Study Title Belantamab Mafodotin, Cyclophosphamide and Dexamethasone in Relapsed/Refractory Multiple Myeloma

Sponsor: University of Maryland

Principal Investigator: Ashraf Badros

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The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements including but not limited to Institutional Review Board/Ethics Committee (IRB/EC) approval.

Confidentiality Statement

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Declaration of Sponsor or Responsible Medical Officer

Title:

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice.

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Declaration of the Investigator

Title: Study Principal Investigator

I have read this study protocol, including all appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), in accordance with the study protocol, the current International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

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1. SYNOPSIS

Study Title: Belantamab Mafodotin, Cyclophosphamide and Dexamethasone in Relapsed/Refractory Multiple Myeloma

Rationale: Multiple myeloma (MM) is an incurable malignancy and accounts for 1% of all cancers and for 10% of all hematologic malignancies. Worldwide, approximately 103,000 new cases are diagnosed annually, and an estimated 30,330 new cases and 12,650 deaths will occur in the US in 2016. Despite significant advances in treatment options, including hematopoietic stem cell transplant (HSCT), and novel therapies like second- and third-generation proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and the recent addition of monoclonal antibodies (mAbs), most MM patients will ultimately develop resistance to existing therapies.

Belantamab mafodotin is a humanized (IgG1) antibody-drug conjugate (ADC) which binds to BCMA, a target widely expressed on malignant plasma cells in MM. The parent anti-BCMA antibody is conjugated to the microtubule inhibitor, MMAF, which is released inside the malignant cell after binding and internalization of the antibody. 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 APRIL, a proliferation-inducing ligand. In DREAMM-1 study, belantamab mafodotin (3.4-mg/kg every 3 weeks) demonstrated promising single-agent activity inducing rapid and durable responses [overall response rate (ORR) of 60% with a median progression free survival (PFS) of 12 months]. In DREAMM-2 study, patients received (2.5-mg/kg or 3.4-mg/kg) with an ORR of 31%-34% and a median progression-free survival of 2.9-4.9 months, for 2.5-mg/kg and 3.4-mg/kg, respectively. The most common adverse events in both studies were eye complications (70% irrespective of the dose) and thrombocytopenia (21% and 44%, which was dose dependent).

Cyclophosphamide was shown to synergistically enhance the therapeutic activities of several antibodies in B cell malignances; for e.g. cyclophosphamide, enhanced rituximab induced B cell toxicity by increasing acute secretory activation phenotype (affecting tumor necrosis factor α, interferon γ as well as interleukin (IL)-6, IL-10, and IL-12.). In addition, cyclophosphamide alters overall immune regulatory cells leading to stimulation of the cytotoxic functions of T lymphocytes (CD-44 lymphocytes), inhibition of regulatory T cells (CD-4/CD-25) and increasing the macrophage induced phagocytosis. In MM, cyclophosphamide has limited activity especially in the relapsed and refractory setting; however, in combination with other agents such as Daratumumab, pomalidomide and carfilzomib it led to enhanced efficacy. It would be very interesting to investigate the impact of the immune modulatory properties of cyclophosphamide on the ophthalmology effects of belantamab. We hypothesize that immune-modulatory properties of cyclophosphamide in combination with Belantamab mafodotin can improve ORR in relapsed/refractory (RR) MM by combining direct tumor kill, with enhanced cytokine profile, cellular toxicity and phagocytosis with no increased toxicities.

Objectives and Endpoints

Primary Objectives:

(1) To characterize the safety and tolerability of chemotherapeutic regimen belantamab mafodotin, cyclophosphamide, and dexamethasone in patients with relapsed/refractory multiple myeloma.

(2) Identifying the maximum tolerated dose and recommended Phase 2 dose.

Primary Endpoints

(1) Incidence of RLTs

(2) Treatment emergent adverse events

(3) Treatment-related adverse events.

Secondary Endpoints

(1) The overall response rate of the better tolerated regimen in an expansion cohort.

(2) The percentage of patients with confirmed partial (or better) response

(3) Duration of response

(4) Time to response

(5) Time to progression

(6) Progression-free survival (PFS)

(7) Overall survival (OS)

Exploratory Endpoints

Obtain exploratory data on cytokine profile in the eye and T cell subsets in the peripheral blood before and after initiation of therapy (cycle 2 day 1).

Overall Study Design: This is a Phase I/II, open-label study to evaluate the efficacy and safety of Belantamab Mafodotin, cyclophosphamide and dexamethasone.

Treatment schedule

Phase I

	Belantamab Mafodotin	**Cyclophosphamide**	**Dexamethasone**	**pts #**
Arm A (cycles repeated every 3 weeks)				
	Day 1	Day 1	Day 1	
Dose level 1	1.9 mg/kg	300 mg	40 mg	3-6
Dose level 2	1.9 mg/kg	500 mg	40 mg	3-6
Arm B (cycles repeated every 6 weeks)				
	Day 1	Day 1	Day 1	
Dose level 1	2.5 mg/kg	300 mg	40 mg	3-6
Dose level 2	2.5 mg/kg	500 mg	40 mg	3-6

- Patients will be assigned to Arm A and B sequentially (one patient to arm A and the next to Arm B); there is no randomization and no stratification.

- 3 patients will be treated at each dose level. Patients will be assessed for RLT defined as:
- Any non-hematological toxicity Grade ≥ 3, except:
    - *Alopecia*
    - *Grade 3 nausea/vomiting or diarrhea for less than 72 hours with adequate antiemetic and other supportive care*
    - *Grade 3 fatigue for less than 1 week*
    - *Grade 3 or higher isolated electrolyte abnormalities that last up to 72 hours, are not clinically complicated, and resolve spontaneously or respond to conventional medical interventions*
    - *Grade 3 or higher amylase or lipase elevation that is not associated with symptoms or clinical manifestations of pancreatitis*
    - *Grade 3 tumor lysis syndrome (TLS) that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions*
- Grade 4 neutropenia lasting more than 5 days
- Febrile neutropenia of any duration (ANC <1.0 x 10^9/L, fever ≥ 38.4°C or ≥ 38° C for 1 hour)
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 4 anemia, unexplained by underlying disease
- Grade 5 event from any cause.
- If 1 of 3 patients within a dose level developed RLT, 3 more will be treated at the same dose level, if no additional toxicity occurs. Proceed to the next dose level if </=1 out of 6 patients experience RLT.
- There is no planned dose escalation for MTD.
- Three patients can be simultaneously enrolled on each arm. Subsequent dose escalation can occur after observation of one cycle in each cohort.
- All concomitant meds will be recorded on each visit.
- All patients will be provided a daily symptom log for reporting side effects.
- Response will be assessed using revised IMWG criteria.

Phase II

Expansion Cohort

- Once tolerability of the highest planned dose is established, patients will be assessed for response rate. The arm with acceptable toxicity and best response will be further assessed in the expansion cohort.

Number of Participants:
- Phase 1; for arm A and B 12-24 patients
- Phase II: 40 patients will be enrolled. If 21 responses are seen, the treatment would be recommended for further study.

Treatment Groups and Duration:

The enrolled patients will be treated with belantamab mafodotin. until any of the following:

- Occurrence of an AE which makes discontinuation from treatment necessary due to protocol-specified safety criteria or desirable in the investigator's and/or the subject´s opinion
- Investigator's decision that a change of therapy is in the subject´s best interest
- Investigator's decision that a subject does not benefit from treatment anymore, e.g., non-response or development of progressive disease
- Intercurrent medical condition, which in the opinion of the investigator or the subject precludes further treatment of the subject
- Withdrawal of subject's consent to further study treatment
- Death
- Lost to follow-up

Inclusion Criteria:

1. Histologically confirmed diagnosis of Refractory MM;

   Has received at least 3 prior classes of anti-myeloma drugs, including an anti-CD38 antibody (e.g., daratumumab) alone or in combination, and is refractory to an IMiD (i.e., lenalidomide or pomalidomide), and to a proteasome inhibitor (e.g., bortezomib, ixazomib or carfilzomib). (*Refractory myeloma is defined as disease that is nonresponsive while on primary or salvage therapy or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve at least minimal response or development of progressive disease (PD) while on therapy).*

2. Has measurable disease with at least one of the following:
   a. Serum M-protein ≥0.5 g/dL (≥5 g/L)
   b. Urine M-protein ≥200 mg/24h
   c. Serum FLC assay: Involved FLC level ≥10 mg/dL and an abnormal ratio (<0.26 or >1.65)
   d. Non secretory myeloma patients can be enrolled if:
      Bone marrow shows > 20% plasma cells
      PET/CT scan is positive for myeloma
3. Provide signed written informed consent
4. 18 years or older (at the time consent is obtained)
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
6. Participants with a history of autologous stem cell transplant or prior BCMA targeted therapy (e.g. CAR-T cells, BiTes) can enroll on the study provided that:
   a. Therapy was >100 days prior to study enrolment
   b. No active infection(s)
7. Adequate organ system function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥1.0 X 10^9/L
Hemoglobin	≥8.0 g/dL
Platelets	≥50 X 10^9/L
Hepatic	
Total bilirubin	≤1.5X ULN Except in patients with congenital bilirubinemia, such as Gilbert syndrome, direct bilirubin ≤1.5 x ULN
ALT	≤2.5 X ULN
Renal eGFR	≥30 mL/min/1.73 m^2
Urine Dipstick Or Albumin/creatinine ratio (from spot urine)	Negative/trace (if ≥ 1+ only eligible if confirmed ≤500 mg/g by albumin/creatinine ratio (spot urine) ≤500 mg/g (56 mg/mmol)

8. Female participants: Contraceptive use for those participating in clinical studies (men or women) should be consistent with local regulations

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

a. Is not a woman of childbearing potential (WOCBP)
OR
b. 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 at least 12 months after the last dose of study intervention 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.

- A WOCBP must have a negative highly sensitive serum pregnancy test (as required by local regulations) within 72 hours before the first dose of study intervention.
- We will review the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with a new undetected pregnancy.

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

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

9. Male participants: contraceptive use 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 during the intervention period and for 6 months after the last dose of study treatment to allow for clearance of any altered sperm:

   a. Refrain from donating sperm PLUS 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 and 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 when having sexual intercourse with a woman of childbearing potential

10. All prior treatment-related toxicities (defined by National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 5.0) must be ≤ Grade 1 at the time of enrollment except for alopecia and Grade 2 peripheral neuropathy.

Exclusion Criteria:

1. Systemic anti-myeloma therapy within ≤14 days or 5 half-lives, whichever is shorter, or plasmapheresis within 7 days prior to the first dose of study drug
2. Systemic treatment with high dose steroids (equivalent to ≥60 mg prednisone daily for ≥4 days) within the past 14 days if administered to treat MM or non- MM disease
3. Prior allogeneic transplant (SCT). NOTE – Participants who have undergone syngeneic transplant may be allowed, if no history of GvHD
4. Current corneal epithelial disease except mild punctate keratopathy
5. Evidence of active bleeding
6. Any major surgery within the last four weeks
7. 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 participants fulfil entry criteria (as defined by inclusion criteria #7)
8. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions (including lab abnormalities) that could interfere participants' safety, obtaining informed consent or compliance with study procedures.
9. Current unstable liver disease per Investigator assessment 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) is acceptable if participant otherwise meets entry criteria.
10. Other malignancies are excluded, except for malignancy from which the patients have been disease-free for more than 2 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, prostate cancer or in situ cervical cancer that has undergone potentially curative therapy.
11. Evidence of cardiovascular disease 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 3 months of screening.
    c) Class III or IV heart failure as defined by the New York Heart Association functional classification system.
    d) Uncontrolled hypertension.
12. Known immediate or delayed hypersensitivity reaction or idiosyncratic reaction to drugs chemically related to belantamab mafodotin, daratumumab, bortezomib, boron or mannitol or any other components of the study treatment.
13. Active infection requiring treatment.
14. Known HIV infection.
15. Presence of hepatitis B surface antigen (HbsAg), or hepatitis B core antibody (HbcAb), at screening or within 3 months prior to first dose of study treatment. Note: presence of Hep B surface antibody (HBsAb) indicating previous vaccination will not exclude a participant.

16. Positive hepatitis C antibody test result or positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment.

    NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained. Hepatitis RNA testing is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.

17. Symptomatic amyloidosis, active POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma proliferative disorder, skin changes) or active plasma cell leukemia at the time of screening.

18. Pregnant or lactating female

19. Concomitant administration of strong P-glycoprotein inhibitors and inhibitors of OATP.

Schedule of Activities (SOA)

Arm A; 3-week (21 Day) cycle[14]

Study Assessments[8]	**Screen** [1]	**Cycle 1-6; day 1**	**>Cycle 6 day 1**	**Once ≥ VGPR**	**End of Treatment**	**30 day Follow-Up**	**PFS Follow-up** [5]	**OS Follow -up**[6]
Window	***30 days***	***± 3 days***	***± 3 days***		***±14 days***	***± 3 days***	***± 7 days***	***± 14 days***
Informed Consent	X							
Demographics	X							
Medical History	X							
Physical Exam	X	X	X	X	X		Q3M	
Concomitant Meds	X	X	X	X	X			
Adverse Events[10]		X	X	X	X	X		
Ocular Exam[7]	X	Every cycle and as clinically indicated			X		Q3M [7]	
ECOG	X	X	X	X	X			
Vitals[4] (BP, HR, Temp)	X	X	X	X	X			
Weight and Height[13]	X	X	X		X			
CBC with diff	X	X	X	X	X			
Chemistry Panel	X	X	X	X	X			
eGFR	X	X	X		X			
Urinalysis (dipstick) OR Spot Urine (albumin/creatinine ratio)[11]	X	X	X		X			
HBsAg, HBcAb, hep C Ab	X				X			
Pregnancy Test[9]	X	X	X	X	X			
Beta2 microglobulin	X			X	X			
Skeletal survey[2]	X	To Confirm ≥ VGPR			X			
Imaging for Extramedullary[3]	X	To Confirm ≥ VGPR						
UPEP/IFE (24 hr. urine)	X	X	X	X	X		Q3M	
SPEP/IFE	X	X	X	X	X		Q3M	
C-reactive protein	X							
Serum FLC levels and ratio	X	X	X	X	X		Q3M	
IgG, IgM, IgA	X	X	X	X	X		Q3M	
BM for FISH	X	To Confirm ≥ VGPR			X			
BM aspirate for BCMA IHC	X				X			
BM for MRD testing								
BM for disease assessment	X				X			
Correlative studies[12]	X	C2D1						
Treatment administration		X	X	X				

Schedule of Activities (SOA)
Arm B; 6-week (42 day) cycle

Study Assessments[8]	**Screen[1]**	**Cycle 1-6; day 1 & 22**	**>Cycle 6 day 1**	**Once ≥ VGPR**	**End of Treatment**	**30 day Follow-Up**	**PFS Follow-up[5]**	**OS Follow-up[6]**
Window	***30 days***	***± 3 days***	***± 3 days***		***±14 days***	***± 3 days***	***± 7 days***	***± 14 days***
Informed Consent	X							
Demographics	X							
Medical History	X							
Physical Exam	X	DAY 1	X	X	X		Q3M	
Concomitant Meds	X	X	X	X	X			
Adverse Events[10]		X	X	X	X	X		
Ocular Exam[7]	X	Day 1 of Every Cycle and as clinically indicated			X		Q3M[7]	
ECOG	X	DAY 1	X	X	X			
Vitals[4] (BP, HR, Temp)	X	Day 1	X	X	X			
Weight and Height[13]	X	X	X		X			
CBC with diff	X	X	X	X	X			
Chemistry Panel	X	X	X	X	X			
eGFR	X	X	X		X			
Urinalysis (dipstick) OR Spot Urine (albumin/creatinine ratio)[11]	X	DAY 1	X		X			
HBsAg, HBcAb, hep C Ab	X				X			
Pregnancy Test[9]	X	DAY 1	X	X	X			
Beta2 microglobulin	X			X	X			
Skeletal survey[2]	X	To Confirm ≥ VGPR			X			
Imaging for Extramedullary[3]	X	To Confirm ≥ VGPR						
UPEP/IFE (24 hr. urine)	X	DAY 1	X	X	X		Q3M	
SPEP/IFE	X	DAY 1	X	X	X		Q3M	
C-reactive protein	X							
Serum FLC levels and ratio	X	DAY 1	X	X	X		Q3M	
IgG, IgM, IgA	X	DAY 1	X	X	X		Q3M	
BM for FISH	X	To Confirm ≥ VGPR			X			
BM aspirate for BCMA IHC	X				X			
BM for MRD testing								
BM for disease assessment	X				X			
Correlative studies[12]	X	C2D1						
Treatment administration		DAY1	X	X				

BM = bone marrow; BP = blood pressure; C1D1 = Cycle 1 Day 1, etc. CRP = C-reactive protein; FISH = fluorescence in situ hybridization; FLC = free light chain; HR= heart rate; Ig = immunoglobulin.

Footnotes for Schedule of Activities

1. *All screening assessments must be performed within 30 days prior to first dose.*
2. *Skeletal Survey should include imaging of bones for lytic lesions by X-ray, CT, or MRI as clinically indicated. .*
3. *PET/CT is indicated for all patients with possible extramedullary disease (symptoms or high LDH [ULN])*
4. *At the first dose of belantamab mafodotin, vital signs must be assessed within 30 min prior to Start of Infusion (SOI), 15 mins after SOI, (±10 min), within 15 min after End of Infusion (EOI), and at 1 h (±10 min) after EOI. On subsequent doses of belantamab mafodotin, vital signs must be assessed within 30 minutes prior to SOI and within 15 min after EOI.*
5. *Progression-Free Survival (PFS) Follow-up Every 3 months (+/- 7 days) for 9 months*
6. *Overall Survival (OS) Follow-up Every 3 months (+/- 14 days) for 9 months*
7. *C1D1 ocular exam does not need to be repeated if within 21 days of screening exam. On treatment ocular exams to be performed Q3W (Arm A),Q 6W (Arm B) prior to each dose. Ocular exam may be performed up to 5 days prior to second dose onwards for belantamab mafodotin.* ***Participants in PFS follow up or OS follow up will only have ocular exams if they had signs or symptoms at EOT. See Section 6.1.3.***
8. *All laboratory tests with values considered clinically significantly or abnormal during participation in the study or within 70 days after the last dose of study treatment should be repeated weekly until the values return to normal or baseline.*
9. *Perform only on women of childbearing potential (WOCBP). A serum pregnancy test must be performed at screening; if the test is completed within 72 hours prior to the first dose of belantamab mafodotin, this assessment does not have to be repeated on C1D1. For questionable cases, follicle-stimulating hormone (FSH) and estradiol (as needed in WOCBP) should be performed at local lab to determine childbearing potential. WOCBP must have a negative highly sensitive serum pregnancy test within 72 hours of dosing on C1D1. Subsequent pregnancy tests on dosing days may be either serum or urine. Final pregnancy test (serum or urine) must be performed in WOCBP at the EOT Visit. Follow up pregnancy assessment by telephone (for WOCBP only) should be performed 4 months after the last dose of belantamab mafodotin.*
10. *AE/SAEs will be collected from the start of study treatment until at least 70 days following EOT, regardless of initiation of new cancer therapy.*
11. *Urine dipstick 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 >2+ on treatment, or with positive protein if urine dipstick protein quantification is not available.*
12. *Correlative studies include obtaining tear drops for cytokine assessment and 5 ml peripheral blood for assessment of T cell profile at Screening, C2D1, and per clinician's discretion.*
13. *Height measure is required only at screening, Arm A and Arm B*
14. *Arm A subject will follow Arm B Schedule of Activities if dosing schedule is changed to Q6W*

2.0 INTRODUCTION

Multiple myeloma (MM) is an incurable malignancy and accounts for 1% of all cancers and for 10% of all hematologic malignancies. Approximately 33,000 new cases are diagnosed annually, and 13,000 deaths will occur in the US. There have been significant advances in treatment for MM, including therapies like second and third -generation proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and monoclonal antibodies (mAbs). Those advances have contributed to incremental gains in PFS and OS, but most MM patients still relapse and ultimately develop resistance to existing therapies highlighting the need for new drugs with novel targets.

B-cell maturation antigen (BCMA) is a member of the tumor necrosis factor (TNF) receptor superfamily and regulates a variety of cellular functions. BCMA is expressed in mature B lymphocytes and binds to two TNF family ligands BAFF (B-cell-activating factor belonging to the TNF family) and APRIL (a proliferation-inducing ligand) which promotes B-cell survival and proliferation. BCMA is expressed on malignant plasma cells in all MM patients. Chimeric Antigen Receptor T-Cells (CAR-T) based therapies targeting BCMA have also demonstrated powerful activity against MM, with substantial albeit reversible risks. Other approaches utilizing bispecific antibodies (BiTe) have also entered development.

2.1 Background of Investigational Product

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

The normal function of BCMA is to promote cell survival by transduction of signals from two known ligands: B cell activating factor from the tumor necrosis factor (TNF) family (BAFF/BLys) and a proliferation inducing ligand (APRIL). BCMA expression is restricted to B cells at later stages of differentiation, with expression on germinal center B cells in tonsil, blood plasma blasts, and long-lived plasma cells. BCMA is expressed in various B cell malignancies, including multiple myeloma (MM), diffuse large B-cell lymphoma (DLBCL), large B-cell lymphoma (LBCL), chronic lymphocytic leukemia (CLL) and Waldenstrom's macroglobulinemia (WM) at varying frequencies. Belantamab mafodotin binds to BCMA, is internalized, and releases free cys-mcMMAF, which disrupts the microtubule network, leading to cell cycle arrest and apoptosis. Belantamab mafodotin also mediates antibody-dependent cell-mediated cytotoxicity (ADCC) effector function directed towards BCMA-expressing cells. The mechanisms of action of belantamab mafodotin are designed to enable anti-tumor activity of cells by ADCC activity (non-dividing), as well as ADC activity (dividing cells). Moreover, ADC-induced apoptosis by belantamab mafodotin was recently shown to be potentially immunogenic as measured by cell surface externalization of calreticulin (CRT) and secretion of high mobility group box 1 (HMGB1) and adenosine triphosphate (ATP).

Clinical and non-clinical data for belantamab mafodotin are discussed in detail in the Investigators Brochure (IB).

2.2 Study Rationale

Patients with MM who relapse after IMiDS, SCT, PI and daratumumab therapy, have few treatment options available and could benefit from treatment with a novel drug such as Belantamab mafodotin. Belantamab mafodotin is a first in class, ADCC enhanced, humanized immunoglobulin G1 (IgG1) antibody-drug conjugate (ADC) that binds specifically to B-cell maturation antigen (BCMA), a target present on mature B cells and on tumor cells in patients with MM. The antibody is conjugated to the microtubule inhibitor monomethyl auristatin-F (MMAF) and is produced as an afucosylated form that generates an enhanced antibody-dependent cellular cytotoxicity (ADCC) response. This novel mechanism of action can be reasonably expected to overcome cross resistance to existing therapies. Single agent Belantamab mafodotin pharmacokinetics were linear over the range of doses tested, with exposure of all analytes increasing proportionately with increasing dose. In DREAMM-1 study, single agent belantamab mafodotin (3.4-mg/kg every 3 weeks) demonstrated promising single-agent activity inducing rapid and durable responses [overall response rate (ORR) of 60% with a median progression free survival (PFS) of 12 months]. In DREAMM-2 study, patients received (2.5-mg/kg or 3.4-mg/kg) with an ORR of 31%-34% and a median progression-free survival of 2.9-4.9 months, for 2.5-mg/kg and 3.4-mg/kg, respectively. The most common adverse events in both studies were eye complications (70% irrespective of the dose) and thrombocytopenia (21% and 44%, which was dose dependent).

Cyclophosphamide synergistically enhanced many therapeutic antibodies in several models of B cell malignances; for e.g. cyclophosphamide, enhanced rituximab induced B cell toxicity by increasing acute secretory activation phenotype (affecting tumor necrosis factor α, interferon γ as well as interleukin (IL)-6, IL-10, and IL-12.). In addition, cyclophosphamide alters overall immune regulatory cells leading to stimulation of the cytotoxic functions of T lymphocytes (CD-44 lymphocytes), inhibition of regulatory T cells (CD-4/CD-25) and increasing the macrophage induced phagocytosis. In MM, cyclophosphamide has limited activity especially in the relapsed and refractory setting; however, in combination with other agents such as Daratumumab, pomalidomide and carfilzomib it led to enhanced activity. It would be very interesting to investigate the impact of the immune modulatory properties of cyclophosphamide on the ophthalmology effects of belantamab.

We hypothesize that immune-modulatory properties of cyclophosphamide in combination with Belantamab mafodotin can improve ORR in relapsed/refractory (RR) MM by combining direct tumor kill, with enhanced cytokine profile, cellular toxicity and phagocytosis with no increased toxicities.

2.3 Study Risk

Corneal AEs have been observed with various ADC drugs and represent the most commonly reported types of AEs associated with Belantamab. As there is no single term which appropriately captures these events, the term ‘corneal events’ includes reported preferred terms (from Eye Disorders System Organ Class) describing events associated with the corneal events related to Belantamab. The most commonly reported corneal events included vision blurred, dry eye, photophobia, and lacrimation increased. More severe cases included keratitis. In most cases the vision returned to baseline after stopping therapy. Interestingly, 90% of participants in Part 2 had corneal findings upon examination. These findings were generally characterized by a superficial punctate keratopathy/keratitis which was often associated with epithelial (microcystic) edema and occasional stromal edema or opacities. Visual acuity declined during treatment in most participants experiencing these clinical findings. Additional information about the known and expected benefits and risks, detailed information of nonclinical and clinical findings information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on Belantamab that may impact participant eligibility is provided in the Investigator’s Brochure.

Cyclophosphamide is a known cancer drug with known side effects that include bone marrow suppression, nausea, vomiting reversible alopecia. The combination with Belantamab has not been studied and will be carefully assessed in the current study.

2.3 Risk Assessment and Management of Belantamab Mafodotin

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

All risks will be considered against the potential benefit to patients who have no other therapeutic options. Patients will be closely monitored on the study; they will continue therapy if the risk/ benefit ratio is favorable and reasonable.

3.0 Objectives and Endpoints

3.1 **Primary Objectives:**

(1) To characterize the safety and tolerability of chemotherapeutic regimen belantamab mafodotin, cyclophosphamide, and dexamethasone in patients with relapsed/refractory multiple myeloma.

(2) Identifying the maximum tolerated dose and recommended Phase 2 dose.

3.2 **Primary Endpoints**

(1) Incidence of RLTs

(2) Treatment emergent adverse events

(3) Treatment-related adverse events.

3.3 Secondary Endpoints

(1) The overall response rate of the better tolerated regimen in an expansion cohort.

(2) The percentage of patients with confirmed partial (or better) response

(3) Duration of response

(4) Time to response

(5) Time to progression

(6) Progression-free survival (PFS)

(7) Overall survival (OS)

3.4. Exploratory Endpoints

Obtain exploratory data on cytokine profile in the eye and T cell subsets in the peripheral blood before and after initiation of therapy (cycle 2 day 1).

4.0 Study Design; This is a Phase I/II, open-label study to evaluate the efficacy and safety of Belantamab Mafodotin, cyclophosphamide and dexamethasone**.**

4.1 Treatment schedule

Phase I

	Belantamab Mafodotin	Cyclophosphamide	Dexamethasone	pts #
Arm A (cycles repeated every 3 weeks)				
	Day 1	Day 1	Day 1	
Dose level 1	1.9 mg/kg	300 mg	40 mg	3-6
Dose level 2	1.9 mg/kg	500 mg	40 mg	3-6
Arm B (cycles repeated every 6 weeks)				
	Day 1	Day 1	Day 1	
Dose level 1	2.5 mg/kg	300 mg	40 mg	3-6
Dose level 2	2.5 mg/kg	500 mg	40 mg	3-6

- Patients will be assigned to Arm A and B sequentially (one patient to arm A and the next to Arm B); there is no randomization and no stratification.
- 3 patients will be treated at each dose level. Patients will be assessed for RLT (defined as grade 3-4 nonhematologic toxicity that fails to recover to grade 1 in 7 days; 7 days delay due to toxicity; treatment related death). If 1 of 3 developed RLT, 3 more will be treated at the dose level, if no additional toxicity 1 out of 6 RLT will proceed to next dose level.
- There is no planned dose escalation for MTD.
- Three patients can be simultaneously enrolled on each arm. Subsequent dose escalation can occur after observation of one cycle in each cohort.
- All concomitant meds will be recorded on each visit.
- All patients will provide a diary symptom log for reporting side effects.
- Response will be assessed using revised IMWG criteria.
- RLT assessment duration will be 3 weeks for arm A and 6 weeks for arm B.
- If ≥2/6 RLT occurs in the lowest dose, the protocol will be placed on hold for unacceptable toxicity until further negotiation/discussion with regulatory bodies (e.g. IRB, FDA) occur.

Phase II; Expansion Cohort

Once tolerability of the highest planned dose is established, patients will be assessed for response rate. The arm with acceptable toxicity and best response will be further assessed in the expansion cohort.

4.2 Number of Participants and duration of therapy:

- Phase 1: for arm A and B 12-24 patients
- Phase II: 40 patients will be enrolled. If 21 responses are seen, the treatment would be recommended for further study.
- Patients will be treated until disease progression or until unacceptable toxicity. For patients who discontinue study treatment for reasons other than PD, disease evaluations will continue to be

performed at monthly intervals until confirmed PD, death, start of a new anticancer treatment, withdrawal of consent, or end of the study whichever occurs first.

5.0 Study Population

5.1 Inclusion Criteria:

1. Histologically confirmed diagnosis of Refractory MM
    a. Has received at least 3 prior classes of anti-myeloma drugs, including an anti-CD38 antibody (e.g., daratumumab) alone or in combination, and is refractory to an IMiD (i.e., lenalidomide or pomalidomide), and to a proteasome inhibitor (e.g., bortezomib, ixazomib or carfilzomib). (*Refractory myeloma is defined as disease that is nonresponsive while on primary or salvage therapy or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve at least minimal response or development of progressive disease (PD) while on therapy).*
2. Has measurable disease with at least one of the following:
    a. Serum M-protein ≥0.5 g/dL (≥5 g/L)
    b. Urine M-protein ≥200 mg/24h
    c. Serum FLC assay: Involved FLC level ≥10 mg/dL and an abnormal ratio (<0.26 or >1.65)
    d. Non secretory myeloma patients can be enrolled if:
    Bone marrow shows > 20% plasma cells
    PET/CT scan is positive for myeloma
3. Provide signed written informed consent
4. 18 years or older (at the time consent is obtained)
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
6. Participants with a history of autologous stem cell transplant or prior BCMA targeted therapy (e.g. CAR-T cells, BiTes) can enroll on the study provided that:
    a. Therapy was >100 days prior to study enrolment
    b. No active infection(s)
7. Adequate organ system function:

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥1.0 X 10^9/L
Hemoglobin	≥8.0 g/dL
Platelets	≥50 X 10^9/L
Hepatic	
Total bilirubin	≤1.5X ULN Except in patients with congenital bilirubinemia, such as Gilbert syndrome, direct bilirubin ≤1.5 x ULN
ALT	≤2.5 X ULN
Renal eGFR	≥30 mL/min
Urine Dipstick Or Albumin/creatinine ratio (from spot urine)	Negative/trace (if ≥ 1+ only eligible if confirmed ≤500 mg/g by albumin/creatinine ratio (spot urine) ≤500 mg/g (56 mg/mmol)

8. Female participants: Contraceptive use for those participating in clinical studies (men or women) should be consistent with local regulations

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

   a. Is not a woman of childbearing potential (WOCBP)
      OR
   b. 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 at least 12 months after the last dose of study intervention 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.

      - A WOCBP must have a negative highly sensitive serum pregnancy test (as required by local regulations) within 72 hours before the first dose of study intervention.
      - We will review the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with a new undetected pregnancy.

   Non-childbearing potential is defined as follows (by other than medical reasons):

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

9. Male participants: contraceptive use 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 during the intervention period and for 6 months after the last dose of study treatment to allow for clearance of any altered sperm:

a. Refrain from donating sperm PLUS 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 and 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 when having sexual intercourse with a woman of childbearing potential

10. All prior treatment-related toxicities (defined by National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 5.0) must be ≤ Grade 1 at the time of enrolment except for alopecia and Grade 2 peripheral neuropathy.

5.2 Exclusion Criteria:

1. Systemic anti-myeloma therapy within ≤14 days or 5 half-lives, whichever is shorter, or plasmapheresis within 7 days prior to the first dose of study drug
2. Systemic treatment with high dose steroids (equivalent to ≥60 mg prednisone daily for ≥4 days) within the past 14 days if administered to treat MM or non- MM disease
3. Prior allogeneic stem cell transplant (SCT). Note: Participants who have undergone syngeneic transplant may be allowed, if no history of GvHD
4. Current corneal epithelial disease except mild punctate keratopathy
5. Evidence of active bleeding
6. Any major surgery within the last four weeks
7. 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 entry criteria (as defined by inclusion criteria #7)
8. 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.
9. Current unstable liver or biliary disease per Investigator assessment 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) is acceptable if participant otherwise meets entry criteria.
10. Other malignancies are excluded, except for malignancy from which the patients have been disease-free for more than 2 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, prostate cancer or in situ cervical cancer that has undergone potentially curative therapy.
11. Evidence of cardiovascular risk including any of the following:

a. Evidence of current clinically significant uncontrolled 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 3 months of screening.

c. Class III or IV heart failure the New York Heart Association functional classification system

d. Uncontrolled hypertension

12. Known immediate or delayed hypersensitivity reaction or idiosyncratic reaction to drugs chemically related to belantamab mafodotin, daratumumab, bortezomib, boron or mannitol or any other components of the study treatment.
13. Active infection requiring treatment.
14. Known HIV infection.
15. Presence of hepatitis B surface antigen (HbsAg), or hepatitis B core antibody (HbcAb), at screening or within 3 months prior to first dose of study treatment. Note: presence of Hep B surface antibody (HBsAb) indicating previous vaccination will not exclude a participant.
16. Positive hepatitis C antibody test result or positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment.

    NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained. Hepatitis RNA testing is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.
17. Symptomatic amyloidosis, active POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma proliferative disorder, skin changes) or active plasma cell leukemia at the time of screening.
18. Pregnant or lactating female
19. Concomitant administration of strong P-glycoprotein inhibitors and inhibitors of OATP.

5.3 Screen Failures

- Screen failures are patients who consent to participate in the study but are not enrolled/treated. Screen failure is expected and will be documented to ensure transparent reporting to meet the Consolidated Standards of Reporting Trials.
- Patients who do not meet the criteria for participation in this study (screen failure) may be rescreened.

6.0 Treatment

Study treatment is defined as any investigational treatment intended to be administered to a study participant according to the study protocol. Belantamab will be administered intravenously. Cyclophosphamide and dexamethasone will be administered orally.

6.1 Belantamab Mafodotin

Belantamab Mafodotin is to be administered at a calculated dose of 1.9 mg/kg on day 1 of 3 weeks cycle arm A or 2.5 mg/kg on days 1 of 6 weeks cycle Arm B as an IV infusion, via an infusion pump. Premedication is not required prior to infusion unless deemed medically necessary by the Investigator and it should be administered according to institutional recommendations.

Dose form Lyophilized powder, 100 mg/vial in single-use vial for reconstitution

Instructions Reconstitute Belantamab lyophilized powder 100 mg/vial 2.0mL of water for injection (WFI); dilute with saline before use.

Route of administration Delivered as IV solution over at least 30 minutes.

Manufacturer: GSK/Baxter

6.1.1 Belantamab Dose Modification

Adjustments Due to Body Weight: The actual body weight in kg at baseline (assessed on Cycle 1 Day 1 prior to dosing) will be used for dose calculation of Belantamab in all patients. If the change of body weight is greater than 10%, the dose must be recalculated based on the actual body weight at the time of dosing.

6.1.2 Belantamab Mafodotin (GSK2857916) Dose Reductions

Starting dose	1st reduction	2nd reduction
Arm A 1.9 mg/kg q3w	1.9 mg/kg day1 q6w	Discontinue treatment permanently
Arm B 2.5 mg/kg q6w	1.9 mg/kg day 1 q6w	Discontinue treatment permanently

If the patient cannot tolerate the drug after the allowed dose reductions, he or she must be withdrawn from the study for lack of tolerability.

If a dose is delayed, the patient should wait for the next scheduled dose to resume treatment; earlier re-start may be considered only for patients who have recovered from toxicity to < G1.

The dose and dosing timing interval changes of administration of belantamab mafodotin (GSK2857916) doesn't occur during the phase I portion (Cohort) of this study (exceptions are Belantamab related corneal adverse events) and only can occur during the phase II portion (Expansion Cohort)

6.1.3 Corneal Supportive Care Guidelines

We have established a close collaboration with an ophthalmologist, a Co-Investigator, who will be responsible for assessing patients managing those who develop a corneal event.

Preservative-free artificial tears *should be used in all patients. 1 drop in each eye every 4-6 hours and can be increased to 1 drop in each eye as frequently as every 2 hours, as needed.*

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

Further information regarding changes in the corneal epithelium associated with belantamab mafodotin, including a grading scale and prophylactic measures are in Appendix 5.

A baseline ocular examination is required for all patients. Patients should undergo on treatment ocular examinations per SOA as defined (Section 8.3). If a participant subsequently develops a change in visual acuity or other ocular symptoms, the participant should be evaluated by an eye care specialist and followed as frequently as clinically indicated. If steroid eye drops are deemed medically necessary and prescribed, intraocular pressure must be monitored if used for >7 days.

Participants who have corneal signs per the Keratopathy Visual Acuity (KVA) scale for treatment-related corneal toxicities present at end of study treatment will continue to be followed every 3 months for up to

12 months, or until full resolution of findings: defined as a return to participant's baseline, or until deemed clinically stable by a qualified eye care specialist, whichever comes first.

6.1.4 Dose Modification for Belantamab-Related Adverse Events

Toxicity	Grade/Symptoms	Recommendations for Belantamab Mafodotin
Elevated serum creatinine not explained by sepsis, TLS, fever, dehydration, etc.	increases from baseline by >0.5 mg/dL	• Repeat within 48 hours • If confirmed: withhold therapy
Serum creatinine	Grade 3-4 (Defined as >3.0x ULN) Or >3.0 mg/dL	• Permanently discontinue belantamab mafodotin

Spot urine (albumin/creatinine ratios)	>2000 mg/g
	(or 224 mg/mmol)
		Re-test (at least 7 days apart).
		• If not confirmed, continue belantamab mafodotin at pre-held dose
		• If confirmed/no evidence of disease progression
		  • Interrupt belantamab mafodotin
		  • Repeat testing within 4 weeks
		  • If spot urine <2000 mg/g (224 mg/mmol), may restart belantamab mafodotin at same dose level
		  • If it remains >2000 mg/g after 4 weeks, discontinue belantamab mafodotin

Urine Dipstick	2+	• May continue belantamab mafodotin dosing • Confirm by quantitative assessment using albumin/creatinine ratio
	>3	• Interrupt treatment and follow up for recovery. Implement quantification of albumin/creatinine ratio
Thrombocytopenia (on days of dosing) Graded according to NCI-CTCAE criteria	Grade 3	• No bleeding: continue treatment with 1 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 1 dose level reduction. • Supportive treatment (e.g., transfusion), as clinically indicated and per local practice.
	Grade 4	• Withhold the dose. Consider restarting with 1 dose level if 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 >25x10^9/L continuing treatment with dose reduction may be considered.
Afebrile Neutropenia Graded according to NCI-CTCAE criteria	Grade 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 pre-held dose once neutropenia recovers to Grade ≤ 2 (ANC ≥ 1.0x10^9/L) on Day 1 of the subsequent cycle. • Prophylactic antibiotics, per physician discretion and local institutional guidance. Consider growth factors.

Toxicity	Grade/Symptoms	Recommendations for Belantamab Mafodotin
		• Local guidance must be followed for hematological monitoring, if more conservative than the protocol specifications. • In cases of frequent recurrent neutropenia (ANC <1.0x10^9/L), consider dose reduction
Febrile neutropenia Graded according to NCI-CTCAE criteria	Grade 3-4 (Defined as: single temp of 38.3 °C and ANC <1.0×10^9/L	• Withhold the dose and immediately hospitalize participant with appropriate management, per local institutional guidance. • Consider additional supportive treatment (e.g. growth factors). • Upon recovery, consider dose reduction of belantamab mafodotin, if neutropenia was drug-related.
Infusion reaction [a] Graded according to NCI-CTCAE criteria	Grade 1/ 2	• Interrupt infusion and provide supportive care. Once symptoms resolve to grade 0/1, resume at lower infusion rate; reduce the infusion rate by at least 50%.
	Grade 3	• Continuation only allowed after recovery to < Grade 1 and with pre-medication, and extension of infusion time to 2-4 hours.
	Grade 4	• Permanently discontinue
Pneumonitis Graded according to NCI-CTCAE criteria	Grade 2	• Withhold treatment with belantamab mafodotin • Upon recovery to Grade 1, restart treatment at 1 dose level reduction dose level.
	Grade 3-4	• Permanently discontinue treatment with belantamab mafodotin

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

6.1.5 Dose Modification Guidelines for Corneal-Related Adverse Events Associated with belantamab mafodotin

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 same 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 after resolution to grade 1 with delays allowed up to 3 months	**Consider permanent discontinuation of belantamab mafodotin.** **If based on benefit risk assessment, 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.

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

6.2 Cyclophosphamide

Chemistry: 2[bis (2chloroethyl)amino]tetrahydro-2H-1,3,2-oxazophosphorine 2-oxide mono-hydrate. Cyclophosphamide (cytoxan) is biotransformed principally in the liver to active alkylating metabolites which cross-link to DNA.

Toxicity from cyclophosphamide includes bone marrow suppression usually occurs 10 to 12 days after administration; nausea, vomiting, anorexia, abdominal discomfort, diarrhea and stomatitis; reversible alopecia; hemorrhagic cystitis which can frequently be prevented with increased hydration; fibrosis of the bladder; cardiac toxicity which may potentiate doxorubicin-induced cardiotoxicity; rare anaphylactic reaction, skin rash, hyperpigmentation, interstitial pulmonary fibrosis, cross sensitivity with other alkylating agents. Treatment with cyclophosphamide may cause significant suppression of the immune system. Second malignancies, most frequently of the urinary bladder and hematologic systems, have been reported when cytoxan is used alone or with other anti-neoplastic drugs. Malignancies may occur several years after treatment has been discontinued. Cyclophosphamide interferes with oogenesis and spermatogenesis and may cause sterility in both sexes which is dose and duration related. Cyclophosphamide is teratogenic, and women of childbearing potential should avoid becoming pregnant. Increased myelosuppression is enhanced with chronic administration of phenobarbital. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination.

This drug is commercially available in 50 mg tablets

6.2.1 Dose Modification for Cyclophosphamide Related Adverse Events

Thrombocytopenia on days of dosing	• Grade $\geq$ 3 o Hold treatment until recover $\leq$ grade 2. o If disease-related (BM > 70%), treat with transfusion support o If persistent after 2 cycles, dose reduce

Febrile neutropenia	• Grade 3 o Withhold Cyclophosphamide o Supportive treatment (GCSF, antibiotics) o On recovery resume at same dose
Neutropenia	• Grade ≥3 o On Day 1 hold Belantamab o On recovery to ≤ Grade 2 resume belantamab at same dose • Recurrent episodes, dose reduce

6.3 Dexamethasone

Dexamethasone (Decadron) is a synthetic adrenocortical steroid and is readily absorbed from the gastrointestinal tract. Chemically, dexamethasone is 9-fluoro-11ß, 17, 21-thrihydroxy-16α-methyl-pregna-1, 4-diene-3, 20-dione. Dexamethasone is insoluble in water.

Possible adverse effects are: fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, exacerbation of infection (e.g., tuberculosis), exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or other hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia, Phenutoin, phenobarbital and ephedrine enhance metabolic clearance of corticosteroids. Corticosteroids should be used cautiously in patients with hypothyroidism, cirrhosis, ocular herpes simplex, existing emotional instability or psychotic tendencies, nonspecific ulcerative colitis, diverticulitis, fresh intestinal anastomoses, peptic ulcer, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Immunization procedures should not be undertaken in patients on corticosteroids. Natural and synthetic glucocorticoids are absorbed from the GI tract. Glucocorticoids have salt-retaining properties, although dexamethasone lacks this property. Anti-inflammatory property can modify the body's immune system. On the other hand, glucocorticoids suppress the body's response to viral as well as bacterial infections.

Formulation: Dexamethasone is available commercially in six potencies (0.25 mg, 0.5 mg, 0.75 mg, 1.5 mg, 4 mg, and 6 mg) in capsule or tablet form.

6.3.1 Dose Modification for Dexamethasone Related Adverse Events

Hypertension	• Grade ≥ 2 o Hold dexamethasone and start therapy for HTN o Restart therapy once BP is grade ≤1
Diabetes	• Grade ≥ 3 o Withhold dexamethasone and treat (oral hypoglycemic) o On recovery to grade ≤1 restart at lower dose
Mood changes	• Grade ≥2 and Recurrent, dose reduce

6.4 Guidelines for Therapy-Related Adverse Events Not Otherwise Specified

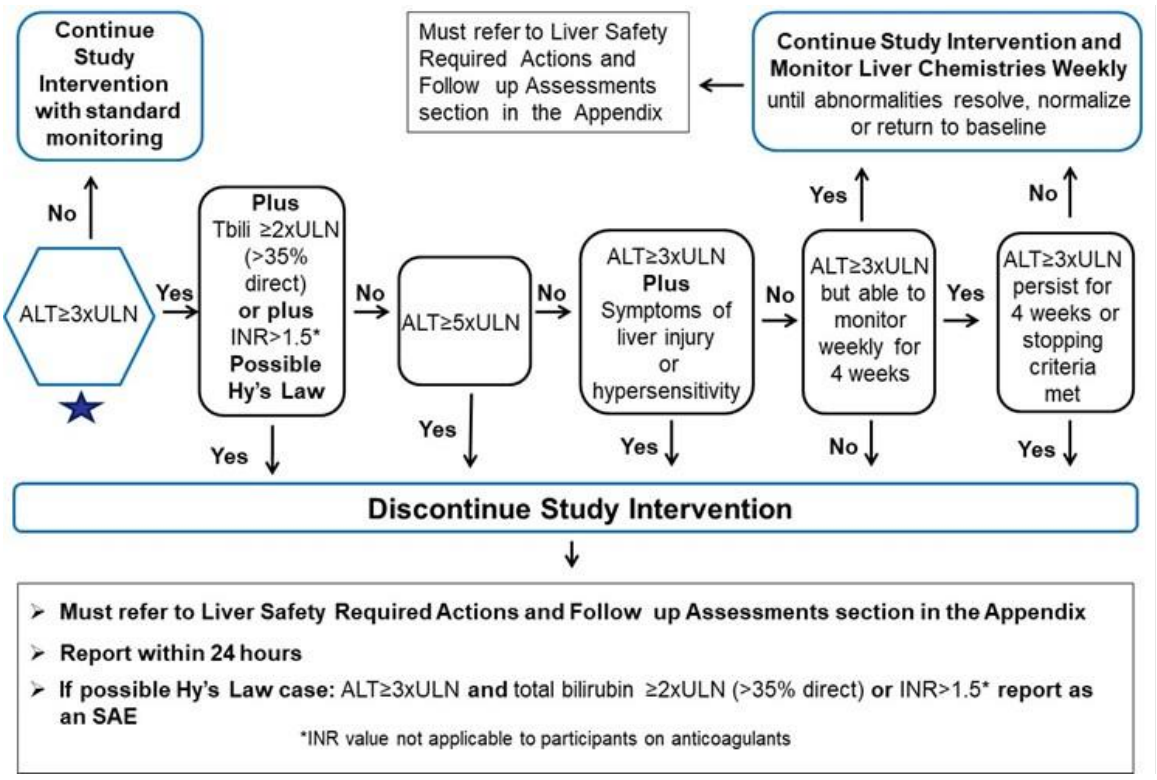
Severity	Management	Follow-up
Grade 1	Administer treatment Close follow-up to evaluate for increased severity, no dose modification necessary	
Grade 2	*Symptoms resolved in ≤7 days: c*ontinue after resolution at the current dose *Symptoms ongoing >7 days or worsening: d*elay therapy or consider dose reductions	

Grade 3	Delay treatment till recovery to G1 or less. Dose reductions as appropriate If resolve to ≤G1 within 48 hours may continue treatment, no dose reductions If resolve > 7 days…continue therapy with dose reductions
Grade 4	Stop therapy and wait until G1 or less…continue therapy with dose reductions If grade 4 persist or recur after dose reduction stopping then discontinue therapy

6.4.1 Liver Chemistry Stopping Criteria

- Designed to assure participant safety and evaluate liver event etiology.
- Liver Safety Required Actions and Follow up Assessments are detailed in Appendix F.
- Discontinuation of study treatment for abnormal liver tests is required when the participant satisfies any of the stopping rules as shown in Figure below.

Stopping and Increased Monitoring Algorithm for Subjects WITH entry criteria ALT ≤2.5xULN



6.5 Therapy Compliance

- Belantamab will be administered intravenously to patients at UMMC. Study treatment is based on body weight calculation and may be reduced for toxicity for individual participants according to protocol guidelines.

- The date and time of each dose administered in the clinic will be recorded. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment and documented in source.
- Cyclophosphamide and dexamethasone will be administered on day 1 only and will be given in infusion.

6.6 Concomitant Therapy

- Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded.

6.7 Discontinuation of Study Treatment

Study treatment may be permanently discontinued for any of the following reasons:

- Disease progression or unacceptable toxicity.
- Participant has met any of the protocol defined safety stopping criteria
- Deviation(s) from the protocol
- Request of the participant or proxy (withdrawal of consent by participant or proxy)
- Investigator's discretion
- Concurrent illness that prevents further administration of study treatment(s)
- Pregnancy
- Patient is lost to follow-up

Safety Stopping Criteria

- Liver toxicity
- Infusion-Related Reactions: Premedication is not required prior to infusion unless deemed medically appropriate by the investigator following evaluation of infusion-related reactions (IRRs). Premedication should be considered in any participant who experienced an IRR at first or any subsequent infusion with belantamab mafodotin. For infusion reactions of any grade/severity, immediately interrupt the belantamab mafodotin infusion and manage symptoms. Once reaction symptoms resolve, resume the infusion at a reduced rate. Premedication may be required with subsequent infusions. A participant that experiences a Grade 4 IRR associated with belantamab mafodotin should be permanently withdrawn from the study.
- For corneal Events follow table above (6.1.4)

7.0 Correlative Studies

Performed by University of Maryland Translational laboratory Shared Services (TLSS) and Flow Cytometry Shared Services (FCSS)

7.1 Tear Film Collection Procedure for Cytokine Assessment

7.1.1 Patients will be instructed to withhold eye drop application at least 4 hours prior to examination. Right eyes will be measured first. Non-stimulated (basal) tear samples will be collected from the inferior-temporal tear film of participants' eyes using a glass microcapillary tube (approximately 5µl/eye). Following collection, samples will be kept on ice and sent to the cytokine lab for centrifugation and storage, until required for cytokine analyses. The time period of storage for all tear samples will be less than 24 months.

7.1.2 Samples will be collected from patients before study entry, on cycle 2- day-1 and at time of development of any corneal events.

7.1.3 We will use BioLegend's LEGENDplex™ platform. This is a bead-based immunoassay that utilizes the same basic principles of sandwich immunoassays, whereby a soluble analyte is captured between two antibodies. The advantage is that a small amount of liquid sample can be analyzed on over 10 cytokine expressions.

7.1.4 We will assess the following Human Essential Immune Response Panel: IL-4, IL-2, CXCL10 (IP-10), IL-1β, TNF-α, CCL2 (MCP-1), IL-17A, IL-6, IL-10, IFN-γ, IL-12p70, TGF-β1 (Free Active), CXCL8 (IL-8).

7.1.5 Methods : tear samples and standard cytokines with known concentration are stained by TLSS on 96 well plate, 50 µL sample is required. 5 µL tear can be diluted to 50 µL, (sensitivity effects will be considered). Standard curve and samples are performed in duplicates. Unfixed samples are used for staining. TLSS fix the samples at the last step before flow cytometry analysis. FCSS will acquire samples on BD Canto II cytometer, generate figures and reports.

7.2 Peripheral Blood Collection for Immune Profile

7.2.1 Blood samples will be collected from patients before study entry, and on cycle 2- day-1. The time period of storage for all blood samples will be less than 24 months.

7.2.2 Blood will be collected and delivered to TLSS in (K2 EDTA tube). TLSS will isolate PBMCs by ficoll gradient. FCSS will prepare antibody cocktail and TLSS stains the cells and fix samples. FCSS will acquire samples on Cytek Aurora cytometer. Data analysis by FCSS, figures and reports generated. Detailed PBMC staining protocol is provided in Appendix I.

7.2.3 PBMC immunophenotyping Panel includes

- Treg: CD25, CD127
- Teff, Tcm, Tnaive, Tem: CD45RA, CCR7.
- Th1, 2, 9, 17, 22: CCR6, CCR4, CCR10, CXCR3, CXCR5.
- NK cells: CD56.
- Activated T cells: HLA-DR, CD27, CD38

8.0 Study Procedures

- A signed, written informed consent form must be obtained before any study procedures
- All screening procedures must be completed within 30 days prior to first dose.
- On-study visits have a ±3-day window
- PFS follow-up visits have a ±7-day window
- Survival follow-up visits have a ±14-day window

8.1 List of Clinical Laboratory Tests

Hematology (each cycle) CBC + automated Differential
Chemistry (each cycle)
BUN/Cr/Electrolytes/ Mag, Phos, eGFR LFTs (AST, ALT, Alk Phos, total Bili); Albumin; total protein; LDH Pregnancy Test (urine or blood- per local practice)
Urine (each cycle) glucose, protein, blood and ketones by dipstick Spot Urine (albumin/creatinine ratio)
At screening C-reactive protein; Troponin I; HBsAg, HbcAb, Hep C antibody.

8.2 Disease Assessment

Standard disease assessments for RRMM will include the following assessments:

- UPEP, Urine Immunofixation, 24 hr. collection for urine M-protein
- SPEP, Serum M-protein, serum immunofixation
- Calcium corrected for albumin
- IgG, IgM, IgA
- Serum Kappa, lambda free LC, FLC ratio
- Bone marrow at screening and to confirm CR.
- Imaging of extramedullary disease if indicated
- Skeletal surveys or PET/CT as clinically indicated at screening and after achieving VGPR or better at 6 months or whichever comes earlier
- Response evaluation with each cycle will be performed according to the IMWG Uniform Response Criteria for Multiple Myeloma

8.3 Ocular Examinations and Procedures

Participants will be assessed by UMM ophthalmologist at screening/baseline in both arms. A full screening/baseline ophthalmic examination for all participants must include for both eyes (OU):

- Best corrected visual acuity.
- Documentation of manifest refraction and the method used to obtain best corrected visual acuity.
- Current glasses prescription (if applicable).
- Anterior segment (slit lamp) examination with focus on the cornea and lens, including fluorescein staining of the cornea
- Intraocular pressure measurement
- Dilated fundoscopic exam.

On treatment and follow-up ophthalmic exam should be performed for both eyes (OU) as described below and in the Schedule of Activities:

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

- Anterior segment (slit lamp) examination with focus on the cornea and lens, including fluorescein staining of the cornea
- Intraocular pressure measurement (if clinically indicated)
- Dilated fundoscopic exam (if clinically indicated)

The end of treatment and last follow-up ophthalmic exam, if required, should match the screening/baseline exam. Additional examinations should be performed at the discretion of the treating eye specialist.

8.4 PFS Follow-up:

Patients who discontinue treatment in absence of disease progression will be followed every 3 months for disease response assessments until new anti-cancer therapy is initiated or progression is documented, or death occurs. Follow up duration is 9 months.

8.5 Overall Survival Follow-up:

Patients who discontinue treatment due to disease progression will be followed for survival and subsequent disease response assessments by chart review every 3 months. Follow up duration is 9 months.

8.6 Reporting Adverse Events

8.6.1 Definitions

Adverse Event: An AE is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The Investigator is responsible for ensuring that any AEs observed by the Investigator or reported by the subject are recorded in the subject's medical record. If a new primary malignancy appears, it will be considered an AE.

An abnormality identified during a medical test [e.g., laboratory parameter, vital sign, electrocardiogram (ECG) data, physical exam] should be defined as an AE only if the abnormality meets 1 of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication or
- the abnormality is clinically significant in the opinion of the Investigator

The Definition of a Serious Adverse Event (SAE):

SAE is defined as any of the following:

- Any death that occurs while the patient is enrolled in the study including the follow-up period or within 28 days of completing the study
- Immediately life-threatening AE
- Requires inpatient hospitalization*
- Prolongation of an existing hospitalization
- Congenital anomaly/birth defect
- Medically important event**
- Disability/incapacity (persistent or significant)
  Associated with liver injury and impaired liver function: ALT ≥3 x ULN and total bilirubin ≥2 x ULN (>35% direct), or ALT ≥3 x ULN and INR >1.5.

**Exception: Preplanned (at time of informed consent) hospitalization for elective procedures, for protocol compliance or social reasons, or for observation will not be considered criteria for an SAE. The reason for the planned hospitalization should be documented. Complications experienced during these hospitalizations must be reported as SAEs if hospitalization is prolonged due to AE, or if the complication meets other serious criteria).*

***Medical and scientific judgment should be exercised in determining whether situations or events should be considered serious adverse events: an important medical event may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the patient or require intervention to prevent one of the above outcomes, as listed above, and these events must be considered serious. Examples of such events are allergic bronchospasm, blood dyscrasias, or convulsions that may require intensive treatment in an emergency room or at home but do not result in hospitalization, or development of drug dependency or drug abuse.*

CTCAE term (AE description) and Grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site.

Attribution of the AE:

- **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.

8.6.2 Adverse Event of Special Interest (AESI) for Belantamab Mafodotin

An Adverse Event of Special Interest (AESI) is defined as any AE (serious or non-serious) that is of scientific and medical concern specific to the study treatment. AESI's for belantamab mafodotin include the following:

- Thrombocytopenia
- Infusion related reactions
- Corneal events

8.6.3 Assessment of Adverse Events

Each AE will be assessed by the Investigator for severity and for a causal relationship with the study treatment as outlined below.

8.6.3.1 **Severity Assessment**

- All AEs will be assessed by the Investigator for severity according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0: 14 June 2010; National Institutes of Health (NIH), National Cancer Institute (NCI). The CTCAE v5.0 is available on the NCI/NIH website.
- Please note that there is a distinction between serious and severe AEs: Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 8.6.1. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe.

8.6.3.2 **Relationship to Study Drug**

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

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

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

8.6.4 **Reporting of Adverse Events**

8.6.4.1 Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting the UMGCCC Data and Safety Monitoring and Quality Assurance Committee (DSM/QAC) and the FDA to any event that seems unusual, even if this event maybe considered an unanticipated.

8.6.4.2 Any adverse experiences which occur at any time during the clinical study or within 30 days of receiving the last dose of study medication, whether or not related to the study drug, will be collected by the study team into the Case Report Forms and submitted to the site Institutional Review Board (IRB) per institutional policy.

8.6.5 **Reporting of Serious Adverse Events**

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 30 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to the protocol therapy, must be reported locally to the site Institutional Review Board (IRB) per local policy. Follow up to a serious adverse event should be reported at least within 7 working days. The event should also be reported locally to the site Institutional Review

Board (IRB) per local policy. The serious adverse event must also be reported to the FDA using FDA Form 3500A (MedWatch Form) within 7 days. If the serious event is unexpected fatal, or life threatening it must be reported to the FDA as soon as possible but no later than 7 calendar days following the initial receipt of the information.

8.6.6 **Reporting to GSK**

- All SAEs, pregnancies, and follow up information must be reported to GSK on an SAE Report Form within 24 hours of becoming aware of the initial event or follow-up information.
- The Sponsor Institution must provide a causality assessment and must sign, and date all SAE Report Forms.
- If supporting documentation is included in the submission to GSK (e.g., hospital reports, consultant reports, death certificates, autopsy reports, etc.), please redact any patient identifiers (including Medical Record number).

GSK SAE and Pregnancy Reporting Information
Email: OAX37649@gsk.com Or eFax number: +44(0) 208754 7822

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

8.6.7 **Collection of Pregnancy Information**

Male participants with partners who become pregnant:

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. 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 GSK within 24 hours of learning of the partner's pregnancy.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female participants who become pregnant:

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

Any female participant who becomes pregnant on study will discontinue treatment.

8.6.8 Reporting Product Complaints for Belantamab Mafodotin

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 GSK within 1 working day of first becoming aware of the possible defect to 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.

9.0 Statistical Analysis

9.1 Study Objectives

The primary objectives of this study are to: (1) characterize the safety and tolerability of chemotherapeutic regimen belantamab mafodotin, cyclophosphamide, and dexamethasone in patients with relapsed/refractory multiple myeloma and (2) Identifying the maximum tolerated dose and recommended Phase 2 dose.

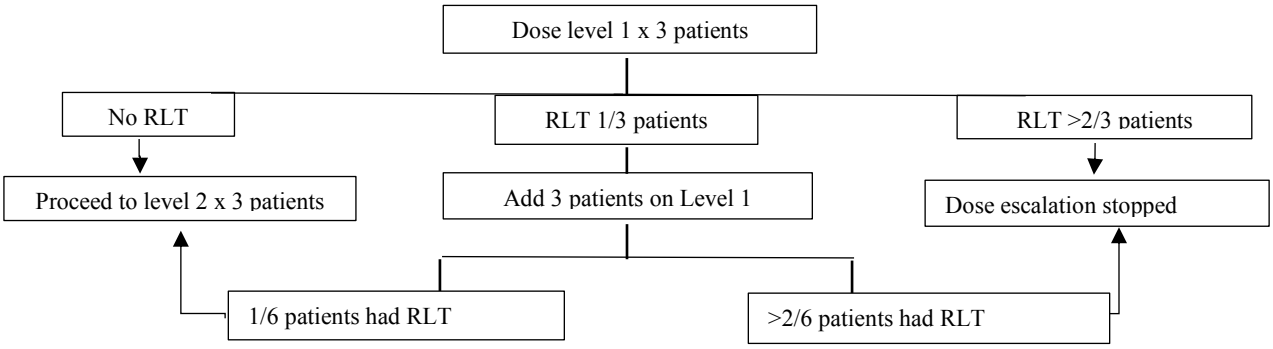
The *primary endpoints* are the occurrence of regimen limiting toxicities (RLTs), treatment-emergent adverse events, treatment-related adverse events, and clinically significant changes as described earlier in the protocol.

The secondary endpoints are the overall response rate of the better tolerated regimen in an expansion cohort, the percentage of patients with confirmed partial (or better) response, duration of response, time to response, time to progression, progression-free survival (PFS), Overall survival (OS) and the percentage of patients with confirmed partial (or better) response.

The exploratory endpoint is to obtain exploratory data on cytokine levels in the tears and T cell subsets in the peripheral blood before and after initiation of therapy (cycle 2 day 1).

9.2 Sample Size

9.2.1 Phase I We will use 3+3 design as shown below



- The total sample size will range from 6 to 24 (3 to 12 per arm), using a standard 3+3 design.
- Arm A: Recruitment will stop if there are 2 or 3 patients with RLT among the first 3 recruited subjects in Dose 1, resulting in a minimum sample size of 3. Otherwise, 3 more patients will be recruited for Dose 2. If there are 2 or 3 RLTs, the trial will stop recruitment. Otherwise, 3 more patients will be recruited. Therefore, the maximum number of patients for Arm A is 12.
- Arm B: The procedures will be similar to Arm A, with sample size ranging from 3 to 12.
- The better tolerated regimen, defined as full dosing for 2 cycles with no dose reductions or grade 3 or higher CTA-defined toxicity will be explored in the expansion cohort.

9.2.2. Phase II (expansion cohort):

- The sample size of the expansion cohort is driven by the study primary endpoint of overall response rate (ORR). We will use a 2-stage Fleming procedure, with a maximum sample size of 40 patients (20 in the each stage). We assume that an ORR less than 40% to be of no interest and 60% of definitive interest. Assuming an 80% power for response detection (type II error = 0.20) and a one-sided type I of 0.05, we will need 20 patients enrolled in each stage. At the completion of stage 1, if there are ≤ 7, the trial will be stopped for futility; if there are ≥ 14 responses, the null hypothesis will be rejected and the regimen will be recommended for further studies. If there are 8 to 13 responses, the trial will continue to stage 2. At the completion of stage 2, ≤ 21 responses will imply no further recommendation for investigation but with ≥ 22 responses, the null hypothesis will be rejected, and the regimen will be recommended for further investigation.

9.2.3 Stopping criteria for Toxicity

- Grade 4 keratopathy > 1% that develop at any time points in the study with no resolution to grade 2 or better in 2 months

- Any Grade 4 nonhematologic toxicity with a cumulative incidence ≥ 5% that last more than 7 days.

- Grade 4 hematologic toxicity (thrombocytopenia, neutropenia and anemia) > 10% that last more than 7 days

- Any study related death > 2% (expected death rate for the study population)

9.3 Statistical analysis:

9.3.1 Phase I:

The analysis will be done on the safety set, which will include all subjects that are enrolled and receive at least 1 cycle of one of either the two regimens. Safety analyses will be conducted on an ongoing basis.

Adverse Events

- The occurrence of all treatment-emergent adverse events will be tabulated by system organ class. Numbers and percentages will be tabulated overall and by dose level and by relationship to study drugs.
- Tables will include reports of adverse events, fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment-emergent adverse events.
- Particular attention will be paid to the main adverse events of the primary adverse events of the drugs included in the regimens, such as corneal epithelium changes and visual acuity.
- Clinical chemistry, hematology, bone marrow, and urinalysis data will be listed and reviewed for each subject. Values outside the normal laboratory reference ranges will be flagged as high or low on the listings. Depending on the size and scope of changes in laboratory data, summaries of laboratory data over time and/or changes from baseline over time may be provided.

9.3.2 Phase II:

- Numbers, percentages, and 95% confidence intervals will be reported for the overall response rates, in the intention to treat set. Safety analyses will be reported, as described earlier. For other covariates, the analyses will include summary statistics, including number and percentage for categorical variables and number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Time-to-event analyses (e.g., time to progression) will be performed using Kaplan-Meier methods with two-sided 95% confidence intervals.

9.3.3 Planned Analyses

- In Phase I, there will be continuous monitoring and reporting of the safety and efficacy data, as they become available.

- In Phase II, the first analysis will be conducted after the conclusion of the first stage, i.e., when the first 21 patients have completed at least 2 cycles on therapy. The second (and final) analysis will be conducted at the completion of the study, when all 40 subjects are enrolled and accessible for efficacy and toxicity.

10.0 STUDY OVERSIGHT AND DATA REPORTING/REGULATORY REQUIREMENTS

10.1 Data Quality Assurance

The University of Maryland Data Safety Monitoring / Quality Assurance Committee (DSM/QAC) is charged with providing peer review and monitoring of local and national research protocols involving cancer patients treated at the University of Maryland Greenebaum Comprehensive Cancer Center (UMGCCC), according to the SOP on file with the IRB and reviewed by NCI. Data specialists coordinate and monitor data generated by Investigator-initiated and pharmaceutical sponsored trials. They are responsible for the timely acquisition and accuracy of all data for the studies to which they are assigned. They work closely with Investigators to collect required data in an accurate and timely manner. In addition, they are responsible for registration and randomization of patients entered on clinical trials. The UMGCCC DSM/QAC will be the Data Safety Monitoring Board of Record for this study. They will review all adverse events recorded for each dose level at all study sites and approve dose escalation to each new level (Safety Monitoring). In addition, cumulative monitoring of all study subjects will occur every 6 months (semi-annual review).

The UMGCCC Clinical Protocol and Data Management/Clinical Trials Office maintains an up-to-date, comprehensive database (OnCore®) of clinical trials conducted by Investigators, accessible to collaborating sites. The UMGCCC Clinical Protocol and Data Management/Clinical Trials Office will be responsible for auditing and collating data from collaborating sites using the OnCore system and examination of primary source documentation.

10.2 SAE and Reporting Definitions

In the event of an SAE (see Section 8.6.1), the first concern will be for the safety of the subject. SAEs will be reported according University of Maryland, Baltimore IRB policies and procedures. If the event meets the criteria for FDA mandatory IND safety reporting (serious + unexpected), UMGCCC will report the event to the FDA using the MedWatch form (FDA Form 3500A). Events which are assessed as "unexpected fatal or life-threatening" should be reported to FDA as soon as possible, but no later than 7 calendar days following the PI's initial receipt of the information. All other unexpected serious suspected adverse reactions suggesting significant risk to human subjects should be reported to FDA no later than 15 calendar days following the PI's initial receipt of the information.

10.3 MedWatch 3500A Reporting Guidelines

A MedWatch 3500A form should be submitted to GSK, the Sponsor, for each SAE. In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event. Description (Section 5 of Part B) of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment and outcome, if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Additional information in follow-up may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e., D.O.B., initials, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report.)

Occasionally, the Sponsor may contact the reporter for additional information, clarification or current status of the subject for whom an adverse event was reported. For questions regarding SAE reporting, you may contact the Sponsor.

10.4 Assessing Causality:

Investigators are required to assess whether there is a reasonable possibility that caused or contributed to an adverse event. The following general guidance may be used.

- Yes: If the temporal relationship of the clinical event to belantamab mafodotin administration makes a causal relationship likely and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.
- No: If the temporal relationship of the clinical event to belantamab mafodotin administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

10.5 Safety Reporting Requirements for IND Holders

The Sponsor will be bound by the following reporting requirements as IND holder, in accordance with 21 CFR 212.32.

10.6 Calendar-Day Telephone or Fax Report:

The Sponsor is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of. belantamab mafodotin. An unexpected adverse event is one that is not already described in the Investigator's Brochure. Such reports are to be telephoned or faxed to the FDA within 7 calendar days of first learning of the event. Each telephone call or fax transmission (fax number for IND Safety Reports: 1 (800) FDA 0178) should be directed to the FDA new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever is responsible for the review of the IND.

10.7 Calendar-Day Written Report:

The Sponsor is also required to notify the FDA and all participating Investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered possibly related to the use of belantamab mafodotin. An unexpected adverse event is one that is not already described in the Investigator's Brochure. New information will be submitted to the IRB as well, according to the policies of the local IRB.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA (fax number for IND Safety Reports: 1 (800) FDA 0178) and all participating Investigators within 15 calendar days of first learning of the event.

IND Annual Reports

In accordance with the regulation 21 CFR § 312.32, the Sponsor shall, within 60 days of the anniversary date that the IND went into effect, submit a brief report of the progress of the investigation according to 21 CFR § 312.32:

10.8 Study Initiation

Before the start of this study and the shipment of investigational agent to the UMGCC, the following documents must be on file:

- U.S. Food and Drug Administration (FDA) Form 1572, signed by the Principal Investigator. The names of any Sub-Investigators must appear on this form. Investigators must also complete all regulatory documentation as required by local regulations
- Current curricula vitae and license of the Principal Investigator
- Final Protocol and ICF
- A signed and dated Investigator's Brochure
- Written documentation of IRB approval of protocol and ICF (identified by title and date of approval)
- Written documentation from the FDA assigning an IND number to the trial and the approval to begin the study
- A signed Confidentiality Agreement
- Approval letter of IND

10.9 Institutional Review Board Approval

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. In addition, any advertising materials must be approved by the IRB. The study will be conducted in accordance with U.S. FDA, applicable national and local health authority and IRB requirements. The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate. An annual progress report will be submitted to the IRB. The Principal Investigator must also keep the IRB informed of any significant adverse events.

Investigators are required to promptly notify the IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to serious adverse events that are not already identified in the Investigator's Brochure and that are considered possibly or probably related to the study drug by the investigator. The Investigator must immediately forward to the IRB any written safety report or update provided by or on behalf of the Sponsor (e.g., IND safety report, Investigator's Brochure, safety amendments, etc.).

10.10 Informed Consent

The informed consent documents must be signed by the patient before his or her participation in the study. The case history for each patient shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent documents must be provided to the patient or the patient's legally authorized representative. If applicable, they will be provided in a certified translation of the local language. Original signed consent forms must be filed in the site study binder or in each patient's study file.

10.11 Study Monitoring Requirements

The Investigator and other appropriate study staff will make available to the Sponsor monitor all documentation relevant to the study. Such documentation includes:

- Case Report Forms—must be legible, accurate, and up to date.
- Serious AE reporting.
- Patient Files—should substantiate the data entered in the CRFs about laboratory data, patient histories, treatment regimens, etc.
- Patient Exclusion Log—should record the reason any patient was screened for the study and found to be ineligible.
- Drug Dispensing Log—should record the total amount of study drug received and returned to the company, and the amount distributed and returned or destroyed. This information must agree with the information entered in the CRFs.
- Informed Consent Forms—completed consent forms from each patient must be available and verified for proper documentation.
- Informed Consent Log—must identify all patients who signed an Informed Consent Form so that the patients can be identified by audit.

10.12 Data Collection

Data recorded on Case Report Forms (CRFs) must be legible and complete. Blue or black ink must be used in completing these forms. CRFs will be completed on a timely basis.

Electronic Data Capture system (REDCap) will be used for CRF entry. The Investigator must review all final CRFs. Upon data base lock, the final eCRF will be printed and signed by the Principal Investigator. The frequency of monitoring may vary depending on enrollment rate and the quality of data collected. The Investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review.

The collected samples will be destroyed if the patients withdraw the consent.

10.13 Study Medication Accountability

All study drug required for completion of this study will be provided by the Sponsor. The recipient, UMGCCC, will acknowledge receipt of the drug by returning the drug receipt form indicating shipment content and condition. Damaged supplies will be replaced.

Study drug accountability records should be maintained by the site in accordance with the regulations. The original drug supply request of belantamab mafodotin will be submitted to the Sponsor or Sponsor's representative along with the form "Approval for Drug Re-Supply", indicating which personnel will be able to submit drug re-supply requests.

All subsequent drug re-supply requests will be directly submitted to the Sponsor or Sponsor's representative from the site. At the time of study closure, the unused, used and expired study drug will be destroyed at the site per Institutional SOPs or returned to the Sponsor or Sponsor's representative.

10.14 Disclosure of Data

Patient medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited. Upon the patient's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his

or her welfare. This medical information must be made available to the Sponsor and authorized representatives of the Sponsor, upon request, for source verification of study documentation.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, local health authorities, the Sponsor and their authorized representative(s), collaborators and licensees and the IRB.

10.15 Retention of Records

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

10.16 Study Completion

The following data and materials are required before a study can be considered complete or terminated:

- Copies of protocol amendments and IRB approval/notification, if appropriate
- Copies of the IRB final report, documentation of submission to the IRB and to the FDA.
- A summary of the study prepared by the Principal Investigator (Study report, manuscript and/or abstract)
- All regulatory documents (e.g. updated curriculum vitae for each Principal Investigator, updated U.S. FDA Form 1572)

This protocol is monitored at several levels, as described in this section. This protocol will be reviewed and approved by the UMGCCC Research Committee (CRC) and UM IRB. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the UMGCCC OnCore Clinical Trials Management System. The protocol will be monitored by the UMGCCC Data Safety Monitoring Committee (DSMB).

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator. In addition, for the Phase 1 portion, the Protocol Principal Investigator will review at least monthly, or more frequently, the accrual, progress, and adverse events and unanticipated problems.

During the Part B Phase 2 portion of the study, the Protocol Principal Investigator will have, at a minimum, quarterly review accrual, progress. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the study Sponsor.

All Study Investigators who register/enroll patients on a given protocol are responsible for timely submission of data via REDCap and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted to UMGCCC via the REDCap system.

This study will be reviewed regularly and monitored closely by the UMGCCC DSMB and per UMGCCC guidelines.

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Appendix A

Ocular Grading Scale

Grade 1:

Mild superficial keratopathy (change from baseline)

Grade 2:

Moderate superficial keratopathy
Peripheral microcysts not involving the central visual axis
Mild central microcysts with peripheral clearing

Grade 3:

Severe superficial keratopathy
Diffuse microcysts involving the central visual axis
Early limbal stem cell deficiency or epithelial irregularity suggestive of limbal stem cell deficiency

Grade 4:

Moderate or greater limbal stem cell deficiency
Corneal epithelial defect or ulceration

Appendix B: ECOG performance status

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

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Appendix C: IMWG Response Criteria

Sustained MRD-negative	MRD negativity in the marrow by next-generation sequencing (NGS) or next-generation flow (NGF), or both, and MRD negativity by imaging for 1 year apart
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS, *and* Disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT
Stringent complete response (sCR)	CR as defined below, *and* *Normal FLC ratio, and* Absence of clonal plasma cells by immunohistochemistry
Complete response (CR)	Negative IFE of serum and urine, *and* Disappearance of any soft tissue plasmacytomas, *and* <5% plasma cells in bone marrow aspirates *In patients in whom the only measurable disease is by sFLC levels,* *CR is defined as a normal FLC ratio (0.26-1.65) in addition to the CR criteria listed above*
Very good partial response (VGPR)	Serum and urine M-protein detectable by IFE but not on electrophoresis, *or* ≥90% reduction in serum M-protein plus urine M-protein <100 mg per 24 hours *In patients in whom the only measurable disease is by sFLC levels,* *VGPR is defined as a >90% decrease in the difference between involved and uninvolved sFLC levels*
Partial response (PR)	≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg *In patients in whom the only measurable disease is by sFLC levels,* *PR is defined as a ≥50% decrease in the difference between involved and uninvolved sFLC levels* If serum and urine M-protein are unmeasurable, and sFLCs are also unmeasurable, ≥50% reduction in bone marrow plasma cells is required in place of M-protein,
Minimal Response	≥25% but ≤49% reduction of serum M-protein, *and* Reduction in 24-h urine M-protein by 50-89%, *and* If present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR or progressive disease
Progressive disease (PD)	Any one or more of the following: Increase of 25% from lowest confirmed response value in any one or more of the following: Serum M-protein (absolute increase must be ≥5 g/L) and/or Urine M-protein (absolute increase must be ≥200 mg/24 hours) and/or *In patients in whom the only measurable disease is by sFLC levels,* *the difference between involved and uninvolved sFLC levels (absolute increase must be >100 mg/L)* If serum and urine M-protein are unmeasurable, and sFLCs are also unmeasurable, bone marrow plasma cell percentage (absolute % must be ≥10%)

Appendix D

Study Monitoring

The Investigator and other appropriate study staff will make available to the Sponsor monitor all documentation relevant to the study. Such documentation includes:

- Case Report Forms—must be legible, accurate, and up-to-date.
- Serious AE reporting.
- Patient Files—should substantiate the data entered in the CRFs with regard to laboratory data, patient histories, treatment regimens, etc.
- Patient Exclusion Log—should record the reason any patient was screened for the study and found to be ineligible.
- Drug Dispensing Log—should record the total amount of study drug received and returned to the company, and the amount distributed and returned or destroyed. This information must agree with the information entered in the CRFs.
- Informed Consent Forms—completed consent forms from each patient must be available and verified for proper documentation.
- Informed Consent Log—must identify all patients who signed an Informed Consent Form so that the patients can be identified by audit.

SAE reporting

- When an AE/SAE occurs, we will review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The Investigator will report all SAE to the IRB, FDA within 7 days of learning of occurrence and within 24 hours of learning of occurrence to GSK.

Appendix E

Permitted Medication

- Patients will continue supportive care during the study, including transfusions of blood products, growth factors, and treatment with antibiotics, anti-emetics, antidiarrheal, and analgesics, as appropriate.
- Concomitant therapy with bisphosphonates and/or Xgeva are allowed.
- Patients may receive local irradiation for pain or stability control.

Prohibited Medications

- Chronic treatment with oral steroids is prohibited; steroids may be used to treat infusion-related reactions. Inhaled steroids are allowed for management of asthma or COPD exacerbations. Chronic low dose replacement therapy (less than or equal to 10 mg prednisolone) is allowed in participants with adrenal insufficiency.

- Administration of live or live-attenuated vaccines are contraindicated 30 days prior to the first dose of study treatment and while on study. Use of live or live-attenuated vaccines is further contraindicated for at least 70 days following the last dose of belantamab mafodotin.

- For participants receiving belantamab mafodotin:

    - Elimination pathways for belantamab mafodotin and cys-mcMMAF have not been characterized in humans. Cys-mcMMAF was not an inhibitor, an inducer, or a good substrate of cytochrome P450 enzymes in vitro. Cys-mcMMAF was shown to be a substrate of P-glycoprotein (P-gp), OATP1B1, and OATP1B3 transporters in vitro.

    - Caution should be exercised when belantamab mafodotin is combined with strong inhibitors of P-gp, and strong inhibitors of OATP1B1 and OATP1B3 should be avoided unless considered medically necessary.

- Elimination pathways for have not been characterized in humans; there is no specific contraindications for P450 inhibitors or inducers

- Plasmapheresis is prohibited from 7 days prior to first dose through the end of study.

- Any other anti-myeloma therapy not specified in this protocol, and any investigational agents are not allowed

- Contact lenses are prohibited while the participant is on study.

Appendix F: Liver Safety

Phase I/II liver chemistry stopping, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT - absolute</td><td>ALT ≥ 5xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥ 3xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥ 3xULN and total bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥ 3xULN and INR>1.5</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions, Monitoring and Follow up Assessments</th></tr>
<tr><td>Actions</td><td>Follow Up Assessments</td></tr>
<tr><td>
• Immediately discontinue study intervention
  • Report the event to GSK within 24 hours
• Complete the liver event form and complete SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments as described in the Follow Up Assessment column
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING)
<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 24-72 hours
• Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline
•
</td><td>
• Viral hepatitis serology[4]
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH), gamma glutamyl transferase [GGT], 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 on the liver event alcohol intake form
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 computerised tomography) to evaluate liver disease; complete Liver Imaging form
• Liver biopsy may be considered and discussed with local specialist if available, for instance:
  ○ In patients when serology raises the possibility of autoimmune hepatitis (AIH)
  ○ In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention
  ○ In patients with acute or chronic atypical presentation:
• If liver biopsy conducted complete liver biopsy form.
</td></tr>
</table>

1. *Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥ 3xULN **and** total bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.*
2. *All events of ALT ≥ 3xULN **and** total bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; the INR threshold value stated will not apply to participants receiving anticoagulants*
3. *New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)*
4. *Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody. In those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody. 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 I/II liver chemistry increased monitoring criteria with continued study intervention

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

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

Appendix G: Ocular Monitoring

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 4 to 8 times daily, beginning on Cycle 1 Day 1 until the subject discontinues treatment. In the event of ocular symptoms (e.g., dry eyes), the use of artificial tears may be increased up to every 2 hours as needed.

Corticosteroid eye drops are not required but can be used if clinically indicated per discretion of an eye-care specialist. Allow at least 5-10 minutes between administration of artificial tears and steroid eye drops (if administered).

While not yet clinically demonstrated, it is theoretically possible that the application of a cooling eye mask during belantamab mafodotin administration, and in the first few hours after infusion may subsequently decrease ocular side effects. On the day of infusion at the discretion of the patient and the physician, the following may be considered:

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

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 7 days.

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

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 1 line on Snellen Visual Acuity	Decline from baseline of 2 or 3 lines (and Snellen Visual Acuity not worse than 20/200)	Decline from baseline by more than 3 lines (and Snellen Visual Acuity not worse than 20/200)	Snellen Visual Acuity worse than 20/200

[a] Mild superficial keratopathy (documented worsening from baseline), with or without symptoms.

[b] Moderate superficial keratopathy with or without patchy microcyst-like deposits, sub-epithelial haze (peripheral), or a new peripheral stromal opacity.

[c] Severe superficial keratopathy with or without diffuse microcyst-like deposits, sub-epithelial haze (central), or a new central stromal opacity.

[d] Corneal epithelial defect such as corneal ulcers (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 PI's assessment of benefit vs. risk based on corneal exam findings following a discussion with the qualified eye care specialist.

BCVA- best corrected visual acuity

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.

Appendix H: Contraceptive Guidance

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**
- 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 I: Human PBMC Staining Protocol

Materials:

- Wash Buffer: PBS + 5% FBS, Brandon prepare
- Zombie NIR: keep frozen until use.
- FcBlock: BD small white vial.
- Ab Cocktail: keep on ice, in dark until use.
- Fix Buffer: Biolegend brown bottle. 15ml aliquot. Room temp when receiving blood.
- BD Brilliant Stain Buffer: to make antibody cocktail.

Method: all steps in BSC

2 million unstained cells will go through the same incubation time and centrifuge, fixation.

1. 3 million PBMC in ~200 µl DPBS. No protein allowed.
2. Add 1 µL Zombie NIR live/dead staining, mix **immediately**. 15 min in dark, room temperature.
3. Add about 500 µL Wash Buffer, gentle mix.
4. 300 x g, 5 min, add 1 µL FcBlock, mix, incubate for 10 min on ice.
5. Add 50 µL Ab Cocktail, gentle mix, 15-30 min on ice, cover in dark.
6. Add ~ 500 µL Wash Buffer, gentle mix
7. 300xg, 5 min. Resuspend in 200 µl Fixation Buffer or > 2 x pellet vol, mix. 40-60 min in dark at room temp.
8. Add ~ 500 µL Wash Buffer, gentle mix, centrifuge. Resuspend in 200 µL Wash Buffer, ready for flow analysis.