is not planned. In case of full resolution of symptoms which lead to dose reduction, further treatment at the previous dose level may be considered by the investigator, after consultation with the sponsor-investigator (cc: MCW Multisite Team email).

Dosing delays are permitted in the case of toxicity, medical/surgical events, or for logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, subject's vacation/holidays, but not for subject's decision to delay treatment). The reason for any dose delay should be documented in the subject's eCRF and clinic record.

Table 3a. Dose modifications

*Note these toxicities are known to be associated with use of belantamab mafodotin. The following actions should be taken whether or not the toxicity may be attributed to other possible causes.

Toxicity	**Grade/description of toxicity**	**Action**
Elevated serum creatinine, which cannot be explained by concomitant sepsis, TLS, other severe condition with fever, or dehydration[a]	If absolute serum creatinine increases from baseline by >0.5 mg/dL	• Repeat serum creatinine or eGFR within 48 hours. • If confirmed: withhold therapy, institute treatment and monitoring as clinically indicated, and follow for resolution. • Discuss any further dosing with study PI (cc: MCW Multisite Team email).
Serum creatinine ≥Grade 3 (compared to baseline)	>3.0 mg/dL from baseline Or 3.0–6.0 X ULN	• Provide appropriate medical treatment. • Hold treatment with belantamab mafodotin. • Discuss with study PI to determine appropriateness of further dosing (cc: MCW Multisite Team email).
Spot urine (creatinine/albumin ratio)	>2,000 mg/g (or 224 mg/mmol)	• Retest (at least seven days apart). • If not confirmed, continue belantamab mafodotin at current dose. • If confirmed on retest and no clear evidence of disease progression.

Toxicity	Grade/description of toxicity	Action
		o Interrupt treatment with belantamab mafodotin. o Repeat testing within four weeks. -If spot urine ≤2,000 mg/g (224 mg/mmol), may restart belantamab mafodotin with one dose-level reduction. - If spot urine remains >2,000 mg/g (224 mg/mmol) after four weeks, permanently discontinue belantamab mafodotin and withdraw participant from study; provide treatment as clinically indicated and follow for resolution.
Urine dipstick	2+	• May continue belantamab mafodotin dosing. • Confirm by quantitative assessment using albumin/creatinine (spot urine from first void). If albumin/creatinine ≥2000 mg/g, at the next cycle follow guidance above for spot urine.
	≥3+	Interrupt treatment and follow-up for recovery. Implement quantification of albumin/creatinine ratio.
Thrombocytopenia (on days of dosing)	Grade 3 (Platelet count 25,000 to less than 50,000/mcL)	• No bleeding: continue treatment with one dose-level reduction. • Consider reverting to previous dose once thrombocytopenia recovered to grade 2, or less.
		• With bleeding: withhold the dose, continue treatment after recovery with one dose-level reduction. • Consider additional supportive treatment (e.g., transfusion), as clinically indicated and per local practice.
	Grade 4 (Platelet count less than 25,000/mcL)	• Withhold the belantamab mafodotin dose. Consider restarting with one dose-level reduction if recovered to ≤ grade 3, only if there is no active bleeding at time of treatment restart.
		• If thrombocytopenia is considered disease related, is not accompanied by bleeding, and recovers with transfusion to >25 x10^9/L, continuing treatment with dose reduction may be considered after discussion with the sponsor-investigator (cc: MCW Multisite Team email).
Febrile neutropenia	Grades 3–4 Defined as: single temperature of 38.3°C, or sustained 38°C for >1 hour AND ANC <1.0×10^9/L	• Withhold belantamab mafodotin and immediately hospitalize participant with appropriate management, per local institutional guidance. • Consider additional supportive treatment per local practice (e.g., growth factors). • Upon recovery, consider a 25% dose reduction of belantamab mafodotin, if neutropenia was drug related.
Afebrile neutropenia	Grades 3–4 (Defined as ANC <1.0x10^9/L)	• If noted on day 1 of any cycle, withhold belantamab mafodotin dose. • Resume belantamab mafodotin at preheld dose once neutropenia recovers to grade ≤2 (ANC ≥1.0x10^9/L) 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 SoA specifications. • In cases of frequent recurrent neutropenia (ANC<1.0x109/L), consider dose reduction of belantamab mafodotin.
Infusion reaction[b]	Grade 2	Stop the infusion, provide medical treatment and continue at slower rate after resolution to grade 0–1.

Toxicity	Grade/description of toxicity	Action
	Grade 3	Further treatment with belantamab mafodotin needs to be discussed with sponsor-investigator. Continuation only allowed after recovery to ≤grade 1 and with premedication, and extension of infusion time to 2–4 hours. Any future infusion needs to be premedicated.
	Grade 4	Permanently discontinue.
Pneumonitis	Grade 1	Continue treatment at the full dose when toxicity resolves to grade < 1.
	Grade 2	• Withhold treatment with belantamab mafodotin. • Upon recovery, restart treatment with one dose-level reduction. • If patient is already at the lowest dose level (1.4 mg/kg), then rechallenge with the same dose; this must be discussed with the study PI.
	Grades 3–4	Permanently discontinue treatment with belantamab mafodotin.
Urine dipstick	2+	• May continue belantamab mafodotin dosing. • Confirm by quantitative assessment using albumin/creatinine (spot urine from first void). • If albumin/creatinine ≥2,000 mg/g, at the next cycle follow guidance above for spot urine.
	≥3+	Interrupt treatment and follow up for recovery. Implement quantification of albumin/creatinine ratio.

[a] These criteria do not apply to participants on dialysis.
[b] 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 should be premedicated for the next scheduled dose.

Table 3b. Dose modifications (other)

*The following actions should be taken only if toxicity may be possibly attributed to belantamab mafodotin.

	Severity	Management	Follow-up
Events Not Otherwise Specified	**Grade 1**	• Administer symptomatic treatment as appropriate. • Continue study drug(s).	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:* • Consult study PI (cc: MCW Multisite Team email) • Delay study drug, or consider one dose level reduction. If recovery takes >3 weeks, consult with study PI (cc: MCW Multisite Team email) • If symptoms continue or worsen to grade 3–4, see below.
	Grade 3	• Provide appropriate medical treatment. • Consider consulting subspecialist.	• Consult study PI (cc: MCW Multisite Team email). • Delay treatment till recovery to grade ≤ 1. • Consider dose reduction. Exceptions: Participants who develop grade 3

			toxicities which respond to standard treatment and resolve to grade ≤ 1 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 if it is agreed between the site investigator and overall study PI (via email, cc: MCW Multisite Team email) that benefits outweigh the risks for a given participant

5.2.3 Dose Modification Related Corneal Adverse Reactions

All belantamab mafodotin dose modifications and stopping criteria are to be based on the Keratopathy Visual Acuity (KVA) Scale for Treatment-related Corneal Toxicities. Corneal events will be graded according to this scale. Refer to reporting section for additional requirements.

Table 4. Corneal adverse reactions and recommendations for belamantab mafodotin dosing.

Grade per KVA scale	Grade 1	Grade 2	Grade 3	Grade 4
***Recommended Dosage Modifications**	Continue treatment at current dose.	Withhold belantamab mafodotin until improvement in **both** corneal examination findings and changes in BCVA to grade 1 or better and resume at current dose.	Withhold belantamab mafodotin until improvement in **both** corneal examination findings and changes in BCVA to grade 1 or better and resume at reduced dose. If already on lowest dose, participant continues treatment at same dose.	Consider permanent discontinuation of belantamab mafodotin. If based on benefit risk assessment and treatment of belantamab mafodotin is being considered, withhold treatment until improvement in **both** corneal examination findings and change in BCVA to grade 1 or better and resume at reduced dose. If already on lowest dose, participant continues treatment at same dose.

Table 5: Keratopathy Visual Acuity (KVA) Scale for treatment-related corneal toxicities

Grade per KVA scale		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Corneal Toxicities	***Corneal examination finding(s)***	Mild superficial keratopathy[a]	Moderate superficial keratopathy[b]	Severe superficial keratopathy[c]	Corneal epithelial defect[d]
	Change in BCVA[e]	Decline from baseline of one line on Snellen Visual Acuity	Decline from baseline of two or three lines (and Snellen Visual Acuity not worse than 20/200)	Decline from baseline by more than three lines (and Snellen Visual Acuity not worse than 20/200)	Snellen Visual Acuity worse than 20/200

Abbreviations: BCVA=Best-Corrected Visual Acuity; KVA=Keratopathy Visual Acuity.

Dose reductions of belantamab mafodotin will be triggered by grade 2 or worse events of ocular exam findings, or decrease in BCVA on day of dosing.

a) Mild superficial keratopathy is mild superficial punctate keratopathy (documented worsening from baseline), **with or without** symptoms.
b) Moderate superficial keratopathy is any/or a combination of moderate superficial punctate keratopathy, patchy microcyst like deposits, subepithelial haze (peripheral), or a new peripheral stromal opacity.
c) Severe superficial keratopathy is any/or a combination of severe superficial punctate keratopathy, diffuse microcyst like deposits involving the central cornea, subepithelial haze (central), or a new central stromal opacity.
d) Corneal epithelial defect such as corneal ulcers: corneal ulcer by definition means an epithelial defect with underlying stromal infiltration.
e) Changes in visual acuity due to treatment-related corneal findings:
   - For participants who have BCVA worse than 20/20 in either eye at baseline, dose modification for that eye will be determined by the worsening of vision from baseline only (not by absolute BCVA at the visits).
   - If a participant has a baseline BCVA of 20/200 or worse in an eye, then belantamab mafodotin-related changes in vision in the other eye will drive the dose modification. If a participant has baseline BCVA of 20/200 or worse in both the eyes, then the decision to delay or reduce belantamab mafodotin dose will be based on site principal investigator's assessment of benefit vs. risk based on corneal examination findings following a discussion with the qualified eye care specialist.

Note: Dose modification should be based on the most severe finding. If eyes differ in severity, dose modification guideline should be applied based on the more severe eye.

VISUAL ACUITY CONVERSION TABLE:

SNELLEN	SNELLEN (METRIC)	logMAR	DECIMAL
No equivalent value[4]			
[1,3]20/20000	6/6000	3.0	0.001
[2,3]20/2000	6/600	2.0	0.010
20/400	6/120	1.3	0.05
20/320	6/96	1.2	0.063
20/250	6/76	1.1	0.08
20/200	6/60	1.0	0.10
20/160	6/48	0.9	0.125
20/150			
20/125	6/38	0.8	0.15- 0.16
20/100	6/30	0.7	0.20
20/80	6/24	0.6	0.25
20/70			
20/63	6/20	0.5	0.3- 0.32
20/60			
20/50	6/15	0.4	0.40
20/40	6/12	0.3	0.50
20/32	6/10	0.2	0.6-0.63
20/30			0.67 – 0.7
20/25	6/7.5	0.1	0.80- 0.9
20/20	6/6	0.0	1.00
20/16	6/5	-0.1	1.2 - 1.25
20/12.5			1.5- 1.6
20/10			2.0

1. Hand motion at 2 feet.
2. Counting fingers at 2 feet.
3. Holladay JT. Visual acuity measurements. J Cataract Refract Surg.2004; 30:287-290
4. Non-snellen acuity of 'light perception' or 'no light perception' do not have corresponding values.

5.2.4 Corneal Supportive Care Guidelines for Belantamab Mafodotin

Corneal events, which commonly manifest as superficial keratopathy, have been observed with antibody drug conjugates, including those conjugated to MMAF. As there is no single term which adequately captures these events, the term "corneal events" includes preferred terms describing corneal events reported with belantamab mafodotin, such as superficial punctate keratopathy, microcyst-like changes, subepithelial haze, corneal erosions and corneal ulcers.

Sites are required to establish a close collaboration with a qualified eye care specialist who will be responsible for assessing participants and managing those who develop corneal examination findings in close communication with the MCW PI (cc: MCW Multisite Team email).

Participants will be assessed by a qualified eye care specialist at screening/baseline and then prior to every dosing of belantamab mafodotin, and 70-day safety visit (assessment window of up to five days prior to dosing, but all effort should be made to schedule as close to belantamab mafodotin dosing as possible).

- If a participant subsequently develops vision changes or other ocular symptoms, the participant should be evaluated by a qualified eye care specialist.

- In case of persistent ophthalmologic exam findings, newly developed ocular symptoms or vision changes, the participants will have further ophthalmologic exams, at least every cycle until resolution (to grade 1 or baseline) or more frequently as clinically indicated by a qualified eye care specialist.
- Participants who have corneal signs per the Keratopathy Visual Acuity (KVA) scale for treatment-related corneal toxicities present at the end-of-study treatment will continue to be followed every three months for up to 12 months, or until full resolution of findings, which is defined as a return to participant's baseline, or until deemed clinically stable by a qualified eye care specialist, whichever comes first.

Ocular Examination and Procedures

Patients will be assessed by ophthalmologist (or an 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. Selected anterior segment (slit lamp) examination with focus on the cornea and lens, including fluorescein staining of the cornea.
5. Intraocular pressure measurement.
6. Dilated funduscopic exam.

The *on-treatment* and *follow-up* ophthalmic exam should be performed for both eyes (OU), as described below and in the schedule of assessments:

1. Best corrected visual acuity.
2. Documentation of manifest refraction and the method used to obtain best corrected visual acuity.
3. Slit anterior segment (slit lamp) examination with focus on the cornea and lens, including fluorescein staining of the cornea.
4. Intraocular pressure measurement (if clinically indicated).
5. Dilated funduscopic exam (if clinically indicated).

All ocular exam procedures/tests (e.g., BCVA, slit lamp, etc.) performed at *screening/baseline* exam should also be obtained at the next ocular exam obtained following treatment discontinuation (e.g., 70-day safety visit). Participants with corneal signs or symptoms at the 70-day safety visit will be followed at least every three months until resolution (to grade 1 or baseline) or more frequently as clinically indicated by the eye care specialist or up to one year (whichever comes first). Clinically stable is defined as changes less than or equal to grade 1 for both Ophthalmic Exam Findings and Visual Acuity according to the Keratopathy Visual Acuity (KVA) Scale criteria for eye disorders. Additional examinations should be performed at the discretion of the treating eye specialist.

Ocular Prophylaxis

Ocular prophylaxis should be instituted for all participants. Ocular prophylaxis includes:

- Prophylactic preservative-free artificial tears must be administered in each eye at least four to eight times daily, beginning on cycle 1 day 1 until the end of belantamab mafodotin treatment.

Participants must not use contact lenses during the study, unless directed by an ophthalmologist (refer to Section 5.6).

Ocular Monitoring — Changes in Corneal Epithelium: Severity Grading and Mitigation Strategy

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 four to eight 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 two 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 five to 10 minutes between administration of artificial tears and steroid eye drops (if administered).

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 or require steroid eye drops for more than seven days.

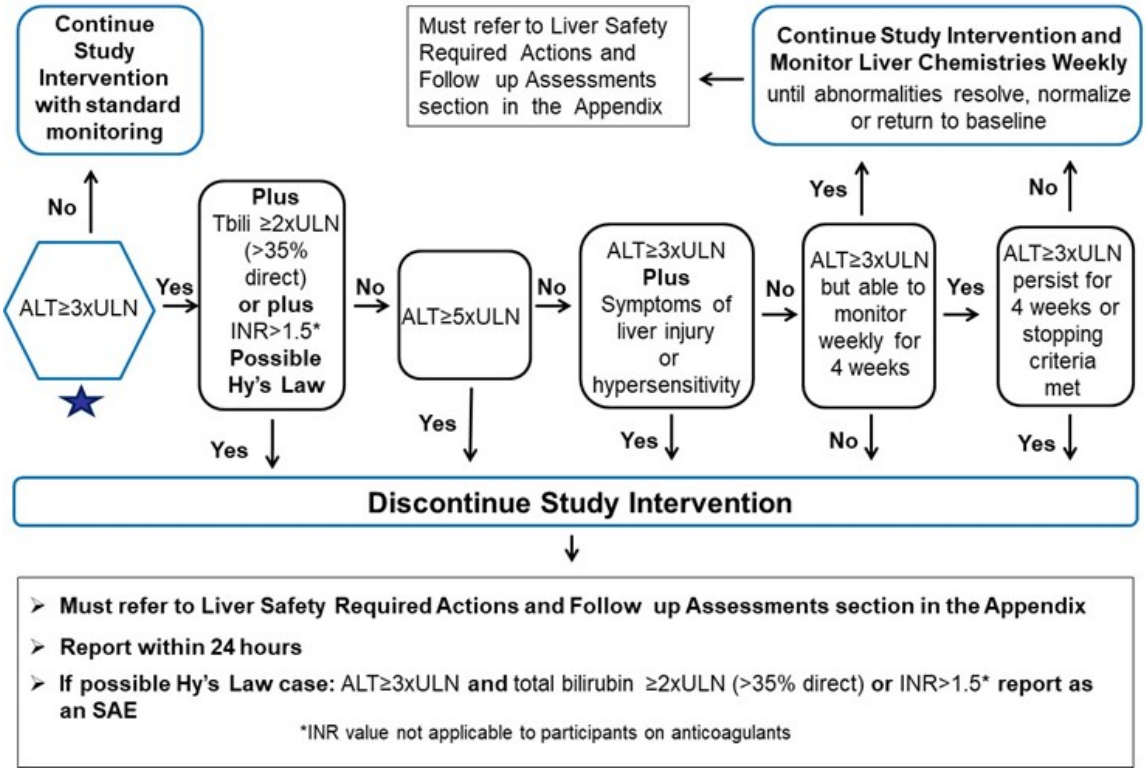
Changes in corneal epithelium must be graded according to the KVA scale (Table 5).

5.3 Safety Stopping Criteria

Liver Chemistry Stopping Criteria

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

Liver chemistry stopping and increased monitoring algorithm for subjects WITH entry criteria ALT ≤2.5xULN



*NOTE – in diagram above, "Appendix" is listed below in this section.

Phase I/II liver chemistry stopping and increased monitoring criteria

Liver chemistry stopping criteria (for patient treatment)	
ALT - absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥ four 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 four 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-upp Assessments**
• **Immediately** discontinue study intervention. • Report the event to study PI **within 24 hours** (refer to reporting section)**.** • Complete the requirement in reporting section and complete SAE 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.	• 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

Liver chemistry stopping criteria (for patient treatment)	
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING**). **<u>MONITORING:</u>** **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)<u>:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up assessments within **24 to 72 hours.** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline.	transferase [GGT], glutamate dehydrogenase [GLDH], 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, on the liver event form. • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs and other over the counter medications. • Record alcohol use. **If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5** obtain the following in addition to the assessments listed above**<u>:</u>** • 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 computerized tomography) to evaluate liver disease. • Liver biopsy may be considered and discussed with local specialist if available, in the following instances: o In participants when serology raises the possibility of autoimmune hepatitis (AIH). o In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention. o In participants with acute or chronic atypical presentation: • If liver biopsy conducted collect all applicable data and report information to study PI (and MCW Multisite Team).

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 AESI (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. 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].

Phase 1-2 Liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3 x ULN **but** <5 x ULN **and** total bilirubin <2 x ULN or INR ≤1.5, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for four weeks.	• Notify the study PI (cc: MCW Multisite Team email) **within 24 hours** (refer to reporting section) of learning of the abnormality to discuss participant safety. • Participant can continue study treatment. • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin and INR) until they resolve, stabilize, or return to within baseline. • If at any time participant meets the liver chemistry stopping criteria, proceed as described above. • If, after four weeks of monitoring, ALT <3 x ULN, bilirubin <2 x ULN and INR 1.5, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

Infusion-Related Reactions 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 for any participant who experienced an IRR at first or any subsequent infusion with belantamab mafodotin. 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 who experiences a grade 4 IRR associated with belantamab mafodotin should be permanently withdrawn from the study treatment and enter follow-up.

5.4 Measurable Residual Disease Assessment

MRD assessment by clonoSEQ® requires an initial marrow sample containing myeloma cells for identification of myeloma-specific sequences in IGH-VDJ, IDH-DJ, and/or IGK. During screening, a fresh bone marrow sample or archive, non-stained bone marrow aspirate slide ("ID sample") will be sent to Adaptive Biotechnologies to be assessed for the presence of myeloma-specific sequences.

For all samples with MRD assessment, MRD will be reported quantitatively as proportion of multiple myeloma-associated sequences. For treatment assignment and clinical trial outcome reporting, we will consider MRD-negative if the burden of MM-associated molecules is $\leq 10^{-5}$.

Subjects who achieve confirmed MRD(-) status with $\leq 10^{-5}$ MM-associated molecules during maintenance will undergo FDG PET/CT scan. FDG PET/CT will be interpreted by the enrolling site and reported on data forms.

5.5 General Concomitant Medication and Supportive Care Guidelines

Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF.

5.6 Prohibited Medications

The following medications are prohibited:

- Any concomitant anticancer therapy to treat the disease under study.
- Any investigational study drug, for any indication.
- Concomitant administration of strong P-glycoprotein (P-gp) inhibitors and strong inhibitors of OATP (see link below) with belantamab mafodotin should be avoided unless considered medically necessary.
    - Refer to list here: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers
- Unless directed by an opthalmologist, contact lenses are not allowed for participants while they are receiving belantamab mafodotin treatment.
    - Contact lens use may be restarted after discontinuation of belantamab mafodotin treatment, provided the eye care specialist confirms there are no other contraindications.
- Administration of live or live-attenuated vaccines are contraindicated 30 days prior to the first dose of study treatment. Use of live or live-attenuated vaccines is further contraindicated for at least 70 days following the last dose of belantamab mafodotin. Killed or inactivated vaccines may be administered; however, the response to such vaccines cannot be predicted.

5.7 Monitoring Subject Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing. Comprehensive instructions may be provided to the patient in order to ensure compliance with dosing procedures.

5.8 Follow-up Period

For patients who discontinue treatment prior to progression, continue standard-of-care follow-up every three months until progression or start of another treatment (whichever comes first), then continue to long term follow-up.

All patients will be followed for survival and follow-up data every six months (± 30 days) until withdrawal of consent, loss to follow-up, death, or the end of the study, whichever occurs first.

Refer to section above regarding ocular examination and procedures during follow-up.

6 ADVERSE EVENTS: DEFINITIONS, COLLECTION, AND REPORTING REQUIREMENTS

6.1 Definitions

6.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. (International Conference on Harmonisation [ICH], E2A, E6).

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, located on the CTEP web site:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures.

6.1.2 Serious Adverse Event (SAE)

Serious adverse event (SAE) means any untoward medical occurrence that results in any of the following outcomes:

- **Death.** Results in death.
- **Life-threatening**. Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- **Hospitalization**. Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph below on planned hospitalizations).
- **Disability/incapacity**. Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- **A congenital anomaly/birth defect.**
- **Medically important event**. This refers to an AE that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include new invasive or malignant cancers

(excluding the disease[s] under study in oncology protocols, e.g., secondary malignancies), allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent. Secondary malignancies should always be considered as serious adverse events.

- **Liver toxicity** (as follows):
    - ALT - absolute ALT ≥ 5xULN.
    - ALT ≥ 3xULN persists for ≥ four weeks.
    - ALT ≥ 3xULN and total bilirubin ≥ 2xULN (>35% direct bilirubin).
        - Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3 x ULN and total bilirubin ≥ 2 x ULN, then the event is to be reported.
    - ALT ≥ 3xULN and INR>1.5.
        - INR testing not required per protocol and the threshold value does not apply to participants receiving anticoagulants. If INR measurement is obtained, the value is to be recorded when reporting.
    - ALT ≥ 3xULN and cannot be monitored weekly for four weeks.
    - ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity.

6.1.3 Attribution of an Adverse Event

For all collected AEs, the site investigator who examines and evaluates the subject will determine the adverse event's causality to all of the study drugs, based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

- **Definitely Related:** There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- **Probably Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- **Possibly Related:** There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events).
- **Unlikely:** A clinical event, including an abnormal laboratory test result, whose temporal relationship to study agent administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).
- **Unrelated:** The AE is completely independent of study agent administration, and/or evidence exists that the event is definitely related to another etiology.

While sites report to the MCW sponsor-investigator based on the above categories, the MCW sponsor-investigator reports to the funder (GSK) based on the categories "related" or "not related" attribution:

- 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.

6.1.4 Expectedness of an Adverse Event

Each site investigator will decide whether an adverse event (AE) is expected or unexpected, but the sponsor is ultimately responsible for determination of expectedness and may therefore override the site investigator's determination of expectedness.

6.2 Collection and Reporting Requirements for Adverse Events and Serious Adverse Events

6.2.1 Collection of Adverse Events

All adverse events (including SAEs) must be recorded in OnCore® data forms. All AEs required to be collected must be graded according to the CTCAE v5. Investigator's or treating physician's assessment of AE attributions must also be documented.

SAEs and AEs will be collected and reported after first treatment dose, through 70 days post last dose of belantamab mafodotin. All conditions prior to treatment will be considered baseline, medical history unless changing in grade after treatment. AEs will be tracked and followed until resolution, subject withdraws consent, or is lost to follow-up (including subjects who discontinue early).

6.2.2 Reporting of Adverse Events, Serious Adverse Events, and AEs of Special Interest (AESI)

Events requiring <u>expedited</u> reporting (i.e., requiring immediate action)	All SAEs (including liver toxicity defined in Section 6.1.2)
	Non-hematological grade 4 AEs not meeting SAE definition.
	Unanticipated problems involving risks to participants or others (UPIRSO).
	Pregnancy.
	Deviations that are "significant" (affect subject safety, such as medication errors) or planned.
	Action letter from sponsor.
	Product complaint.
	Subject trial withdrawal.
Events requiring <u>routine</u> reporting (i.e., entered into OnCore® in a timely manner)	All grade 1–4 AEs (unless in an above category), including all lab abnormalities (regardless of clinical significance) and AEs of special interest (AESI). Non-significant deviations.

6.3 Serious Adverse Event (SAE)

IMPORTANT NOTE — refer to liver toxicity events defined as an SAE in Section 6.1.2.

SAEs are reported in the following manner:

- All SAEs (occurring after the subject has received first dose of study drug through the 70 days after the last dose of belantamab mafodotin) will be reported within 24 hours of study staff awareness, using OnCore® (entered in the SAE tab) and GSK SAE form. Supporting de-identified documents (e.g., admission and discharge note) will be uploaded to shared site study folder and emailed (see below). An email notice with the SAE or pregnancy PDF report from OnCore® as well as the GSK SAE form (provided by the multisite team) will be sent to the MCW study PI and MCW Multisite Team (via the MCW Multisite Team email) who will report to GSK (MCW will email to OAX37649@gsk.com).
- In addition, if the SAE is unexpected and possibly, probably, or definitely related to study drugs, sites must create a reportable event notice with the sIRB, and complete a MedWatch 3500A and send it in an email to the study PI and MCW Multisite Team email.
  - US FDA MedWatch 3500A found here: *http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm*
- All grade 4 and 5 SAEs and any other expedited SAE reports to the IRB must also be reported to DSMC within five calendar days of study staff's awareness by the MCW Multisite Team.
- All SAEs will be followed until satisfactory resolution, or until the site investigator deems the event to be chronic. Any significant update/resolution should be updated in OnCore® follow-up SAE report (update the sIRB and MedWatch report, if a SUSAR). The SAE OnCore® PDF follow-up SAE form should be reported in the same manner as the SAE process above.

6.4 Adverse Events Not Meeting SAE Definition

Adverse Events

Any medical condition that is present at the time that the participant is screened will be considered a baseline condition and captured on the baseline OnCore® CRF form and not reported as an AE (though all SAEs that occur after starting treatment are reported in an expedited manner; see below). All new or worsening AEs that occur after starting study drug until 70 days post last dose of belantamab mafodotin will be tracked and followed until resolution, subject withdraws consent, or is lost to follow-up (including subjects who discontinue early).

Changes in the grade of an AE will be documented in the AE CRF to allow an assessment of the duration of the event at each level of severity. Information to be collected includes event description, time of onset, clinician's assessment of severity, expectedness, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event.

Adverse Event of Special Interest (AESI)

An adverse event of special interest (AESI) is an adverse event (serious or non-serious) of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. AESIs may be added or removed during a study by protocol amendment.

Current list of AESIs:

- Elevated serum creatinine (increases from baseline by >0.5 mg/dL).
- Serum creatinine >3.0 mg/dL from baseline OR 3.0-6.0 X ULN.
- Thrombocytopenia.
- Infusion-related reactions.

- Pneumonitis grade 2.
- Corneal events (severity of corneal events will be graded according to the KVA scale).

All AESIs that meet the definition of an SAE will be reported according to the manner above for SAEs. All AESIs that do not meet the definition of an SAE (or grade 4, see below) must be reported in a routine manner on data forms (which indicate the event is an AESI).

Grade 4 AEs

Any grade 4 AE that meets the definition of an SAE will be reported according to the manner above for SAEs. A hematological grade 4 AE that does not meet the definition of an SAE will be routinely reported.

Any non-hematological grade 4 AE that does not meet the definition of an SAE will be reported within 24 hours of study staff awareness in the following manner:

- Enter the AE into OnCore® AE CRF.
- Email the MCW Study PI and MCW Multisite Team (via the Multisite Team email; the Multisite Team will notify DSMC coordinator, if required) detailing the following information:
    - Case/sequence number of the subject.
    - Date of event.
    - CTCAE term.
    - CTCAE grade.
    - Relationship to study drug(s).
    - Expectedness.
    - Any clinical action taken or planned.

6.5 Unanticipated Problem Involving Risk to Subject or Other (UPIRSO)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meet all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (sIRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied.
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

6.6 DSMC Reporting

All internal reports to the DSMC and subsequent DSMC review letters will be available to participating sites (e.g., shared site study folder). For those internal events that do not meet the definition of an SAE but are required by the protocol to be reported to the DSMC, the participating site will report according to the protocol.

6.7 Reporting Pregnancy

Male participants with partners who become pregnant:

- Investigator will attempt to collect pregnancy information on any female partner of a male study participant who becomes pregnant while participating in this study and for six 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 submit it to study PI, MCW Multisite Team, and GSK within 24 hours of learning of the partner's pregnancy.
- Participating sites should report the pregnancy in OnCore® as a grade 3 SAE and complete the pregnancy report form (provided by sponsor as an additional document), and email both PDF reports to the study PI, MCW Multisite Team (via the MCW Multisite Team email), and commercial manufacturers within 24 hours of staff awareness.
- 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 within 24 hours of study staff awareness.
- Generally, follow-up will be no longer than six to eight 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 four months following the last dose of belantamab mafodotin.
- Information will be recorded and submitted to study PI, MCW Multisite Team, and GSK within 24 hours of learning of a participant's pregnancy.
- Participating sites should report the pregnancy in OnCore® as a grade 3 SAE and complete the pregnancy report form (provided by sponsor as an additional document), and email both PDF reports to the study PI, MCW Multisite Team (via the MCW Multisite Team email), and commercial manufacturers within 24 hours of staff awareness. 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 within 24 hours of study staff awareness. Generally, follow-up will not be required for longer than six to eight 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 study PI, MCW Multisite Team, and GSK within 24 hours of study staff awareness. according to the SAE reporting process above.

6.8 Protocol Deviations and Medication Errors

Significant deviations are defined, but not limited to, the following:

- Enrolling an ineligible subject.
- Non-compliance: violates federal regulations or institutional policies regarding informed consent or research conduct which impacts subjects' rights, welfare and/or safety or affect the scientific integrity of the project.
- Deviations that have an impact on primary objectives of the study.
- Prohibited medications which pose a safety risk to the patient or integrity of the data.

Planned deviations are defined as follows:

- Any temporary protocol deviation that is anticipated to occur but hasn't occurred yet.
- Sites must follow the sIRB policies regarding acknowledgment prior to deviation initiation.

Significant and/or planned deviations and medication errors are reported in the following manner:

- Participating sites enter the deviation into OnCore® and email the PDF report to the MCW Multisite Team (via the MCW Multisite Team email) within five calendar days of staff awareness.
- Participating sites report to the sIRB.

Any other deviation that is not significant or planned is to be reported in OnCore® in a timely manner (refer to Section 6).

The following actions may occur due to persistent or significant deficiencies:

- Telephone call between the MCW Multisite Team and site staff to discuss resolution or possible prevention of future deficiencies.
- Schedule additional, or short interval, monitoring visits and/or training sessions with the MCW Multisite Team.
- Formal notification to participating site PI of deficit with request for corrective action plan, and/or due date for outstanding items to be completed.
- Warning of potential suspension of participating site accrual until corrective action is completed.
- Suspension of accrual at participating site.
- Participating site accrual closure.

6.9 Staff, Subject, and Product Complaint Reporting

If a complaint is received by anyone on the study staff, it will be addressed on a case-by-case basis. The site PI will be notified of any complaints. Complaints will be reported to the sIRB and MCW PI if required. If the subject has questions about his or her rights as a study subject, wants to report any problems or complaints, obtain information about the study, or offer input, the subject can call the research subject advocate. This information is provided to the subject in their consent.

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of the product. The following are examples of product complaint types:

- Labeling Complaints
    - Damaged or defective label.
    - Batch number/expiry date issues (for example, not able to read or missing).

    - Directions for use not easy to understand.
- Packaging Complaints
    - Defective packaging.
    - Dose difficult to dispense.
- Vial Complaints
    - Broken, dirty, or cracked vial.
- Stopper Issues
    - Coring, damaged, or pushed into vial.
- Appearance Complaints
    - Vials cloudy.
    - Dissolution difficulty.
    - Vials contain foreign material.
    - Dusty capsules.
    - Capsule or tablet color.
    - Capsule difficult to swallow.
    - Drug delivery system complaints.
    - Leaking after injection.
    - Dose knob difficult to push.
    - Pen is jammed.
    - Error codes.
    - Difficult to attach/detach needle.
    - Unable to set dose.
    - Electronic malfunction.

Study staff who identify a product complaint situation for any study agent should report the complaint within 24 hours of study staff awareness, in the following manner:

- Complete the study-specific product complaint form.
- Email GSK (as relevant), and also the MCW Multisite Team (via the MCW Multisite Team email) the product complaint form and upload it into shared site study folder.
- File the original completed product complaint form in the shadow chart.
- Return product sample, if requested by drug manufacturer, with a copy of the product complaint form.
- Any written, electronic or oral communication that alleges dissatisfaction related to manufactured clinical drug product with regards to its manufacturing, testing, packaging, or shipping, must be reported by the sponsor institution or qualified designee to study PI, MCW Multisite Team, and GSK within one working day of first becoming aware of the possible defect (email of GSK QA at gsk-rd.complaints@gsk.com). The product and packaging components in question, if available, must be stored in a secure area under specified storage conditions until it is determined whether the product is required to be returned for investigation of the defect. If the product complaint is associated with an SAE, the SAE must be reported separately in accordance with the protocol, and the SAE report should mention the product quality complaint.

Product complaints in and of themselves are not reportable events. If a product complaint results in an SAE, an SAE form should be completed according to the SAE reporting requirements.

Reporting information is collected for:

- A product complaint unrelated to an adverse event.
- A product complaint associated with a serious or non-serious adverse event.

Submit a product complaint if there is any alleged deficiency with the drug delivery system:

- Complaints can be expressed directly by the subject or by the MCW PI or Study Chair and staff, based on evaluation of the issue.
- The MCW PI or Study Chair should check the box on the product complaint form: "Adverse Event associated with complaint," when he/she suspects the product complaint may have led to the adverse event.

6.10 Subject Withdrawal

The MCW Multisite Team (via the MCW Multisite Team email) must be notified via email within 24 hours of discontinuation of study drugs or study intervention (preferably prior to discontinuation, in case the study PI could recommend an intervention or clarification), describing the nature of the discontinuation. OnCore® subject status updates (off-treatment date and follow-up start date) and discontinuation eCRF must be completed within 24 hours of discontinuation.

6.11 Reporting UPIRSO to Participants

The MCW Multisite Team, DSMC, drug manufacturers, and/or MCW or sIRBs may make the determination that an event requires reporting to subjects, either verbally/written documentation or reconsent.

6.12 External or Internal Auditing at Participating Sites

Sites must inform the MCW Multisite Team (via the MCW Multisite Team email) of any other external or internal audit/QA review (outside that performed according to this protocol's monitoring and auditing plans) prior to its occurrence, and send the final findings/report, along with any corrective action plan, to the MCW Multisite Team and MCW PI.

6.13 Known Adverse Events List

Please see the latest version of the belantamab mafodotin investigator's brochure.

7 PHARMACEUTICAL INFORMATION

7.1 Belantamab Mafodotin

7.1.1 Description

	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 2.0 mL of water for injection (WFI); dilute with saline before use.
Manufacturer/ source of procurement:	GSK/Baxter

7.1.2 Storage

Belantamab Mafodotin Solution, 20 mg/mL, 1.5 mL drug product is supplied as a frozen liquid in a 2R glass vial. Detailed instructions for preparation and administration of doses are provided in the site instruction manual. Prepared doses of belantamab mafodotin in the range of 0.2 – 2.0 mg/mL in 0.9% NaCl should be used as soon as possible and no later than 8 hours from the time of dose preparation including administration because the product does not contain an antimicrobial preservative.

The recommended storage condition of belantamab mafodotin Solution, 20 mg/mL, 1.5 mL drug product is -50°C to -15°C, protected from light. The expiry date, where required, is stated on the product label.

7.1.3 Biochemical and Structural Information

GSK2857916 is an afucosylated humanized IgG1 monoclonal antibody conjugated with an average of four maleimidocaproyl monomethyl auristatin F (mcMMAF [SGD-1269]) that binds to BCMA.

7.1.4 Molecular Weight

Theoretical mass of protein containing carbohydrate conjugated with four drug linker molecules are 152.1 kDa (intact mass).

7.1.5 Physical Form

Clear to opalescent; colorless to yellow to brown liquid.

7.1.6 Handling and Drug Accountability

Belantamab Mafodotin for Injection, 100 mg drug product is supplied as a lyophilized powder for solution for infusion. Detailed instructions for preparation and administration of doses are provided in the site instruction manual. Prepared doses of belantamab mafodotin in the range of 0.2 – 2.0 mg/mL in 0.9% NaCl should be used as soon as possible and no later than 6 hours from the time of dose preparation including administration because the product does not contain an antimicrobial preservative.

The recommended storage condition is 2-8°C, protected from light. The expiry date, where required, is stated on the product label. Before use, remove the drug product vial(s) from the refrigerator and allow to stand for approximately 10 minutes to reach room temperature (68°F to 77°F [20°C to 25°C]).

Each vial of the drug product is reconstituted with 2.0 mL of sterile WFI before use. Once reconstituted, the drug product solution in vial(s) should be used to prepare the dose as soon as possible. If the reconstituted solution is not used immediately, store the vial(s) refrigerated at 36ºF to 46ºF (2ºC to 8ºC) or at room temperature (68ºF to 77ºF [20ºC to 25ºC]) for up to 4 hours in the original container. Do not freeze. Discard the reconstituted DP vial(s) if not used to prepare diluted dosing solution within 4 hours.

Visually inspect the reconstituted solution for particulate matter and discoloration. The reconstituted drug product solution in vial should be clear to opalescent, colourless to yellow to brown liquid. Discard the reconstituted vial if extraneous particulate matter other than translucent to white proteinaceous particles is observed.

GSK2857916 (belantamab mafodotin) dose rounding instructions:

Participant's weight in kilograms (kg) should be entered to one decimal place and the total dose (mg) will be calculated to two decimal places.

Example:

Total Dose (mg) = 97.2 kg * 1.9 mg/kg

Total Dose (mg) = 184.68 mg

The quantity of vials dispensed will depend on the participant's weight and dose level.

For dose preparation, withdraw calculated volume of reconstituted DP from the vial(s) for each dose and add to 250 mL IV bag containing 0.9% sodium chloride. The diluted dosing solution is stable at 0.2 mg/mL to 2 mg/mL in 0.9% sodium chloride for injection for a maximum of 6 hours (including infusion time) when stored at room temperature (68ºF to 77ºF [20ºC to 25ºC]).

The diluted dosing solution is compatible with the following contact materials: polyvinylchloride and polyolefin IV bags/administration sets and polyurethane catheter. Filtration is not mandatory, but if using a filter use a 0.2 um polyethersulfone (PES) filter. If a closed system transfer device (CSTD) is used, instructions provided by the manufacturer must be followed to ensure intended dose is delivered. If the diluted solution is not used immediately, it may be stored in a refrigerator 36ºF to 46ºF (2ºC to 8ºC) for up to 24 hours prior to administration. If refrigerated, allow the diluted solution to equilibrate to room temperature prior to administration. The diluted solution should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The diluted infusion solution should be clear and colorless. Discard if particulate matter is observed.

Density of reconstituted belantamab mafodotin after addition of 2 mL sterile WFI to lyophilized powder (50mg/mL) is 1.0418 g/cm3 at room temperature 68°F to 77°F (20°C to 25°C).

The site PI is fully responsible for the investigational products at the trial site. Dispensing of investigational products will be delegated to site staff. The person responsible for dispensing the investigational products will be accountable for maintaining adequate control of the investigational products and for documenting all transactions with them.

The site PI, or a responsible party designated by the site PI, will maintain a careful record of the inventory and disposition of all agents. Each participating site PI, or authorized designee, is responsible for maintaining a careful record of inventory and disposition of all investigational agents received at the site. Use of the NCI Drug Accountability Record Form is recommended, but sites may use their own accountability logs per institutional standards. Sites must ensure accountability records capture the same information as the NCI Drug Accountability Record Form and in addition, capture the preparation time. Any used or partially used vials may be destroyed on-site per the institutional standard of practice. Expired vials remaining at the end of the study may be destroyed onsite per institutional standards.

7.1.7 Drug Supply

Provided by funder, drug manufacturer.

Belantamab mafadotin will be provided by GSK through ALMAC, a vendor managing the labeling and shipping of drug. The initial shipment of drug will be initiated by GSK and resupply orders will be the responsibility of each participating site. WebEZ is only used to order drug, it does not require any patient information.

8 STATISTICAL CONSIDERATIONS

8.1 General Description

This phase II study will be conducted using an optimal two-stage design based on the methods of Huang (35). The enrollment target will be 45 subjects, with an interim analysis for futility after 23 patients have been enrolled, and followed for 12 months post diagnosis. Enrollment of new subjects will continue during that period.

The design is based on a modification of a binomial two-stage design that allows incorporation of data from subjects with less than full follow-up at the interim analysis (Huang, 2010). The study will enroll up to 45 subjects with an interim analysis performed when 23 patients have been treated and followed to the 12th month after CAR-T. The futility decision will use the Kaplan-Meier estimate of the 12-month progression-free conditional survival using the data from the first 23 subjects and any subject who have been enrolled during the follow-up period of the 23rd subject. The study will be stopped for futility, if the one-sided z-test comparing the 12-month progression-free conditional survival to 54% defined by the null hypothesis has a p-value of 0.54 or higher. The study has a 70% probability of stopping for futility if the underlying 12-month conditional PFS equals to the null-hypothesis value of 54%.

If the study is not stopped for futility, study enrollment will continue until 45 subjects are enrolled. The final analysis will be performed when all subjects have been followed to 12 months after CAR-T. The Kaplan-Meier estimate of the 12-month progression-free conditional survival will be compared to 54% using a one-sided z-test at a 5% significance level.

8.2 Determination of Sample Size and Accrual Rate

8.2.1 Primary Endpoint

The primary endpoint of the study is the 12-month progression-free survival (PFS) with time counted from the CAR-T infusion conditional on being alive and progression-free at day +90 post CAR-T. An event will be defined as documented progression or death for any cause, subjects without an event will be censored at the last date known to be alive without progression. Left truncation at the time of the start of study treatment will be used to adjust for "immortal time" after day +90 before study enrollment.

8.2.2 Primary Hypothesis

We hypothesize that, with belantamab mafodotin maintenance, the 12-month PFS conditional on being progression-free at day +90 will exceed 54%.

The comparison value was selected based on published and preliminary data from the KarMMa2 trial, with three-month PFS of 74%, and 12-month PFS of 40%, resulting in a conditional PFS of 0.4/0.74=0.54. A 5% one-sided type I error rate will be used.

8.2.3 Sample Size Justification

The sample size was computed using 80% power at a one-sided 5% significance level to detect a significant effect if the conditional PFS exceeds the historical value by 20%, that is 74%. Assuming a 74% three-month PFS, this corresponds to a 12-month PFS of 55%.

The OptInterim R package was used to compute the optimal two-stage design that minimizes the expected sample size, assuming exponential PFS and recruitment of one patient/month during year 1, and two patients/months afterwards. The optimal design recruits a total of 45 subjects, with an interim analysis after 23 subjects have been enrolled, and followed for 12 months post-CAR-T. Recruitment will not be paused during for the interim analysis, and the information from all treated subjects (even those with incomplete

follow-up) will be used in the interim analysis. This design achieves an 84% power in the hypothesized setting, which exceeds the target due to the discreteness of the design space,

We conducted simulation studies to confirm that the actual study design maintains the target type I error and power under a range of scenarios, including non-exponential survival, up to 10% censoring, and an enrollment window of 1.5 months without additional adjustment of the sample size.

8.2.4 Analysis Populations

The overall study population will consist of all subjects enrolled into the study. This population will be used in study flowcharts and patient disposition summaries.

The efficacy population will consist of all enrolled subjects who received at least one dose of the study treatment and had at least one response evaluation after the start of the treatment. This population will be used for the primary efficacy.

The safety population will consist of all enrolled subjects who received at least one dose of the study treatment.

8.2.5 Statistical Analysis Plan

Primary outcome
PFS will be estimated by the Kaplan-Meier (KM) estimator, and presented with pointwise 90% confidence intervals. An event will be defined as documented progression or death for any cause, subjects without an event will be censored at the last date known to be alive without progression. Left truncation at the time of the start of study treatment will be used to adjust for "immortal time" before study enrollment.

The primary efficacy hypothesis of 12-month PFS exceeding 54% will be evaluated by comparing the KM-estimate to the null-hypothesis values using a one-sided z-test.

The primary outcome will also be summarized separately for subjects with ≤PR, and VGPR at the initiation of treatment. No between-group comparisons will be performed.

Secondary outcomes
Time-to-event outcomes, such duration of response, time to progression/relapse, progression-free survival, and overall survival will be described using the Kaplan-Meier estimator. Left truncation at the start of study treatment will be used. Best objective response on the trial and negative MRD prevalence at specific timepoints will be summarized as counts with percentages. Quality of life scores will be summarized at each timepoint with descriptive statistics and analyzed using mixed effect models with a random subject intercept.

Safety analyses
Safety analyses will be performed on the entire safety population. The incidence of severe adverse events will be reported for all subjects who received at least one dose of the study treatment. The proportion of patients experiencing an SAE will be reported overall, as well as classified by grade and organ system.

Formal toxicity monitoring will be performed for the following adverse events:

- SAEs that are possibly, probably or definitely related to treatment, with 30% acceptable rate
- Treatment-related grade 4 or higher non-hematologic toxicity, with 10% acceptable rate
- Grade 4 corneal adverse events, with 5% acceptable rate

- Treatment-related death, i.e., grade 5 hematologic or non-hematologic toxicity, with 3% acceptable rate

The monitoring rules will suggest stopping the study when there is sufficient evidence that the proportion of patients with a specific adverse event exceeds the acceptable rate. Specifically, a Bayesian toxicity monitoring approach will be used, recommending stopping if the posterior probability of the event rate exceeding the acceptable rate is at least 80%. A Beta distributed prior with effective sample size of 1 and prior mean equal to the acceptable event rate was used for each event.

The tables assume that monitoring will be conducted after every five patients. Table 6 shows the cutoffs for the number of events that would trigger a stopping rule. For example, the third row shows that if 15 patients have been enrolled and 3 or more treatment-related non-hematologic AEs have occurred, then there is evidence to indicate that the proportion of these AEs exceeds the acceptable rate of 10%.

Table 6. Cutoffs for the number of patients with a specific adverse event indicating excessive rate of adverse event as a function of number of subjects in the study.

Subjects	Outcome			
	Treatment-related SAE (30%)	Treatment-related grade 4+ non-hematologic AE (10%)	Grade 4 corneal AE (5%)	Treatment-related death (3%)
5	≥ 3	≥ 2	≥ 2	≥ 1
10	≥ 5	≥ 3	≥ 2	≥ 2
15	≥ 7	≥ 3	≥ 2	≥ 2
20	≥ 8	≥ 4	≥ 3	≥ 2
25	≥ 10	≥ 5	≥ 3	≥ 2
30	≥ 12	≥ 5	≥ 3	≥ 3
35	≥ 13	≥ 6	≥ 4	≥ 3
40	≥ 15	≥ 6	≥ 4	≥ 3
45	≥ 17	≥ 7	≥ 4	≥ 3

Table 7 shows the operating characteristics of the boundaries listed in Table 6 for several values of true underlying probability of the adverse event. For example, if the true proportion of treatment-related SAEs is 40%, then the monitoring rule will be triggered over 83.6% of the time.

Table 7. Overall probability of crossing the boundaries defined in Table 6 with up to 45 subjects as a function of the underlying probability of the adverse event (cells with extremely low or high probabilities are left empty for clarity)**.**

Underlying probability of event	Outcome (acceptable rate of adverse events)			
	Treatment-related SAE (30%)	Treatment-related grade 4+ non-hematologic AE (10%)	Grade 4 corneal AE (5%)	Treatment-related death (3%)
2%	-	0.6%	4.9%	16.9%
3%	-	1.7%	11.3%	28.9%
5%	0.1%	6.2%	29.7%	52.9%

7.5%	0.4%	17.4%	55.0%	75.7%
10%	1.0%	33.8%	75.0%	88.9%
20%	9.8%	90.0%	99.1%	99.8%
30%	42.4%	99.6%	-	-
40%	83.6%	-	-	-
50%	98.6%	-	-	-

8.3 Accrual Estimates

MCW is required (per MCW sIRB) to activate prior to other sites, whose activation times will vary due to internal activation timelines. Accrual is expected at one subjects/month during year 1, and two subjects/month afterwards. Therefore, enrollment is expected to last 29 months; last subject, last dose and assessment are expected to take another 11 months. Therefore, total trial duration would be approximately 40 months.

The study will reach study completion in approximately 10 years (five years for completion of treatment for all patients, and five years of long-term survival follow-up) from the time the study opens to accrual.

9 OPERATIONAL CONSIDERATIONS, MULTISITE ADMINISTRATION, SOURCE DOCUMENTS, AND DATA MANAGEMENT

9.1 Staff Training, Changes, and Delegation of Authority Log

Documentation of training completion for required items of training (i.e., training log, CITI completion certification, etc.) and the delegation of authority (DOA) or local context form (as appropriate) must be maintained at each site for all study staff members, uploaded into the shared site study folder, and sent to the MCW Multisite Team upon request.

All site study staff must be adequately trained to perform the delegated task(s) approved by the participating site PI, as recorded in the delegation of authority log, or local context form (as appropriate), and training log (or online training log).

Inform the MCW Multisite Team (via the MCW Multisite Team email) immediately if a change in PI is planned.

9.2 Monitoring Plan

The MCWCC DSMC is responsible for monitoring data quality and subject safety for all MCWCC investigator-initiated clinical trials, according to the approved MCW DSMP.

Unless otherwise specified in the contract/budget, the following monitoring plan will occur under the direction of the MCW Multisite Team:

- Onsite monitoring or remote monitoring within two to four weeks of the first subject enrollment (if applicable, as determined by the MCW Multisite Team).
- Onsite monitoring or remote monitoring (if applicable, as determined by the MCW Multisite Team) visits and outstanding data reports approximately every three months until the MCW PI and DSMC approve that routine monitoring is no longer required.

- Consents, source documents supporting eligibility, primary and secondary objectives, drug accountability/temperature/shipping/receiving logs (if applicable), and key data points should be provided to the MCW Multisite Team. The monitor may verify certain data points at his/her discretion.
- Data lock at time of interim analysis.
- Study updates via a videoconference meeting may occur (depending upon accrual rate and complexity of trial, at the discretion of the MCW Multisite Team and MCW PI).

9.3 Audit Plan

Audit plans are determined by the DSMP according to risk category:

- Approximately 30% of enrolled subjects per site randomly selected for review (a maximum of 10 subjects per site at each review).
- Consent, eligibility, and objective-based data are reviewed for all files selected.
- One subject file per site (of the 30% mentioned above) randomly selected for a comprehensive review at each time point.
- 100% of regulatory documents.
- The auditor reserves the right to select other subject(s) if deemed necessary (i.e., in case of a significant or repetitive finding).
- An audit occurs every year until the DSMC determines that future audits may be deferred.

Audits may be performed by either the MCW QA department, a contracted business partner, and/or another entity specified in the consent, contract, or budget. Directed audits, outside of those regularly scheduled, may be requested at any time by the MCW Multisite Team or applicable regulatory agency. Studies are subject to random or for-cause audits from the sIRB.

Participating sites must promptly inform the MCW Multisite Team (via the MCW Multisite Team email) of any other external or internal audit/review of this trial prior to its occurrence and send the final findings/report with any corrective action plan to the MCW Multisite Team (via the MCW Multisite Team email).

9.4 Audit and Monitoring Report and Corrective Action Plan (CAP)

Audit or monitoring reports occur in the following manner:

- Sites follow local SOP/practices and communicate with MCW as appropriate.
- Sent to the participating site PI after the date of the audit or monitoring visit.
- Must be shared with any other required entity, as required per local SOPs and policies (e.g., DSMC, sIRB, etc.).
- Include a brief description of findings.
- Address whether a corrective action plan (CAP) is required, and when it is required.
- Indicate if another short-term audit or monitoring visit is necessary, and within what time frame it should occur.

9.5 Deidentified Source Documents, Remote Access to Records, and Shadow Charts

Regulatory authorities, the sIRB, and/or sponsor may request access to all source documents, data capture records and other study documentation for audit or inspection. Direct access to these documents must be guaranteed by the investigators, who must provide support at all times for these activities.

The following (but not limited to) source documentation should be provided to the MCW Multisite Team (via the online shared study folder and/or email):

- Supporting documents for all eligibility criteria (including consent and documentation of consent process).
- Supporting documents for important data points (e.g., primary or secondary endpoints).
- Source(s) indicating all expedited reported events.
- SAE and AESI supporting source documents (e.g., admission/discharge notes and other applicable procedures) and SAE/AESI email confirmations.
- Pharmacy drug accountability/temperature/shipping/receiving logs (uploaded prior to monitoring visits or as requested (or applicable access to these records via institutional practice, e.g., Vestigo).
- Investigator attribution determination (e.g., AE log signoff, etc.)

If a participating site allows monitors and auditors remote or onsite access to their electronic health record (EMR), staff will adhere to their local SOPs. Shadow charts (e.g., paper or electronic copies of the EMR) are maintained according to local SOPs and policies.

9.6 Transferring Subjects

If a participant decides to transfer from the enrolling site to another new participating site, the following occurs:

- The current enrolling site contacts the MCW Multisite Team (via the MCW Multisite Team email) and new participating site.
- Both site PIs agree to the transfer and follow institutional SOPs.
- All data and queries must be completed before transfer.
- After official transfer, documents have been finalized.
    - All applicable source documents are transferred.
    - Data capture system access is transferred.
    - The new participating site PI becomes responsible for the participant.

9.7 Retention of Study Documents

Study documents must be retained according to the following requirements:

- Participating sites must maintain all study records according to FDA and applicable regulatory requirement(s).
- Records are retained for at least two years after the last marketing application approval or two years after formal discontinuation of the clinical development of study drugs or according to applicable regulatory requirement(s), whichever is longest. In either case, sites must inform the MCW PI and MCW Multisite Team (via the MCW Multisite Team email) of any intention to no longer retain study records.
- Record retention may be extended per local institution policy or sponsor request.
- If the participating site PI withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility.
- The MCW Multisite Team must be notified in an email (via the MCW Multisite Team email) if a custodial change might occur, and approval must be obtained prior to the change.

9.8 Publication and Data Sharing Policy

Publication and data sharing requirements are detailed in the clinical trial agreement. The MCW study PI determines authorship in a multifaceted manner, based on substantial intellectual input, effort, and participation:

Authorship guidelines are as follows:

- First author requirements:
  - MCW study PI/Co-PI.
  - Writes the primary manuscript.
- Participating site PI authorship:
  - Each participating site investigator with at least one enrollment may be eligible for authorship.
  - Order determined by top accruing sites.
- Last author:
  - Most senior position who contributed to the protocol development (unless otherwise specified).
- Acknowledgements:
  - The MCW study PI may include other staff or colleagues, as applicable.
  - Sponsorship from the drug manufacturer(s) per the drug manufacturer(s)'s contractual requirements.
- Journal or publication author number limitations:
  - Authors will be removed in reverse order of original order, as determined by the MCW study PI.

9.9 Electronic Data Capture and Timely Data Entry

Participating sites enter electronic data into OnCore®, under the supervision and responsibility of the site investigator. Study-specific case report forms (CRFs) will document outcomes. All study data will be entered into OnCore® via standardized CRFs, in accordance with the study calendar, using single data entry with a secure access account. Designated study staff will complete the CRFs as soon as possible upon completion of the study visit; the investigator will review and approve the completed CRFs. The information collected on CRFs shall be identical to that appearing in original source documents.

Timely data entry is defined as follows (unless otherwise specified in the contract/budget):

- OnCore® entry must occur within 24 hours of consent, enrollment, and withdrawal (for any reason).
- Protocol visit time point data should be entered within four weeks of visit occurrence, unless otherwise requested by the MCW Multisite Team (e.g., prior to DSMC reviews, audit, etc.).
- Deviations should be entered within four weeks of discovery, if not requiring expedited reporting (refer to Section 6).
- Refer to Section 6 for timely reporting of events requiring expedited reporting.

10 REGULATORY COMPLIANCE, ETHICS, AND MANAGEMENT

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4).

This study will be conducted in compliance with:

- The protocol.

- Federal regulations, as applicable, including: 21 CFR 50 (Protection of Human Subjects/Informed Consent); 21 CFR 56 (Institutional Review Boards) and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children), and all applicable regulatory requirements. The sIRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

10.1 Activation Letter for Participating Institutions

Study conduct must not occur until an official activation letter has been received at the participating site. After all required institutional and regulatory approvals have been obtained, the MCW PI and MCW Multisite Team issue an activation letter to the participating site. Then, study conduct may begin.

10.2 CAP, CLIA, and Reference Ranges

Participating sites should ensure their laboratory maintains CAP (if applicable) and CLIA certification. The MCW Multisite Team may request reference ranges as necessary.

10.3 Scientific Review Committee

The MCW Scientific Review Committee (SRC) has the following responsibilities:

- Establishing and maintaining a review committee of sufficient size and breadth of expertise to conduct a critical and fair scientific review of institutional cancer-related research involving human subjects.
- Conducting a thorough scientific review of all non-peer-reviewed, cancer-related clinical protocols using a standard format based on specific, predetermined review criteria.
- Assisting MCWCC investigators in the development of scientifically and clinically sound research through well-written protocols.
- Considering protocol feasibility with regard to budget, resources, and competing trials.
- Establishing clear criteria for determining whether ongoing clinical trials are making sufficient scientific progress, including the attainment of adequate subject accrual rates.
- Monitoring all cancer-related research protocols based on the criteria established by the SRC and terminating protocols that do not meet these expectations.
- Ensures that clinical trials are scientifically sound and that approved trials maintain subject accrual goals and scientific progress.

The levels of reviews are full, expedited, or exempt (based on the chair's discretion). Amendments may require SRC review or be exempt from review depending on whether the changes are major or administrative. The SRC may approve, approve with modifications, defer, or disapprove a trial. Furthermore, the SRC identifies low-accruing studies and either warns the disease-oriented team (DOT) chair and MCW PI of low accrual or recommends study closure.

Participating sites will adhere to their local policies regarding scientific review committee approvals.

10.4 Data and Safety Monitoring Committee

The MCW PI only reports DSMC letters to all other participating sites if they meet the FDA definition of requiring reporting (i.e., unanticipated problem), are required to be reported to other sites by the DSMC, and/or result in a significant finding/recommendation/action (e.g., change in study conduct, study closure, study hold). However, all DSMC reports can be sent to participating sites upon request.

After DSMC review of a participating site event, the MCW PI reports the DSMC letter to the participating site where the pertinent event occurred. The most recently approved MCW Data and Safety Monitoring Plan (DSMP) documents must be followed by all participating sites.

The MCW Data and Safety Monitoring Committee (DSMC) has the following responsibilities:

- Reviews the clinical trials for data integrity and safety.
- Reviews all unexpected grade 3, and all grade 4, and 5 adverse events, as well as any others requiring expedited reporting as defined in this protocol.
    - Non-hematological grade 4 and all grade 5 events must be reported to the DSMC within five calendar days of MCW study staff's knowledge. Hematological grade 4 events can be routine reported.
- Reviews all DSM reports.
- Submits a summary of any recommendations related to study conduct.
- Terminates the study if deemed unsafe for subjects.
- Informs the MCW Multisite Team (via the MCW Multisite Team email) of finalized reports/letters to be sent to the participating sites.

The DSMC will review reports no less than biannually (unless otherwise specified/approved by the DSMC). MCW institutional monitoring of multisite trials will be conducted according to the approved data and safety monitoring plan (DSMP), under the responsibility of the associate director for clinical research (ADCR).

10.5 Subject Confidentiality and Access to Source Documents/Data

Participant confidentiality and privacy are strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests, in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (sIRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing sIRB, institutional policies, or sponsor requirements.

Study participant research data, which are for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in OnCore®. This will not include the participant's contact or identifying information from participating sites outside MCW. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management

systems used by clinical sites and by MCW research staff will be secured and password protected. At the end of the study, all study databases will be archived at the Medical College of Wisconsin.

10.6 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the sIRB mechanism and the informed consent process. The sIRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The sIRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

10.7 Changes in the Protocol, Consent, or other Trial Document

A participating site may request changes to trial documents in the following manner:

- Major site-specific changes to the consent and ancillary documents are highly discouraged, though some changes are necessary (e.g., accrual goal updates, local context changes, etc.).
- Any change must be clearly indicated, then submitted to the MCW Multisite Team (via the MCW Multisite Team email) for approval by the MCW PI, the drug manufacturer(s) (if required), and sIRB, prior to implementation.
- MCW PI and sIRB approval must occur prior to implementation of any change, unless all of the following obtains:
    - Approval cannot be obtained in a reasonable time frame for subject safety and must be implemented immediately for subject safety.
    - The MCW PI, Multisite Team (via the MCW Multisite Team email), and applicable agencies (SRC, DSMC, sIRB as applicable) are informed as soon as possible, if they cannot be informed before implementation.
    - The investigator must then notify the sIRB in writing within five working days after implementation.

The sIRB may provide, if applicable regulatory authority(ies) permit, expedited review, and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB. The investigator will submit all protocol modifications to the drug manufacturer(s) and the regulatory authority(ies) in accordance with the governing regulations. Changes to the protocol may require approval from the drug manufacturers.

APPENDIX 1. 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 2. SUBJECT LOST TO FOLLOW-UP LETTER

Date: _____

Dear _____,

The research study team has been unable to contact you regarding the clinical trial ("A Multicenter Phase II Study of Maintenance Belantamab Mafodotin (Blenrep®) after BCMA-directed Chimeric Antigen Receptor-T Cell Therapy in Patients with Relapsed and/or Refractory Multiple Myeloma (RRMM)") you participated in.

We would like to discuss how you are doing and if we may continue contacting you.

Please contact us at

_____

Sincerely,

_____

APPENDIX 3. IMWG MULTIPLE MYELOMA RESPONSE CRITERIA

(Based on Kumar et al., 2016)

Stringent complete response (sCR)	Complete response (defined below) AND normal free light chain (FLC) ratio and absence of clonal cells in marrow by IHC.
Complete response (CR)	Negative immunofixation (serum and urine) AND disappearance of any plasmacytomas AND <5% plasma cells in marrow by IHC.
Very good partial response (VGPR)	Serum and urine M-protein detectable by immunofixation but not by electrophoresis; greater than or equal to 90% reduction in serum M-protein level AND urine M-protein level less than 100 mg per 24 hr.
Partial response (PR)	50% or greater reduction of serum M-protein AND reduction in 24 hr urinary M-protein by 90% or greater or to less than 200 mg/24 hr; if serum and urine M-protein are unmeasurable, must have a 50% or greater reduction in the difference between involved and uninvolved FLC level; if M-proteins and FLC assays are non-contributory, a 50% or greater reduction in plasma cells is required.
Minimal response	Reduction in serum-protein by 25 to 49% AND reduction in urine M-protein by 50 to 89%.
Stable disease (SD)	Not meeting any of the definitions listed in this table for response or PD.
Progressive disease (PD)	Increase of 25% from lowest confirmed response value (one or more of the following): Serum M-protein (absolute increase must be ³ 0.5 g/dL); Serum M-protein increase ³ 1 g/dL, if the lowest M component was ³ 5 g/dL; Urine M-protein (absolute increase must be ³ 200 mg/24 hr.); appearance of a new lesion.

APPENDIX 4. CONTRACEPTIVES USE

CONTRACEPTIVES 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[a]

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
- 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 5. CORRELATIVE SAMPLE INSTRUCTIONS AND REQUISITION FORM

Methods for Preparation of Samples

1.0 Bone Marrow

A. ~10 ml of bone marrow aspirate from each patient should be collected in heparinized tube at each of the timepoints below, stored at room temperature, and shipped overnight at room temperature.

2.0 Serum

A. 15 ml of whole blood from each patient should be collected in a serum separator tube (SST) at each of the time points below.
B. The serum should be separated as soon as possible (ideally within two hours) and placed into a labeled cryotube and stored at -20°C until shipment.

3.0 Timepoints

A. Screening (bone marrow aspirate and serum)
B. Cycle 3, Day 1
C. Cycle 7, Day 1
D. 70 days post-last dose safety visit (or at time of progression, whichever is earlier)
E. Diagnostic BM samples. If available, after enrollment is confirmed and subject has relapsed.
    - Diagnostic BM samples may be difficult to obtain. If available, the study team requests 5-10 diagnostic BM slides (e.g., ID sample, recuts are allowed/permitted from the institution those samples were obtained), if any additional/obtainable samples are available to be sent for study correlatives (and only if/when the subject has relapsed).

Shipping Instructions

A. All samples should be securely packaged in a container designed for shipping human biospecimens.
B. All sample labels should include the following information:
    - Patient study ID number.
    - Center identification.
    - Collection date.
    - Study day and time point.
    - Initials of the individual who collected the specimen,
C. Marrow samples should be shipped express overnight (day of collection) at room temperature.
D. Serum samples should be shipped on dry ice and can be sent in batches (upon request from the MCW Multisite Team, when approximately half of enrollments are completed).
E. Site study budget includes shipping costs (please use your site account to ship FedEx/UPS/etc.)
    - Shipping Address:
      MCW Cell Therapy Laboratory
      Attention: Immune Monitoring Lab
      Froedtert Hospital Pavilion, Room 304
      9200 W. Wisconsin Ave.
      Milwaukee, WI 53226
      Laboratory telephone: 414-805-6143
F. Email the MCW Cell Therapy Laboratory (celltherapyresearch@mcw.edu) and call 414-805-6143 between the hours of 7 a.m. and 6 p.m. central time to let them know a specimen is coming.
G. **Ship samples Monday through Thursday only.** Specimens will only be received Tuesday through Friday (except holidays).

MCW EMBRACE TRIAL – REQUISITION FORM

Participating site name:		**Checkbox**	**Sample Type**
Patient Study Number #		☐	Bone Marrow
Date of Sample Collection		☐	Serum
Time of sample collection (Please use 24-hour time)			

Timepoint
☐ Diagnostic BM
☐ Screening
☐ Cycle 3, Day 1
☐ Cycle 7, Day 1
☐ 70-days post-last dose Safety Visit (or at time of progression, whichever is earlier)
Site Information:
Site staff contact (full name): _____
Site staff contact phone number: _____
Site staff contact email: _____
Person Filling out Requisition (print full name): _____

APPENDIX 6: PATIENT-REPORTED OUTCOMES (PRO)

EORTC-QLQ-MY20 and EORTC QLQ-C30
OCULAR SURFACE DISEASE INDEX (OSDI)

EORTC QLQ – MY20

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had bone aches or pain?	1	2	3	4
32. Have you had pain in your back?	1	2	3	4
33. Have you had pain in your hip?	1	2	3	4
34. Have you had pain in your arm or shoulder?	1	2	3	4
35. Have you had pain in your chest?	1	2	3	4
36. If you had pain did it increase with activity?	1	2	3	4
37. Did you feel drowsy?	1	2	3	4
38. Did you feel thirsty?	1	2	3	4
39. Have you felt ill?	1	2	3	4
40. Have you had a dry mouth?	1	2	3	4
41. Have you lost any hair?	1	2	3	4
42. Answer this question only if you lost any hair: Were you upset by the loss of your hair?	1	2	3	4
43. Did you have tingling hands or feet?	1	2	3	4
44. Did you feel restless or agitated?	1	2	3	4
45. Have you had acid indigestion or heartburn?	1	2	3	4
46. Have you had burning or sore eyes?	1	2	3	4

Please turn to next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
48. Have you been thinking about your illness?	1	2	3	4
49. Have you been worried about dying?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4

/

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): 31 _____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4

9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

OCULAR SURFACE DISEASE INDEX ©

(US English version of the OSDI)

Please answer the following questions by checking the box that best represents your answer.

Have you experienced any of the following **during the last week:**

		All of the time	Most of the time	Half of the time	Some of the time	None of the time
1	Eyes that are sensitive to light?					
2	Eyes that feel gritty?					
3	Painful or sore eyes?					
4	Blurred vision?					
5	Poor vision?					

Have problems with your eyes limited you in performing any of the following **during the last week**:

		All of the time	Most of the time	Half of the time	Some of the time	None of the time	Not applicable
6	Reading?						
7	Driving at night?						
8	Working with a computer or bank machine (ATM)?						
9	Watching TV?						

Have your eyes felt uncomfortable in any of the following situations **during the last week:**

		All of the time	Most of the time	Half of the time	Some of the time	None of the time	Not applicable
10	Windy conditions?						
11	Places or areas with low humidity (very dry)?						
12	Areas that are air conditioned?						

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