TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Phase I/II Single Arm Open-Label Study to Explore Safety and Clinical Activity of GSK2857916 Administered in Combination with Pembrolizumab in Subjects with Relapsed/Refractory Multiple Myeloma (DREAMM 4)

Protocol Number:	205207/Amendment 04
Compound Number:	GSK2857916
Development Phase:	I/II
Sponsor Name and Legal Registered Address:	GlaxoSmithKline Research & Development Limited 980 Great West Road Brentford Middlesex, TW8 9GS UK

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Medical Monitor Name and Contact Information: Can be found in Study Reference Manual

Regulatory Agency Identifying Number(s):

Registry	**ID**
IND number	119333
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Effective Date: 21-FEB-2022

SPONSOR SIGNATORY

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21-FEB-2022

Timothy Crossman, BMBS MRes — Date

Group Sr. Director, Clinical Development Lead

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment No. 4	21-FEB-2022	TMF-14344600
Amendment No. 3	27-AUG-2021	TMF-12902367
Amendment No. 2	26-FEB-2020	2016N273410_02
Amendment No. 1	26-SEP-2018	2016N273410_01
Original Protocol	11-MAY-2017	2016N273410_00

Amendment [04] [21-FEB-2022]

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The protocol has been amended to provide updates including the addition of the end of study definition section (Section 5.5.2) and continued access to study intervention after the end of the study section (Post Analysis Continued Treatment [PACT]) (Section 6.13).

Section # and Name	Description of Change	Brief Rationale
Section 1: PROTOCOL Synopsis for Study 205207	Additional content to the overall study has been added which includes PACT implementation and End of Study definition	To allow continued treatment of study participants post final analysis
Section 2.2.5.1: Pharmacokinetics and Pharmacodynamics	Revision of pharmacokinetics and pharmacodynamics section as per latest information available in IB	Section updated as per latest information available in IB
Section 4.6.1: Risk Assessment and Mitigation Strategy	Additional content added to keratopathy, nephrotoxicity, and ovarian toxicity	Updated the data/rationale for risk assessment
Section 5.5.2: End of Study Definition	End of Study section added to align with PACT implementation and additional content added related to PACT	To allow continued treatment of study participants post final analysis
Section 6.13: Continued Access to Study Intervention after the End of the Study	New section added to align to PACT implementation and additional content added related to PACT	To allow continued treatment of study participants post final analysis

Section # and Name	Description of Change	Brief Rationale
Section 7.3.1.1: Time Period and Frequency for Collecting AE and SAE Information	Additional content added to align to PACT implementation	To allow continued treatment of study participants post final analysis

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1. PROTOCOL SYNOPSIS FOR STUDY 205207

Rationale

This is a phase I/II, single arm, open label, two-part study that will assess safety, tolerability and clinical activity of belantamab mafodotin (previously referred to as GSK2857916) given in combination with a programmed cell death-1 (PD-1) inhibitor pembrolizumab in patients with relapsed/refractory multiple myeloma (RRMM).

Belantamab mafodotin is a humanized (IgG_1) antibody drug conjugate (ADC), which binds specifically to B cell maturation antigen (BCMA). The antibody is conjugated to the microtubule inhibitor monomethyl auristatin-F (MMAF) to result in an ADC molecule. Belantamab mafodotin has been produced in an afucosylated form to generate an enhanced antibody dependent cellular cytotoxicity (ADCC). This dual mechanism of action is expected to improve clinical activity by targeting dividing (ADC) and non-dividing tumor cells (ADCC).

B-cell maturation antigen expression is restricted to B cells at later stages of differentiation [Darce, 2007] and according to GSK internal data all patients with MM express various levels of BCMA on the surface of the tumor cells. In addition, GSK2857916 belantamab mafodotin was shown to induce immunogenic cell death (ICD) characterized by expression of ecto-Calreticulin, release of adenosine tri phosphate (ATP), and secretion of HMGB1 in BCMA expressing multiple myeloma cell line (GSK unpublished data). Treatment of mice harbouring syngeneic tumors derived from the EL4 lymphoma cell line expressing human BCMA (EL4-hBCMA) with belantamab mafodotin delays tumor growth and promotes durable regressions. Mice which responded remained immune to re-challenge suggesting an engagement of the host immune system and immunologic memory, providing a strong rationale for clinical combinations with immuno-modulatory agents (GSK unpublished data). Exposure of dendritic cells to tumor cells undergoing ICD evokes an inflammatory phenotype (innate response), where mature dendritic cells (DCs) are activated and may induce an antigen-specific T cell response. It is hypothesized that the T cell dependent anti-tumor response induced by belantamab mafodotin can be further augmented by PD-1 inhibitor, pembrolizumab when both drugs are used in combination.

Objective(s)/Endpoint(s)

Part 1: Dose Escalation

Objectives	Endpoints
Primary	
• To determine safety, tolerability and to establish the recommended Phase 2 dose (RP2D) of the combination of belantamab mafodotin and pembrolizumab in subjects with RRMM	• Percent of subjects with adverse events (AEs), changes in clinical signs and laboratory parameters • Number of subjects with dose limiting toxicities (DLTs)

Objectives	Endpoints
Secondary	
• To evaluate clinical activity of the combination of belantamab mafodotin and pembrolizumab in subjects with RRMM	• Overall Response Rate (ORR), defined as the percentage of subjects with a confirmed partial response (PR) or better (i.e., PR, very good partial response [VGPR], complete response [CR] and stringent complete response [sCR]), according to the International Myeloma Working Group (IMWG) Response Criteria [Kumar, 2016]
• To evaluate the pharmacokinetic profile of belantamab mafodotin when administered intravenously in combination with pembrolizumab[1]	• Pharmacokinetic (PK) parameters following IV administration as data permit.
• To assess anti-drug antibodies (ADAs) against belantamab mafodotin[1]	• Incidence and titers of ADAs against belantamab mafodotin
Exploratory	
• To assess Minimal Residual Disease (MRD) in subjects who achieve ≥VGPR or better	• Minimal Residual Disease (MRD) negativity rate, defined as: the percentage of subjects who are MRD negative in subjects who achieve VGPR or CR
• To characterize the relationship between clinical response and other biologic characteristics	• BCMA expression levels on malignant cells, serum sBCMA levels, serum cytokines, and immune cell characterization and their relationship to clinical response (Protein, RNA, DNA analysis)
• To investigate the relationship between genetic variants in the host and response to belantamab mafodotin in combination with pembrolizumab	• Possible relationship between host genetic variation and response to belantamab mafodotin in combination with pembrolizumab
• To evaluate the tolerability of belantamab mafodotin in combination with pembrolizumab based on patient self-report of symptomatic adverse effects	• Symptomatic adverse effects as measured by the Patient-reported outcome version of the Common Term Criteria for Adverse Events (PRO-CTCAE) • Impact of ocular adverse effects on quality of life as measured by the Visual Function questionnaire(s): National Eye Institute 25-item Visual Function Questionnaire (NEI-VFQ-25) and Ocular Surface Disease Index (OSDI)
• To evaluate disease and treatment related symptoms and associated impacts on function and health-related quality of life	• Exit Interview

1. PK and ADA samples for pembrolizumab will be collected and stored during the trial. The analysis will be triggered only in case of unexpected clinical findings.

Part 2: Expansion

Objectives	Endpoints
Primary	
• To assess the clinical activity of the combination treatment with belantamab mafodotin and pembrolizumab in subjects with RRMM	• Overall Response Rate (ORR), defined as the percentage of subjects with a confirmed PR or better (i.e., PR, VGPR, CR and sCR), according to the IMWG Response Criteria [Kumar, 2016].
Secondary	
• To further evaluate safety of belantamab mafodotin administered in combination with pembrolizumab in subjects with RRMM	• Number (percent) of subjects with AEs, changes in clinical signs and laboratory parameters • Ocular findings on ophthalmic exam
• To further characterize the clinical activity of the combination treatment with belantamab mafodotin and pembrolizumab in subjects with RRMM	• Clinical benefit rate (CBR), defined as the percentage of subjects with a confirmed minimal response (MR) or better per IMWG • Duration of response (DoR), defined as: the time from first documented evidence of PR or better to the time when disease progression (PD) is documented per IMWG, or death due to PD among subjects who achieve an overall response, i.e. confirmed PR or better. • Time to response (TTR), defined as: the time between the date of first dose and the first documented evidence of response (PR or better) among subjects who achieved a confirmed response of PR or better. • Time to best response, defined as the time between the date of first dose and the first best documented response (PR or better) among subjects who achieve a confirmed response of PR or better. • Progression-free survival (PFS), defined as: the time from first dose to the earliest date of PD per IMWG, or death due to any cause. • Time to disease progression (TTP), defined as: the time from first dose until the earliest date of PD per IMWG, or death due to PD. • Overall Survival (OS), defined as the time from first dose to death due to any cause
• To evaluate the pharmacokinetic profile of belantamab mafodotin when administered intravenously in combination with pembrolizumab[1]	• Pharmacokinetic (PK) parameters following IV administration as data permit.
• To assess anti-drug antibodies (ADAs) against belantamab mafodotin[1]	• Incidence and titers of ADA to belantamab mafodotin

Objectives	Endpoints
Exploratory	
• To assess Minimal Residual Disease (MRD) in subjects who achieve ≥VGPR or better	• Minimal Residual Disease (MRD) negativity rate, defined as: the percentage of subjects who are MRD negative in subjects who achieve VGPR or CR
• To characterize the relationship between clinical response and other biologic characteristics	• BCMA expression levels on malignant cells, serum sBCMA levels, serum cytokines, and immune cell characterization and their relationship to clinical response (Protein, RNA, DNA analysis)
• To investigate the relationship between genetic variants in the host and response to belantamab mafodotin in combination with pembrolizumab	• Possible relationship between host genetic variation and response to belantamab mafodotin in combination with pembrolizumab
• To explore the effect of the combination therapy of belantamab mafodotin with pembrolizumab on symptoms and health-related quality of life in subjects with RRMM	• Changes from baseline in symptoms and health-related quality of life as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module (EORTC-QLQ-C30) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma Module (EORTC-QLQ-MY20)
• To evaluate the tolerability of belantamab mafodotin in combination with pembrolizumab based on patient self-report of symptomatic adverse effects	• Symptomatic adverse effects as measured by the PRO-CTCAE • Impact of ocular adverse effects on quality of life as measured by the Visual Function questionnaire(s): NEI-VFQ-25 and OSDI
• To evaluate disease and treatment related symptoms and associated impacts on function and health-related quality of life	• Exit Interview

1. PK and ADA samples for pembrolizumab will be collected and stored during the trial. The analysis will be triggered if unexpected clinical findings have been identified.

Overall Study Design

This is a phase I/II, single arm, open label, two-part study to determine the recommended Phase 2 dose (RP2D) of belantamab mafodotin in combination with pembrolizumab, and to evaluate safety and clinical activity of the combination in subjects with RRMM.

Type and Number of Subjects

The study will enroll adult subjects with RRMM, who have undergone stem cell transplant or who are considered transplant ineligible. Subjects must have been previously treated with at least 3 prior lines that include the following: an

immunomodulatory imide drug -IMiD (eg. lenalidomide or pomalidomide), proteasome inhibitor -PI (eg. bortezomib, ixazomib or carfilzomib) and an anti-CD38 antibody alone or in combination. Line of therapy are defined by consensus panel of the International Myeloma Workshop [Rajkumar, 2011].

Overall, it is estimated that up to 40 evaluable subjects will be enrolled in this two-part study (up to 12 in Part 1, and 28 in Part 2).

End of Treatment and End of Study Definitions:

A final data cut-off will occur when all participants have either died, progressed, withdrawn consent, or have been followed for a minimum of 24 months from the time the last participant receives their first dose of study treatment (LSFD).

Following 24 months post LSFD, a Post Analysis Continued Treatment (PACT) will be implemented. At this time, the collection of data for all recruited participants who no longer receive study treatment will stop entirely and clinical trial database will be closed. Those participants still benefiting from belantamab mafodotin in the opinion of their treating physician may continue to receive study drug and only SAEs, overdose and pregnancy cases, and pre-specified ocular data will be reported directly to GSK.

Key Inclusion Criteria

Subjects eligible for enrolment in the study must meet all of the following criteria:

- Provide signed written informed consent, which includes compliance with the requirements and restrictions listed in the consent form
- Male or female, 18 years or older (at the time consent is obtained)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- Histologically or cytologically confirmed diagnosis of MM as defined according to IMWG, 2014 [Rajkumar, 2014], and
  - Has undergone stem cell transplant or is considered transplant ineligible, and
  - Has been treated with at least 3 prior lines of anti-myeloma treatments, including: an IMiD (eg. lenalidomide or pomalidomide), proteasome inhibitor (eg., bortezomib, ixazomib or carfilzomib) and an anti-CD38 antibody, alone or in combination. Line of therapy are defined by consensus panel of the International Myeloma Workshop [Rajkumar, 2011].
  - Has measurable disease defined as 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 (≥100 mg/L) and an abnormal serum free light chain ratio (<0.26 or >1.65)
- Subjects with a history of autologous stem cell transplant (SCT) are eligible for study participation provided the following eligibility criteria are met:
  a) Transplant was > 100 days prior to study enrolment.
  b) No active infection (s).
  c) Subject meets the other eligibility criteria outlined in this protocol.
- Subject has adequate organ system functions defined in the Table below:

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)[1]	≥ 1.0 X 10^9/L
Hemoglobin	≥ 8.0 g/dL
Platelets	≥ 75 X 10^9/L
Hepatic	
Total bilirubin	≤1.5X ULN (Isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
AST and ALT	≤2.5 X ULN
Renal	
eGFR[2] Spot urine (albumin creatinine ratio)	≥40 mL/min ≤500 mg/g (56 mg/mmol)
Cardiac	
LVEF (Echo)	≥50%
QTcF interval[3]	< 470 msecs

1. Without any Growth factor support (e.g.colony stimulating factors (including granulocyte colony stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GMCSF], recombinant erythropoietin) or any thrombopoietin receptor agonists) within 2 weeks before the first dose of study drug.
2. As calculated by Modified Diet in Renal Disease (MDRD) formula
3. The QT interval should be corrected for heart rate by Fridericia's formula (QTcF)

- All prior treatment-related toxicities (defined by National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.03, 2010) [NCI, 2010] must be ≤ Grade 1 at the time of enrollment except for alopecia, and Grade 2 neuropathy.
- A female subject is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP)

    OR
  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 8 during the intervention period and for 4 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. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

    A WOCBP must have a negative highly sensitive serum pregnancy test (as required by local regulations) within 72 hours of dosing on C1D1 and agree to use effective contraception during the study and for 4 months after the last dose of study medication.

Additional requirements for pregnancy testing during and after study intervention are located in Appendix 8.
The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

- Male Subjects:
  - Male subjects are eligible to participate if they agree to the following from the time of first dose of study until 6 months after the last dose of study treatment to allow for clearance of any altered sperm :
    - 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 as detailed below
    - Agree to use a male condom, even if they have undergone a successful vasectomy, and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Appendix 8 when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.
    - Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Key Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

- Systemic anti-myeloma therapy or an investigational drug ≤14 days or five half-lives, whichever is shorter, preceding the first dose of study drug
- Plasmapheresis within 7 days prior to the first dose of study drug
- Prior treatment with a monoclonal antibody within 30 days of receiving the first dose of study drugs
- Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137) and was discontinued from that treatment due to a Grade 3 or higher immune related adverse event (irAE)
- Current corneal epithelial disease except mild punctate keratopathy
- Any major surgery within the last four weeks prior to the first dose of study therapy
- Presence of active renal condition (infection, requirement for dialysis or any other condition that could affect subject's safety). Subjects with isolated proteinuria resulting from MM are eligible, provided they fulfil criteria for adequate renal function defined in the inclusion criteria

- Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions (including lab abnormalities)
- Has received prior radiotherapy within 2 weeks of start of study therapy. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-central nervous system (CNS) disease.
- History of (non-infectious) pneumonitis that required steroids or current pneumonitis
- Current active 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 chronic liver disease (Gilbert's syndrome or asymptomatic gallstones) or hepatobiliary involvement of malignancy is acceptable if subject otherwise meets entry criteria
- Malignancies other than disease under study are excluded, except for any other malignancy from which the subject has been disease-free for more than 2 years and, in the opinion of the principal investigators and GSK Medical Monitor, will not affect the evaluation of the effects of this clinical trial treatment on the currently targeted malignancy (RRMM). Subjects with curatively treated non-melanoma skin cancer are allowed
- Has known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study therapy
- Evidence of any cardiovascular risk defined in the protocol
    - QTcF interval ≥470 msecs
    - Evidence of current clinically significant uncontrolled arrhythmias;
        - including clinically significant electrocardiogram (ECG) abnormalities including 2nd degree (Type II) or 3rd degree atrioventricular (AV) block.
    - History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within six months of Screening.
    - Class III or IV heart failure as defined by the New York Heart Association functional classification system
    - Uncontrolled hypertension
    - Presence of cardiac pacemaker (or defibrillator) with a predominantly ventricular paced rhythm, limiting ECG/QTcF analysis.
    - Abnormal cardiac valve morphology (≥Grade 2) documented by echocardiogram (subjects with grade 1 abnormalities CCI [redacted] can be entered on study). Subjects with moderate valvular thickening should not be entered on study.
- Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to belantamab mafodotin or pembrolizumab, or any of the components of the study treatment.

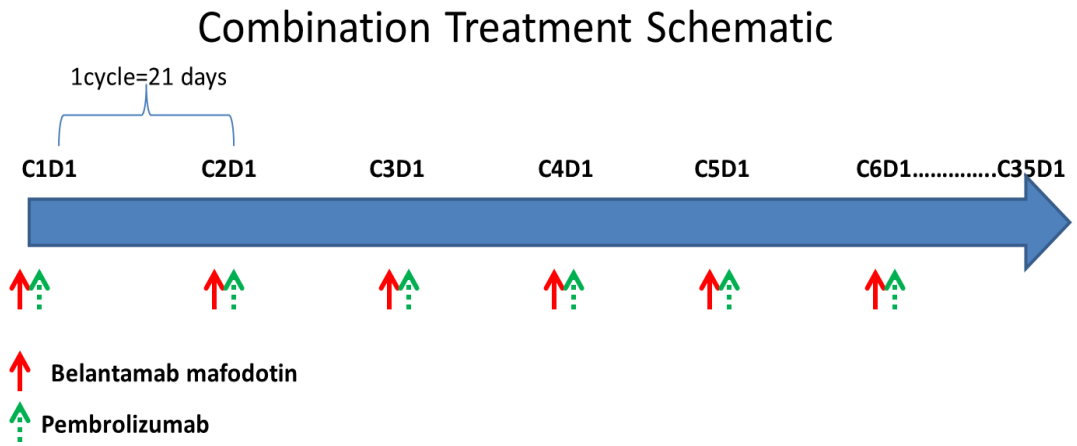
- Pregnant or lactating female
- Known active infection requiring antibiotic, antiviral, or antifungal treatment
- Known HIV infection
- Presence of hepatitis B surface antigen (HBsAg), or hepatitis B core antibody (HBcAb at screening or within 3 months prior to first dose of study treatment)
- Positive 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: Subjects with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained
  NOTE: Hepatitis RNA testing is optional and subjects with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing
- Has received a live-virus vaccination within 30 days of planned start of study therapy
- Active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment
- Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study therapy
- Has a known psychiatric or substance abuse disorder that would interfere with the subject's ability to cooperate with the requirements of the study.
- Has had an allogenic tissue/solid organ transplant

Study Treatment and Duration

Product name:	Belantamab mafodotin	Pembrolizumab
[Formulation description:]	20 mg/mL, 1.5 mL/vial	100 mg/4 mL
Route of Administration	Delivered as IV infusion. Refer to Study Reference Manual (SRM) for details.	Delivered as 30 min IV infusion

Treatment Duration

Belantamab mafodotin and pembrolizumab will be administered via intravenous (IV) infusion on day 1 of each 21-day cycle (once every 3 week dosing schedule). Subjects enrolled in Part 1 and 2 will be treated until disease progression, intolerable toxicity, informed consent withdrawal, or for a maximum of 35 cycles (approximately 2 years, See Combination Treatment Schematic below).



Dosing:

-Belantamab mafodotin and pembrolizumab on D1 of each cycle
-Belantamab mafodotin first, Pembrolizumab as second iv infusion (1hr apart)
-If IRR related to GSK2857916, the PD1 dosing will be delayed
-Max treatment duration: 35 cycles combination treatment

Subjects who discontinued treatment for reasons other than PD will be followed up every 3 weeks until confirmed PD, initiation of a new anticancer therapy or death. All subjects with confirmed PD will be followed for OS every 3 months until the end of study. End of study is defined as when all subjects have been followed for 36 months from first dose of study treatment, or died, or withdrew consent, or are lost to follow-up, or the study is early terminated, whichever occurs first. The next subsequent therapy will be collected for all subjects who have confirmed PD before initiation of new anticancer therapy.

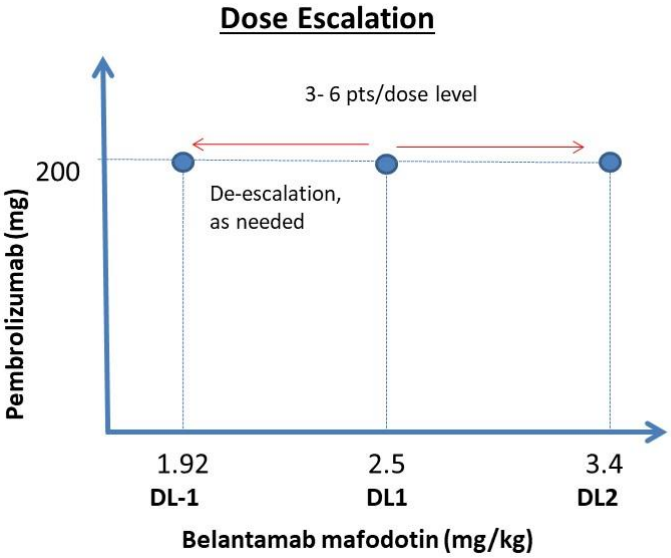
Treatment Arms

The study will comprise of two parts: Part 1- dose escalation and Part 2- expansion.

Part 1: Dose Escalation

Part 1 dose escalation will characterize the safety and tolerability of escalating doses of belantamab mafodotin in combination with 200 mg pembrolizumab to establish the RP2D. The following dose levels of belantamab mafodotin in combination with 200 mg pembrolizumab are planned to be studied: 2.5 mg/kg (dose level [DL] 1) and 3.4 mg/kg (DL2) (as outlined in Dose Escalation Schematic for Part 1 below). Additionally, other dose levels may also be explored. Dose level 1.92 mg/kg may be tested if dose level 2.5 mg/kg is not cleared. During the dose escalation, at least 3 evaluable subjects will be studied per dose level. In Part 1, any subject who received at least one treatment cycle of the combination will be evaluated for DLTs. Subjects who have received only belantamab mafodotin or have been withdrawn from the study for reasons other than toxicity but prior to completion of DLT observation period will be replaced.

Dose Escalation Schematic for Part 1



Dose Limiting Toxicity Criteria (Part 1 only)

The DLT observation window will be 21 days (=1 cycle). Any subject in Part 1 who received at least one treatment cycle of the combination of belantamab mafodotin and pembrolizumab will be evaluated for DLTs using National Cancer Institute (NCI) CTCAE Version 4.03 [NCI, 2010]. In addition, for belantamab mafodotin treatment related corneal events, the GSK grading scale for corneal events (Appendix 9) should be used for evaluation of DLT.

A DLT is defined as an AE that meets at least one of the criteria defined below and is considered by the investigator to be clinically relevant and attributed (definitely, probably, or possibly) to the study therapy during the 21 day DLT observation period.

1. Any Grade 4 non-hematologic toxicity
2. Any Grade 3 non-hematologic toxicity, with the following exceptions (i.e., the following will not be considered a DLT): Grade 3 diarrhea, nausea, or vomiting that responds to standard of care within 72 hours; Grade 3 hypertension (controlled following addition of 1 antihypertensive medication); and Grade 3 tumor lysis syndrome
3. Any Grade 3 or greater non-hematologic laboratory value if either:
   - The laboratory abnormality persists for >48 hrs despite supportive treatment, or
   - The abnormality leads to hospitalization
4. Hematologic toxicity:
   - Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia:
     - Grade 4 thrombocytopenia of any duration
     - Grade 3 thrombocytopenia associated with clinically significant bleeding
   - Grade 3 or greater febrile neutropenia lasting >48 hours despite adequate treatment:

5. Nephrotoxicity requiring dialysis, and not considered to be due to disease under study (ie. myeloma) based on investigator's assessment
6. Liver toxicity meeting pre-specified GSK liver stopping criteria
7. Prolonged delay (>14 days) in initiating Cycle 2 due to any treatment (pembrolizumab or belantamab mafodotin) related toxicity, with the exception of Grade 1-2 corneal events (GSK grading scale for belantamab mafodotin treatment related corneal events)
8. Any treatment-related toxicity that causes the subject to discontinue treatment during Cycle 1
9. Any other toxicity considered to be dose-limiting that occurs beyond 21 days will be considered in the selection of the dose to recommend for expansion cohorts
10. Any other event which in the judgment of the investigator and GSK Medical Monitor is considered to be a DLT

A subject who develops a DLT will be allowed to continue on study treatment if the toxicity did not meet predefined stopping criteria and recovered to ≤ Grade 1 within 14 days if the investigator and medical monitor agree that for a given subject the potential benefits may outweigh the risks.

The dose escalation will complete when RP2D is determined. The RP2D will be the maximum pre-specified dose of 3.4 mg/kg, or a lower dose that provides adequate PK exposure, tolerability and clinical activity.

Recommended Phase 2 Dose (RP2D)

All available data from Part 1 will be analyzed after the last cohort of subjects complete the 21-day DLT observation period. Data considered for RP2D selection will include, but not be limited to: safety, available PK profile, and observed signs of clinical activity. A dose level below maximum pre-specified dose (3.4 mg/kg) may be selected as RP2D if compelling safety and encouraging clinical activity can be demonstrated at dose levels below 3.4 mg/kg.

Part 2: Expansion

Once the RP2D has been identified, an expansion cohort (Part 2) will open for enrollment of up to 28 subjects with RRMM in order to confirm the safety profile and to evaluate the clinical activity of the combination.

If necessary, alternative schedules and/or additional dose(s) can be explored after RP2D is identified.

Safety Assessment

Safety assessments during the study will include, but not limited:

- AEs, SAEs, AEs leading to discontinuation of study treatment
- Clinical laboratory safety assessments, including hematology and clinical chemistry data
- Other safety measures, including data for vital signs, the performance status of the ECOG scale, ECG, echocardiogram (ECHO), and serum pregnancy test for female subjects of childbearing potential
- Ocular exam

Corneal Supportive Care Guidelines (belantamab mafodotin)

Corneal events, which commonly manifest as a superficial microcystic keratopathy, have previously been observed with antibody drug conjugates, including those conjugated to MMAF. It is required that sites establish a close collaboration with an ophthalmologist (or optometrist, if ophthalmologist is not available) who will be responsible for assessing subjects on study and managing subjects who develop a corneal event in close communication with the GSK Medical Monitor and possibly a GSK ophthalmologist.

Subjects will be assessed by ophthalmologists (or optometrist, if ophthalmologist is not available) at baseline, and then every three weeks prior to each dose of belantamab mafodotin for the first 4 doses. After the 4th dose of belantamab mafodotin, if there are no significant ocular symptoms or vision changes, the frequency of ophthalmologic exams may be decreased to once every 6 months until end of study treatment. In case of persistent or newly developed ocular symptoms or vision changes, the subject will have further ophthalmologic exams, at least every 3 months until resolution (to Grade 1 or baseline) or more frequently as clinically indicated by the eye care specialist.

Further information regarding corneal event associated with belantamab mafodotin, including a grading scale and prophylactic measures are in Appendix 9.

Clinical Activity Assessment

Standard disease assessments for MM will include laboratory tests (serum and urine M protein test, sFLC, and corrected calcium), bone marrow core biopsy and aspirate (in case of suspected CR or to demonstrate progression), immunohistochemistry (IHC) of bone marrow samples to confirm sCR to confirm stringent CR) or imaging, and minimal residual disease by Next Generation Sequencing (NGS; in subjects with achieve confirmed VGPR or CR). Response evaluation will be performed according to the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma 2016 [Kumar, 2016]. Minimal residual disease negative rate will be assessed in those subjects who achieve a VGPR or CR.

Pharmacokinetic assessments

Blood PK samples will be collected during the trial and analysed for belantamab mafodotin (ADC and total antibody) and cys-mcMMAF concentrations. Blood samples for pembrolizumab measurements will be collected and stored, but will only be analyzed in case of unexpected clinical findings.

Translational Research

BCMA expression in plasma cells from bone marrow aspirates will be evaluated at baseline, and at additional timepoints if available, by IHC. IHC markers may include but will not be limited to: BCMA, Blimp1, CD138, and CD38.

Soluble BCMA (sBCMA) concentrations in serum will be evaluated in all subjects.

Additionally, bone marrow tumor tissue may be evaluated for any DNA/RNA changes correlating with clinical response.

Value Evidence and Outcome

The impact of potential ocular toxicity will be assessed using the selected items from the Questionnaire of NEI-VFQ-25 and OSDI.

A subset of items selected from the PRO-CTCAE Version 1.0 Item library will be applied to evaluate symptomatic toxicity in subjects.

Subjects enrolled in Part 2 only will self-complete additional questionnaires to assess the symptoms related to multiple myeloma and its treatment, and the impact of these symptoms on daily functioning. Symptoms will be assessed using two questionnaires: EORTC-QLQ-C30 and EORTC-QLQ-MY20.

To further evaluate disease and treatment related symptoms and associated impacts on function and health-related quality of life, subjects enrolled in both Part 1 and 2 will participate in an Exit Interview conducted via telephone subsequent to the End of Treatment visit.

Statistical Analysis

For part 1, no formal statistical hypotheses are being tested. In Part 1, the dose escalation decisions will be guided by the Modified Toxicity Probability Interval (mTPI) approach, as well as the totality of the safety data. After the last cohort of subjects in Part 1 completes the 21-day DLT observation period, a formal interim analysis will be performed to support the RP2D decision, except for scenarios where RP2D is clearly defined by the toxicity profile.

The primary goal of Part 2 is to confirm safety and to characterize clinical activity of the combination and to detect if meaningful overall response rate (ORR) can be achieved.

During part 2 of the study, treatment-rated Grade 4 or higher AEs will be continuously monitored starting from when 5 subjects are dosed. If observed toxicity level is significantly higher than 12% at 1-sided alpha of 0.025, the study may be terminated early based on totality of safety data. The 12% threshold is chosen based on 11% Grade 4 or higher AE observed in study BMA117159.

For Part 2, futility analyses for ORR will start when 10 subjects are evaluable. Enrollment may stop if the stopping rule is met based on totality of data.

Primary analysis of the data captured in Part 1 and Part 2 will be performed approximately 15 months from the last subject first visit (LSFV) to test the hypothesis that a meaningful response rate (ORR) can be achieved of the combination. Participants may discontinue the study treatment if meaningful response rate (ORR) cannot be achieved. For primary analysis, data may be combined from parts 1 and 2.

Final analysis of the data captured in Part 1 and Part 2 will be undertaken after all subjects meet at least one of the following criteria: have reached the end of study or died. End of study is defined as when all subjects have been followed for 36 months from first dose of study treatment or died or withdrew consent or are lost to follow-up or the safety stopping criteria is met, whichever occurs first.

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2. INTRODUCTION

2.1. Study 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 U.S. in 2016 [Siegel, 2016]. Despite significant advances with current novel therapies and hematopoietic stem cell transplantation (HSCT), novel therapies like second- and third-generation proteasome inhibitors (PIs), immunomodulatory agents, and recent addition of monoclonal antibodies (mAbs), most MM patients will relapse and ultimately develop resistance to existing therapies [Laubach, 2014]. Thus, there is a need to develop treatments with novel mode of action (MOA) which could potentially prevent the cross resistance to existing therapies.

Before the introduction of daratumumab, patients with disease refractory to both immunomodulatory agents and PIs had a median overall survival (OS) ranging from 9 months [Kumar, 2012] to 12 months [San Miguel, 2013].

Daratumumab [DARZALEX, 2017], is a human IgGk monoclonal antibody that was granted accelerated approval as monotherapy for the treatment of relapsed/refractory multiple myeloma (RRMM) in the US in November 2015 based on the results from a Phase II monotherapy study (n=106), which reported 29.2% overall response rate (ORR) and median progression free survival (mPFS) of 3.7 months in patients with RRMM [Lonial, 2016]. The median number of prior lines of treatment reported in this study was 5.

Daratumumab has also been approved in combination with lenalidomide/dexamethasone or bortezomib/dexamethasone for patients who were previously treated with at least one prior line of therapy, and in combination with pomalidomide and dexamethasone for patients previously treated with at least 2 prior lines of therapy based on improvement in mPFS and ORR [DARZALEX, 2017; Janssen-Cilag International NV, 2016].

While the data with daratumumab indicates that prolongation of PFS can been achieved, patients continue to relapse after treatment with daratumumab; additional treatment options to control the disease are needed. Patients with RRMM who relapse after daratumumab, IMiD, and PI based therapies, have few treatment options available.

B cell maturation antigen (BCMA, also referred to as TNFRSF17 or CD269) 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 influence B cell survival and proliferation. Mice deficient for BCMA are viable, have normal B cell development, and exhibit normal humoral responses [Xu, 2001]. BCMA is widely expressed on malignant plasma cells in MM and to a lesser degree in other B cell malignancies [Tai, 2006]. A soluble form of BCMA has been identified in serum from MM patients and shown to correlate with progressive disease [Sanchez, 2016]. Since all malignant plasma cells express various

levels of BCMA, MM has a biologically based rationale as a key indication for anti-BCMA therapy.

Belantamab mafodotin (previously referred to as GSK2857916) is a humanized immunoglobulin G1 (IgG1) antibody-drug conjugate (ADC) that binds specifically to B cell maturation antigen (BCMA). The parent antibody (GSK2857914) competes with the BCMA ligands APRIL and BAFF and is conjugated to the microtubule inhibitor monomethyl auristatin-F (MMAF), resulting in an ADC molecule. The conjugate is produced in an afucosylated form to generate enhanced antibody-dependent cellular cytotoxicity (ADCC). In addition, when MM cells expressing BCMA are exposed to belantamab mafodotin, immunogenic cell death (ICD) markers are induced. Exposure of dendritic cells to tumor cells undergoing ICD may result in antigen-specific T-cell response, enabling the patient's own immune response against the MM tumor.

Of the four proposed mechanisms of action (MOA) for belantamab mafodotin, the ADC and ADCC MOAs have been linked to efficacy in non-clinical models: *in vitro* and *in vivo* against multiple myeloma cell lines, and *ex vivo* against primary patient myeloma samples. Inhibition of BCMA signaling has been demonstrated biochemically; however, functional effects on myeloma cells have not been demonstrated. ICD markers on cells are induced by belantamab mafodotin both *in vivo* and *in vitro*, but effects on efficacy have not been established in non-clinical models. These different mechanisms may enable belantamab mafodotin to deliver anti-tumour activities targeting both dividing and non-dividing tumour cells and associate the cell kill with an adaptive immune response; these MoA characteristics clearly differentiate belantamab mafodotin from existing approved treatments [GlaxoSmithKline Document Number 2013N175128_09, 2021**]**

Belantamab mafodotin is a very good candidate for combining with immunomodulating drugs, including programmed cell death 1 (PD-1) inhibitors, due to auristatin-induced immunogenic cell death (ICD) on target MM tumor cells (GSK unpublished data). ICD is characterized by induction of the endoplasmic reticulum (ER) stress response and exposure of danger-associated molecular patterns (DAMPs), many of which are Toll-like receptor ligands. Exposure of dendritic cells to tumor cells undergoing ICD evokes an inflammatory phenotype (innate response) including an increase in co-stimulatory markers CD86 and MHC Class II antigens, and activation of NFκB, an intermediate of inflammatory signalling pathways. Mature dendritic cells (DCs) play key roles in priming robust immune responses in tumor-bearing hosts and ICD can induce an effective anti-tumor immune response through activation of DCs and consequent activation of specific T cell response, by priming of tumor antigen-specific T cells [Kroemer, 2013; Muller, 2014]. The T cell anti-tumor response can be further augmented by pembrolizumab.

Programmed cell death-1 (PD-1) expressed on T cells is a member of the CD28 superfamily that delivers negative signals upon interaction with its two ligands, programmed cell death ligand 1 (PD-L1) or programmed cell death ligand 2 (PD-L2). Physiologically PD-1 and its ligands are broadly expressed and exert a wider range of immunoregulatory roles in T cell activation and tolerance. Recent studies show that PD-1/PD-L1 interaction regulates the induction and maintenance of peripheral tolerance and

protect tissues from autoimmune attack. PD-1 and its ligands are also involved in attenuating tumor immunity, and facilitating tumor progression.

Many tumors, including MM use various escape mechanisms to evade the immune control and to promote tumor growth and clonal tides [McLaughlin, 2016]. One of those mechanisms is the expression of PD-1 ligands (PD-L1). Recent advances in cancer treatment include successful checkpoint blockade by using antibodies binding to PD-1 or PD-L1 (e.g., pembrolizumab, nivolumab). The anti-PD-1 and anti-PD-L1 antibodies have a favorable safety profile and have resulted in durable responses in a variety of cancers, including melanoma, kidney cancer, lung cancer, and Hodgkin lymphoma. The agents continue to be evaluated in various solid tumors and hematological malignancies, alone or in combination with other therapies [Dolan, 2014]. There is also growing body of data demonstrating broad expression of PD-1 and its ligands in the microenvironment of MM, and indicating an important role of the PD-1 pathway [Liu, 2011; Kuranda, 2010; Atanackovic, 2014; Benson, 2010]. Although, so far, anti-PD-1 treatment alone has not been effective in MM [Lesokhin, 2014; Suen, 2006].

The KEYNOTE-023 study examined whether an anti-PD-1 treatment (Keytruda [pembrolizumab]) in combination with immunomodulatory agents may create synergism, in this case lenalidomide and dexamethasone. Lenalidomide doses of 10 mg and 25 mg were examined, with the 25 mg dose further explored. Of the subject's evaluable for efficacy (N=40), 88% of subjects had a decrease in M protein. The ORR for this population was 50%, including a 38% ORR for subjects who were lenalidomide refractory [Mateos, 2016]. Based on these findings, the KEYNOTE-183 and KEYNOTE-185 studies were initiated, exploring combinations of pembrolizumab with immunomodulatory agents.

Following review of both studies by data monitoring committees, KEYNOTE-183 and KEYNOTE-185 were placed on full clinical hold. In both studies, it was determined that the benefit-risk was unfavorable for the combination of pembrolizumab with immunomodulatory agents. The US FDA also placed Cohort 1 (combination with lenalidomide and dexamethasone) of KEYNOTE-023 on full clinical hold as a result of the data from KEYNOTE-183 and KEYNOTE-185. Please refer to Section 2.3.3 for additional information.

This study will evaluate the safety and anti-myeloma activity of belantamab mafodotin in combination with pembrolizumab. Safety will be closely monitored with dose modification guidelines in Section 6.5. GSK will also use an internal Safety Review Committee (iSRC) as described in Section 10.9.1. for review of safety. We hypothesize that given the immunogenic properties of the cell death induced by belantamab mafodotin an augmented anti-tumor activity will be observed in MM subjects, when treated with combination of belantamab mafodotin and pembrolizumab.

2.2. Belantamab mafodotin

2.2.1. Nonclinical Pharmacology

In vitro, belantamab mafodotin demonstrated both ADC and ADCC cytotoxicity against all MM cell lines tested, including those with low BCMA expression. Further, belantamab mafodotin activity was demonstrated under conditions designed to mimic the human target cells and microenvironment in the bone marrow, including in the presence of physiological concentrations of BCMA ligands, the presence of shed BCMA, a large range of BCMA expression levels, and at concentrations of belantamab mafodotin hypothesized to be achievable in humans. The presence of the drug conjugate on the antibody had no impact on the Fc receptor engagement, with identical ADCC potency of the ADC compared to the unconjugated mAb. Likewise, afucosylation of the mAb portion had no impact on the ADC activity compared to the wild type (WT) fucosylated molecule. Belantamab mafodotin significantly inhibited tumor growth in xenograft models of female mice bearing human MM NCI-H929, OPM2, and MM1Sluc cells. Additionally, a single dose male monkey study showed a pharmacodynamic effect on BCMA expressing cells in the blood.

In vivo safety pharmacology studies were not conducted with belantamab mafodotin. Evaluations of potential cardiovascular effects were performed in the 3-week toxicology studies. Electrocardiograms (ECG) were monitored in monkeys for up to 24 hours following repeat dosing and did not produce any evidence of test-article induced electrocardiographic waveform abnormalities, arrhythmias or QTc changes. Serum cardiac troponin I was also measured in the rat and monkey 3-week studies and no treatment-related effects were observed.

2.2.2. Nonclinical Pharmacokinetics Metabolism of Belantamab Mafodotin

Detailed information is available in the Investigator's Brochure [GlaxoSmithKline Document Number 2013N175128_09, 2021].

2.2.3. Toxicology of belantamab mafodotin (GSK2857916)

A range of nonclinical toxicology studies have been conducted to support the intravenous administration of belantamab mafodotin to humans. Detailed information is available in the Investigator's Brochure [GlaxoSmithKline Document Number Number 2013N175128_09, 2021].

2.2.4. Genotoxicity of belantamab mafodotin (GSK2857916)

Intact biopharmaceutical therapeutics, such as monoclonal antibodies and antibody drug conjugates, do not directly interact with DNA or other chromosomal material. Therefore, genetic toxicology studies with belantamab mafodotin were not performed [ICH S6(R1), 2011]. The active moiety of belantamab mafodotin is MMAF cytotoxin which is expected to be genotoxic in mammalian systems given it is a microtubule disrupting agent.

2.2.5. Effects in Humans (belantamab mafodotin)

Data from two belantamab mafodotin single agent studies conducted in heavily pre-treated RRMM patients (Q3W schedule via IV administration) is summarized below.

In the FTIH study DREAMM 1 (BMA117159) (NCT02064387), as of 28 August 2018 primary analysis data cut-off, a total of 73 subjects with RRMM received at least 1 dose of belantamab mafodotin frozen drug product ranging from 0.03 mg/kg to 4.6 mg/kg once every 3 weeks [GlaxoSmithKline Document Number 2013N175128_09, 2021]. Subjects were heavily pre-treated: 57% of subjects had 5 or more prior lines of therapy. Data from DREAMM 1 demonstrates a manageable safety profile with thrombocytopenia and corneal events being the most frequently reported AEs. All subjects in Part 2 (MM patient population) initiated belantamab mafodotin treatment at 3.4 mg/kg and experienced at least one AE. The most common events occurring in ≥30% of subjects were corneal events, thrombocytopenia (including the preferred term platelet count decreased), nausea, fatigue, anemia, and aspartate aminotransferase increased. In Part 2, Grade 3/4 AEs were reported in 29/35 subjects (83%) and SAEs were reported in 17/35 (49%) subjects. The most common SAEs were lung-associated infections, pneumonia, pyrexia, and IRR.

Corneal events are the most frequently reported adverse events associated with belantamab mafodotin in the clinic, which include keratopathy (microcyst-like superficial deposits in the corneal epithelium), blurred vision, dry eyes and photophobia. These findings are consistent with those previously reported with other antibody drug-conjugates utilizing monomethyl auristatin F in terms of manifestation and incidence of events [Donaghy, 2016; Eaton, 2015]. In Part 2 of DREAMM 1, corneal events were reported in 24/35 (69%) subjects, most commonly blurred vision (18/35; 51%), dry eye (13/35; 37%) and photophobia (10/35; 29%). Most subjects experienced Grade 1 or 2 corneal events (19/35; 54%); 5 (14%) subjects had Grade 3 events. The median duration of corneal events for subjects with a resolution date (n = 16) was 35 days (range 5–442). Corneal events led to dose reduction in 16 (46%) subjects, and dose interruptions or delays in 17 (49%) subjects [Trudel, 2019].

Thrombocytopenia/platelet count decreased was reported in a total of 40 subjects (55%) in the All Treated Population (N=73), and 22 subjects (63%) in Part 2 (N=35). Belantamab mafodotin may cause transient worsening of thrombocytopenia in some subjects, but in most cases these events are resolved during between-dosing intervals. In the Part 2 MM population, two serious bleeding events were reported: intracranial hemorrhage in a subject with a history of an intracranial bleeding in the setting of disease progression, and hematuria in a subject with a large bladder mass in the setting of progressive disease.

As of the efficacy cut-off date of 31 August 2018, a total of 35 subjects were treated at the 3.4 mg/kg dose in Part 2 of the ongoing DREAMM 1 study. The ORR was 60% (95% CI: 42.1, 76.1): comprised of PR, 6%; VGPR, 40%; CR, 9%; and stringent CR (sCR), 6%. The median duration of response (DoR) was 14.3 months (95% CI: 10.6, NR). The median PFS (mPFS) in this population was 12.0 months (95% CI: 3.1, NR). For subjects refractory to both immunomodulatory agents and PIs (n = 32/35), the confirmed ORR

was 56% (95% CI: 37.7, 73.6) and mPFS was 7.9 months (95% CI: 2.3, Not Estimable [NE]) [Trudel, 2019].

A Bayesian logistic regression model (BLRM) was used to determine the dose-response relationship for both ORR and ≥Grade 2 corneal event rate (as determined by NCI-CTCAE grading Version 4.0) based on data from all 73 subjects with RRMM in DREAMM 1. The model showed that the posterior probability of observing an ORR ≥30% is 100% in the 3.4 mg/kg dose group and 83% in the 2.5 mg/kg dose group. Similarly, the posterior probability of observing ≥Grade 2 corneal event rate is also higher in the 3.4 mg/kg dose group. Based on this analysis, these two doses (2.5 and 3.4 mg/kg) were selected for further evaluation.

The ongoing Phase II study 205678/DREAMM 2 (NCT03525678) is evaluating these two IV single agent doses (2.5 and 3.4 mg/kg) administered Q3W until disease progression in subjects who have failed at least 3 prior lines of anti-myeloma therapy, including an anti-CD38 antibody, and who are refractory to an immunomodulatory agent and a proteasome inhibitor. A total of 194 subjects received frozen drug product in the main cohort and 24 subjects received 3.4 mg/kg lyophilized drug product. Preliminary data from this study indicated no new safety signals, and the profile of adverse events was similar to the experience in the DREAMM 1 study for both arms. Both dose levels, 2.5 and 3.4 mg/kg, were shown to have a positive benefit/risk profile.

2.2.5.1. Pharmacokinetics and Pharmacodynamics

The pharmacokinetics and pharmacodynamics of belantamab mafodotin (antibody-drug conjugate, including complex with soluble BCMA (sBCMA)) and total monoclonal antibody (total mAb; including complex), and cys-mcMMAF were investigated in 291 participants with RRMM following IV administration at doses from 0.03 to 4.6 mg/kg Q3W in Study BMA117159 (n=73) and at doses of 2.5 or 3.4 mg/kg Q3W in Study 205678 (n=218).

Maximum concentrations (Cmax) of belantamab mafodotin and total monoclonal antibody were observed at or shortly after the end of infusion (EOI), while cys-mcMMAF Cmax values were generally observed on Day 2. On a molar basis, plasma concentrations of cys-mcMMAF were <1% of belantamab mafodotin concentrations. There was limited accumulation (less than 2-fold) of belantamab mafodotin or cys-mcMMAF during subsequent cycles.

Belantamab mafodotin pharmacokinetics were well described by a linear, two compartment population model, with a time-varying decrease in clearance in a population pharmacokinetic analysis. At Cycle 1, belantamab mafodotin had a systemic clearance of 0.92 L/day, steady-state volume of distribution of 10.8 L, and an elimination half-life of 12 days in participants with RRMM in Study 205678. Over time, clearance was reduced by 28%, resulting into 0.72 L/day, with an elimination half-life of 14 days. The time to 50% change in clearance was approximately 50 days.

No clinically significant differences in the pharmacokinetics of belantamab mafodotin or cys-mcMMAF were observed based on age (34 to 89 years), sex, race (African American/Black and White), body weight (42 to 130 kg), mild or moderate renal

impairment (eGFR ≥30 mL/min/1.73m^2) or mild hepatic impairment (NCI-ODWG classification). Higher serum levels of β_2-microglobulin, IgG, and soluble BCMA (sBCMA) and lower levels of albumin are associated with more advanced multiple myeloma or a higher multiple myeloma disease burden. Higher baseline IgG and sBCMA levels, and lower baseline albumin levels were associated with higher belantamab mafodotin clearance leading to lower average and trough concentrations (Ctau) of belantamab mafodotin. Higher baseline IgG and sBCMA levels were associated with higher cys-mcMMAF central volume of distribution leading to lower cys-mcMMAF Cmax.

In nonclinical studies, cys-mcMMAF had limited metabolic clearance. In vitro data suggested that belantamab mafodotin and cys-mcMMAF are unlikely to perpetrate a drug-drug interaction or to be a victim of a drug-drug interaction with inhibitors or inducers of cytochromes (CYP) P450. Cys-mcMMAF was an in vitro substrate of organic anion transporting polypeptides (OATP)1B1 and OATP1B3, multidrug resistance associated proteins MRP1, MRP2, and MRP3, a borderline substrate of bile salt export pump (BSEP), and a possible substrate of P-glycoprotein (P-gp). Following the administration of belantamab mafodotin to participants with RRMM, only intact cys mcMMAF was detected in pooled human urine, with no evidence of other MMAF related urinary metabolites.

Free sBCMA levels were measured in Study BMA117159 and Study 205678. All participants exhibited reductions in free sBCMA concentration at end of infusion compared to baseline at Cycle 1, with a return to near-baseline level by seven days after dosing, reflecting binding of belantamab mafodotin to sBCMA. Maximum decreases ranged from 2% to 97%, which were qualitatively dose-dependent, with larger reductions in free sBCMA at higher doses.

Exposure-response analyses performed for Study 205678 and/or Study BMA117159 found that ocular safety endpoints were most strongly associated with belantamab mafodotin exposure, while efficacy endpoints had a weaker association with belantamab mafodotin exposure. Both safety and efficacy endpoints were associated with patient characteristics. Belantamab mafodotin Ctau was associated with probability of corneal events and keratopathy, and cys-mcMMAF Cmax was associated with probability of thrombocytopenia. Probability of occurrence of dry eye, blurred vision, neutropenia and infusion related reaction were not associated with an exposure measure. In addition, the results of the analysis of concentration against corrected QT interval (QTc), concentration-QTc analysis, demonstrated that belantamab mafodotin or cys-mcMMAF did not have a significant effect on cardiac repolarization.

Additional information related to belantamab clinical PK, PD, and exposure-response relationships can be found in the Investigator's Brochure [GlaxoSmithKline Document Number 2013N175128_09, 2021]

2.3. Pembrolizumab

2.3.1. Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [Disis, 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded *ex vivo* and reinfused, including durable objective tumor responses in cancers such as melanoma [Dudley, 2005; Hunder, 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and CTLA-4, which has been shown to negatively regulate antigen receptor signalling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, 2005; Okazaki, 2001].

The structure of murine PD-1 has been resolved [Zhang, 2004]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail, which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T cell signaling cascade [Okazaki, 2001; Chemnitz, 2004; Sheppard, 2004; Riley, 2009]. The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from that of CTLA-4, because both molecules regulate an overlapping set of signalling proteins [Parry, 2005; Francisco, 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in RRMM.

2.3.2. Pre-Clinical Pharmacology of Pembrolizumab

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interactions enhance infiltration of tumor-specific CD8+ T cells and ultimately lead to tumor rejection, either as a monotherapy or in combination with other treatment modalities [Hirano, 2005; Blank, 2004; Weber, 2010; Strome, 2003;Spranger, 2014; Curran, 2010; Pilon-Thomas, 2010]. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal

carcinoma [Strome, 2003; Curran, 2010; Pilon-Thomas, 2010; Nomi, 2007; Zhang, 2004]. In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function *in vivo* [Curran, 2010]. Experiments have confirmed the *in vivo* efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the Investigator's Brochure [IB], Keytruda IB, 2021).

2.3.3. Pembrolizumab Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator brochure.

Keynote-183 was a randomized trial which evaluated pomalidomide and low-dose dexamethasone with or without pembrolizumab in subjects with relapsed and refractory multiple myeloma. The ORR was 34% in the pembrolizumab containing arm versus 40% in the control arm without pembrolizumab; however, there was no difference in time-to-progression between arms. There were 29 deaths in the pembrolizumab arm compared to 21 in the control arm, reflecting an overall survival hazard ratio of 1.61 (95% CI: 0.91, 2.85) [Krauss, 2018]. An analysis conducted with the removal of subjects with high-risk disease characteristics (high-risk cytogenetics, plasmacytoma and quadruple refractory status) resulted in a similar number of deaths (n=13) in both arms [Mateos, 2018].

Keynote-185 was a randomized trial which evaluated lenalidomide and dexamethasone with or without pembrolizumab in subjects with newly diagnosed multiple myeloma. The ORR was 64% in the pembrolizumab containing arm versus 62% in the control arm without pembrolizumab; however, there was no difference in time-to-progression between arms. There were 19 deaths in the pembrolizumab arm compared to 9 in the control arm, reflecting an overall survival hazard ratio of 2.06 (95% CI: 0.93, 4.55) [Krauss, 2018].

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475 [KEYTRUDA Product Information, 2018; Keytruda IB, 2021].

2.4. Assessment of Nonclinical Data for Belantamab Mafodotin when Co-Administered with Pembrolizumab

The current nonclinical and clinical safety information for both belantamab mafodotin and pembrolizumab, used as single agents, provide support for their use in combination in the target patient population. Based on the mechanism of action of belantamab mafodotin (following engagement with both target and the FcγRIIIA, leading to ADCC

activity and the potential for cytokine release as a result of inflammation secondary to non-specific cytotoxicity) and the identified potential for pembrolizumab to cause cytokine release *in vitro*, there may be a potential risk for cytokine release when these agents are administered in combination. The risk is considered to be low. To ensure the safety of subjects, a careful dose escalation of belantamab mafodotin will be implemented where no more than one subject will be dosed per day.

In addition, the starting dose of belantamab mafodotin in this combination regimen has been selected to be 1 dose level below a dose that has been shown to be well tolerated during the belantamab mafodotin monotherapy dose escalation and should provide a sufficient safety margin when pembrolizumab is added at 200 mg. In addition, close clinical monitoring will be implemented.

3. OBJECTIVE(S) AND ENDPOINT(S)

Part 1: Dose Escalation

Objectives	Endpoints
Primary	
• To determine safety, tolerability and to establish the RP2D of the combination of belantamab mafodotin with pembrolizumab in subjects with RRMM	• Percent of subjects with AEs, changes in clinical signs and laboratory parameters • Number of subjects with dose limiting toxicities (DLTs)
Secondary	
• To evaluate clinical activity of the combination of belantamab mafodotin and pembrolizumab in subjects with RRMM	• Overall Response Rate (ORR), defined as the percentage of subjects with a confirmed partial response (PR) or better (i.e., PR, very good partial response [VGPR], complete response [CR] and stringent complete response [sCR]), according to the International Myeloma Working Group (IMWG) Response Criteria [Kumar, 2016].
• To evaluate the pharmacokinetic profile of belantamab mafodotin when administered intravenously in combination with pembrolizumab[1]	• Pharmacokinetic parameters following IV administration as data permit.
• To assess anti-drug antibodies (ADAs) against belantamab mafodotin [1]	• Incidence and titers of ADAs against belantamab mafodotin
Exploratory	
• To assess Minimal Residual Disease (MRD) in subjects who achieve ≥VGPR or better	• Minimal Residual Disease (MRD) negativity rate, defined as: the percentage of subjects who are MRD negative in subjects who achieve VGPR or CR

Objectives	Endpoints
• To characterize the relationship between clinical response and other biologic characteristics	• BCMA expression levels on malignant cells, serum sBCMA levels, serum cytokines, and immune cell characterization and their relationship to clinical response (Protein, RNA, DNA analysis)
• To investigate the relationship between genetic variants in the host and response to belantamab mafodotin in combination with pembrolizumab	• Possible relationship between host genetic variation and response to belantamab mafodotin in combination with pembrolizumab
• To evaluate the tolerability of belantamab mafodotin in combination with pembrolizumab based on patient self-report of symptomatic adverse effects	• Symptomatic adverse effects as measured by the Patient-reported outcome version of the Common Term Criteria for Adverse Events (PRO-CTCAE) • Impact of ocular adverse effects on quality of life as measured by the Visual Function questionnaire(s): National Eye Institute 25-item Visual Function Questionnaire (NEI-VFQ-25) and Ocular Surface Disease Index (OSDI)
• To evaluate disease and treatment related symptoms and associated impacts on function and health-related quality of life	• Exit Interview

1. PK and ADA samples for pembrolizumab will be collected and stored during the trial. The analysis will be triggered only in case of unexpected clinical findings.

Part 2: Expansion

Objectives	Endpoints
Primary	
• To assess the clinical activity of the combination treatment with belantamab mafodotin and pembrolizumab in subjects with RRMM	• Overall Response Rate (ORR), defined as the percentage of subjects with a confirmed PR or better (i.e., PR, VGPR, CR and sCR), according to the IMWG Response Criteria [Kumar, 2016].
Secondary	
• To further evaluate the safety of belantamab mafodotin administered in combination with pembrolizumab in subjects with RRMM	• Number (percent) of subjects with AEs, changes in clinical signs and laboratory parameters • Ocular finding on ophthalmic exam
• To further assess the clinical activity of the combination treatment with belantamab mafodotin and pembrolizumab in subjects with RRMM	• Clinical benefit rate (CBR), defined as the percentage of subjects with a confirmed minimal response (MR) or better per IMWG • Duration of response (DoR), defined as: the time from first documented evidence of PR or better, to the time when disease progression (PD) is documented per IMWG; or death due

Objectives	Endpoints
	to PD occurs among subjects who achieve an overall response, i.e. confirmed PR or better • Time to response (TTR), defined as: the time between the date of first dose and the first documented evidence of response (PR or better) among subjects who achieved a confirmed response of PR or better • Time to best response, defined as the time between the date of first dose and the first best documented response (PR or better) among subjects who achieved a confirmed response of PR or better • Progression-free survival (PFS), defined as: the time from first dose until the earliest date of PD per IMWG, or death due to any cause • Time to disease progression (TTP), defined as: the time from first dose until the earliest date of PD per IMWG, or death due to PD • Overall Survival (OS), defined as the time from first dose until death due to any cause
• To evaluate the pharmacokinetic profile of belantamab mafodotin when administered intravenously in combination with pembrolizumab[1]	• Pharmacokinetic parameters following IV administration as data permit.
• To assess ADAs against belantamab mafodotin[1]	• Incidence and titer of ADA to belantamab mafodotin
Exploratory	
• To assess Minimal Residual Disease (MRD) in subjects who achieve ≥VGPR or better	• Minimal Residual Disease (MRD) negativity rate, defined as: the percentage of subjects who are MRD negative in subjects who achieve VGPR or CR
• To characterize the relationship between clinical response and other biologic characteristics	• BCMA expression levels on malignant cells, serum sBCMA levels, serum cytokines, and immune cell characterization and their relationship to clinical response (Protein, RNA, DNA analysis).
• To investigate the relationship between genetic variants in the host and response to belantamab mafodotin in combination with pembrolizumab	• Possible relationship between host genetic variation and response to belantamab mafodotin administered in combination with pembrolizumab
• To explore the effect of belantamab mafodotin in combination with pembrolizumab on symptoms and health-related quality of life in subjects with RRMM	• Changes from baseline in symptoms and health-related quality of life as measured by the European Organisation for Research and Treatment of Cancer Quality of Life

Objectives	Endpoints
	Questionnaire 30-item Core Module (EORTC-QLQ-C30) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma Module (EORTC-QLQ-MY20)
• To evaluate the tolerability of belantamab mafodotin in combination with pembrolizumab based on patient self-report of symptomatic adverse effects	• Symptomatic adverse effects as measured by the PRO-CTCAE • Impact of ocular adverse effects on quality of life as measured by the Visual Function questionnaire(s): NEI-VFQ-25 and OSDI
• To evaluate disease and treatment related symptoms and associated impacts on function and health-related quality of life	• Exit Interview

1. PK and ADA samples for pembrolizumab will be collected and stored during the trial. The analysis will be triggered if unexpected clinical findings have been identified.

4. STUDY DESIGN

4.1. Overall Design

This is a phase I/II, single arm, open label, two-part study to determine the RP2D of belantamab mafodotin administered in combination with 200 mg of pembrolizumab, and to evaluate safety and clinical activity of the combination in subjects with RRMM. The study will be conducted in two parts: Part 1: dose escalation of belantamab mafodotin with a constant dose of pembrolizumab at 200 mg, and Part 2: expansion cohort at RP2D of belantamab mafodotin in combination with 200 mg pembrolizumab. A total of up to 40 evaluable subjects with RRMM will be enrolled into this study (up to 12 in Part 1, and 28 in Part 2).

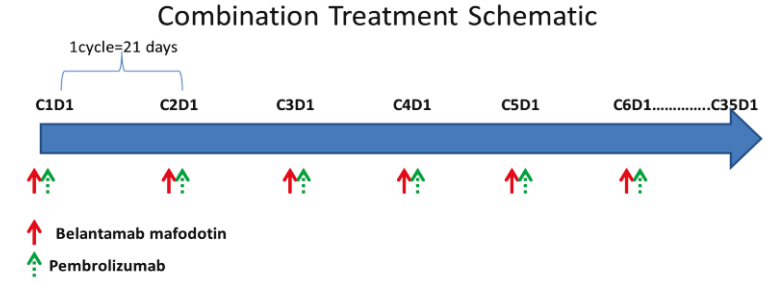
4.2. Study Treatment and Duration

4.2.1. Study Treatment

The treatment schematic is depicted in Figure 1.

This is a single arm, open label study. Subjects in Part 1 and in Part 2 will receive belantamab mafodotin and pembrolizumab via IV infusion on day 1 of each 21-day cycle. Belantamab mafodotin will be administered first, as an IV infusion, followed by at least 1 hour rest. Refer to the SRM for details on belantamab mafodotin infusion. Provided there is no infusion related reaction (IRR) warranting a prolonged interval between dosing, pembrolizumab will be administered as second drug over approximately 30 min via IV infusion. If a subject develops IRR during or after belantamab mafodotin infusion, he or she will be treated according to institutional guidelines. In such cases the infusion of pembrolizumab may have to be delayed until IRR has recovered to Grade 1 or less, and investigator considers it safe to continue with infusion with pembrolizumab. The infusion of pembrolizumab may be delayed for up to the +3 day window from scheduled visit to allow for recovery of IRR, and to accommodate scheduling conflicts. If a subject does not recover from IRR to Grade 1 or less within the +3 day window, the dosing of pembrolizumab will be skipped in a given cycle, and may be resumed in the next cycle.

Figure 1 Study Treatment Schematic



Dosing:
-Belantamab mafodotin and pembrolizumab on D1 of each cycle
-Belantamab mafodotin first, Pembrolizumab as second iv infusion (1hr apart)
-If IRR related to GSK2857916, the PD1 dosing will be delayed
-Max treatment duration: 35 cycles combination treatment

4.2.2. Duration of Treatment

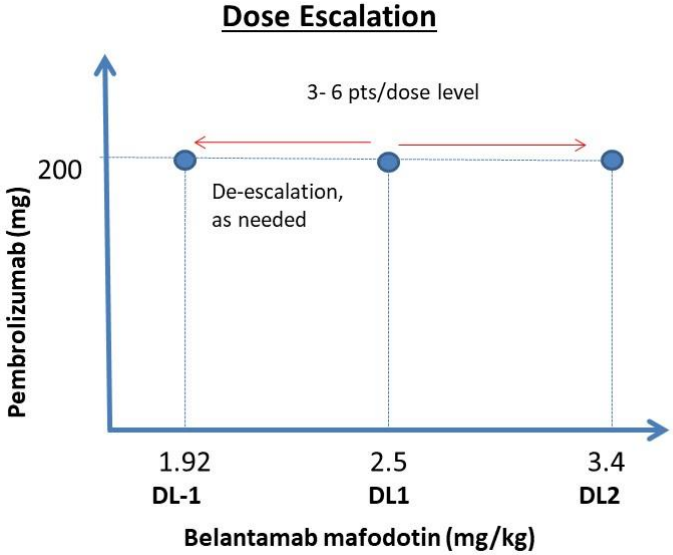
Subjects will be treated until disease progression, intolerable toxicity, informed consent withdrawal, or for a maximum of 35 cycles (approximately 2 years).

After the study treatment discontinuation, subjects will undergo end of treatment assessments 30 days (±7 days) after the last dosing, or prior to the start of new anti-cancer treatment (whichever occurs first). Subjects who discontinued treatment for reasons other than PD, will be followed up every 3 weeks until confirmed PD, initiation of a new anticancer therapy or death. All subjects with confirmed PD will be followed for OS and subsequent anti-cancer therapy every 3 months until the end of study. End of study is defined in Section 5.5.2.

4.2.3. Part 1: Dose-Escalation

Part 1 dose escalation will characterize the safety and tolerability of escalating doses of belantamab mafodotin in combination with 200 mg pembrolizumab to establish the RP2D. In the currently ongoing FTIH study (ClinicalTrials.gov Identifier: NCT02064387), no DLTs were observed up to the highest tested dose level of 4.6 mg/kg of belantamab mafodotin and 3.4 mg/kg was selected as RP2D dose. The following dose levels of belantamab mafodotin in combination with 200 mg pembrolizumab are to be tested in this study: 2.5 mg/kg and 3.4 mg/kg (as outlined in Figure 2). Additionally, other dose levels may also be tested if emerging data suggests a beneficial risk/benefit profile at those dose levels. The RP2D from the monotherapy FTIH study (3.4 mg/kg (ClinicalTrials.gov Identifier: NCT02064387)) will not be exceeded in this combination study. During the dose escalation, at least 3 evaluable subjects will be tested per dose level, and escalation will be guided by the modified Toxicity Probability Interval (mTPI) approach.

Figure 2 Dose Escalation Schematic for Part 1



The mTPI design assumes the true underlying toxicity rate for maximum tolerated dose (MTD) of belantamab mafodotin falls within the range from 25% to 35% and centered at 30%. The monitoring rules for guiding dose escalations are provided in Table 1. Columns provide the numbers of subjects treated at the current dose level, and rows provide the corresponding numbers of subjects experiencing toxicity. The entries of the table are dose-finding decisions (i.e., E, S, and D) representing escalating the dose, staying at the same dose, and de-escalating the dose. In addition, decision U means that the current dose level is unacceptable because of high toxicity; the current dose level and any higher dose level should be excluded from the trial. For example, when one of three subject's experiences toxicity, the decision can be located at row 1 and column 3, which is S – to stay at the current dose level. Consequently, the next cohort of subjects will be treated at the same dose level currently being used. If 0 of 3 subjects experiences toxicity, the decision is at row 0 and column 3, which is E – to escalate. Thus, the next cohort of subjects will be treated at the next-higher dose level. If three of three subjects experiences toxicity, the decision is DU – to de-escalate to the next-lower dose level, and exclude the current dose and any higher dose from the trial, because the high toxicity level is unacceptable. In dose escalation (E)/de-escalation (D), no dose skipping is allowed.

Table 1 Dose-Escalation Monitoring Rules for Part 1 Using the mTPI Method

Number of DLTs	Number of Subjects treated at current dose					
	1	2	3	4	5	6
0	E	E	E	E	E	E
1	D	S	S	S	S	E
2		DU	D	S	S	S
3			DU	DU	D	S
4				DU	DU	DU
5					DU	DU
6						DU

The table was generated based on a beta/binomial model and precalculated before trial initiation. The letters in different colors are computed based on the decision rules under the mTPI method and represent different dose-finding actions. In addition to actions de-escalate the dose (D), stay at the same dose (S), and escalate the dose (E), the table includes action unacceptable toxicity (DU), which is defined as the execution of the dose-exclusion rule in mTPI. Excerpted from Ji et al . [Ji, 2010]

The DLT observation period for subjects in Part 1 is 21 days after the first dose of the study treatment. The complete safety data from DLT observation period of at least 3 subjects are needed for dose escalation decisions. Subjects who have only received belantamab mafodotin or have been withdrawn from the study for reasons other than toxicity but prior to completion of DLT observation period will be replaced.

In Part 1, dose escalation/de-escalation decisions will take into account all available safety and tolerability data. The decisions will be informed by the mTPI approach and will occur following review of these data and joint discussion by the GSK Study Team and investigators.

The dosing may be adjusted to expand any cohort to further evaluate safety at a given dose level, or to add cohorts to evaluate additional, intermediate dose levels of

GSK2858916 after discussion between GSK study team and investigators. The study procedures for these additional subject(s) or cohort(s) will be the same as that described in Section 5 and Section 7. The dose of pembrolizumab will be kept constant at 200 mg throughout the study.

4.2.3.1. Dose-Limiting Toxicity Criteria (Part 1 only)

Any subject in Part 1 who received at least one treatment cycle of belantamab mafodotin in combination with pembrolizumab will be evaluated for DLTs.

All toxicities will be graded using National Cancer Institute (NCI) CTCAE Version 4.03 [NCI, 2010]. In addition, for belantamab mafodotin treatment related corneal events, the GSK Grading Scale (Appendix 9) should be used for evaluation of DLT.

A DLT is defined as an AE that meets at least one of the criteria defined below and is considered by the investigator to be clinically relevant and attributed (definitely, probably, or possibly) to the study therapy during the 21 day DLT observation period.

- Any Grade 4 non-hematologic toxicity
- Any Grade 3 non-hematologic toxicity, with the following exceptions (i.e., the following will not be considered a DLT): Grade 3 diarrhea, nausea or vomiting that responds to standard of care within 72 hours; Grade 3 hypertension (controlled following addition of 1 antihypertensive medication); and Grade 3 tumor lysis syndrome
- Any Grade 3 or greater non-hematologic laboratory value if either:
  - The laboratory abnormality persists for >48 hrs despite supportive treatment or,
  - The abnormality leads to hospitalization
- Hematologic toxicity:
  - Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia:
    - Grade 4 thrombocytopenia of any duration
    - Grade 3 thrombocytopenia associated with clinically significant bleeding
  - Grade 3 or greater febrile neutropenia lasting >48 hours despite adequate treatment:

    CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.
- Nephrotoxicity requiring dialysis, and is not considered to be due to disease under study (i.e., myeloma) based on investigator's assessment
- Liver toxicity meeting pre-specified GSK liver stopping criteria (see Section 5.4.1.1)
- Prolonged delay (>14 days) in initiating Cycle 2 due to any treatment (pembrolizumab or belantamab mafodotin) related toxicity, with the exception of Grade 1-2 corneal events (GSK grading scale for belantamab mafodotin treatment related corneal events; Table 17)
- Any treatment-related toxicity that causes the subject to discontinue treatment during Cycle 1

- Any other toxicity considered to be dose-limiting that occurs beyond 21 days will be considered in the selection of the dose to recommend for expansion cohorts
- Any other event which in the judgment of the investigator and GSK Medical Monitor is considered to be a DLT

A subject who develops a DLT will be allowed to continue on study treatment if the toxicity did not meet predefined stopping criteria (Section 5.4) and recovered to ≤ Grade 1 within 14 days, if the investigator and medical monitor agree that for a given subject the potential benefits may outweigh the risks.

4.2.3.2. Completion of Dose Escalation and the Recommended Phase 2 Dose (RP2D)

The dose escalation will complete when RP2D is determined. A dose level at or below the pre-specified max dose of 3.4 mg/kg may be selected as RP2D in combination with the fixed dose of 200 mg pembrolizumab. All available data from Part 1 will be analyzed. The totality of the data including, but not be limited to, safety, available PK profile, and observed signs of clinical activity will be considered for the RP2D selection of belantamab mafodotin to be administered in combination with pembrolizumab. If necessary, alternative doses and schedules can be explored to determine additional clinically active regimens.

Once the RP2D has been identified, an expansion cohort (Part 2) will open for enrollment of up to 28 subjects with RRMM in order to confirm the safety profile and to evaluate the clinical activity of the combination.

If necessary, alternative schedules and/or additional dose(s) of belantamab mafodotin can be explored after RP2D is identified.

4.3. Type and Number of Subjects

The study will enroll adult subjects with RRMM, who have undergone stem cell transplant, or are considered transplant ineligible, and who have been previously treated with at least 3 prior lines that include the following: an immunomodulatory agent (i.e. lenalidomide or pomalidomide), proteasome inhibitor (i.e. bortezomib, ixazomib or carfilzomib) and an anti-CD38 antibody alone or in combination. Line of therapy are defined by consensus panel of the International Myeloma Workshop [Rajkumar, 2011].

Overall, it is estimated that up to 40 evaluable subjects will be enrolled in this two-part study (up to 12 in Part 1, and 28 in Part 2).

4.4. Design Justification

This is the first clinical study in which belantamab mafodotin will be administered in combination with pembrolizumab. Therefore, a two-part study design is implemented to allow for careful safety assessments during dose escalation. Part 1 will consist of dose escalation to establish the RP2D of belantamab mafodotin in combination with 200 mg of pembrolizumab. Once RP2D has been established, Part 2 will enroll an additional 28 subjects with RRMM to further confirm safety and to assess the clinical activity of the

combination at the RP2D of belantamab mafodotin. Futility analyses will be conducted from when response data is available from 10 subjects. Details of the futility analysis are described in Section 9.5.2.

4.5. Dose Justification

4.5.1. Belantamab Mafodotin Starting Dose Justification

The starting dose for belantamab mafodotin will be 2.5 mg/kg administered intravenously Q3W on Day 1 of each 21-day Cycle. Careful dose escalation and monitoring will be implemented to protect subjects' safety throughout the study.

The 2.5 mg/kg dose is considered to be appropriate starting dose for combination with a fixed dose of 200 mg pembrolizumab:

- The starting dose of 2.5 mg/kg is one dose level below the 3.4 mg/kg, which had an acceptable safety profile in FTIH trial;
- Per currently available data, it is anticipated that the starting dose of 2.5 mg/kg will be well tolerated and is not expected to result in an excessive toxicity;
- Based on the non-specific clearance mechanism with large capacity of both: belantamab mafodotin and pembrolizumab, the likelihood for drug-drug interactions from combining belantamab mafodotin with pembrolizumab is low.

4.5.2. Pembrolizumab Dose Justification

The dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W), representing an approximate 5 to 7 fold exposure range (refer to the IB) [Keytruda IB, 2021].
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W.
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg

Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other subject covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.6. Benefit: Risk Assessment

Pembrolizumab

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on pembrolizumab that may impact subject eligibility is provided in the pembrolizumab approved labelling. For detailed background information on pembrolizumab refer to [Keytruda SmPC, 2017 and KEYTRUDA PI, 2018, Keytruda IB, 2021].

Belantamab Mafodotin

Summaries of non-clinical findings and information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on belantamab mafodotin that may impact subject eligibility is provided in the Investigator's Brochure [GlaxoSmithKline Document Number 2013N175128-09, 2021]

4.6.1. Risk Assessment

The risk assessment and risk mitigation plan for belantamab mafodotin and study procedures are summarized in Table 2. Refer to Table 5 for pembrolizumab guidance.

There is a risk of overlapping toxicities with the combination of belantamab mafodotin and pembrolizumab. Potential overlapping toxicities and risk mitigation plans are provided in Table 2. The frequency and intensity of these assessments will allow Investigators and GSK to identify and to react to potential worsening of toxicities.

Table 2 Risk Assessment and Mitigation Strategy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential overlapping toxicities for belantamab mafodotin in combination with pembrolizumab)		
Keratopathy (changes to the corneal epithelium, potentially resulting in vision changes) **Eye disorders associated with pembrolizumab**	**Belantamab mafodotin**: Changes in corneal epithelium on ocular examination have been frequently observed with belantamab mafodotin. This was most commonly associated with: blurred vision, dry eyes, photophobia, and changes in visual acuity. Participants with a history of dry eye were more prone to develop changes in the corneal epithelium. Based on available follow-up data, visual acuity returned to, or near baseline in most cases and no permanent loss of vision reported. **Pembrolizumab**: Eye disorders including dry eye, uveitis, and rarely Vogt-Koyanagi-Harada syndrome, have been reported with pembrolizumab.	Active monitoring for corneal events according to Table 4. Timely evaluation and management by an ophthalmologist (or an optometrist if an ophthalmologist is not available) upon developing corneal related events (see Section 6.5.1 and Appendix 9). In the event of new-onset eye-related symptoms (such as pain, significant loss of visual acuity, or bothersome foreign body sensation), participants are to urgently seek medical attention by a qualified eye care specialist (appropriate testing includes slit lap examination [includes fluorescein staining] and measurement of visual acuity). Appropriate management should be initiated immediately as defined in Section 6.5.1. Recommendations for dose delays / reductions are provided in Section 6.5.1.
Infusion related reaction	**Belantamab mafodotin**: IRRs were reported in patients treated with belantamab mafodotin. Most IRRs observed to date were Grade 1 to 2 and manageable with medical treatment. **Pembrolizumab**: Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug	Subjects will be closely monitored for signs of IRR. Premedication prior to first infusion of belantamab mafodotin is not mandatory but may be considered based on investigator judgement. If an IRR occurs during belantamab mafodotin administration, management may follow guidance in Table 4

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	infusion and generally resolve completely within 24 hours of completion of infusion.	or local standard of care. Management of pembrolizumab infusion reactions is provided in Table 6.
Thrombocytopenia	**Belantamab mafodotin**: Thrombocytopenic events of all grades (1-4) are among the most common AEs associated with belantamab mafodotin. **Pembrolizumab**: Thrombocytopenia has been reported with pembrolizumab therapy. .	Hematological panels are assessed frequently. Supportive therapy (including transfusions) is provided according to standard medical practice, and dose reductions or treatment discontinuations are outlined in Section 6.5.
Neutropenia	**Belantamab mafodotin**: Neutropenic events, including febrile neutropenia have been observed with treatment with belantamab mafodotin, In a study of belantamab mafodotin in combination with lenalidomide/ dexamethasone, two fatal cases of severe infections associated with neutropenia have been observed. **Pembrolizumab**: Neutropenia has been reported with pembrolizumab therapy.	Hematological panels are assessed frequently. Consider prophylactic antibiotics, per physician discretion and local institutional guidance, in subjects with Grade 3-4 neutropenia CCI [redacted] even if afebrile. Immediately hospitalize subjects with febrile neutropenia and initiation appropriate management, per local institutional guidance. Consider additional supportive treatment(s) per local practice (e.g., growth factors). Dose reductions or treatment discontinuations are outlined in Section 6.5
Potential for cardiotoxicity related to an inflammatory	**Belantamab mafodotin**: Nonclinical studies, predominantly in monkey, increased activation of macrophages was noted in a number of organs at ≥3 mg/kg/week, reflective of a systemic inflammatory response. Minimal inflammatory changes (inflammatory cell infiltrate and/or	Subjects with significant cardiac risk factors will be excluded from study participation.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
response with belantamab mafodotin **Cardiac disorders associated with pembrolizumab**	haemorrhage) were also noted in hearts (atrial epicardium, ventricle endocardium) of single monkeys, which were nonadverse and reversible. Incidence of cardiac events reported to date with belantamab mafodotin was relatively low and mostly grade 1-2. **Pembrolizumab**: Cardiac disorders including pericarditis, pericardial effusion, and myocarditis, have been reported with pembrolizumab therapy.	Close monitoring of vital signs and ECG, troponin, and ECHO will be performed. Treatment as medically indicated. Monitoring of other cardiac parameters as clinically indicated. Dose modifications for myocarditis with pembrolizumab are provided in Table 5.
Hepatotoxicity	**Belantamab mafodotin**: In nonclinical studies liver is a target organ for toxicity, with increased liver weights and/or raised hepatobiliary enzymes and transaminases observed I both rat and monkey. These changes in the liver were without clinical consequence in the shorter duration studies and in the rat 13-week study. In the monkey 13-week study, progression of liver toxicity to include minimal multifocal hepatocellular necrosis was observed at all doses administered (≥3 mg/kg/week). Mild elevations of liver enzymes have been reported in some patients treated with belantamab mafodotin. **Pembrolizumab**: Hepatitis has been reported with pembrolizumab treatment.	Only subjects with well-preserved liver function per the inclusion/exclusion criteria will be allowed on study. Subjects with Hepatitis B (HBV) and C will be excluded. Liver function tests will be frequently monitored. In case of liver abnormalities, management will be implemented according to clinical practice. Subjects that meet liver stopping criteria (Section 5.4.1.1) will be withdrawn from the study.
Nephrotoxicity	**Belantamab mafodotin**: Non-clinical safety studies have demonstrated dose dependent and reversible primary glomerular injury and tubular degeneration (in rat and monkey), accompanied by large molecular proteinuria (albuminuria) and enzymuria. Single cell necrosis of the kidney and bladder urothelium was also noted in the 13-week monkey study. Severe tubular degeneration/regeneration and marked glomerulonephritis exacerbated by immune complex disease, likely	Subjects will be monitored for kidney function by assessing creatinine, eGFR, electrolytes, and albumin/creatinine rations (spot urine). Subjects will be educated about the need of maintaining adequate urinary output.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	associated with ADA, led to the early euthanasia of one monkey following 5 weekly doses of 10 mg/kg. Increased albumin/creatinine ratio (albuminuria) not indicative of disease progression has been reported in clinical trials and named patient programs with belantamab mafodotin. **Pembrolizumab**: Renal disorders, including nephritis and acute kidney injury, have been reported with pembrolizumab treatment.	Management will be implemented according to clinical practice. Dose reductions and treatment stopping criteria will be applied according to Section 6.5. Dose modifications for nephritis and renal dysfunction with pembrolizumab are provided in Table 5.
Pulmonary toxicity (pneumonitis)	**Belantamab mafodotin**: Nonclinical safety experiments have demonstrated the presence of progressive microscopic changes in the lungs (prominent alveolar macrophages associated with eosinophilic material; mixed perivascular/neutrophilic inflammation) in rats at all doses tested. Cases of pneumonitis, including fatal events, have been observed with belantamab mafodotin although a causal association has not been established. **Pembrolizumab**: Pneumonitis has been reported with pembrolizumab treatment.	Monitoring for clinical signs and symptoms potentially related to pulmonary toxicity. If a participant experiences new or worsening pulmonary symptoms, (e.g., cough, dyspnea) without obvious etiology, appropriate diagnostic evaluation should performed (see protocol section 6.5.1) and further treatment with belantamab mafodotin delayed (refer to protocol section 6.5.1). An overall benefit/risk assessment should be considered for the participant prior to continuing belantamab mafodotin treatment. Dose modifications for pembrolizumab are provided in Table 5.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential for Other Laboratory abnormalities	**Belantamab mafodotin**: An increased magnitude of AST relative to ALT consistent with increased skeletal troponin I was observed in the single dose monkey study. Increased skeletal troponin I and/or creatine kinase and aldolase was observed in the rat 3-week study. Cases of elevated aspartate aminotransferase (AST), lactic dehydrogenase (LDH) and creatine kinase (CK) alone or concomitant with no clear clinical correlate have been observed in clinical studies. **Pembrolizumab**: AST and ALT increase have been reported with pembrolizumab treatment.	Laboratory parameters will be monitored as outlined in Section 7. Subjects with significant laboratory elevations (≥x3 ULN) should, where possible, have a sample sent to central testing of CK and LDH isoenzyme levels. Dose modifications for pembrolizumab ALT and AST elevations are provided in Table 5.
Embryo-Fetal Toxicity	**Belantamab mafodotin**: Nonclinical reproductive studies with belantamab mafodotin have not been conducted. Embryo-fetal toxicity is expected due to the cytotoxic component, cys-mcMMAF via nonspecific uptake and/or BCMA-mediated toxicity (due to reports of BCMA expression in human placental cells [Langat, 2008]). Use of belantamab mafodotin in pregnant women may cause fetal harm. **Pembrolizumab**: Animal reproduction studies have not been conducted with pembrolizumab; however, in murine models of pregnancy blockade of PD-L1 signaling has been shown to disrupt tolerance to the foetus and to result in an increased fetal loss. These results indicate a potential risk, based on its mechanism of action, that administration of pembrolizumab during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth.	See Contraception requirements in Section 6.11.1.
Risks Related to Belantamab mafodotin not listed under potential overlapping toxicities		
Immunosuppression	In non-clinical studies belantamab mafodotin has been associated with decrease in immunoglobulins in monkeys at all doses. An increase in	Subjects who have active infection will be excluded.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	immunoglobulins was seen in rats (rats are not an antigen specific species for belantamab mafodotin). MM subjects frequently are immunodeficient due to the underlying condition. Assessment of changes in immunoglobulin levels is challenging in patients with MM.	Subjects will be monitored for infections and those who develop infection will receive immediate treatment according to standard practice.
Impaired Male and Female Fertility	In animal studies, belantamab mafodotin treatment has resulted in testicular toxicity and adverse effects on spermatogenesis. Reversibility of testicular and ovarian toxicity is unknown at this time. Ovarian toxicity (luteinized non-ovulatory follicles) was observed in a 3-week rat study (weekly dosing) and was not observed following 12 weeks off dose. In a 13-week rat study where drug was administered once every 3 weeks, these changes were not observed.	Men who may wish to father children in the future will be advised to have sperm samples frozen and stored before treatment. Women of child bearing potential who may desire offspring in the future will be counselled about the option of having eggs frozen before treatment. See Contraception requirements in Section 6.11.1
Study Procedures		
Bone marrow aspiration/biopsy	Pain, infection, bleeding may occur after the procedure	Subjects will be treated according to institution's practice
Incidental findings during imaging data acquisition	During the acquisition of imaging data (e.g.., MRI, CT, PET, ECHO), non-MM disease or drug related clinical abnormalities could be found by the radiographer or echocardiographer performing the exams.	Copies of all medical images that include non-disease, and clinically relevant abnormalities will be shared with the site for storage.

4.6.2. Benefit Assessment

Currently there is no cure for MM, and after exhausting available treatment options patients frequently relapse, become refractory, and ultimately die of their disease. This study will test a novel combination of belantamab mafodotin and pembrolizumab to assess safety, tolerability and clinical activity of this treatment. Belantamab mafodotin has been shown to induce immunogenic cell death phenomenon of MM cells in vitro, which provides a rationale for testing it in combination with pembrolizumab. It is reasonable to hypothesise that such combination will benefit MM patients, who are refractory to currently available treatments.

4.6.3. Overall Benefit: Risk Conclusion

Although there is limited human experience with belantamab mafodotin, and no clinical experience with the combination of belantamab mafodotin with pembrolizumab, given the currently available safety data and the low likelihood of drug-drug interactions between belantamab mafodotin and pembrolizumab, combination therapy may have an acceptable safety profile. Additionally, the combination may provide anti-tumor effect in subjects with MM; but this is unknown.

Of note, excess deaths were noted with pembrolizumab in combination with lenalidomide and dexamethasone (Keynote-185) or in combination with pomalidomide and dexamethasone (Keynote-183) leading the FDA to suspend these phase 3 trials, in addition to other trials of anti-PD[L] therapies in combination with immunomodulatory agents in myeloma or non-Hodgkin's lymphoma were suspended . Please refer to Section 2.3.3 for additional information. This statement does not apply to patients taking KEYTRUDA (pembrolizumab) for an approved indication. The safety and efficacy of using KEYTRUDA (pembrolizumab) for approved, on-label uses have been proven. (www.fda.gov/Drugs/DrugSafety/ucm574305.htm). Considering the measures taken and described in Section 7, to minimize risk to subjects, the potential risks associated with belantamab mafodotin in combination with pembrolizumab noted in Section 4.6.1 are justified by the anticipated benefits that may be afforded to subjects with MM.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on belantamab mafodotin that may impact subject eligibility is provided in the Investigator's Brochure [GlaxoSmithKline Document Number 2013N175128_09, 2021].

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on pembrolizumab that may impact subject eligibility is provided in the pembrolizumab approved labelling. For detailed background information on pembrolizumab refer to [Keytruda SmPC,2017 and KEYTRUDA PI, 2018].

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. Provide signed written informed consent, which includes compliance with the requirements and restrictions listed in the consent form
2. Male or female, 18 years or older (at the time consent is obtained)
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix 2)
4. Subjects must:
   - Has histologically or cytologically confirmed diagnosis of MM, as defined by IMWG, 2014 [Rajkumar, 2014], and
   - Has undergone stem cell transplant or is considered transplant ineligible, and
   - Has been treated with at least 3 prior lines of prior anti-myeloma treatments including an IMiD (eg. lenalidomide or pomalidomide), a proteasome inhibitor (eg. bortezomib, ixazomib or carfilzomib) and an anti-CD38 antibody alone or in combination. Line of therapy are defined by consensus panel of the International Myeloma Workshop [Rajkumar, 2011].
   - Has measurable disease defined as one 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 (≥100 mg/L) and an abnormal serum free light chain ratio (<0.26 or >1.65)
5. Subjects with a history of autologous stem cell transplant are eligible for study participation provided the following eligibility criteria are met:
   a) transplant was > 100 days prior to study enrolment
   b) no active infection (s)
   c) subject meets the remainder of the eligibility criteria outlined in this protocol
6. Adequate organ system functions as defined in Table 3

Table 3 Adequate Organ System Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)[1]	≥ 1.0 X 10^9/L
Hemoglobin	≥ 8.0 g/dL
Platelets	≥ 75 X 10^9/L
Hepatic	
Total bilirubin	≤1.5X ULN (Isolated bilirubin >1.5 xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
AST and ALT	≤2.5 X ULN
Renal	
eGFR[2] Spot urine (albumin creatinine ratios)	≥40 mL/min <500 mg/g (56 mg/mmol)
Cardiac	
LVEF (Echo)	≥50%
QTcF interval[3]	< 470 msecs

1. Without any Growth factor support (e.g.colony stimulating factors (including granulocyte colony stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GMCSF], recombinant erythropoietin) or any thrombopoietin receptor agonists) within 2 weeks before the first dose of study drug.
2. As calculated by Modified Diet in Renal Disease (MDRD) formula
3. The QT interval should be corrected for heart rate by Fridericia's formula (QTcF)

NOTE: Laboratory results obtained during Screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the investigator may retest the subject and the subsequent within range screening result may be used to confirm eligibility. If laboratory results were obtained more than 72 hours before first dose, laboratory results must be redone within 72 hours prior to first dose to confirm eligibility.

7. All prior treatment-related toxicities (defined by National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.03, 2010) [NCI, 2010] must be ≤ Grade 1 at the time of enrollment except for alopecia and Grade 2 neuropathy.
8. A female subject is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
   - Is not a woman of childbearing potential (WOCBP)
     OR
   - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 8 during the intervention period and for at least 9 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. Contraceptive use by

women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

A WOCBP must have a negative highly sensitive serum pregnancy test (as required by local regulations) within 72 hours of dosing on C1D1 and agree to use effective contraception during the study and for 4 months after the last dose of study medication.

Additional requirements for pregnancy testing during and after study intervention are located in Appendix 8.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

9. Male subjects:
   - Male subjects are eligible to participate if they agree to the following from the time of first dose of study until 6 months after the last dose of study treatment to allow for clearance of any altered sperm:
     - 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 as detailed below:
     - Agree to use a male condom, even if they have undergone a successful vasectomy, and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Appendix 8 when having sexual intercourse with a woman of childbearing potential who is not currently pregnant
     - Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies

5.2. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Systemic anti-myeloma therapy or an investigational drug ≤14 days or five half-lives, whichever is shorter, preceding the first dose of study drug
2. Plasmapheresis within 7 days prior to the first dose of study drug
3. Prior treatment with a monoclonal antibody within 30 days of receiving the first dose of study drugs
4. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g.,

CTLA-4, OX 40, CD137) and was discontinued from that treatment due to a Grade 3 or higher immune related adverse event (irAE)

5. Current corneal epithelial disease except mild punctate keratopathy
6. Any major surgery within the last four weeks prior to the first dose of study therapy
7. Presence of active renal condition (infection, requirement for dialysis or any other condition that could affect subject's safety). Subjects with isolated proteinuria resulting from MM are eligible, provided they fulfil criteria given in Table 3
8. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions (including lab abnormalities) that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures.
9. Has received prior radiotherapy within 2 weeks of start of study therapy. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.
10. History of (non-infectious) pneumonitis that required steroids, or current pneumonitis
11. Current active 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 chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) or hepatobiliary involvement of malignancy is acceptable if subject otherwise meets entry criteria
12. Malignancies other than disease under study are excluded, except for any other malignancy from which the subject has been disease-free for more than 2 years and, in the opinion of the principal investigators and GSK Medical Monitor, will not affect the evaluation of the effects of this clinical trial treatment on the currently targeted malignancy (RRMM). Subjects with curatively treated non-melanoma skin cancer are allowed.
13. Has known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study therapy
14. Evidence of cardiovascular risk including any of the following:
    a. QTcF interval ≥470 msecs.
       NOTE: The QT interval should be corrected for heart rate by Fridericia's formula (QTcF).
    b. Evidence of current clinically significant uncontrolled arrhythmias;
       i. including clinically significant ECG abnormalities including 2nd degree (Type II) or 3rd degree atrioventricular (AV) block.
    c. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within six months of Screening.
    d. Class III or IV heart failure as defined by the New York Heart Association functional classification system (Appendix 4)
    e. Uncontrolled hypertension
    f. Presence of cardiac pacemaker (or defibrillator) with a predominantly ventricular paced rhythm, limiting ECG/QTcF analysis.

g. Abnormal cardiac valve morphology (≥Grade 2) documented by echocardiogram (subjects with grade 1 abnormalities CCI [redacted] can be entered on study). Subjects with moderate valvular thickening should not be entered on study.

15. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to belantamab mafodotin or pembrolizumab, or any of the components of the study treatment.
16. Pregnant or lactating female.
17. Known active infection requiring antibiotic, antiviral, or antifungal treatment.
18. Known HIV infection.
19. 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
20. 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: Subjects with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained
    NOTE: Hepatitis RNA testing is optional and subjects with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing
21. Has received a live-virus vaccination within 30 days of planned start of study therapy. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist) are live attenuated vaccines, and are not allowed.
22. Active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
23. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other chronic form of immunosuppressive therapy within 7 days prior the first dose of study therapy
24. Has known psychiatric or substance abuse disorder that would interfere with the subject's ability to cooperate with the requirements of the study.
25. Has had an allogenic tissue/solid organ transplant

5.3. Screening Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened subjects must be assigned a new unique subject number that is different from the initial number.

5.4. Withdrawal/Stopping Criteria

Subjects will receive study treatment until disease progression, death or unacceptable toxicity (including but not restricted to meeting stopping criteria for significant toxicity as outlined in Section 5.4.1), or completion of pre-assigned treatment by reaching a maximum of 35 treatment cycles. In addition, study treatment may be permanently discontinued for any of the following reasons:

- recurrent Grade 2 pneumonitis
- subject has met any of the protocol defined safety stopping criteria (Section 5.4.1)
- deviation(s) from the protocol
- request of the subject or proxy (withdrawal of consent by subject or proxy)
- investigator's discretion
- concurrent illness that prevents further administration of study treatment(s)
- study treatment must be permanently discontinued in case of pregnancy
- subject is lost to follow-up
- study is closed or terminated

The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and electronic case report form (eCRF)

If the subject withdraws the consent and discontinues from treatment due to toxicity, 'adverse event (AE)' will be recorded as the primary reason for permanently discontinuation on the eCRF.

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be re-entered the study.

After the study treatment discontinuation, subjects will undergo end of treatment assessments 30 days (±7 days) after the last dosing, or prior to the start of new anti-cancer treatment (whichever occurs first). Subjects who discontinued treatment for reasons other than PD will be followed up every 3 weeks until confirmed PD, until initiation of a new anti-cancer therapy or death. All subjects with confirmed PD will be followed for OS and next subsequent anti-cancer therapy every 3 months until the end of study. End of study is defined in Section 5.5.2.

The following actions must be taken for subjects who fail to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3

telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

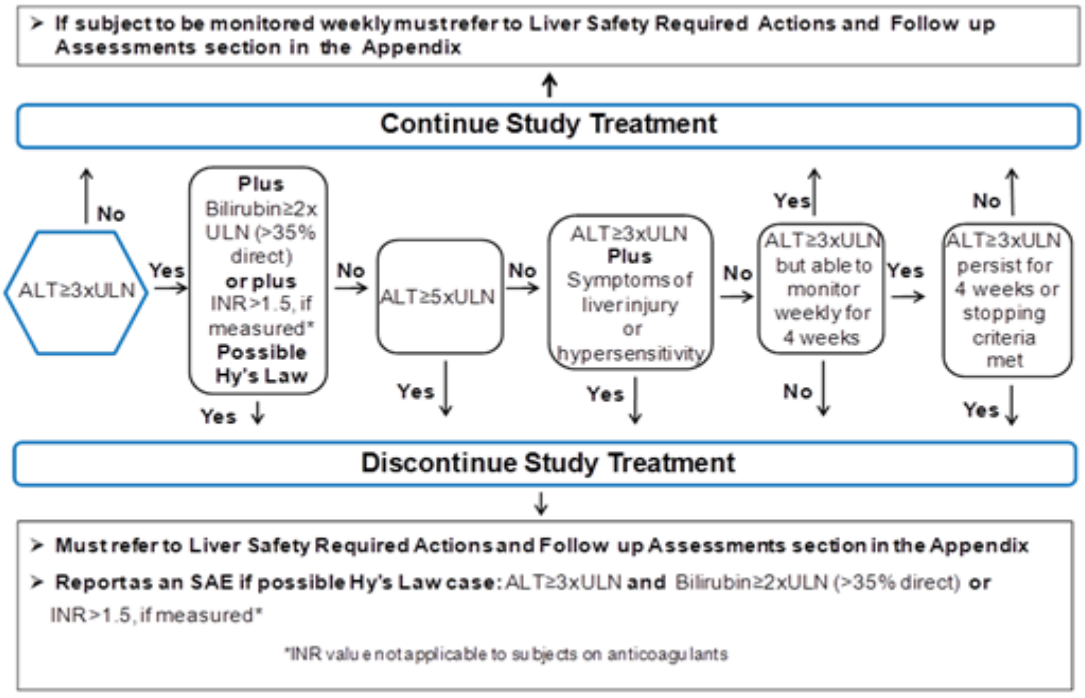
5.4.1. Safety stopping criteria

5.4.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology.

The diagram below illustrates Liver Stopping Event Algorithm (Figure 3).

Figure 3 Liver Stopping and Monitoring Even Algorithm



Refer to Appendix 5 for required Liver Safety Actions and Follow up Assessments.

5.4.1.2. Study Treatment Restart or Rechallenge

If subject meets liver chemistry stopping criteria do not restart/rechallenge subject with study treatment unless:

- GSK Medical Governance approval is granted (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

If GSK Medical Governance approval to restart/rechallenge subject with study treatment is not granted, then subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments.

5.4.1.3. QTc Stopping Criteria

If a subject that meets the corrected QT (QTc)[1] interval duration criteria below, study treatment(s) will be withheld.

- QT interval corrected for heart rate by Fridericia's formula (QTcF = QT / CubeRootRR) >530 msec

  OR

- Increase of QTcF by ≥60 msec from baseline

[1]Based on average QTc value of triplicate ECGs to include manual over-read. For example, if an ECG demonstrates a prolonged QT interval, obtain 2 additional ECGs over a brief period (e.g., within approximately 10 minutes of the abnormal ECG, if possible, and approximately 10 minutes apart from each other), and then use the averaged QTc values of the 3 ECGs to determine whether the subjects should have study treatment(s) withheld.

The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

5.4.1.4. Left Ventricular Ejection Fraction (LVEF) stopping criteria

Echocardiography (ECHO) must be performed at Screening and as outlined in the Time and Events Table (Table 7). Subjects who have an asymptomatic, absolute decrease of >15% in LVEF compared with baseline or an absolute decrease of >10% in LVEF compared with baseline and the ejection fraction is below 50% should temporarily interrupt study treatment and have a repeat evaluation of LVEF within 1 week. ECHO should be repeated every 1 to 2 weeks for 4 weeks or until LVEF recovery to within 15% of baseline or to above 50% and within 10% of baseline depending on which stopping criteria above were met.

- If the LVEF recovers (defined as absolute decrease ≤15% compared to baseline or ≥50% and absolute decrease ≤10% compared with baseline) at any time during the next 4 weeks, after consultation and approval of the GSK Medical Monitor, the subject may be restarted on belantamab mafodotin at a reduced dose. For such

subjects, monitoring of LVEF will be performed 2, 4, and 8 weeks after rechallenge, and then per protocol

- If LVEF does not recover within 4 weeks, treatment with the combination of belantamab mafodotin and pembrolizumab should be permanently discontinued. Ejection fraction should be monitored every 4 weeks for a total of 16 weeks or until resolution

Subjects with Grade 3 or 4 symptomatic left ventricular systolic dysfunction must discontinue treatment with the combination of belantamab mafodotin and pembrolizumab. Ejection fraction should be monitored every 4 weeks for a total of 16 weeks or until resolution. Copies of all ECHOs and cardiology consultations performed on subjects who experience a >15% decrease in LVEF from baseline or >10% decrease in LVEF from baseline and whose cardiac ejection fraction is <50% will require review by a GSK medical monitor. Instructions for submitting qualifying ECHOs/MUGAs are provided in the Study Reference Manual (SRM).

5.4.1.5. Troponin Evaluation and Stopping Criteria

If post-screening, the local troponin is >Institutional ULN it is recommended that subjects undergo urgent evaluation of cardiac ischemia symptoms and ECG should be performed to rule out cardiac ischemia. An urgent repeat of troponin value and collection of sample for central lab evaluation should be obtained within 24 hours.

Asymptomatic subject:

If the second value of troponin is ≤ULN the subject can continue on study with close follow up of symptoms, ECG, and further troponin measurements as clinically indicated If the second value of troponin remains >ULN treatment with belantamab mafodotin should be interrupted. The subject should undergo cardiac evaluation including ECHO testing for cardiac function. Any re-start of study treatment must be discussed with the GSK medical monitor who will consult with a member of the internal cardiotoxicity panel prior to restart. If the second value of troponin exceeds the threshold for MI according to local lab parameters, obtain cardiology consultation immediately. Permanently discontinue belantamab mafodotin and withdraw the subject from the study.

Symptomatic subject:

Obtain cardiology consultation immediately. Permanently discontinue belantamab mafodotin and withdraw the subject from the study.

5.4.1.6. Valvular Toxicity Stopping Criteria

Subjects who have a new asymptomatic, moderate regurgitation or stenosis by ECHO (Grade 2 mitral/tricuspid/aortic valvular toxicity per National Cancer Institute- Common Toxicity Criteria for Adverse Events [NCI-CTCAE], version 4.03, [NCI, 2010]) should temporarily discontinue study treatment and have a repeat evaluation by ECHO within 1 week. ECHO should be repeated every 1 to 2 weeks for 4 weeks or until valve recovery to baseline.

- If the valve recovers to baseline any time during the next 4 weeks after consultation and approval of the Medical Monitor, the subject may be restarted on belantamab mafodotin at a reduced dose(s). For such subjects, monitoring of the valve via ECHO will then be performed 2 and 4 weeks after rechallenge, and then per protocol.
- If repeat ECHO does not reveal valve recovery to baseline within 4 weeks, then the subject should permanently discontinue study treatment . The valve should continue to be monitored via ECHO every 4 weeks for 16 weeks or until resolution.
- Subjects with a Grade 3 or 4 CCI [redacted] valvular toxicity must discontinue study treatment. Valvular toxicity should continue to be monitored every 4 weeks for 16 weeks or until resolution. If recovery occurs (return to baseline via imaging AND symptom resolution) within 4 weeks, the subject may receive belantamab mafodotin at a reduced dose after consultation and approval of the Medical Monitor.

Echocardiogram must be performed as outlined in the Time and Event tables (Table 7, Table 8, and Table 10). Copies of all ECHO(s) and cardiology consultations performed on subjects who experience valvular toxicity will be required by GSK for review. Instructions for submitting qualifying ECHOs are provided in the SRM.

5.4.1.7. Corneal Toxicity Stopping Criteria

Corneal events should be graded according to the guidelines provided in Appendix 9.

Subjects who develop Grade 4 corneal toxicity have to be discussed in detail between the treating ophthalmologist (or optometrist, if an ophthalmologist is not available), the GSK Medical Monitor, and possibly a GSK ophthalmologist, in order to determine whether the subject can be allowed to continue treatment with belantamab mafodotin, or should be permanently removed from study. If subject is allowed to continue on study, the dose of belantamab mafodotin will be reduced by 1 dose level. The decision will be documented in study files, together with individual assessment of risk-benefit. For details on re-start guidance, see Table 4.

5.4.1.8. Infusion-Related Reactions

Infusion-Related Reactions Associated with Belantamab Mafodotin

Premedication is not required prior to infusion of belantamab mafodotin unless deemed medically appropriate by the investigator following evaluation of infusion related reactions. Premedication should be considered in any subject who experienced an infusion related reaction at first or any subsequent infusion with belantamab mafodotin

Infusion-related reactions should be managed by guidelines provided in Table 4. A subject that experiences a Grade 4 IRR after belantamab mafodotin, should be permanently withdrawn from the study.

Infusion-Related Reactions Associated with pembrolizumab

If an IRR occurs during and/or after the infusion of pembrolizumab, refer to Table 6 for further guidance.

5.4.1.9. Allergic and Anaphylactic reaction stopping criteria

All subjects will be monitored carefully for evidence of allergic response. A subject that exhibits signs or symptoms of severe hypersensitivity or anaphylaxis will receive appropriate medical treatment and be permanently withdrawn from the study.

Additional stopping criteria in case of significant toxicity are provided in Section 6.5.1

5.5. Subject and study Completion

5.5.1. Subject completion

For Part 1 and Part 2, a subject is considered to have completed the study if they received at least 1 cycle of combination study treatment, and:

- The subject is followed until death, or
- The subject is followed until the end of study

The end of study is defined in Section 5.5.2. The end of study analyses will be performed at that time.

The eCRF should continue to be completed during the follow up period (every 3 months (±7 days) until the end of study. Please refer to Table 10 for assessments to be completed during PFS follow-up visits or OS follow-up. OS follow-up data can be based on contacting subjects via phone calls/e-mails/or, other means of communication. Subjects who cannot be contacted will be considered lost to follow up. Follow-up data will be entered into the eCRF.

5.5.2. End of Study Definition

A final data cut-off will occur when all participants have either died, progressed, withdrawn consent, or have been followed for a minimum of 24 months from the LSFD.

Following 24 months post LSFD, PACT will be implemented. At this time, the collection of data for all recruited participants who no longer receive study treatment will stop entirely and clinical trial database will be closed. Those participants still benefiting from belantamab mafodotin will continue to receive study drug as assessed by the investigator, or can choose to discontinue belantamab mafodotin and only SAEs, overdose and pregnancy cases, and pre-specified ocular data will be reported directly to GSK.

Dispensing of study treatment following 24 months post LSFD, will utilize a manual resupply option, and drug accountability assessment will be performed at the site. All participants will be monitored and will receive follow-up care in accordance with standard local clinical practice. For participants who do continue to receive belantamab

mafodotin beyond the time of the final data cut-off, investigators will continue to report all SAEs, pregnancy and overdose cases up to 70 days after last dose of study treatment, and pre-specified ocular data (see SRM) will be reported until resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow up. Additionally, any SAE and pre-specified ocular event that are ongoing at the time of this data cut-off must be followed up to resolution, unless the event is considered by the investigator unlikely to resolve, or the patient is lost to follow-up. GSK retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

5.5.3. Treatment after the End of Study

The investigator is responsible for ensuring that consideration has been given for the post-study care of the subject's medical condition whether or not GSK is providing specific post-study treatment. If a subject remains on treatment at the time end of study is achieved they may be offered an option to extend treatment.

6. INVESTIGATIONAL PRODUCT

The term of "Study Treatment" are used throughout the protocol to describe belantamab mafodotin and pembrolizumab as the investigational products (IP)

6.1. Investigational Products

Product name:	Belantamab Mafodotin	Pembrolizumab
[Formulation description:]	Solution containing 20 mg/mL, 1.5 mL/vial	Solution containing 100 mg/4 mL
Dosage form:	20 mg/mL solution for infusion Supplied as frozen liquid. Protect from light.	100 mg/4 mL solution that should be stored under refrigeration at 2-8°C (36-46°F). Protect from light. Do not freeze. Do Not Shake.
Unit dose strength(s)/Dosage level(s):	20 mg/mL, 1.5 mL/vial	100 mg/4 mL
Route of Administration	Delivered as IV infusion over at least 30 minutes. Infusions may be prolonged in the event of an infusion reaction. If subjects experience clinically significant infusion reactions, the infusion rate may be slowed for all future administrations of study treatment(s) for each subject. Should a global change in infusion rate be required, it will be communicated to sites in writing.	Delivered as 30 min IV infusion

Dosing instructions:	Dilute belantamab mafodotin solution in normal 0.9% saline to the appropriate concentration for the dose. See SRM for detailed preparation procedures.	Dilute pembrolizumab injection (solution) prior to intravenous Administration in 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) or 5% Dextrose Injection, USP. See SRM for detailed preparation procedures.
Manufacturer/ Source of Procurement:	GSK/Baxter	Merck

6.2. Medical Devices

Not applicable.

6.3. Treatment Assignment

Dose level allocation will be performed by GSK after subject has given written informed consent and has completed the necessary screening assessments. Eligible subjects will be enrolled to receive GSK2857916 at an assigned dose in combination with 200 mg of pembrolizumab.

Additional details are outlined in the SRM.

6.3.1. Study Treatment Administration

For belantamab mafodotin, please refer to the SRM for additional details on administration. For pembrolizumab, the study medical staff should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the belantamab mafodotin and pembrolizumab infusion and administration of infusion solution.

6.3.1.1. Belantamab Mafodotin Administration

Belantamab mafodotin will be administered to subjects intravenously as mg/kg calculated dose at the study site . The dose to be administered is based on actual body weight calculation, and may be reduced for toxicity according to protocol guidelines.

Administration will be documented in the source documents and reported in the eCRF. The time of start and end of infusion will be documented in eCRF.

Belantamab mafodotin will be administered over at least 30 minutes on Day 1 of each cycle at the assigned dose. Premedication is not required prior to infusion unless deemed medically necessary by the investigator, in which case it should be administered

according to institutional recommendations. In case of infusion related reactions related to belantamab mafodotin the rules outlined in Section 5.4.1.8 and in Table 6 should be followed.

After the infusion of belantamab mafodotin has been completed subject will be required to enter at least 1 hour rest period before start of pembrolizumab infusion. In case of IRR during belantamab mafodotin infusion, subject needs to recover to Grade 1 or less in order to be able to receive pembrolizumab infusion.

6.3.1.2. Pembrolizumab administration

Pembrolizumab will be administered using IV infusion on Day 1 of each 3-week treatment cycle after all procedures and assessments have been completed.

Pembrolizumab will be administered as a dose of 200 mg using a 30 min IV infusion after at least approximately 1 hour rest period after completion of belantamab mafodotin infusion. Premedication is not required prior to infusion unless deemed medically necessary, in which case it should be administered according to institutional recommendations.

In case of IRR during or after preceding belantamab mafodotin infusion, the administration of pembrolizumab will be delayed to allow for recovery to Grade 1 or less. In total, the infusion of pembrolizumab may be delayed for up to the allowed +3 day window from the scheduled dose date to allow for recovery, and to accommodate scheduling conflicts in a given cycle. If the subject does not recover from IRR to Grade 1 or less within the +3 day window, the dosing of pembrolizumab will be skipped in a given cycle, and may be resumed in the next cycle.

All subjects are required to remain under observation at the study site for at least three hours post-infusion of the last study drug administered for the first two study treatment dosing visits. At subsequent study treatment dosing visits, for subjects who experience infusion-related reactions, the post-infusion observation time should remain as at least three hours; for subjects who do not experience infusion reactions, these subjects should remain under observation for a time period not shorter than one hour (or longer as per the judgement of the investigator or as per institutional guidelines.)

In case of IRR during pembrolizumab administration –please refer to Table 6 for management guidelines.

Detailed information on the preparation and administration, refer to [Keytruda SmPC, 2017 and KEYTRUDA PI, 2018].

6.4. Planned Dose Adjustments

6.4.1. Adjustments due to body weight

The actual body weight in kg at the baseline (assessed on the Cycle 1 Day prior to dosing) will be used for dose calculation of belantamab mafodotin in all subjects during

the treatment period. However, if the change of body weight is greater than 10%, the dose should be re-calculated based on the actual body weight on the day of dosing.

A fixed dose of pembrolizumab will be used during the study.

6.4.2. Intra subject dose escalation

For subjects enrolled in Part 1 intra-subject dose escalations of belantamab mafodotin may be considered on a case-by-case basis, provided that the subject completed at least 2 cycles at originally assigned dose, has tolerated treatment well, and did not experience the treatment related Grade 3 or higher toxicity. A subject's dose may be increased to that of a completed cohort that has not exceeded the maximum pre-specified dose of 3.4 mg/kg. Approval must be obtained from a GSK Medical Monitor. Dose-escalation decisions will be documented on a Dose Escalation/De-escalation Decision Form (see SRM).

6.5. Subject Specific Dose Adjustment Criteria

6.5.1. Dose modifications and management for belantamab mafodotin-related toxicity

Subjects should have their dose (including the first dose and subsequent doses) delayed or reduced for toxicities according to the recommendations as listed in Table 4. Dose reductions are only allowed for belantamab mafodotin.

In individual cases where, in the judgement of an investigator, waiting a full planned Cycle (21 days) to resume treatment after delays due to toxicities would be detrimental to the subjects' health, the Medical Monitor should be contacted to discuss an earlier re-start. An earlier re-start may be considered only for subjects who have recovered from toxicity to Grade 1 or less. Dosing cannot occur more frequently than every 21 days (±3 days). In such cases, efficacy and safety assessments must remain every 3 weeks from the initial efficacy and safety assessments (Cycle 1 Day 1), which may result in 2 separate visits (1 for disease assessment [Table 8] and 1 for dosing [Table 9]).

No dose reductions are allowed for pembrolizumab. Dose Modification Guidelines for Pembrolizumab-Related Adverse Events are listed in Table 5.

If belantamab mafodotin is held or discontinued for any toxicity, pembrolizumab is to be held or discontinued.

For drug related toxicities which are not listed in Table 4 and Table 5, the general rule of withholding the dose at Grade 3 or greater toxicity should be followed.

Resuming treatment will be possible with or without dose reduction after the toxicity has resolved to Grade 1 or less, and in agreement between PI and GSK Medical Monitor.

Table 4 Dose Modification Guidelines for Belantamab Mafodotin-Related Adverse Events

Toxicity	Grade	Recommendations to belantamab mafodotin	Recommendations to pembrolizumab
Serum creatinine elevation or decrease in eGFR which cannot be explained by concomitant sepsis, TLS, other severe infection with fever or dehydration	If absolute serum creatinine increase from baseline of >0. 5 mg/dL	• Repeat serum creatinine within 48 hours • If confirmed: withhold therapy, institute treatment and monitoring as clinically indicated, and follow for resolution • Discuss any further dosing with Medical Monitor[a]	See Table 5 for guidance on pembrolizumab
Serum creatinine≥Grade 3 (acute kidney injury)	>3.0mg/dL from baseline Or 3.0-6.0xULN	• Provide appropriate medical treatment. • Permanently discontinue treatment with belantamab mafodotin	Resume treatment with pembrolizumab only if treatment with belantamab mafodotin may be continued
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 current dose • If confirmed on re-test and no clear evidence of disease progression[c] ○ Interrupt treatment with belantamab mafodotin ○ Repeat testing within 4 weeks ○ If spot urine <2000 mg/g (224/mg/mmol) may restart belantamab mafodotin with one dose level reduction ○ If spot urine remains >2000 mg/g (224/mg/mmol) after 4weeks; permanently discontinue belantamab mafodotin and discontinue study treatment; provide treatment as clinically indicated and follow for resolution	Resume treatment with pembrolizumab only if treatment with belantamab mafodotin may be continued
Thrombocytopenia (on days of dosing))	3-4	• Withhold treatment until thrombocytopenia recovered to Grade 2 or less (≤G2). • If Grade 3-4 thrombocytopenia is considered disease-related, treatment may be continued with dose reduction and more	Delay treatment until the next belantamab mafodotin dose

Toxicity	Grade	Recommendations to belantamab mafodotin	Recommendations to pembrolizumab
		frequent hematology monitoring, until recovery to Grade 2 or less. • Implement supportive treatment (e.g. transfusion) as clinically indicated and per local practice.	
Febrile neutropenia	Defined as: single temp of 38.3°C, or sustained 38°C for >1 hr AND ANC <1.0x10^9/L	• Withhold belantamab mafodotin and pembrolizumab and hospitalize subject with appropriate management, per local institutional guidance • Consider additional supportive treatment per local guidance (e.g., growth factors) • Upon recovery, consider a dose reduction of belantamab mafodotin, if neutropenia was drug related	• Delay treatment until the next belantamab mafodotin dose
Neutropenia	≥3 (Defined as ANC <1.0x10^9/L	• If noted on Day 1 of any cycle, withhold belantamab mafodotin. Repeat hematology (CBC) as clinically indicated until recovery to Grade 2 or less. • Resume belantamab mafodotin at pre-hold dose once neutropenia recovers to Grade ≤2 CCI [redacted] on Day 1 of the subsequent cycle. • Implement supportive care as clinically indicated per local practice	• Delay treatment until the next belantamab mafodotin dose
	In case of recurrence of frequent episodes of neutropenia CCI [redacted]	• Consider dose reduction of belantamab mafodotin, if it was drug-related.	• Delay treatment until the next belantamab mafodotin dose
Belantamab mafodotin Treatment Related Corneal events[b]	Corneal Management Care Regardless of Grade	**Preservative-free artificial tears**: • Increase to 1 drop as frequently as every 2 hours, as needed	
	Grade 1 per GSK Scale	• Continue treatment with current treatment with belantamab mafodotin	• None

Toxicity	Grade	Recommendations to belantamab mafodotin	Recommendations to pembrolizumab
	Grade 2 per GSK Scale	• If Grade 2 finding (visual acuity and/or exam finding) and the subject is **asymptomatic,** continue dosing with belantamab mafodotin. • If Grade 2 finding (visual acuity and/or exam findings) and the patient is **symptomatic**. ○ **DOSE REDUCE** and continue treatment. ○ If already on 1.92 mg/kg, subject may continue at current dose. • Upon improvement of either visual acuity or ophthalmic exam findings to ≤Grade 1 and improvement in symptoms, dose may be re-escalated to previous dose.	• Hold/Delay treatment until the next belantamab mafodotin dose
	Grade 3 per GSK Scale	• If Grade 3 finding (exam finding) and the subject is **asymptomatic**: continue dosing with belantamab mafodotin. • If Grade 3 exam finding and the subject is **symptomatic or Grade 3 visual acuity**: ○ HOLD belantamab mafodotin . Upon improvement of either visual acuity or ophthalmic exam findings to ≤ Grade 2 and improvement in symptoms continue treatment with dose **REDUCTION**. ○ If already on 1.92 mg/kg subject may continue at current dose • If after event resolution eye symptoms are considered stable for at least 3 cycles consider re-escalation to previous dose.	• Hold/Delay treatment until the next belantamab mafodotin dose
	Grade 4 per GSK Scale	• Hold treatment with belantamab mafodotin. • Treatment re-start may be possible after discussion and agreement between the treating ophthalmologist*, treating physician, the GSK Medical Monitor • *or optometrist, if an ophthalmologist is not available	• Stop treatment with pembrolizumab. • Further treatment only possible if belantamab mafodotin is allowed to restart

Toxicity	Grade	Recommendations to belantamab mafodotin	Recommendations to pembrolizumab
Infusion Reaction[c]	2	Stop the infusion, provide medical treatment and continue at slower pace after resolution to Grade 0-1	See Table 6 for guidance on pembrolizumab
	3	Further treatment with belantamab mafodotin needs to be discussed with Medical Monitor. Continuation only allowed after recovery to ≤Grade 1 and with pre-medication, and extension of infusion time to 2-4 hours. Any future infusion needs to be pre-medicated	
	4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Continue when toxicity resolves to Grade 0-1	See Table 5 for guidance on pembrolizumab
	Grade 3-4	Permanently discontinue	Permanently discontinue

a. Medical Monitor may consult GSK's nephrotoxicity panel about plans to continue therapy
b. Corneal toxicity should be graded according to GSK scale for belantamab mafodotin treatment related Corneal Events (Appendix 9).
c. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose

6.5.2. Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab combination exposure, including coadministration with additional compounds, may represent an immune-related response. These immune related AEs (irAEs) may occure shortly after the first dose or several months after the last dose of pembrolizumab combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 5.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, to belantamab mafodotin alone, or to pembrolizumab alone, for adverse events listed in Table 5, both interventions must be held according to the criteria in [Table 5].

Holding Study Interventions:

When study interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

Restarting Study Interventions:

Subjects may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 5.If the toxicity does not resolve or the criteria for resuming treatment are not met, the subject must be discontinued from all study interventions.If the toxicities do resolve and conditions are aligned with what is defined in Table 5, the combination of belantamab mefodotin and pembrolizumab may be restarted at the discretion of the investigator.

Table 5 Dose Modification Guidelines for Pembrolizumab-Related Adverse Events

General instructions:

1. Severe and life-threatening irAEs, should be treated with IV corticosteroids fllowed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if AE does not resolve or the corticosteroid dose is ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤Grade 1 after corticosteroid taper.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.03)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment •
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.03)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
				sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased Bilirubin	Grade 2[1]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3[2] or 4[3]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[4]	• Initiate insulin replacement therapy for subjects with T1DM • Administer an antihyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[4]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue[1]		

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.03)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis; grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology, and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1)	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology, or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.03)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
	Grade 3	Withhold or discontinue based on event[5].		
	Recurrent Grade 4 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal;; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

NOTES**:** Non-irAE will be managed as appropriate, following clinical practice recommendations.

1. AST/ALT: >3.0 - 5.0 x ULN if baseline normal; >3.0 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal
2. AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal
3. AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal
4. The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed. .
5. Events that require discontinuation include but are not limited to: encephalitis, and other clinically important irAEs (eg. Vasculitis and sclerosing cholangitis).

6.5.3. Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are in Table 6.

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6.6. Blinding

This is an open-label study.

6.7. Packaging and labelling/Preparation/Handling/Storage

The contents of the label will be in accordance with all applicable regulatory requirements.

Open label vials of belantamab mafodotin solution 20 mg/mL, 1.5 mL, each carton contains 1 x vial.

Open label vials of pembrolizumab solution (100 mg/4 mL), each carton contains 1 x vial.

6.7.1. Belantamab Mafodotin

Preparation

Belantamab mafodotin Solution for Infusion, 20 mg/mL, 1.5 mL is supplied as a frozen liquid. Before use, thaw each vial of belantamab mafodotin and prepare infusion solution. Refer to the SRM for further details on preparation of belantamab mafodotin.

Handling

Under normal conditions of handling and administration, investigational product (IP) is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

In the case of unintentional occupational exposure notify the study monitor, the GSK Medical Monitor and/or the study manager.

Refer to the SRM for detailed procedures for the disposal and/or return of unused study treatment(s).

Administration

Belantamab mafodotin is compatible with polyvinylchloride-lined or polyolefin-lined intravenous infusion administration sets, 0.2 micron polyethersulfone filters, or optionally a polyurethane catheter. Doses of belantamab mafodotin are to be administered as an IV infusion via an infusion pump that can ensure precision to the decimal point of a mL for the infusion rate at lower doses. It is recommended to prime the IV tubing with at least 15 mL prior to dosing.

Storage

Belantamab mafodotin must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the belantamab mafodotin will be limited to the investigator and authorized site staff. Belantamab mafodotin must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

Belantamab mafodotin is to be stored at a temperature range of -50°C to -15°C. Maintenance of a temperature log is required.

6.7.2. Pembrolizumab

Preparation

Pembrolizumab will be provided in a single-use vial at 100 mg/4 mL (25 mg/mL).

Preparation for intravenous infusion: withdraw the required volume from the vials of pembrolizumab and transfer into an intravenous (IV) bag containing 0.9% sodium chloride injection, USP or 5% dextrose injection, USP. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL. Refer to the SRM for further details on preparation of pembrolizumab.

Handling

Under normal conditions of handling and administration, investigational product (IP) is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

In the case of unintentional occupational exposure notify the study monitor, the GSK Medical Monitor and/or the study manager.

Refer to the SRM for detailed procedures for the disposal and/or return of unused study treatment(s).

Administration

Pembrolizumab infusion solution should be intravenously administered over 30 minutes through an intravenous line containing a sterile, non-pryogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes -5 min/+10 min).

Storage

The vials of pembrolizumab (100 mg/4 mL) solution should be stored under refrigeration at 2-8°C (36-46°F) in original carton to protect from light. Do not freeze and do not shake.

6.8. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product (IP) and other study treatments dispensed and/or administered to study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study. Refer to the SRM for further detailed instructions on product accountability.

6.9. Compliance with Study Treatment Administration

Both study drugs: belantamab mafodotin and pembrolizumab will be administered intravenously to subjects at the study site. The dose of pembrolizumab will be 200 mg. The dose of belantamab mafodotin is based on body weight calculation, and will be escalated from 2.5 mg/kg to 3.4 mg/kg in Part 1. The dose of GSK1857916 in Part 2 will be the RP2D as established in Part 1. The dose of belantamab mafodotin may be reduced for toxicity according to protocol guidelines.

6.10. Treatment of Investigational Product Overdose

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the sponsor within 24 hours of awareness.

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined below – Treatment of Overdose, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial.

For this study, an overdose of pembrolizumab will be defined as 1000 mg or ≥5 times the indicated dose.No specific information on the treatment of overdose of pembrolizumab and belantamab mafodotin.

In the event of an overdose (defined as administration of more than the protocol-specified dose) of belantamab mafodotin and pembrolizumab, the investigator should:

- contact the GSK Medical Monitor immediately
- closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until belantamab mafodotin can no longer be detected systemically (at least 3 months)
- obtain a plasma sample for pharmacokinetic (PK) analysis within 24 hours of the event if requested by the GSK Medical Monitor (determined on a case-by-case basis)
- document the quantity of the excess dose as well as the duration of the overdosing in the eCRF

6.11. Lifestyle and/or Dietary Restrictions

6.11.1. Contraception

Belantamab mafodotin and pembrolizumab may have adverse effects on a fetus in utero. The cytotoxic component of belantamab mafodotin, MMAF, disrupts microtubule function, is genotoxic, and can be toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity and should not be administered to pregnant or lactating women [GlaxoSmithKline Document Number 2013N175128_09, 2021]. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study.

6.11.1.1. Female Subjects

In order to participate in the study, WOCBP must adhere to the contraception requirement (from the day of study medication initiation) during the study and for 9 months after the last dose of study treatment. If there is any question that a WOCBP will not reliably comply with the requirements for contraception, that subject should not be entered into the study. Full details are in Appendix 8.

6.11.1.2. Male Subjects

Male subjects with female partners of child bearing potential must comply with the contraception requirements highlighted in Section 5.1 from the time of first dose of study medication until 140 days after the last dose of belantamab mafodotin. Details on contraceptive options for subjects with a partner of childbearing potential are in Appendix 8.
Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration from the time of first dose of study until 6 months after the last dose of study treatment to allow for clearance of any altered sperm.

6.11.1.3. Lactation Restrictions

Female subjects who are lactating must discontinue nursing prior to the first dose of study treatment and must refrain from nursing throughout the treatment period and for 4 months following the last dose of study treatment.

6.11.2. Subjects with Contact Lenses

Contact lenses are prohibited while on the study treatment (from first dosing to the end of study treatment). Contact lens use may be restarted after the ophthalmologist (or an optometrist if an ophthalmologist is not available) confirms there are no other contraindications.

Use of bandage contact lenses is permitted during study treatment as directed by the treating ophthalmologist (or optometrist if an ophthalmologist is not available).

6.12. Concomitant Medications/Vaccinations and Non-Drug Therapies

Subjects will be instructed to inform the investigator prior to starting any new medications from the time of first dose of study treatment until the end of the treatment visit. Any concomitant medication(s), including non-prescription medication(s) and herbal product(s), taken during the study will be recorded in the eCRF. Additionally, a complete list of all prior anti-cancer therapies will be recorded in the eCRF.

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by GSK and stored in the study file. The SRM will be updated to include this information. Any such changes will be communicated to the investigative sites in the form of a letter.

6.12.1. Permitted Medication(s)

Subjects should receive full supportive care during the study, including transfusion of blood products, growth factors, and treatment with antibiotics, anti-emetics, antidiarrheals, and analgesics, as appropriate.

Concomitant therapy with bisphosphonates and RANKL inhibitors are allowed.

Subjects may receive local irradiation or elective surgery, eg. for pain control after discussion with the medical monitor.

6.12.2. Tumor Lysis Syndrome (TLS) Prevention and Treatment Recommendations

Subjects with a high tumor burden with a high proliferative rate might be at risk for TLS and should be monitored for clinical and laboratory signs of tumor lysis. Specifically, all subjects with elevated uric acid (>8 mg/dL, or >476 mmol/L) should receive prophylaxis with allopurinol, or rasburicase. All subjects should be hydrated to reduce risks for renal toxicity and tumor lysis syndrome (TLS) with belantamab mafodotin treatment. Adequate fluid volume status should be maintained throughout treatment and blood chemistries should be monitored as indicated in the Time and Events Tables in Section 7 or more frequently if clinically indicated. Prior to the first dose in Cycle 1, all subjects should receive at least 250- 500 mL of intravenous normal saline or other appropriate intravenous fluid. Additionally, 250-500 mL of intravenous fluid should be given as needed following belantamab mafodotin administration. Intravenous hydration should be continued, as needed, in subsequent cycles and subjects should be monitored for fluid overload during this period.

If the constellation of clinical and/or laboratory signs tested on Cycle 2 Day 1 indicates a possibility of developing TLS, subjects should be hospitalized with frequent monitoring of clinical signs and clinical chemistries and treated accordingly.

6.12.3. Supportive Care Guidelines for Corneal Events (Belantamab Mafodotin)

Corneal events, which commonly manifests as a superficial microcystic keratopathy, has previously been reported with antibody drug conjugates, including those conjugated to MMAF [Tannir, 2014; Eaton, 2012; Younes, 2012]. It is required that the sites establish a close collaboration with an ophthalmologist (or optometrist, if ophthalmologist is not available) who will be responsible for assessing subjects on study and managing subjects who develop corneal toxicity in close communication with GSK Medical Monitor and possibly a GSK ophthalmologist.

Subjects will be assessed by ophthalmologists (or optometrist, if an ophthalmologist is not available) at baseline, and then every three weeks prior to each dose of belantamab mafodotin for the first 4 doses. After the 4th dose of belantamab mafodotin, if there are no significant ocular symptoms or vision changes the frequency of ophthalmologic exams may be decreased to once every 6 months until end of study treatment. In case of persistent or newly developed ocular symptoms or vision changes, the subject will have further ophthalmologic exams, at least every 3 months until resolution (to Grade 1 or baseline) or more frequently as clinical indicated by the eye care specialist.

Subjects who have signs or symptoms of corneal toxicity present at end of study will continue to be followed monthly for up to 12 months, or until deemed clinically stable by an ophthalmologist (or optometrist, if ophthalmologist is not available), whichever comes first. Clinically stable is defined as:

- Any GSK Grade 1 exam finding (CCI keratopathy) and a one-line change in vision when compared to baseline or,
- No exam findings, and a one-line change when compared to baseline or,
- Any GSK Grade 1 exam finding (CCI keratopathy) and no change in vision from baseline

Further information regarding corneal toxicity associated with belantamab mafodotin, including a grading scale and prophylactic measures are in Appendix 9.

6.12.4. Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in 6.5.2. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance. Refer to Table 5 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

6.12.5. Prohibited Medication(s)

Chronic treatment with oral steroids is prohibited while the subject is on study, unless for treatment of acute complications related to study treatment, or pre-medication prior to belantamab mafodotin, or pembrolizumab infusion. Steroids may be used to treat infusion related reactions. Inhaled steroids are allowed for management of asthma, or COPD.

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 (CYP) enzymes in vitro. Cys-mcMMAF was shown to be a substrate of P-glycoprotein (P-gp), and strong inhibitors of OATP1B1 and OATP1B3 should be avoided unless considered medically necessary.

A list of Prohibited Concomitant Medications is provided in SRM, based on known interactions or characteristics of each component of the Study Treatment.

Other Prohibited Therapies:

- Plasmapheresis is prohibited from 7 days prior to study entry through the end of study.
- Anti-cancer therapies other than those referred to as Study Treatment that include but are not limited to chemotherapy, immunotherapy, biologic therapy, hormonal therapy (other than physiologic replacement), surgery, and radiation therapy (other than palliative intervention as described in Section 6.12.1). Radiation therapy or surgery may be permitted after mutual agreement of the investigator, the sponsor and the subject.
- Investigational agents other than pembrolizumab and belantamab mafodotin
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. Flu - Mist) are live attenuated vaccines, and are not allowed.

6.13. Continued Access to Study Intervention after the End of the Study

Participants receiving belantamab mafodotin following 24 months post LSFD (at the time of study completion) may continue to receive belantamab mafodotin, if, in the opinion of their treating physician, they are continuing to derive clinical benefit from continued treatment. Study treatment will continue until a study discontinuation criterion (see Protocol Section 5.4) as assessed by the investigator has been met. Investigators will report all SAEs, overdose and pregnancy cases until 70 days after receipt of their last

dose of study treatment and pre-specified ocular data (see SRM) will be reported until resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow up. Post EOS, data cut-off, recording and follow up of SAEs and pre-specified ocular data will be done via paper forms. Drug accountability data will also be collected at site. Assessments will revert to standard of care at their particular site.

7. STUDY ASSESSMENTS AND PROCEDURES

A signed, written informed consent form must be obtained from the subject prior to any study-specific procedures or assessments being performed.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

The timing of each assessment is listed in the Time and Events Tables (Table 7, Table 8, Table 9, and Table 10). The timing and number of the planned study assessments may be altered during the course of the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring for the following assessments: safety, PK, or other assessments. The change in timing or addition of time points for any of the planned study assessments listed above must be approved and documented by GSK, but this will not constitute a protocol amendment. The IRB or EC will be informed of any safety issues that require alteration of the safety monitoring scheme. The maximum amount of blood collected in Screening and during the first Cycle 1 from each subject for the Dose Escalation and for the Dose Expansion is no more than 120 mL of blood (the details will be provided in SRM).

Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time. Detailed procedures for obtaining each assessment are provided in the SRM.

Table 7 Time and Events Table: Part 1 and Part 2 – Screening Assessments

Study Assessments[1]	Screen[2]
Informed Consent	X
Baseline Demographics	X
Medical History	X
Physical Exam	X
Concomitant Medications	X
ECOG Performance Status	X
	Safety
Ocular Exam	X[3]
Vital Signs (BP, HR, Body Temperature)	X
Weight and Height	X
Pregnancy Test	X[4]
Hematology	X
Clinical chemistry	X
eGFR	X[5]
Urinalysis	X
Spot Urine (albumin / creatinine ratio)	X[6]
CRP	X
HBsAg, HBcAb, HCV tests	X
Troponin	X[7]
BNP	X[8]
12-lead ECG	X[9]
LVEF and valves assessment (ECHO)	X[10]
	Disease Evaluation
Beta2 microglobulin	X
Skeletal Survey	X[11]
UPEP 24 hr urine collection	X
Urine immunofixation	X
SPEP	X
Serum Immunofixation	X
Extramedullary Plasmacytoma Assessment (by whole body CT or whole body MRI or CT/PET)	X[12]

Notes

1. All assessments will apply to Part 1 and 2 unless stated otherwise. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified.
2. All Screening assessments must be performed within 28 days prior to first dose unless otherwise specified. Informed Consent must be signed before any study-specific assessments are performed. Screening Assessment do not need to be repeated on C1D1 unless otherwise specified.
3. Screening ocular examination to be performed by an ophthalmologist (or an optometrist if an ophthalmologist is not available) within 28 days prior to the first dosing. See Section 7.3.5 for list of ophthalmic exam procedures.
4. Perform only in women of child-bearing potential. A serum pregnancy test must be performed at screening. If test is completed within 72 hours prior to the first dose, this assessment need not be repeated on C1D1. For questionable cases, follicle-stimulating hormone (FSH) and estradiol (as needed in women of non-childbearing potential only) should be performed at local lab.
5. eGFR as calculated by Modified Diet in Renal Disease (MDRD) formula (Appendix 3)
6. Albumin / creatinine ratios (spot urine from first void).
7. Troponin will be measured at the local lab (troponin I or T) and a central lab (troponin I).
8. BNP to be measured locally at screening; if cardiac workup is required due to safety concerns during the study, BNP should be measured.
9. Triplicate ECG measurement.
10. LVEF may be performed within 28 days prior to first dose. To be sent for central imaging storage.
11. Skeletal Survey: Imaging of bones for lytic lesions by a method aligned with the institutional guidance (X-ray, CT, or MRI). Skeletal survey results within 28 days prior to C1D1 may be used for screening. Same modality used at Screening must be used throughout study.
12. In subjects with known or suspected extramedullary disease. May be performed up to 28 days prior to C1D1 as screening value. Needs to be performed by the same method throughout the study as was done at baseline (i.e. if CT/PET scan was used as baseline, subject needs to be followed by CT/PET scans). Selected target lesion needs to be measured and followed over time. For sites in Germany, only MRI is allowed as imaging modality.

Study Assessments[1]	Screen[2]	Notes
Serum Kappa, Lambda free Light chain, FLC ratio	X	13. Only required for subjects with IgD/E myeloma If patient has IgD or IgE myeloma, then IgG/A/M testing is not required. 14. FISH testing at least for: t(4;14), t(14;16), amp (1q), del(1p) and 17p13del. FISH results from samples taken within 60 days prior to first dose are acceptable. 15. Samples from within 28 days prior to first dose are acceptable. A portion of the aspirate collected for disease assessment will be used for biomarker research (BM aspirate clot is preferred for BCMA analysis), for FISH testing, and MRD testing. MRD testing will be performed by a central lab. 16. Archival samples are acceptable; however, they should not replace fresh BM biopsies/aspirates
Calcium corrected for albumin (serum)	X	
IgG, IgM, IgA	X	
IgD/E	X[13]	
	Bone Marrow (BM) Aspiration/Biopsy	
BM aspirate for FISH testing	X[14]	
BM aspirate for BCMA expression and immune cell characterization	X[15]	
BM aspirate for MRD testing	X[15]	
BM aspirate/biopsy for percent malignant plasma cell	X[15, 16]	
	Health Outcomes	
PRO-CTCAE	X	
NEI-VFQ-25 and OSDI	X	

Abbreviations:
BP = Blood pressure; BNP = B-type natriuretic peptide; CRP = C-reactive protein; CT = Computed tomography; eGFR = Estimated glomerular filtration rate; ECG = Electrocardiogram; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; FISH = Fluorescence in situ hybridization; FLC = Free light chain; HBsAg = surface antigen of Hepatitis B virus; HBcAb = Hepatitis B core antibody; HCV = Hepatitis C virus; HR = Heart rate; Ig = Immunoglobulin; LVEF = Left Ventricular Ejection Fraction; MRD = Minimal residual disease; MRI = Magnetic resonance imaging; NEI-VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; OSDI = Ocular Surface Disease Index; PET = Positron emission tomography; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Term Criteria for Adverse Events; SPEP = Serum protein electrophoresis; UPEP = Urine protein electrophoresis

Table 8 Time and Events Table: Part 1 and Part 2 – On Study Assessments Completed Independent of Dosing

Study Assessments[1]	C1 Day 1 (Week 1)	C1 Day 8 (Week 2)	Treatment Period: Q3W from Wk 4 until EOT
Physical Exam	X		X
Vital Signs (BP, HR, Body Temperature)	X[2]	X	X[2]
Adverse Events[3]	Ongoing		
Concomitant Medications	Ongoing		
Genetics[4]	X		
ECOG Performance Status			X
			Safety
Ocular Exam			X[5]
Hematology	X[6]	X[7]	X[7]
Clinical chemistry	X[6]	X	X
eGFR[8]	X[6]	X	X
Urinalysis	X[6]		X
CRP			X
Free T3, Free T4 and TSH	X		X[9]

1. All assessments will apply to Part 1 and 2 unless stated otherwise. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. Assessments for C1D8 can be performed up to +3 days of the scheduled date. All assessments from Cycle 2 can be performed ±3 days of the scheduled date unless otherwise specified.
2. Single vital sign assessment required if dosing is held. Refer to Table 9 for additional vital sign assessments to be completed if dosing.
3. AEs/SAEs will be collected from first study dose up to 45 days post the last dose All related SAEs are to be collected from consent through OS follow-up. AEs/SAEs will be followed until the event is resolved, stabilized, otherwise explained or subject is lost to follow up.
4. Informed consent for optional sub studies (e.g. genetic research) must be obtained before collecting a sample. The sample will be collected on C1D1 prior to infusion.
5. On-study ocular exams to be performed up to 5 days before scheduled study dose by an ophthalmologist (or an optometrist if an ophthalmologist is not available) every three weeks prior to each dose of belantamab mafodotin for the first 4 doses. See Section 7.3.5 for list of ophthalmic exam procedures. After the 4th dose of belantamab mafodotin, f there are no significant ocular symptoms or vision changes, the frequency of ophthalmologic exams may be decreased to once every 6 months until end of study treatment. In case of persistent or newly developed ocular symptoms or vision changes, the subject will have further ophthalmologic exams, at least every 3 months until resolution (to Grade 1 or baseline) or more frequently as clinically indicated by the eye care specialist.
6. If completed within 72 hrs prior to the first dose, this assessment does not need to be repeated on Day 1 of Cycle 1. Refer to Table 11 for comprehensive list of lab tests.
7. For subjects that develop Grade 3 or 4 thrombocytopenia and/or neutropenia, blood counts should be monitored more frequently until resolution to a ≤Grade 2. In addition, subects should be monitored for signs and symptoms of bleeding, infection and other associated events and evaluated promptly. Institute supportive care (e.g transfusion, growth factors) and other treatments as clinically indicated and in accordance with local institutional guidelines.
8. eGFR as calculated by Modified Diet in Renal Disease (MDRD) formula (Appendix 3)
9. Every 6 weeks from first dose while on study.

Study Assessments[1]	C1 Day 1 (Week 1)	C1 Day 8 (Week 2)	Treatment Period: Q3W from Wk 4 until EOT
LVEF and valves assessment (ECHO)[10]			X[10]
			Disease Evaluation
Skeletal Survey			X[11]
UPEP 24 hr urine collection	X[6]		X
Urine immunofixation	X[6]		X[12]
SPEP	X[6]		X
Serum Immunofixation	X[6]		X[12]
Extramedullary Plasmacytoma Assessment (by whole body CT or whole body MRI or CT/PET)			X[13]
Serum Kappa, Lambda free Light chain, FLC ratio	X[6]		X
Calcium corrected for albumin (serum)	X[6]		X
IgG, IgM, IgA	X[6]		X
IgD/E[14]	X[6]		X
			Bone Marrow (BM) Aspiration/Biopsy
BM aspirate for BCMA expression and immune cell characterization		X[16]	X[15,16]
BM aspirate for MRD testing			X[17]
BM aspirate and biopsy for disease assessment			X[18]
BM biopsy to assess sCR			X[19]
			Health Outcomes
PRO-CTCAE	X	X	X
NEI-VFQ-25 and OSDI	X	X	X[20]

Notes

10. ECHOs to be done locally up to 7 days prior to scheduled visit. On treatment ECHOs will occur every 12 weeks from C1D1 (e.g., Week 13, W25, W37, etc.) and will continue regardless of dose delays. All ECHOs will be sent for central imaging storage.
11. At the time of suspected disease progression or as clinically indicated. Same modality used at Screening must be used throughout study.
12. At time of first achieving SPEP or Urine M protein ~ 0g/dl (suspected CR) and until suspected PD after CR or sCR.
13. **Q12 weeks (±3 weeks) through 1 year and then as clinically indicated .** To be performed by the same method throughout the study as was done at baseline (i.e. if CT/PET scan was used as baseline, subject needs to be followed by CT/PET scans). Selected target lesion needs to be measured and followed over time. For sites in Germany, only MRI is allowed as imaging modality. Imaging is from Cycle 1 Day 1.
14. Only required for subjects with IgD/E myeloma. If patient has IgD or IgE myeloma, then IgG/A/M testing is not required.
15. Bone marrow aspirate sample to be collected at C3D1 (± 7 days). BM aspirate clot is preferred for BCMA analysis and immune cell characterization/profiling.
16. Optional additional bone marrow aspirate samples may be collected at C1D8 or during any 3 week period, or at time of Progressive Disease for biomarker assessments.
17. MRD assessment to be performed by a central lab at the time of first achieving VGPR or CR. Repeat MRD testing 6 and 12 months after achieving VGPR or CR (provided VGPR/CR is maintained). Additional samples to be collected for biomarker research are encouraged, as part of the same BM draw.
18. At the time of suspected CR for confirmation of PC% <5% (always) or at time of suspected PD (only if not evident otherwise). Bone marrow core biopsy is preferred.
19. IHC only to confirm sCR at the time of confirmation of CR bone marrow biopsy/aspirate is performed. IHC to confirm sCR on BM biopsy when CR is achieved. Absence of clonal cells in BM biopsy by IHC is required to determine sCR.
20. Additional assessments may be conducted for those subjects who experience worsening in visual function.

Study Assessments[1]	C1 Day 1 (Week 1)	C1 Day 8 (Week 2)	Treatment Period: Q3W from Wk 4 until EOT	Notes
EORTC-QLQ-C30 and EORTC-QLQ-MY20 **(Part 2 only)**	X[21]		X[21]	21. Collected pre-dose every **Q6 weeks** from C1 until EOT

Abbreviations:
AE = Adverse Event; BP = Blood pressure; CR = Complete response; CRP = C-reactive protein; CT = Computed tomography; eGFR = Estimated glomerular filtration rate; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module; EORTC-QLQ-MY20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma Module; FLC = Free light chain; HR = Heart rate; Ig = Immunoglobulin; IHC = Immunohistochemistry; MRD = Minimal residual disease; MRI = Magnetic resonance imaging; NEI-VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; OSDI = Ocular Surface Disease Index; PC = clonal plasma cells; PD = Progressive disease; PET = Positron emission tomography; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Term Criteria for Adverse Events; Q3W = Every 3 weeks; sCR = Stringent complete response; SAE = Serious adverse event; SPEP = Serum protein electrophoresis; T3 = Triiodothyronine 3; T4 = Triiodothyronine 4; TSH = Thyroid Stimulating Hormone; UPEP = Urine protein electrophoresis; VGPR = Very good partial response

Table 9 Time and Events Table: Part 1 and Part 2 – On Study Assessments with Dosing Days (Cycles)

Study Assessments[1]	C1 Day 1 (Week 1)	C1 Day 8 (Week 2)	Day 1 of C2 – C35 (IF DOSING) Cycles = 21 days	Notes
			Safety	1. All assessments will apply to Part 1 and 2 unless stated otherwise. Assessments should be done prior to drug administration, unless otherwise specified. Assessments for C1D8 can be performed +3 days of the scheduled date. From Cycle 2, assessments can be performed ±3 days of the scheduled date unless otherwise specified.
Infusion Related Vital Signs (BP, HR, Body Temperature)			X[2]	2. For the first infusion, Infusion vital signs must be assessed for each infusion (belantamab mafodotin and pembrolizumab) at: pre-dose (within 30 min prior to SOI); at the end of infusion (EOI) (+15 min); and 1 hr (±10 min) post EOI. For subsequent infusions, infusion vital signs must be assessed for each infusion (belantamab mafodotin and pembrolizumab) at pre-dose (within 30 min prior to SOI); at EOI (+15 min), and 30 min (±10 min) post EOI. **On dosing days with PK sampling time points, vital signs should be assessed prior to PK samples being drawn**. See Section 7.3.7.
Weight	X		X	
Pregnancy Test	X[3]		X[3]	3. Perform only in women of child-bearing potential. Pregnancy tests may be either pre-dose serum or urine and should be performed within 72 hours prior to dosing.
Troponin		X	X[4]	4. Pre-dose. Troponin will be measured at the local lab (troponin I or T) and a central lab (troponin I).
Spot Urine (albumin / creatinine ratio)	X[5, 6]		X[5]	5. Albumin / creatinine ratios (spot urine from first void).
Triplicate 12-lead ECG	X[7]	X	X[7]	6. If completed within 72 hrs prior to the first dose, this assessment does not need to be repeated on Day 1 of Cycle 1. Refer to Table 11 for comprehensive list of lab tests.
			PK and ADA	7. Triplicate ECGs to be performed at pre-dose (within 30 minutes prior to SOI belantamab mafodotin) and at EOI (within 30 min **after** belantamab mafodotin EOI) at each cycle. ECG recordings should be made after at least 10 min rest and collected no more than 2 min apart. On days with PK sampling time points, ECGs should be performed prior to PK samples being drawn.
Pharmacokinetics[8] for belantamab mafodotin and pembrolizumab	X[8]	X[8]	X[8]	8. PK samples to be obtained at as described in Section 7.4.1. The sBCMA samples must be taken at the same time of any belantamab mafodotin PK sample.
Immunogenicity (ADA)	X		X[9]	9. Pre-dose belantamab mafodotin (within 30 min prior to SOI) at C1 Day1 (week 1), C2, C5 and every 3 cycles thereafter (i.e., C8, C11,..) until EOT for both belantamab mafodotin and pembrolizumab ADA samples. If belantamab mafodotin is administered but pembrolizumab is planned to be held during any of the above Cycle timepoints, pre-dose pembrolizumab ADA should still be collected.
			Biomarker	10. Serum sBCMA samples will be collected each cycle at pre-dose (within 30 minutes prior to SOI), at every time a PK sample is collected, as indicated in Section 7.4.1., and at every MRD assessment timepoint.
Soluble BCMA	X[10]	X[10]	X[10]	

Study Assessments[1]	C1 Day 1 (Week 1)	C1 Day 8 (Week 2)	Day 1 of C2 – C35 (IF DOSING) Cycles = 21 days	Notes
Serum cytokines/ chemokines[11]	X	X	X[11]	11. Collect a cytokine/chemokine serum sample during C1D1 at pre-dose (within 30 minutes prior to SOI belantamab mafodotin), EOI of pembrolizumab (within 30 minutes after EOI) (even when infusion is interrupted or halted), 4 h after belantamab mafodotin SOI, 24 h after belantamab mafodotin SOI (±1 h); at C1D8 (+3 days, on same day as PK sample collection) dose, and pre-dose belantamab mafodotin (within 30 min prior to SOI) at C2D1 and C5D1. 12. Collect pre-dose belantamab mafodotin (within 30 min prior to SOI) at C1D1, at every 12 weeks thereafter (pre-dose belantamab mafodotin), and at every MRD assessment timepoint. 13. Collect pre-dose belantamab mafodotin (within 30 min prior to SOI) at C1D1, C1D8 (+3 days, on same day as PK sample collection), and pre-dose belantamab mafodotin (within 30 min prior to SOI) at C2D1 and C5D1. 14. Collect during C1D1 at pre-dose (within 30 minutes prior to SOI belantamab mafodotin), EOI of pembrolizumab (within 30 minutes after EOI) (even when infusion is interrupted or halted), 4 h after belantamab mafodotin SOI, 24 h after belantamab mafodotin SOI (±1 h); at C1D8 (+3 days, on same day as PK sample collection) and pre-dose belantamab mafodotin (within 30 min prior to SOI) at C2D1 and C5D1. 15. A window of ± 3 days is acceptable for administration of study treatment after C1. Belantamab mafodotin will be administered first as IV infusion, followed by 1 hr rest period. Refer to SRM for details. Pembrolizumab will be administered as second, in a 30 min infusion, 1 hr after belantamab mafodotin EOI, provided subject did not develop IRR requiring intervention. If planned Cycle treatment is delayed due to toxicities which have resolved, if in the judgement of the investigator, treatment needs to be initiated prior to next planned Cycle, this can be discussed with the medical monitor. Dosing cannot occur more frequently than every 21 days (±3 days). 16. Premedication should be considered in any subject who experienced an infusion related reaction at first or any subsequent infusion with belantamab mafodotin and pembrolizumab. 17. Corneal management information: - Prophylactic preservative-free artificial tears must be administered in each eye at least 4-8 times daily beginning on Cycle 1 Day 1 until end of treatment. - At the start of each infusion, subjects may apply cooling eye masks to their eyes for approximately 1 hour as long as tolerated.
Plasma-cfDNA	X[12]		X[12]	
Whole blood RNA	X[13]	X[13]	X[13]	
Cryopreserved PBMCs	X[14]	X[14]	X[14]	
			Treatment	
Administration of belantamab mafodotin[15]	X		Day 1 of each cycle	
Administration of pembrolizumab[15]	X		Day 1 of each cycle	
Premedication if needed[16]	X		X (at the start of each cycle)	
Corneal events management: preservative-free artificial tears and cooling masks[17]	X[17]		X[17]	

Abbreviations:
ADA = Antibody Drug Antibody; BP = Blood pressure; cfDNA = Circulating free DNA; ECG = Electrocardiogram; EOI = End of Infusion; HR = Heart rate; IRR = Infusion related reaction; PBMC = peripheral blood mononuclear cell ; PK = Pharmacokinetics; QID = 4 times a day; SOI = start of infusion

Table 10 Time and Events Table: Part 1 and Part 2 – End of Treatment and Follow-up Assessments

Study Assessments[1]	End of Treatment Visit[2]	PFS Follow-up[3]	OS Follow-up[4]	Notes
Physical Exam	X	X		1. All assessments will apply to Part 1 and 2 unless stated otherwise. 2. Safety follow up to occur within 30 days from the last dose, or prior to the new anti-MM treatment (whichever occurs first). 3. PFS follow-up every 21 days (±7 days) for subjects who discontinue IP for a reason other than PD. Disease evaluations will continue until confirmed PD, death, start of a new anticancer treatment, withdrawal of consent, or end of the study whichever occurs first. Once subject progresses, move to OS Follow-up. 4. The survival for MM will be documented in medical charts. No visit necessary. Contacts will be made via phone calls, emails or other means of communications every 12 weeks (± 14 days) until end of study (Section 5.5.2). Subject does not need to come in for visit unless they are being followed for corneal signs that are present at the end of study treatment. 5. AE/SAEs will be collected to 45 days post the last dose. All related SAEs are to be collected from first dose through OS follow-up. AEs/SAEs will be followed until the event is resolved, stabilized, otherwise explained or subject is lost to follow up. 6. If a subject develops signs / symptoms, or they require additional treatment, e.g. topical steroid for more than 7 days, additional assessment by an ophthalmologist (or optometrist, if ophthalmologist is not available) will be implemented. Intraocular pressure should be monitored if steroid eye drops are used more than 7 days. See Section 7.3.5 for list of exams. 7. Subjects with decreased visual acuity or corneal signs or symptoms at the end of study treatment visit will have follow-up ophthalmic exams at 3 and 6 weeks from the last dose of study treatment and then every 6 weeks (±7 days) until deemed clinically stable by an eye care professional, or up until 1 year (whichever comes first). See Section 7.3.5 for list of exams. 8. Perform only in women of child-bearing potential. May be either serum or urine. 9. Final pregnancy test (serum or urine) must be performed in women of childbearing potential 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. eGFR as calculated by Modified Diet in Renal Disease (MDRD) formula (Appendix 3) 11. Albumin / creatinine ratios (spot urine from first void).
Adverse Events[5]	X	Related SAEs only	Related SAEs only	
Concomitant Medications	X	X		
	Safety			
Ocular Exam	X[6,7]	X[7]	X[7]	
ECOG Performance Status	X			
Hematology	X			
Clinical chemistry	X	X		
Pregnancy Test	X[8]	X[9]	X[9]	
eGFR[10]	X			
Urinalysis	X			
CRP	X			
Spot Urine (albumin / creatinine ratio)[11]	X			

Study Assessments[1]	End of Treatment Visit[2]	PFS Follow-up[3]	OS Follow-up[4]	Notes
Troponin[12]	X			12. Troponin will be measured at the local lab (troponin I or T) and a central lab (troponin I). 13. Obtain a triplicate ECG measurement. 14. Sent for central imaging storage. 15. At the time of suspected disease progression or as clinically indicated. Same modality used at Screening must be used throughout study. 16. At time of first achieving SPEP or Urine M protein ~ 0g/dl (suspected CR) and until suspected PD after CR or sCR 17. In subjects with extramedullary MM, if the last radiographic assessment occurred ≥8 weeks prior withdrawal from study treatment, and PD has NOT been documented otherwise, a new assessment should be obtained at the time the subject withdrew from study treatment. To be performed by the same method throughout the study as was done at baseline (i.e. if CT/PET scan was used as baseline, subject needs to be followed by CT/PET scans). Selected target lesion needs to be measured and followed over time. For sites in Germany, only MRI is allowed as imaging modality. 18. As clinically indicated with same method as was done at baseline. 19. Only required for subjects with IgD/E myeloma. If patient has IgD or IgE myeloma, then IgG/A/M testing is not required. 20. One PK sample for belantamab mafodotin and pembrolizumab should be collected at the end of treatment visit. 21. Collect one ADA at least 8 weeks post last dose.
Free T3, Free T4 and TSH	X			
12-lead ECG	X[13]			
LVEF and valves assessment (ECHO)	X[14]			
	Disease Evaluation			
Skeletal survey	X[15]	X[15]		
UPEP 24 hr urine collection	X	X		
Urine immunofixation	X[16]	X[16]		
SPEP	X	X		
Serum Immunofixation	X[16]	X[16]		
Extramedullary Plasmacytoma Assessment (by whole body CT or whole body MRI or CT/PET	X[17]	X[18]		
Serum Kappa, Lambda free Light chain, FLC ratio	X	X		
Calcium corrected for albumin (serum)	X	X		
IgG, IgM, IgA	X	X		
IgD/E[19]	X	X		
Subsequent anti-MM Treatment		X	X	
	PK and ADA			
Pharmacokinetics for belantamab mafodotin and pembrolizumab	X[20]			
Immunogenicity (ADA)	X	X[21]		
	Biomarkers			
Soluble BCMA	X			
Plasma-cfDNA	X			

Study Assessments[1]	End of Treatment Visit[2]	PFS Follow-up[3]	OS Follow-up[4]	Notes
	Bone Marrow (BM) Aspiration/Biospy			22. MRD assessment to be performed by a central lab at the time of first achieving VGPR or CR, repeat testing at 6 and 12 months after achieving VGPR or CR (provided VGPR/CR is maintained). Additional samples to be collected for biomarker research are encouraged, as part of the same BM draw. MRD testing will be performed by a central lab. 23. Only to confirm CR or suspected PD at this visit. 24. Bone marrow aspirate sample to be collected at EOT. BM aspirate clot is preferred for BCMA analysis and immune cell characterization/profiling. 25. Subjects who discontinue participation in the study will continue to be assessed during follow-up until resolution of visual symptoms. Continue to follow-up with subjects via telephone who are still experiencing visual symptoms even after study discontinuation. 26. Exit Interview should be performed within approximately 21 days of end of treatment visit
BM aspirate for MRD testing	X[22]	X[22]		
BM aspirate and biopsy for disease assessment	X[23]	X[23]		
BM biopsy to assess sCR	X[23]	X[23]		
BM aspirate for BCMA expression and immune cell characterization	X[22, 24]	X[22]		
	Health Outcomes			
PRO-CTCAE	X			
NEI-VFQ-25 and OSDI	X	X[25]	X[25]	
EORTC-QLQ-C30 and EORTC-QLQ-MY20 **(Part 2 only)**	X			
Exit Interview	X[26]			

Abbreviations:
AE = Adverse Event; ADA = Antibody Drug Antibody; BP = Blood pressure; cfDNA = Circulating free DNA; CR = Complete response; CRP = C-reactive protein; CT = Computed tomography; eGFR = Estimated glomerular filtration rate; ECG = Electrocardiogram; ECHO = Echocardiogram; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module; EORTC-QLQ-MY20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma Module; FLC = Free light chain; HR = Heart rate; Ig = Immunoglobulin; MRD = Minimal residual disease; MRI = Magnetic resonance imaging; NEI-VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; OS = Overall survival; OSDI = Ocular Surface Disease Index; PD = Progressive disease; PET = Positron emission tomography; PFS = Progression free survival; PK = Pharmacokinetics; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Term Criteria for Adverse Events; sCR = Stringent complete response; SAE = Serious Adverse Event; SPEP = Serum protein electrophoresis; T3 = Triiodothyronine 3; T4 = Triiodothyronine 4; TSH = Thyroid Stimulating Hormone; UPEP = Urine protein electrophoresis; VGPR = Very good partial response

7.1. Screening and Critical Baseline Assessments

The following demographic parameters will be captured during Screening: date of birth, gender, race and ethnicity.

Medical/medication history assessed as related to the eligibility criteria listed in Section 5.

Baseline (at Screening and/or on Day 1 prior to belantamab mafodotin infusion) assessments obtained will include:

- Complete physical examination, including height (in cm) and weight (in kg).
- Vital signs (blood pressure, body temperature, pulse rate)
- Ocular exam
- Eastern Cooperative Oncology Group (ECOG) performance status
- Clinical laboratory tests outlined in Table 11
- Serum beta-human chorionic gonadotropin (β-HCG) pregnancy test for female subjects of childbearing potential only
- 12-lead electrocardiogram (ECG)
- Echocardiogram (ECHO)
- Imaging studies CT, MRI or PET-CT (for subjects with extramedullary disease)
- BM aspirate/biopsy for disease assessment, FISH, BCMA
- Serum (soluble BCMA, chemokines/cytokines, and anti-drug-antibodies)
- Plasma cfDNA
- Review of concomitant medications
- PRO-CTCAE

Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

Cardiovascular medical history/risk factors will be assessed at baseline.

7.2. Efficacy

Standard disease assessments for MM will include the following assessments:

- UPEP (24 hour), with M protein
- Urine Immunofixation
- SPEP, with M protein
- Serum immunofixation
- Corrected Calcium
- Quantitative Immunoglobulins (IgG, IgA, and IgM and for subjects with IgD or IgE myeloma, quantitative IgD or IgE)
- Serum kappa and lambda free light chains and FLC ratio

- Bone marrow aspirate and/or core biopsy at screening for baseline PC percentage and FISH analysis; and for disease response assessment at time of suspected CR/sCR, or PD
- At time of VGPR or CR, MRD testing on bone marrow aspirate
- Imaging by CT, MRI, CT/PET or X-ray to assess EMP and bone lesions. For sites in Germany, only MRI is allowed as imaging modality
- Skeletal survey (Screening and as clinically indicated). For sites in Germany, only MRI is allowed as imaging modality

Response evaluation will be performed according to the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma 2016 [Kumar, 2016].

Clinical activity measured as ORR which is defined as follows:

The percentage of subjects with confirmed sCR, CR, VGPR, and PR as assessed by 2016 recommendations of the International Myeloma Working Group (IMWG)) [Kumar, 2016]. Other assessments of interest like CBR, PFS, TTR, DOR, and OS may also be considered. Minimal residual disease negative rate will be assessed in those subjects who achieve a VGPR or CR.

In subjects with extramedullary myeloma- the disease assessments have to include imaging (e.g., computed tomography [CT] scan, magnetic resonance imaging [MRI], or PET/ CT scan) and physical examination (as indicated for palpable/superficial lesions). For subjects with skin only involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the Sum of the Products of the maximal perpendicular diameters of measured lesions (SPD).

Baseline serum disease assessment will be completed during screening period (within 28 days prior to the fist dose of study medication) and baseline imaging within 28 days prior to the first dose of study treatment. On study serum and urine based assessments (M-protein, FLC, immunofixation) and imaging, for extramedullary disease, will be performed as required. The final assessments will be performed during final study visit (End of treatment visit). See the Time and Events Tables (Table 7, Table 8, and Table 10) for the schedule of assessments of anti-cancer activity. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. For post-baseline assessments, a window of ±3 days is permitted to allow for flexible scheduling. For imaging assessments, a window of Q12 weeks (±3 weeks) through 1 year and then as clinically indicated.

In subjects with extramedullary MM: if the last radiographic assessment was more than 8 weeks prior to the subject's withdrawal from study and progressive disease has not been documented, a disease assessment should be obtained at the time of withdrawal from study.

MRD negativity rate (defined as: the percentage of subjects who are MRD negative by clonoSEQ). During treatment, testing will be performed for subjects achieving VGPR or CR. In subjects who have achieved MRD negativity, the testing will be repeated after 6 and 12 months (provided CR is maintained) from time of first documented negative

MRD result to assess sustained MRD negativity. MRD testing will be performed by a central lab.

7.3. Safety

Planned time points for all safety assessments are provided in the Time and Events Tables (Table 7, Table 8, Table 9, and Table 10).

7.3.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of an AE or SAE can be found in Appendix 7 (Section 12.7)

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an adverse event (AE) or serious adverse event (SAE) as outlined in Section 7.3.1.2.

7.3.1.1. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

All AEs will be collected from the time the first dose of study treatment is administered until 45 days following cessation of treatment regardless of initiation of new anticancer therapy.

All SAEs will be collected from the time the first dose of study treatment is administered until 45 days following cessation of study treatment. In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment or GSK concomitant medication must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 7.3.1.7.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. At any time after 45 days the investigator may report any AE that they believe possibly related to study treatment.

Investigator is no longer required to to review and approve SAEs in InForm within 72 hours of awareness of event. They will continue to record casuality assessment for SAEs in source notes.

Following 24 months post LSFD, participants still deriving clinical benefit in the opinion of their treating physician may continue to receive belantamab mafodotin. For these participants, GSK will continue to collect safety information including SAEs, overdose and pregnancy cases and pre-specified ocular data via paper forms which will be reported directly to GSK. For these participants, SAEs, overdose and pregnancy cases will be

reported during the treatment period and for up to 70 days after last dose and pre-specified ocular data will be reported until resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow up.

7.3.1.2. Method of Detecting AEs and SAEs

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

"How are you feeling?"

"Have you had any (other) medical problems since your last visit/contact?" or for pediatric studies, "Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?"

"Have you taken any new medicines, other than those provided in this study, since your last visit/contact?" or for pediatric studies, "Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?"

Definition of an AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits, abuse, or misuse. Examples of events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE).

"Lack of efficacy" or "failure of expected pharmacological action" *per se* is not to be reported as an AE or SAE. However, any signs and symptoms and/or clinical sequelae resulting from "lack of efficacy" will be reported as an AE or SAE, if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that led to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

Definition of an SAE

An SAE is any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-subject setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.
f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may

jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Protocol-Specific SAEs:

- All events of possible study treatment-induced liver injury with hyperbilirubinemia defined as alanine aminotransferase (ALT) ≥3 times upper limit of normal (ULN) **and** bilirubin ≥2 times ULN (>35% direct) (or ALT ≥3 times ULN and international normalization ratio (INR) >1.5, if INR is measured) or termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants).

NOTE: Bilirubin fractionation should be performed.

- Any new primary cancers

Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided.

In addition, an associated AE or SAE is to be recorded for any laboratory test result or other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay.

Any new primary cancer must be reported as a SAE.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

7.3.1.3. Follow up on AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 7.

7.3.1.4. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) are first reported.

7.3.1.5. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to disease progression) does not need to be reported as a SAE. Death due to disease under study is to be recorded on the Death eCRF. However, if the underlying disease (i.e., progression) is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study treatment(s) or protocol design or procedures and the disease progression, then this must be reported as a SAE.

7.3.1.6. Adverse Events of Special Interest

Adverse events of special interest (AESI) for belantamab mafodotin are corneal events, thrombocytopenia and infusion related reactions. The severity of all AESI will be graded utilizing the National Cancer Institute Common Toxicity Criteria for Adverse Events (Version 4.03 [NCI, 2010]). Severity of belantamab mafodotin treatment related corneal events will also be graded using the GSK scale for corneal events provided in Table 17. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in Table 4.

For pembrolizumab, an overdose as defined in Section 6.10 that is not associated with clinical symptoms or abnormal laboratory results is an AESI.

7.3.1.7. Regulatory reporting requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/EC, if appropriate according to local requirements.

Prompt Reporting of SAEs and Other Events to GSK

Serious adverse events (SAEs), pregnancies, and liver function abnormalities and any other events meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the following table once the investigator determines the event meets the protocol definition for that event.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
"CV events" and/or "death"	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	24 Hours	Pregnancy Notification Form	2 Weeks	Pregnancy Followup- Form
Liver chemistry abnormalities:				
ALT ≥3 times ULN and bilirubin ≥2 times ULN (>35% direct) (or ALT ≥3 times ULN and INR >1.5, if INR is measured)[c]	24 hours[a]	SAE data collection tool; Liver Event eCRF and liver imaging and/or biopsy eCRFs if applicable[b]	24 hours	Updated SAE data collection tool. Updated Liver Event eCRF[b]
ALT ≥5 times ULN; ALT ≥3 times ULN with hepatitis or rash **or** 3 times ULN ≥4 weeks	24 hours[a]	Liver Event eCRF[b]	24 hours	Updated Liver Event eCRF[b]
ALT ≥3 times ULN and <5 times ULN and bilirubin <2 times ULN	24 hours[a]	Liver Event eCRF does not need to be completed unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[b]		

a. GSK to be notified at onset of liver chemistry elevations to discuss subject safety.
b. Liver event documents should be completed as soon as possible
c. INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.

Methods for detecting, recording, evaluating, and following up on AEs and SAEs are provided in the SRM.

7.3.2. Pregnancy

Do not collect pregnancy information for female subjects known to be pregnant during the screening phase or before exposure to study.

The need for a screening pregnancy test depends on whether a female subject is of childbearing potential or non-childbearing potential.

If a female subject is of childbearing potential, she must have a serum β-human chorionic gonadotropin (β –HCG) pregnancy test performed within 72 hours prior to the first dose of study treatment. Subjects with positive pregnancy test result must be excluded from the study. Subjects with negative pregnancy test result must agree to use an effective contraception method as described below during the study and for 4 months following the last dose of study treatment.

Details of all pregnancies in female subjects will be collected after the start of study treatment and for 4 months following last dose of belantamab mafodotin.

Details of all pregnancies for female partners of male subjects will be collected after the start of study treatment and 6 months following last dose of belantamab mafodotin.

If a pregnancy is reported, the investigator must inform GSK within 24 hours of learning of the pregnancy and must follow the procedures outlined in Appendix 8.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure (4 months after the last dose of belantamab mafodotin) and correspond with the time frame for female subject contraception in Section 5.1.

7.3.3. Medical Device Incidents (including malfunctions)

Not applicable for this study

7.3.4. Physical Exams

At screening and on dosing days, a full physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. Height and weight will also be measured and recorded.

During interim visits and at the end of study, a brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

7.3.5. Ocular Examinations and Procedures

Study sites must establish a close collaboration with an ophthalmologist (or an optometrist if an ophthalmologist is not available) who will be responsible for assessing subjects while they are on study and managing subjects who develop treatment-related

changes in vision associated with belantamab mafodotin. Management of subjects with treatment-related changes in vision must be performed in close communication with the GSK Medical Monitor and the coordinating ophthalmologist (or an optometrist if an ophthalmologist is not available).

Subjects will be assessed by eye care specialist (ophthalmologist, or an optometrist if an ophthalmologist is not available) at screening/baseline.

A full ***screening/baseline*** ophthalmic examination for all subjects must include for both eyes (OU):

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

The ***on treatment*** **and** ***follow-up*** ophthalmic exam should be performed for both eyes (OU) as described below and in the Time and Events Tables (Section 7):

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

The *end of study treatment visit* ophthalmic exam should match the *baseline (screening)* exam.

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

7.3.6. ECOG Performance Status

The performance status will be assessed using the ECOG scale (Appendix 2) as specified in the Time and Events Tables (Table 7, Table 8, and Table 10).

7.3.7. Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, temperature, and pulse rate. Vital signs should be measured after resting for at least 5 minutes. Vital signs will be measured more frequently if warranted by the clinical condition of the subject. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.

First Infusion:

Monitoring intervals: Vital signs must be monitored at pre-dose (within 30 minutes prior to start of each infusion), and at the end of each infusion, and 1 hour post end of infusion.

Subsequent Infusions:

Monitoring intervals: Vital signs must be monitored at pre-dose (within 30 minutes prior to start of each infusion) and at the end of each infusion, and 30 min post the end of infusion.

In case of infusion related reactions or cytokine storm, monitoring will be performed with higher frequency (as clinically indicated).

7.3.8. Electrocardiogram

Triple 12-lead ECGs will be obtained at designated time points specified in the Time and Events Table (Table 7, Table 9, and Table 10) during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. At each assessment, a 12-lead ECG will be performed by qualified personnel at the site after the subject has at least a 10 minute rest.

For triplicate ECGs, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.

The QT interval should be corrected for heart rate by Fridericia's formula (QTcF). Refer to Section 5.4.1.3 for QTc withdrawal criteria. ECGs will be collected and stored centrally. Refer to the SRM for details regarding ECG procedures.

7.3.9. Echocardiogram

Echocardiograms (ECHOs) will be performed at baseline to assess cardiac ejection fraction and cardiac valve morphology for the purpose of study eligibility, as specified in the Time and Events Table (Table 7). Additional ECHO assessments will be performed at specified time points indicated in the Time and Events Table (Table 8 and Table 10) or if clinically warranted. The evaluation of the echocardiographer should include an evaluation for LVEF and both right and left-sided valvular lesions.

Copies of all ECHOs performed on subjects will be stored in a central location if further evaluation is warranted.

7.3.10. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in (Table 11), should be performed according to the Time and Events Table (Table 7, Table 8, Table 9, and Table 10) Details for the preparation and shipment of samples will be provided in the SRM.

Prior to administration of the first dose of study treatment, results of laboratory assessments should be reviewed. Any laboratory test with a value outside the normal range may be repeated (prior to the first dose) at the discretion of the investigator.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in patient management or are considered clinical significant by the Investigator (for example SAE or AE or dose modification) the results must be recorded in the subject's CRF. Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All laboratory tests with values that are significantly abnormal during participation in the study or within 45 days after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

Asymptomatic elevations of lactate dehydrogenase (LDH) and creatine kinase (CK) and AST have been observed in study BMA117159. Subjects with significant elevations (≥x3 ULN) should, where possible, have a sample sent for central testing of CK and LDH isoenzyme levels.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 11.

Table 11 List of Clinical Laboratory Tests

Hematology			
Platelet Count	*RBC Indices*:	*Automated WBC Differential:*	
Red blood cell (RBC) Count	MCV	Neutrophils	
White blood cell (WBC) Count (absolute)	MCH	Lymphocytes	
Hematocrit	MCHC	Monocytes	
Hemoglobin		Eosinophils	
		Basophils	
Clinical Chemistry			
Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin
Creatinine	Chloride	Alanine aminotransferase (ALT)	Uric Acid
Glucose	Total carbon dioxide (CO_2)/ bicarbonate	Gamma glutamyl transferase (GGT)	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein
Magnesium	Phosphorous	Creatine kinase (CK)	LDH
Troponin	BNP	T3, T4 and TSH	
Routine Urinalysis			
Specific gravity			
pH, glucose, protein, blood and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
24-hour urine protein			
Spot urine (albumin / creatinine ratio)[1]			
Other screening tests			
Hepatitis B (HBsAg)			
Hepatitis B core antibody (HBcAb)			
Hepatitis C (Hep C antibody -- if second generation Hepatitis C antibody positive, a hepatitis C PCR test should be performed)			
Follicle stimulating hormone (FSH) and estradiol (as needed in women of non-child bearing potential only)			
FISH analysis[2]			
Other Laboratory Tests			
eGFR	Pregnancy test (urine or blood – according to local practice)	IgG, IgM, IgA	C-reactive protein (CRP)
Beta2 microglobulin	Kappa, lambda free LC, FLC ratio	ADA	Genetic Sample[3]
Immunofixation	Serum Protein Electrophoresis (SPEP)	Urine Protein Electrophoresis (UPEP)	MRD testing
Serum M-protein calculation	Corrected calcium with albumin	LDH and CK isoenzymes[4]	
Biomarker Measurements			
Soluble BCMA (sBCMA) (serum)	Serum cytokines/chemokines	cfDNA (plasma)	Peripheral blood mononuclear cell
Whole Blood RNA			

1. Obtained from first void
2. FISH testing at least for: t(4;14), t(14/16), 17p13del. Biopsy samples from within 60 days prior to first dose are acceptable.
3. Informed consent for optional sub studies (e.g. genetic research) must be obtained before collecting a sample
4. Subjects with significant elevations (≥x3 ULN) and performed by central laboratory

7.3.11. Suicidal Risk Monitoring

Not applicable for this study

7.3.12. Patient-Reported Outcome Version of the Common Term Criteria for Adverse Events (PRO-CTCAE)

The PRO-CTCAE is a patient-reported outcome measure developed to evaluate symptomatic toxicity in subjects on cancer clinical trials [Basch, 2014]. The PRO-CTCAE was designed to be used as a companion to the CTCAE, the standard lexicon for adverse event reporting in cancer trials. The PRO-CTCAE includes an item library of 124 items representing 78 symptomatic toxicities drawn from the CTCAE. PRO-CTCAE provides a systematic yet flexible tool for descriptive reporting of symptomatic treatment side effects in cancer clinical trials. In the present study, a subset of items selected from the PRO-CTCAE Version 1.0 Item library will be administered. The PRO-CTCAE will be administered to select subjects based on the availability of translated versions.

7.3.13. Visual Function Questionnaires (VFQ) and Ocular Surface Disease Index (OSDI).

The impact of potential ocular toxicity will be assessed with the use of a visual function questionnaire. The visual function questionnaire will include select items from the NEI-VFQ-25 and OSDI. The NEI-VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question [Mangione , 2001]. The NEI-VFQ-25 generates the following vision-targeted sub-scales: global vision rating (1), difficulty with near vision activities (3), difficulty with distance vision activities (3), limitations in social functioning due to vision (2), role limitations due to vision (2), dependency on others due to vision (3), mental health symptoms due to vision (4), driving difficulties (3), limitations with peripheral (1) and color vision (1), and ocular pain (2). In addition to the 25 items from the NEI-VFQ-25, additional questions will be administered to further assess the impact of ocular toxicity on visual function.

The OSDI is a 12-item questionnaire designed to assesses both the frequency of dry eye symptoms and their impact on vision-related functioning [Schiffman, 2000]. The OSDI has demonstrated good reliability, validity, sensitivity, and specificity, and can be used as a complement to other clinical and subjective measures of dry eye disease by providing a quantifiable assessment of dry eye symptom frequency and the impact of these symptoms on vision-related functioning.

All subjects will use the Self-Administered version, unless their vision prevents them from being able to complete the questionnaire on their own. Subjects who are not able to complete the questionnaire on their own and require assistance should use the Interviewer Administered format. If the Interviewer Administered format is being used, it should be read to the subjects verbatim, and subject responses should be recorded directly without

any interpretation. For any additional assessments conducted via telephone (either during participation in the treatment period or during follow-up), the Interviewer Administered format should be used.

The NEI-VFQ-25 and OSDI will be administered to subjects in different regions based on the availability of translated versions.

7.4. Pharmacokinetics

7.4.1. Blood Sample Collection for Pharmacokinetics

Blood samples for pharmacokinetic (PK) analysis of belantamab mafodotin (ADC and total monoclonal antibody [mAb]), cys-mcMMAF and corresponding blood samples for sBCMA as well as pembrolizumab will be collected at the time points indicated in Table 12. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring and need to be accompanied by a corresponding sBCMA sample. Note that sBCMA samples will also be collected independent from PK samples, as described in the Time and Events table. Samples for pembrolizumab will be collected and stored. Pembrolizumab PK samples will only be analysed if clinical observations warrant it (e.g. to rule out or confirm suspicion of DDI).

Each PK sample should be collected as close as possible to the planned time relative to the dose (i.e., time zero) administered to the subject on PK days. The actual date and time of each blood sample collection will be recorded. All PK, sBCMA, and anti-drug antibody (ADA) samples once collected (regardless of dosing) may be analyzed if the sample date and time have been recorded.

Table 12 Pharmacokinetic and sBCMA blood sampling times

Cycle Day	Sampling Times	Belantamab Mafodotin	sBCMA	Pembrolizumab	Sampling window
C1D1	**Pre-dose belantamab mafodotin**	X	X		Within 30 minutes prior to start of infusion
	EOI belantamab mafodotin	X	X		Within 30 min **after** EOI
	Pre-dose Pembrolizumab[1]			***P***	Within 30 minutes prior to start of infusion
	EOI Pembrolizumab[1]			***P***	Within 30 min **after** EOI
	2 hr SOI belantamab mafodotin	X	X		±15 min
	24 hr SOI belantamab mafodotin	X	X		±1 hr
C1D4	**Any time**	X	X		±1 day
C1D8	**Any time**	X	X		+3 days
C2D1 & C5D1	**Pre-dose belantamab mafodotin**	X	X		Within 30 minutes prior to start of infusion

Cycle Day	Sampling Times	Belantamab Mafodotin	sBCMA	Pembrolizumab	Sampling window
	EOI belantamab mafodotin	X	X		Within 30 min **after** EOI
	Pre-dose Pembrolizumab[1]			***P***	Within 30 minutes prior to start of infusion
	EOI Pembrolizumab[1]			***P***	Within 30 min **after** EOI
C8D1 & C11D1	**Pre-dose belantamab mafodotin**	X	X	X	Within 30 minutes prior to start of infusion
	EOI belantamab mafodotin	X	X		Within 30 min **after** EOI
C14D1 and every 3 cycles thereafter (i.e., C17, 20, until EOT)	**Pre-dose belantamab mafodotin**	X	X	X	Within 30 minutes prior to start of infusion
End of Treatment		X	X	X	

EOI = end of the infusion; SOI = start of the infusion, EOT = end of treatment;
X = time relative to belantamab mafodotin dose; P = time relative to pembrolizumab dose
1. To be obtained pre- and post- first dose of pembrolizumab irrespective of any dose delay

Details on PK blood sample collection including blood volumes, processing, storage and shipping procedures are provided in the SRM.

7.4.2. Pharmacokinetic Sample Analysis

Plasma analysis will be performed under the control of the GSK Bioanalysis Immunogenicity and Biomarkers (BIB) group, the details of which will be included in the SRM. Concentrations of belantamab mafodotin (ADC and total mAb) and cys-mcMMAF will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the plasma has been analysed for belantamab mafodotin (ADC and total mAb) any remaining plasma may be analysed for other compound-related metabolites and the results reported under a separate GSK BIB protocol.

If analysis is warranted, concentrations of pembrolizumab in serum will be performed under the control of Merck, the details of which will be included in the SRM. Raw data will be archived at Merck's data repository, OpenLab (detailed in the SRM).

7.5. Biomarkers

7.5.1. sBCMA Analysis

To measure any changes in soluble BCMA (sBCMA) concentration during the study, serum will be collected at the time points specified in the Time and Events Tables (refer to Table 9 and Table 10) and per PK Table 12.

7.5.2. Cytokine and Chemokine Analysis

Cytokines in the blood have been found to correlate with tumor pathway activation. A broad panel of cytokines/chemokines will be evaluated as outlined in the Time and Events Table (refer to Table 9).

7.5.3. Subject Stratification/Predictive Biomarkers

This is an open-label and single-arm study, no subject stratification will be performed. BCMA exhibits varied expression across haematological malignancies and therefore, BCMA expression at baseline may be an important predictor of response to belantamab mafodotin in combination with pembrolizumab. Though the majority of MM subjects express BCMA, the intensity of expression varies. To evaluate whether BCMA expression has utility in patient stratification, BCMA protein expression will be measured by IHC in malignant plasma cells at baseline, and other timepoints if available, and will be correlated with clinical outcomes and potentially other biomarker or disease assessments. Because BCMA can also be detected in circulation, the soluble form (sBCMA) has the potential to serve as a surrogate marker of BCMA at the cell surface. This study will correlate subjects sBCMA levels with BCMA cell surface expression and clinical response.

Any blood and bone marrow samples collected during this study may be used for the purposes of measuring novel biomarkers to identify factors that may influence scientific advances in multiple myeloma, hematological malignancies and/or medically related conditions, as well as the biological and clinical responses to belantamab mafodotin in combination with pembrolizumab. If relevant, this approach may be extended to include the identification of biomarkers associated with AEs.

Unless stated otherwise, these investigations may be performed irrespective of whether a response to belantamab mafodotin in combination with pembrolizumab is observed.

Samples will be collected at the time points indicated in the Time and Events Tables (Table 7, Table 8, Table 9 and Table 10). The timing of the collections may be adjusted on the basis of emerging data from this study or other new information, in order to ensure optimal evaluation of the pharmacodynamic and/or biomarker endpoints. Novel or emerging candidate biomarkers associated with the biological response to advanced multiple myeloma, hematological malignancies and/or medically related conditions, as well as biological and clinical responses to belantamab mafodotin in combination with pembrolizumab, may also be evaluated. These analyses may include but are not limited to:

- Tumor/bone marrow BCMA receptor expression by IHC and/or by RNA analyses.
- Soluble factors, including circulating cfDNA, blood and derivatives including cytokine/chemokine analysis of serum
- Immune cell characterization and/or profiling of peripheral blood and/or bone marrow aspirate samples by protein and/or RNA analyses
- Additional soluble marker measurements that include serum levels of sBCMA

- RNA/DNA/gene and/or protein analysis of tumor tissue/bone marrow aspirates or samples in circulation

7.5.4. Tumor Biomarker Analysis

To further characterize the subject population, biomarkers (e.g. expression of genes and proteins) related to the activity of the investigational compound may be assessed in malignant cells.

BCMA expression in plasma cells from bone marrow aspirates or trephines will be evaluated at baseline, and other timepoints if available, by IHC. Analysis of the immune context (immune cell characterization) of bone marrow aspirate samples may also be performed to analyse the tumor microenvironment. Additional bone marrow aspirate samples may be taken during the treatment period for biomarker research. All bone marrow aspirate samples collected may be evaluated for additional DNA/RNA/protein biomarker analyses.

7.5.5. Circulating Cell Free DNA (cfDNA) Analysis

Tumor specific circulating nucleic acid (cfDNA) levels detected in plasma or serum have been found to correlate with increasing tumor burden and decline following therapy. cfDNA in cancer subjects can harbour many genetic alterations (mutations, microsatellite alterations, aberrant methylation), which are generally consistent with the tumor. Tumor-specific circulating cfDNA has the potential to be a useful biomarker of therapeutic response as well as offering a less invasive blood based technique for identifying and selecting subjects for certain treatments. Given this promise, cfDNA will be explored to determine whether mutations in cfDNA can be identified. This test will also be explored to correlate increasing cfDNA levels with increasing tumour burden.

7.5.6. Immunogenicity Assessments

Serum samples for determination of anti-belantamab mafodotin and anti-pembrolizumab antibodies will be taken from all subjects at the time-points specified in the Time and Events Table in Table 9.

Samples will be analyzed for the presence of anti-belantamab mafodotin antibodies using validated immunoassays. Samples collected for pembrolizumab will be collected and stored. Analysis of pembrolizumab samples will only be performed if considered clinically indicated. All samples will be tested in screening assay, and positive samples will be further characterized for specificity and antibody titers. Details of blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the SRM. For each subject, immunogenicity results, including the incidence and titers, will be reported.

7.6. Genetics

Information regarding genetic research is included in Appendix 6 (Section 12.6)

An important exploratory objective of the clinical study is genetic research. Participation in genetic research is optional but all subjects who are eligible for the clinical study will be given the opportunity to participate. Subjects may decline participation without effect on their medical care or care during the clinical study. A separate consent signature is required for genetic research.

Subjects who provide consent will have a blood sample taken for analysis. The presence/absence of genetic variations in host DNA will be analyzed to determine their relationship with response (safety, tolerability, pharmacokinetics (PK) and efficacy) to treatment with the combination of belantamab mafodotin and pembrolizumab.

Information regarding genetic research is included in Section 12.6. In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the genetic research described in Section 12.6 unless otherwise indicated. Where required by regulatory authorities, approval of the genetic assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the genetic assessments is being deferred and the study, except for genetic assessments, can be initiated. When genetic assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, genetic assessments will not be conducted.

7.7. Value Evidence and Outcome

Three Health-Related Quality-of-Life (HRQoL) assessments will be performed in this study. More details about all patient questionnaires can be found in the SRM. The following assessments will be administered to subjects in different regions based on the availability of translated versions.

7.7.1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module (EORTC QLQ-C30)

The EORTC QLQ-C30 is a 30-item questionnaire containing both single- and multi-item measures [Aaronson, 1993]. These include five functional scales (Physical, Role, Cognitive, Emotional, and Social Functioning), three symptom scales (Fatigue, Pain, and Nausea/Vomiting), a Global Health Status/QoL scale, and six single items (Constipation, Diarrhea, Insomnia, Dyspnea, Appetite Loss, and Financial Difficulties). Scores for each scale and single-item measure are averaged and transformed linearly to a score ranging from 0–100. A high score for functional scales and for Global Health Status/QoL represent better functioning ability or HRQoL, whereas a high score for symptom scales and single items represents significant symptomatology [Proskorovsky, 2014].

7.7.2. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma module (EORTC QLQ-MY20)

The EORTC QLQ-MY20 is a supplement to the QLQ-C30 instrument used in patients with multiple myeloma [Aaronson, 1993; Cocks, 2007]. The module comprises 20

questions that address four myeloma-specific HRQoL domains: Disease Symptoms, Side Effects of Treatment, Future Perspective, and Body Image. Three of the four QLQ-MY20 domains are multi-item scales: Disease Symptoms (includes bone aches or pain, back pain, hip pain, arm or shoulder pain, chest pain, and pain increasing with activity); Side Effects of Treatment (includes drowsiness, thirst, feeling ill, dry mouth, hair loss, upset by hair loss, tingling hands or feet, restlessness/agitation, acid indigestion/heartburn, and burning or sore eyes); and Future Perspective (includes worry about death and health in the future, and thinking about illness). The Body Image scale is a single-item scale that addresses physical attractiveness. As with the QLQ-C30, QLQ-MY20 domain scores are averaged and transformed linearly to a score ranging from 0–100. A high score for Disease Symptoms and Side Effects of Treatment represents a high level of symptomatology or problems, whereas a high score for Future Perspective and Body Image represents better outcomes [Proskorovsky, 2014].

7.7.3. Exit Interview

All subjects in Parts 1 and 2 will participate in an Exit Interview. The Exit Interview will be conducted to further evaluate disease and treatment related symptoms and their associated impacts on function and health-related quality of life. The Exit Interview will be conducted by a trained interviewer via telephone subsequent to the End of Treatment visit. The Exit Interview should be scheduled to be completed within approximately 21 days of the end of treatment visit.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system].
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

Statistical considerations and data analysis may be performed separately and/or combined for Part 1 and Part 2.

9.1. Hypothesis(es)

9.1.1. Part 1: Dose-Escalation Phase

No formal statistical hypotheses are being tested in Part 1. Analysis of the data obtained from Part 1 will only utilize descriptive methods.

9.1.2. Part 2: Expansion cohort

The primary goal of Part 2 is to characterize clinical activity of the combination and to detect if meaningful response rate (ORR) can be achieved. Based on historical information [Lokhorst, 2015] and clinical judgement, the null hypothesis has been defined as ORR ≤40%. The alternative hypothesis has been defined as ORR ≥60% based on clinically meaningful improvement of 20%.

In Part 2, treatment-related Grade 4 or higher AEs will be continuously monitored starting from when 5 subjects are dosed. Based on the 11% Grade 4 or higher AEs observed in the FTIH study (BMA117159), it is considered that the combination treatment has unacceptable toxicity if observed treatment-related Grade 4 or higher AEs is significantly higher than 12% at 1-sided alpha of 0.025.

9.2. Sample Size Considerations

9.2.1. Part 1: Dose-Escalation Phase

The total number of subjects to be enrolled into Part 1 will depend on the number of subjects needed to characterize individual dose cohorts. The sample size is not driven by statistical considerations. However, based on assumptions that 2 different dose levels will be tested (up to 6 subjects per dose level) it is anticipated that up to 12 evaluable subjects will be enrolled in Part 1.

9.2.2. Part 2: Expansion Cohort

Sample size for Part 2 is estimated based on hypothesis specified in Section 9.1.2 using the Predictive Probability design [Lee, 2008]. Details of sample size calculation are provided in Appendix 12. The optimal design has Nmax = 28, type I error rate of 0.10 and power of 80.6%. The expansion cohort may be stopped early for futility if the predicted probability of success is less than 1.5%. If the true ORR is 40%, the expected sample size is 20 and the probability of early termination is 86.1%; if the true ORR is 60%, the expected sample size is 28 and the probability of early termination is 15.6%.

9.3. Sample Size Sensitivity

There is no need to perform sample size sensitivity analysis.

9.3.1. Sample Size Re-estimation or Adjustment

Sample size re-estimation is not planned for this study.

9.4. Data Analysis Considerations

9.4.1. Analysis Populations

All Treated Population: will consist of all subjects who received at least one dose of study drug(s). Safety and clinical activity data will be evaluated based on this population.

The Pharmacokinetic Population: This will consist of those subjects in All Treated Subjects Population from whom at least one PK sample is obtained and analyzed.

DLT Evaluable Population: will consist of subjects fulfilling the 'All Treated' population criteria during part 1 (Dose Escalation) and are followed up for a 21-day period or withdrawn within 21 days due to an AE meeting the definition of a DLT as defined in Section 4.2.3.1.

All Evaluable Population: This is the population used for decision-making at the futility analysis during part 2 (Expansion Cohort). This will be the population for Bayesian predictive adaptive design as defined in Section 9.5.2 and summaries of response if data warrant. In general, subjects are evaluable if they have received at least 1 dose of treatment for both drugs and the time from the first dose to the time of data cut-off is more than 66 days, i.e., reached the time of three planned disease assessments. Details on deriving the evaluable population will be provided in the RAP.

Additional analysis populations may be defined in the Reporting and Analysis Plan (RAP).

9.5. Interim Analysis

9.5.1. Part 1: Dose Escalation

During dose escalation, no formal interim analysis will be performed. Data will be reviewed through data visualization tools to inform dose escalation decisions. The mTPI design will be utilized to guide dose escalation/de-escalation decisions. More details of the dose escalation procedure are described in Section 4.2.3.1.

After the last cohort of subjects in Part 1 complete the DLT observation period, a formal interim analysis will be performed to support the RP2D decision, except for scenarios where RP2D is clearly defined by the toxicity profile. Data considered to support RP2D decision will include but not be limited to safety, available PK profiles and observed signs of clinical activity. Details of the interim analysis will be provided in the RAP.

9.5.2. Part 2: Expansion

Continuous safety monitoring will be conducted for the expansion cohort starting from when 5 subjects are dosed. The observed number of treatment-related Grade 4 or higher AEs will be compared against the safety stopping rule in Table 13. Enrollment may stop if the safety stopping rule is met based on totality of safety data. For example, if there are 3 events out of 5 dosed subjects, enrollment may stop after review of all safety data, if

there is 2 or fewer events out of 5 dosed subjects, enrollment will continue. Operating characteristics for the safety stopping rule are provided in Appendix 11.

Table 13 Safety Stopping Rules for the Expansion Cohort

Number of dosed subjects	Stop if treatment related Grade 4 or higher AEs larger or equal to this number
5	3
6-10	4
11-14	5
15-19	6
20-25	7
26-28	8

Interim analyses for ORR will start when at least 10 subjects are evaluable as defined in Section 9.4.1. Subjects who initially received RP2D in Part 1 may also be included. The observed number of subjects with unconfirmed response of PR or better will be compared with the stopping boundary in Table 14. Enrolment may stop if the stopping rule is met. Final decision will be based on the totality of data. For example, if there are 2 unconfirmed responses out of 10 evaluable subjects, enrolment may stop after review of all available data; if there are 3 or more unconfirmed responses out of 10 evaluable subjects, enrolment will continue.

Table 14 Decision Making Criteria for Futility Analysis

Number of Evaluable Subjects	≤ This Number of Responses to Stop Early for Futility	Probability of continuing enrolling when ORR=0.4	Probability of continuing enrolling when ORR=0.6
10	2	83.3%	98.8%
11	2	83.3%	98.8%
12	3	75.5%	98.1%
13	3	75.5%	98.1%
14	4	68.6%	97.5%
15	4	68.6%	97.5%
16	5	62.3%	96.9%
17	6	52.9%	95.7%
18	6	52.9%	95.7%
19	7	46.7%	94.9%
20	7	46.7%	94.9%
21	8	41.6%	94.2%
22	9	34.6%	92.8%
23	9	34.6%	92.8%
24	10	30.2%	91.9%
25	11	24.4%	90.2%
26	12	18.8%	87.7%
27	13	13.9%	84.5%

Number of Evaluable Subjects	≤ This Number of Responses to Stop Early for Futility	Probability of continuing enrolling when ORR=0.4	Probability of continuing enrolling when ORR=0.6
28	14	0.0%	0.0%

9.6. Primary Analysis

Primary analysis will be conducted approximately 15 months from the last subject first visit (LSFV). If meaningful response rate (ORR) cannot be achieved, participants may discontinue the study treatment and will undergo end of treatment and follow-up assessments as defined in Section 4.2.2. Statistical considerations and data analysis may be performed separately and/or combined for Part 1 and Part 2.

9.7. Final Analysis

Final analysis of the data captured in Part 1 and Part 2 will be undertaken at the end of study (Section 5.5.2). Data from the two parts may be combined for some analyses at the end of the trial, as appropriate.

9.8. Key Elements of Analysis Plan

Data will be listed and summarized according to GSK reporting standards, where applicable. Complete details will be documented in the RAP. Any deviations from, or additions to the original analysis plan described in this protocol will be documented in the RAP and final study report.

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative, data from all participating centers will be pooled prior to analysis.

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment.

As the duration of treatment for a given subject will depend on efficacy and tolerability, the duration of follow-up will vary between subjects. Consequently, there will be no imputation for missing data.

Demographic and baseline characteristics will be summarized.

9.8.1. Clinical Activity Analyses

The primary endpoint ORR and other applicable secondary endpoints (e.g., CBR, DoR, TTR, TTP, PFS) will be based on the responses assessed by the investigator.

At futility interim and the primary analysis, the primary endpoint (ORR) will be analyzed based on the All Evaluable population. Otherwise, all efficacy endpoints will be analyzed based on the All Treated population unless otherwise specified. The analytical methods planned for each endpoint are described in Table 15.

Table 15 Statistical Analysis Methods for Clinical Activity Endpoints (Part 2)

Endpoint	Statistical Analysis Methods
Primary	Overall Response Rate (ORR) is defined as the percentage of subjects with a confirmed PR or better (i.e. PR, VGPR, CR and sCR), according to the International Myeloma Working Group (IMWG) Response Criteria). The number and percentage of subjects in the following response categories will be presented: sCR, CR, VGPR, PR, overall response (sCR+CR+VGPR+PR), minimal response (MR), stable disease (SD), progressive disease (PD), and not evaluable (NE). The corresponding 95% CI for ORR will also be provided. Subjects with unknown or missing responses will be treated as non-responders, i.e., these subjects will be included in the denominator when calculating percentages of response.
Secondary	Secondary clinical activity endpoints of Part 2 of this study are CBR, DoR, TTR, PFS, TTP and MRD Negative Rate. **Clinical benefit rate (CBR),** defined as the percentage of subjects with a confirmed minimal response (MR) or better per IMWG. **Duration of response (DoR)** is defined as the time from first documented evidence of PR or better until disease progression (PD) per IMWG, or death due to PD among subjects who achieve an overall response (i.e. confirmed PR or VGPR or CR or sCR). Responders without disease progression will be censored at the censoring time point for TTP. **Time to response (TTR)** is defined as the time between the date of first dose and the first documented evidence of response (PR or better) for subjects who achieve an overall response (i.e. confirmed PR or VGPR or CR or sCR). **Time to best response,** defined as the time between the date of first dose and the first best documented response (PR or better) for subjects who achieve an overall response (i.e. confirmed PR or VGPR or CR or sCR). **Progression-free survival (PFS)** is defined as the time from first dose until the earliest date of disease progression (PD) per IMWG, or death due to any cause. Determination of dates of PFS event and dates for censoring will be described in the RAP. **Time to disease progression (TTP)** is defined as the time from first dose until the earliest date of PD per IMWG, or death due to PD. Determination of dates of TTP event and dates for censoring will be described in the RAP. For all the TTE endpoints described above, median TTE with 95% CI will be estimated employing the Kaplan-Meier method. A Kaplan-Meier survival curve will be generated. The number and percentage of subjects who had the event or were censored will also be reported. In addition, PFS rate with 95% CI at 6, 12 and 18 months will be estimated using Kaplan-Meier methods for the PFS endpoint. **OS** is defined as the time from first dose until death due to any cause. Subjects who withdraw consent from the study or are lost to follow-up will be censored at the time of withdrawal or lost to follow-up. Subjects who are still alive at the clinical cut-off date for the analysis will be censored at the last known alive date or last contact date. The last contact date will be determined by the maximum collection/assessment date from

Endpoint	Statistical Analysis Methods
	among selected data domains within the clinical database. Survival rate 12, 18 and 24 months will be reported from Kaplan-Meier analysis as data permits. .

9.8.2. Safety Analyses

The All Treated Population will be used for the analysis of safety data. All serially collected safety endpoints (e.g. laboratory tests, vital signs, ECGs) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a "worst-case" analysis. Complete details of the safety analyses will be provided in the RAP.

9.8.2.1. Exposure Duration

The number of subjects administered study treatment will be summarized according to the duration of therapy.

9.8.2.2. Adverse Events

Adverse events (AEs) will be coded using the standard MedDRA and grouped by system organ class. Adverse events (AEs) will be graded by the investigator according to the National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), (version 4.03, [NCI, 2010]). In addition, for belantamab mafodotin treatment related corneal events, the GSK grading scale for corneal events (Appendix 9) should be used.

Events will be summarized by frequency and proportion of total subjects, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, and SAEs and AEs leading to discontinuation of study treatment. Adverse events (AEs), if listed in the NCI-CTCAE (version 4.03, [NCI, 2010]) will be summarized by the maximum grade. Otherwise, the AEs will be summarized by maximum intensity.

Characteristics (e.g. number of occurrences, action taken, grade, etc) of the following AEs of special interest will be summarized separately:

- Corneal events
- Thrombocytopenia
- Infusion related reactions

The incidence of deaths and the primary cause of death will be summarized.

9.8.2.3. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) (Version 4.03, [NCI, 2010]). Laboratory test results outside the reference ranges that do not have associated NCI-CTCAE criteria will be summarized using proportions. Further details will be provided in the RAP.

9.8.2.4. Other Safety Measures

Data for vital signs, ECGs, and ECHOs will be summarized based on predetermined criteria identified to be of potential clinical concern (PCI). Further details will be provided in the RAP.

9.8.3. Pharmacokinetic Analyses

9.8.3.1. Concentration Time Data

Linear and semi-logarithmic individual concentration-time profiles and mean and median profiles (when applicable) by belantamab mafodotin dose will be plotted for belantamab mafodotin (ADC and total mAb), cys-mcMMAF, and pembrolizumab (if tested) in Part 1.

Concentrations of belantamab mafodotin (ADC and total mAb), cys-mcMMAF, and pembrolizumab (if tested) will be listed for each subject and summarized (when appropriate) by planned time point and dose cohort in Part 1 and Part 2.

9.8.3.2. Derived Pharmacokinetic Parameters

Pharmacokinetic analyses will be the responsibility of Clinical Pharmacology Modeling and Simulation, GSK.

For Cycle 1, belantamab mafodotin, total mAb, cys-mcMMAF, and pembrolizumab (if measured) concentration-time data will be analyzed by standard non-compartmental methods, if data permit. Calculations will be based on the actual sampling times recorded during the study.

From the plasma concentration-time data, the following PK parameters will be determined for belantamab mafodotin, total mAb, and pembrolizumab (if measured) for each participant after each dose of belantamab mafodotin or of pembrolizumab, as data permit:

- Maximum observed plasma concentration (Cmax), time to Cmax (tmax), concentration at the end of infusion (C-EOI), and concentration prior to next dose (Ctrough)
- For Cycle 1: area under the plasma concentration-time curve from time 0 to the end of the dosing interval [AUC(0-τ)], last time point where the concentration is above the limit of quantification (tlast)

For cys-mcMMAF, Cmax, tmax, C-EOI, tlast, and area under the plasma concentration-time curve from time 0 to 168 h after dosing [AUC(0-168)] will be computed at Cycle 1, as data permit.

Pharmacokinetic parameters will be listed and summarized descriptively (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, CV% and 95% confidence interval of log-transformed parameters) by dose cohort in Part 1 and Part 2.

Belantamab mafodotin data from this study may be analyzed using a population pharmacokinetic approach. If performed, the initial analysis will use the most current population pharmacokinetic model and will include computation of systemic clearance (CL), volume of distribution, and/or terminal phase half-life (t½). The results of the population PK analysis may be provided in a separate report.

9.8.4. Pharmacokinetic/Pharmacodynamic Analyses

If deemed appropriate and if data permit, exposure-response relationships between belantamab mafodotin, cys-mcMMAF, and/or pembrolizumab (if measured) exposure measures (e.g., dose, concentration, Cmax, or AUC) and clinical activity (e.g., ORR) and/or toxicity may be explored by population methods. Results of this analysis may be provided in a separate report.

9.8.5. Translational Research Analyses

The results of translational research investigations will be reported either within or separately from the main clinical study report (CSR). All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Further details on the translational research analyses will be addressed in the RAP.

9.8.5.1. Novel Biomarker(s) Analyses

The results of these biomarker investigations may be reported separately from the main clinical study report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Additional exploratory analyses may be performed to further characterize novel biomarkers.

9.8.5.2. Genetic Analyses

Further details on genetic analyses will be addressed in Section 7.6

Exploratory Response Prediction Biomarkers

Cell surface BCMA and sBCMA pre dosing will be quantified as a potential predictive biomarker for clinical activity. Post dosing sBCMA will be quantified to assess dynamics during treatment.

If the data permit, an attempt will be made to identify a statistically and clinically meaningful threshold for BCMA expression which serves as an indicator for potential efficacy. Full details of analysis approaches will be provided in the RAP.

9.8.5.3. Exploratory analyses of DNA, and Protein

Exploratory analyses may be performed on remaining study samples for analyses of DNA, RNA and protein to understand changes in response to the combination treatment with belantamab mafodotin and pembrolizumab.

The results of exploratory investigations will be reported separate from the main clinical study report (CSR). All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

9.8.6. Immunogenicity Assessment

For each subject, the results and titers of anti-belantamab mafodotin binding antibodies will be listed for each assessment time point with time-matched belantamab mafodotin plasma concentration. The frequency and percentage of subjects with positive and negative results will be summarized for each assessment time and overall for each subject by dose cohort. The detailed information will be included in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Clinicaltrials.gov

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.

- Signed informed consent must be obtained for each subject prior to participation in the study
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

10.3. Urgent Safety Measures

If an event occurs that is related to the conduct of the study or the development of the IP, and this new event is likely to affect the study of subjects, the Sponsor, and the investigator will take appropriate urgent safety measures to protect subjects against any immediate hazard.

The Sponsor will work with the investigator to ensure the Institutional review board (IRB)/ethics committee (EC) is notified.

10.4. Quality Control (Study Monitoring)

In accordance with applicable regulations, Good Clinical Practice (GCP) and GSK procedures, the site will be contacted prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents and to allocate their time and the time to their staff to monitor to discuss findings and any issues.

Monitoring visits will be conducted in a manner to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.5. Quality Assurance

To ensure compliance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and all applicable regulatory requirements, GSK may conduct quality assurance audits of the site. Regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

10.6. Study and Site Closure

The end of the study will be defined as the date of the last visit of the last subject enrolled.

Upon completion or termination of the study, the monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, International Conference on Harmonization Good Clinical Practice (ICH GCP), and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/EC promptly and provide the reason(s) for the suspension/termination.

10.7. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that

an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

10.8. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The results summary will be posted to the GSK Clinical Study Register no later than eight months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

10.9. Review Committees

10.9.1. Internal Safety Review Committee

An Internal Safety Review Committee (iSRC) will be utilized in this study and comprise individuals who are not members of the clinical study team. The iSRC are positioned to offer an internal, independent review of safety data to protect the interests of subjects and ensure their safety. All efforts will be made to maintain the study integrity and validity of study data. The schedule of planned reviews of safety data and the analysis plan for iSRC review is described in the iSRC Charter, which is available upon request.

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12. APPENDIX

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ADCC	Antibody dependent cellular cytotoxicity
ADC	Antibody drug conjugate
AE	Adverse Event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APRIL	A proliferation-inducing ligand
AST	Aspartate aminotransferase
ATP	Adenosine tri phosphate
AUC	Area under the curve
AUC(0-t)	Area under the concentration-time curve
AV	Atrioventricular
BAFF	B-cell-activating factor belonging to the TNF family
BCG	Bacillus Calmette-Guerin
BCMA	B cell maturation antigen
BP	Blood Pressure
BNP	B-type natriuretic peptide
BUN	Blood urea nitrogen
CBR	Clinical Benefit Rate
cfDNA	Circulating Cell Free deoxyribonucleic acid
CK	Creatine kinase
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CO_2	Carbon dioxide
CPK	Creatinine phosphokinase
CRF	Case Report Form
CR	Complete Response
CRP	C-reactive protein
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CT	Computed tomography
Ctrough	Concentration at trough
CV	Coefficient of variation
CYP	Potent cytochrome P450
DAMPs	Danger-associated molecular patterns
DCs	Dendritic cells
DDI	Drug-Drug interaction
DKA	Diabetic ketoacidosis
DLT	Dose limiting toxicities
DNA	Deoxyribonucleic acid

DOR	Duration of Response
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ER	Endoplasmic reticulum
EMA	European Medicines Agency
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module
EORTC-QLQ-MY20	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma module
EOS	End of Study
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridization
FLC	Free light chain
FNRP	Female of non-childbearing potential
FRP	Female of reproductive potential
FSH	Follicle stimulating hormone
FTIH	First Time in Human Trial
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GSK	GlaxoSmithKline
GVHD	Graft-versus-host disease
HBcAb	Hepatitis B core antibody
HBsAg	Surface antigen of Hepatitis B virus
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human Immunodeficiency Virus
HNSTD	Highest non-severely toxic dose
HRT	Hormone replacement therapy
HSCT	Hematopoietic stem cell transplantation
IB	Investigator Brochure
ICD	Immunogenic cell death
ICH GCP	International Conference on Harmonization Good Clinical Practice.
IFN-γ	Increased interferon-γ
IL-2	Interleukin-2
IMWG	International Myeloma Working Group
IND	Investigational new drug
IgG	ImmunoglobulinG
IgM	ImmunoglobulinM
IgA	ImmunoglobulinA

INR	International normalization ratio
IP	Investigational product
ITIM	immunoreceptor tyrosine-based inhibition motif
IRB	Institutional review board
IRR	Infusion related reaction
ITSM	immunoreceptor tyrosine-based switch motif
IV	Intravenous
IVRS	Interactive voice response system
LDH	Lactate dehydrogenase
LSFD	Last subject first dose
LSLV	Last subject's last visit
LSLV	Last subject last visit
mAb	Monoclonal antibody
mTPI	Modified Toxicity Probability Interval
MM	Multiple myeloma
MMAF	Monomethyl auristatin-F
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
NCI	National Cancer Institute
NEI-VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
NYHA	New York Heart Association
ORR	Overall Response Rate
OTC	Over the counter
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PACT	Post Analysis Continued Treatment
PCR	Polymerase chain reaction
PCI	Potential clinical concern
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death Ligand 1
PD-L2	Programmed cell death Ligand 2
PFS	Progression Free Survival
PI	Principal Investigator
PK	Pharmacokinetics
PRO-CTCAE	Patient-Reported Outcome Version Of Common Toxicity Criteria for Adverse Events
PR	Partial response
PTS	Platform Technologies and Science
QTcF	Corrected QT interval for heart rate by Fridericia's formula
RAMOS	Registration and Medication Ordering System

RAP	Reporting and Analysis Plan
RBC	Red blood cell
REM	Rapid eye movement
RIBA	Recombinant immunoblot assays
RP2D	Recommended Phase 2 Dose
RNA	Ribonucleic acid
SAE	Serious adverse event
SAS	Statistical Analysis System
SEB	Staphylococcal enterotoxin B
SOI	Start of infusion
SOP	Standard operating procedure
SPEP	Serum Protein Electrophoresis
SRM	Study Reference Manual
STD_{10}	Severely toxic dose 10
T1DM	Type 1 diabetes mellitus
TLS	Tumor Lysis syndrome
TTP	Time to Disease Progression
TTR	Time to (best) Response
TNF	Tumor necrosis factor
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
USP	United States Pharmacopeia
VGPR	Very good partial response
WBC	White blood cell
WT	Wild type

Trademark Information

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12.2. Appendix 2: ECOG Performance Status[1]

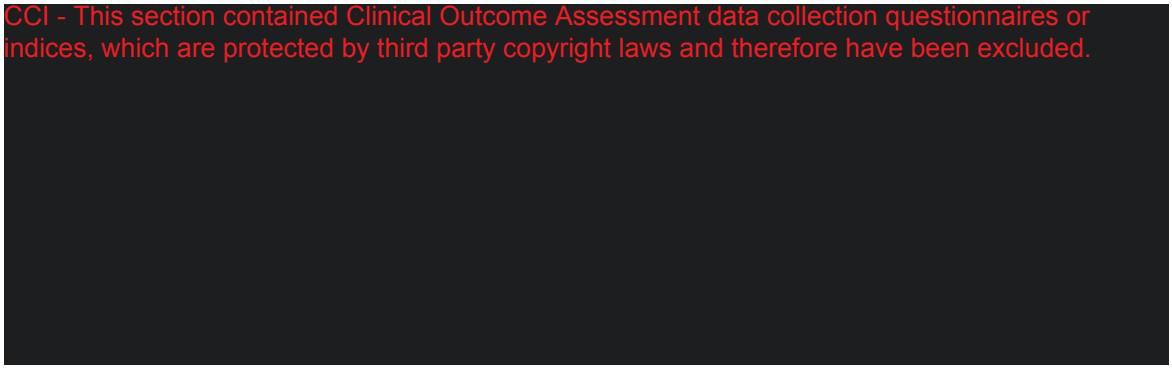
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

12.3. Appendix 3: Modified Diet in Renal Disease Formula

MDRD	eGFR = 175 × $(S_{cr})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American) GFR is expressed in mL/min/1.73 m2, SCr is serum creatinine expressed in mg/dL, and age is expressed in years. The link below will auto-calculate the creatinine clearance: http://nephron.org/cgi-bin/MDRD_GFR/cgi

12.4. Appendix 4: NYHA Functional Classification System

The **New York Heart Association (NYHA) Functional Classification: Class I, II, III or IV Heart Failure** [NYHA, 1994] provides a simple way of classifying the extent of heart failure. It places subjects in one of 4 categories based on the level of limitation experienced during physical activity:



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The Criteria Committee of the New York Heart Association (NYHA). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, Mass: Little, Brown & Co.; 1994:253-256.

12.5. Appendix 5: Liver chemistry stopping and monitoring criteria and required actions and follow up assessments

12.5.1. Liver chemistry stopping criteria

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

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

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE**²** • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to language within this appendix) • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may	• Viral hepatitis serology[4] • Only 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[5]. • Blood sample for pharmacokinetic (PK) analysis, if it can be obtained within 45 days after the last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • 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 AE report form • Record use of concomitant medications on the concomitant medications report form including

continue subject in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	acetaminophen, herbal remedies, other over the counter medications • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</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 HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** 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** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects 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. Includes: 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
5. 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].
6. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase I/II Oncology liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, **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 subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

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12.5.2. Liver Safety Drug Restart or Rechallenge Guidelines

If subject meets liver chemistry stopping criteria do not restart/rechallenge subject with study treatment unless:

- GSK Medical Governance approval **is granted** (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

If GSK Medical Governance approval to restart/rechallenge subject with study treatment **is not granted**, then subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments

12.5.2.1. Rechallenge Following Liver Stopping Events that are Possibly Related to Study Treatment

Following drug-induced liver injury, **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies**.[1] Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered within one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- hypersensitivity[1] with initial liver injury (e.g. fever, rash, eosinophilia)
- jaundice or bilirubin >2xULN with initial liver injury (direct bilirubin >35% of total)
- subject currently exhibits severe liver injury defined by: ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total), or INR≥1.5
- serious adverse event or fatality has earlier been observed with drug rechallenges[2,3]
- evidence of drug-related preclinical liability (e.g. reactive metabolites; mitochondrial impairment[3])

Rechallenge refers to resuming study treatment following drug induced liver injury (DILI). Because of the risks associated with rechallenge after DILI this should only be considered for a subject for whom there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit:risk assessment of rechallenge is considered to be favourable.

Approval by GSK for rechallenge with study treatment can be considered where:

- Investigator requests consideration of rechallenge with study treatment for a subject who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.
- Ethics Committee or Institutional Review Board approval for rechallenge with study treatment must be obtained, as required.
- If the rechallenge is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable

liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.

- If after study treatment rechallenge, subject meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.

- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment rechallenge.

- GSK to be notified of any adverse events, as per Section 7.3.1.

12.5.2.2. Restart Following Transient Resolving Liver Stopping Events NOT Related to Study Treatment

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with HLA markers of liver injury.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Possible study treatment-induced liver injury has been excluded by the investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where a study treatment has an identified genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate), the presence of the marker should be excluded. If study treatment-related liver injury cannot be excluded, the guidance on rechallenge in Section 12.5.2 will apply.
- There is no evidence of alcoholic hepatitis.
- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.

- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.
- GSK to be notified of any adverse events, as per Section 7.3.1.

References:

- [1]Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.
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12.6. Appendix 6: Genetic Research

Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [Gorin, 2012] with certain variants reported to influence treatment response [Chen, 2002]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including belantamab mafodotin or any concomitant medicines;
- Multiple myeloma susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 mL blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

12.7. Appendix 7: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. • The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

1. Results in death

a. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

b. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

c. Results in disability/incapacity

NOTE:

• The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
d. Is a congenital anomaly/birth defect
e. Other situations: • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
f. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.
• Refer to Appendix 5 for the required liver chemistry follow-up instructions

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias

- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.
- Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category

utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- [If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.](if performed)
- New or updated information will be recorded in the originally completed CRF.

- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the [Medical Monitor or the SAE coordinator]
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the [Medical Monitor or the SAE coordinator] by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

SAE reporting to GSK via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the [Medical Monitor or the SAE coordinator]
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE data collection tool sent by overnight mail
- Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE receipt can be found at this beginning of the protocol on the Sponsor/Medical Monitor Contact Information page.

SAE reporting to GSK via PIMS

• Facsimile transmission of the following PIMS listings for the corresponding subject is the preferred method to transmit SAE information to the [Medical Monitor or protocol contact]:
  • SAE listing
  • Demographic listing
  • Study treatment listing
• In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of all required information sent by overnight mail.
• If the PIMS system is unavailable when the SAE occurs, the site will use the paper SAE form and fax that to the [Medical Monitor or protocol contact]. The site will enter the SAE data into PIMS as soon as the system becomes available.

12.8. Appendix 8: Contraceptive Guidance and Collection of Pregnancy Information Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's: review of the subject's medical records, medical examination, or medical history interview.
- Postmenopausal female
- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

a.	**CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
b.	**Highly Effective Methods[b] That Have Low User Dependency**
c.	Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
d.	Intrauterine device (IUD)
e.	Intrauterine hormone-releasing system (IUS)[c]
f.	Bilateral tubal occlusion
g.	Vasectomized partner
h.	*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.*
i.	**Highly Effective Methods[b] That Are User Dependent**
j.	Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
k.	oral
l.	intravaginal
m.	transdermal
n.	injectable
o.	Progestogen-only hormone contraception associated with inhibition of ovulation[c]
p.	oral
q.	injectable
r.	Sexual abstinence
s.	*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 subject*

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 amenorrhoea 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)

Collection of Pregnancy Information

Male subjects with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male subject's female partner of a male study subject who becomes pregnant while participating in this study, and for 6 months following last dose of belantamab mafodotin. This applies only to male subjects 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 Subjects who become pregnant

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study, and for 4 months following last dose of belantamab mafodotin.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on subject 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 subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will discontinue study intervention.

12.9. Appendix 9: Belantamab Mafodotin associated Corneal Event Severity Grading and Mitigation Strategy

Prophylactic preservative-free artificial tears should be administered in each eye at least 4-8 times daily, beginning on Cycle 1 Day 1 until the End of Treatment (EOT). Allow at least 5-10 minutes between administration of artificial tears and steroid eye drops. 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.

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 subject and the investigator, the following may be considered:

- Beginning with the start of each belantamab mafodotin infusion, subjects may apply cooling eye masks to their eyes for approximately 1 hour or as much as tolerated.
- Subjects 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.

Subjects must avoid the use of contact lenses during the study.

An ophthalmology (or optometrist, if an ophthalmologist is not available) consult is required for all subjects who develop signs or symptoms of corneal toxicity.

A summary of prophylactic interventions for corneal toxicity associated with belantamab mafodotin is provided in Table 16. Corneal toxicity must be graded according to the guidelines provided in Table 17. Additional guidance on grading visual acuity changes provided in Table 18.

Table 16 Prophylactic measures for corneal Events associated with Belantamab Mafodotin

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

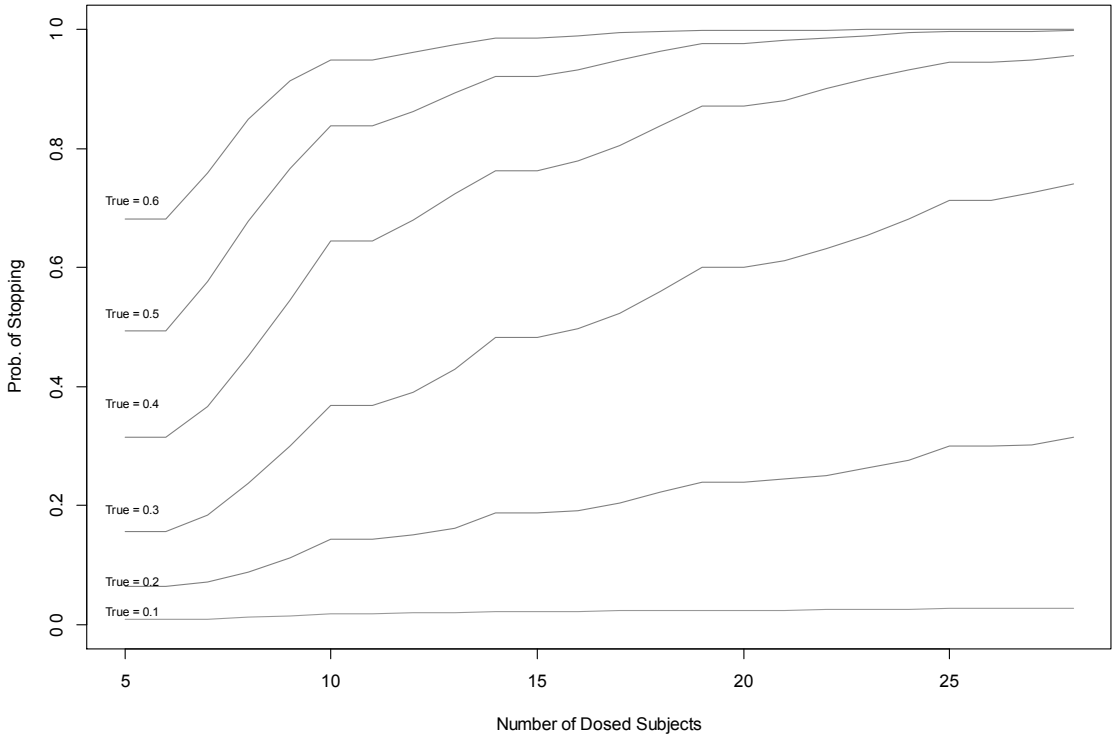
a. Dose modifications and treatment for ocular toxicities are discussed in Section 6.5.

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

12.10. Appendix 10: Country Specific Requirements

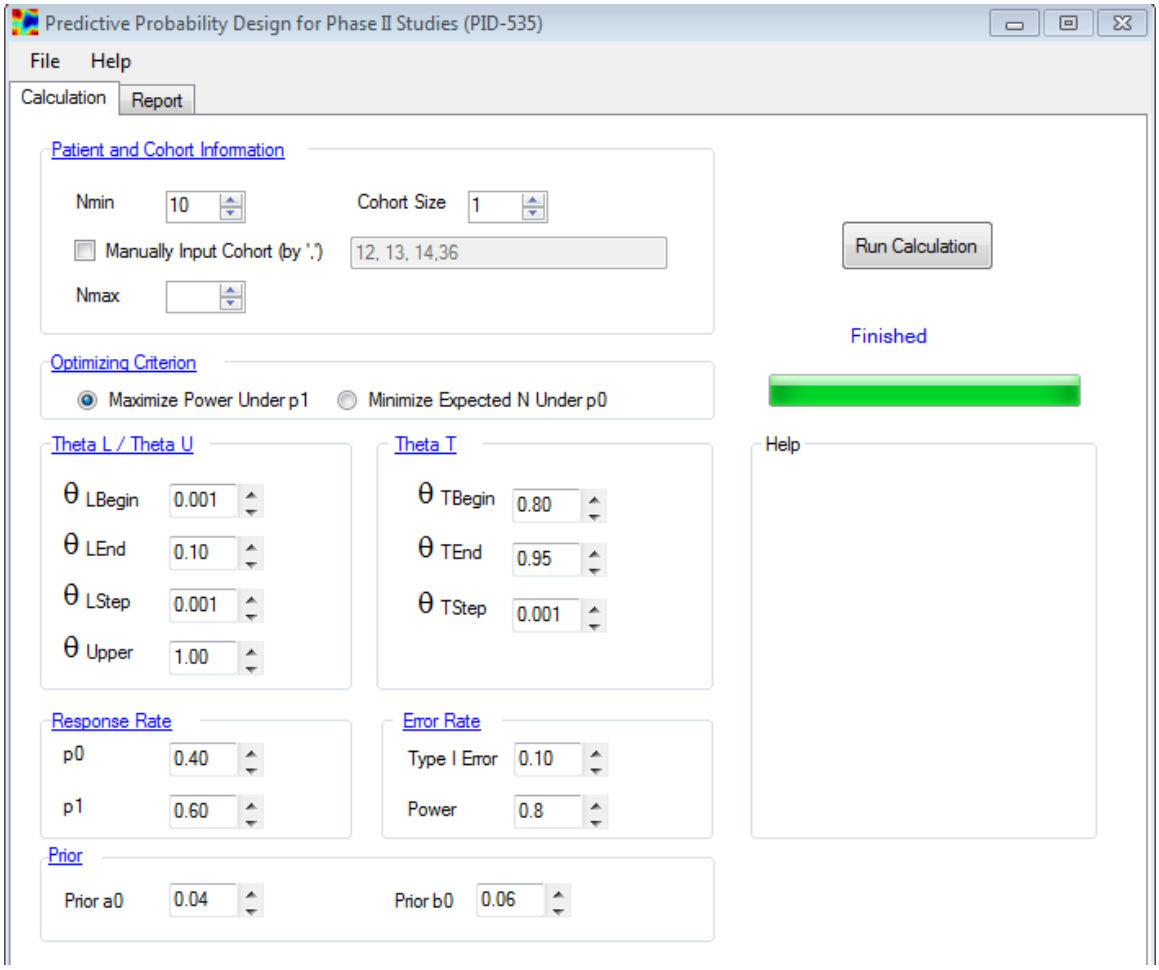
No country-specific requirements exist.

12.11. Appendix 11: Operating Characteristics of Safety Stopping Rule for Expansion Cohort



12.12. Appendix 12: Sample Size Calculation for the Expansion Cohort

Sample size is calculated using the Predictive Probability Design for Phase II studies software. The optimal design is identified by specifying interim looks starting from a minimum of 10 evaluable subjects, "maximizing power under the alternative hypothesis' as the optimizing criterion, Thetha_L(threshold of early futility stopping)/Theta_U(threshold of early efficacy stopping)/Theta T(threshold) as default, a weakly informative beta prior Beta (0.04, 0.06) representing information from 0.1 subject with a mean response of 40%, type I error rate controlled at 0.10, and power of 80%. The design with smallest N_{max} that controls the type I and type II error rate is the optimal design.



12.13. Appendix 13: Data Management/Monitoring

Source Data Verification/Source Document Review (SDV/SDR)

During periods in which on-site monitoring is not permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution and in accordance to with local law and regulatory guidance documents.

Remote SDV/SDR will be proposed to study sites to meet a patient and/or critical data quality need, e.g., to assess patient safety or to ensure data integrity. The study specific monitoring plan will be updated in accordance with remote monitoring practices adopted for the country/study. The subject informed consent will be updated in line with local regulations to permit remote monitoring practices. In case of remote SDV/SDR, GSK will work with the site to ensure subject privacy.

eCRF/CRF Final or Interim Sign off Process:

The Principal Investigator (PI) is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study patient is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 and 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing the eDC platform) using his/her unique eCRF login credentials.

Essential Document Sign Off Process:

If an investigator is unable to print and sign essential documents such as Protocol/Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK. Please note that unblinding procedures remain the same as those documented in the protocol and other study-related documents.

12.14. Appendix 14: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

2016N273410_01	**26-SEP-2018**	**Amendment No. 1**
Amendment 1 applies to all global sites. The following changes were based on review and comments from the FDA: • Revised line of setting from 2nd line to 4th line; updated associated sections in the synopsis, protocol body, and inclusion/exclusion criteria • Revised dose limiting toxicity (DLT) wording as directed by FDA • Removed the lowest dose level (1.92 mg/kg) during dose escalation. Maintained 2.5 and 3.4 mg/kg doses during dose escalation. Due to lowest dose removal, revised study number to 40 overall subjects. Associated revisions made in statistical section • Addition of statement to add clarity that pembrolizumab will be held or discontinued when belantamab mafodotin is held or discontinued • Addition of Part 2 stopping criteria In addition to the requests from the FDA, the following revisions were also included: • Update to the Sponsor Information section • Addition of EudraCT number • Inclusion of additional wording to the Rationale and Background section to further support combination with pembrolizumab and to support move to 4th line therapy • Revision of dose escalation objective/endpoints to move overall response rate to secondary from exploratory and addition of minimal residual disease negativity rate (based on current guidelines); revision of dose expansion objectives/endpoints to add clarity to endpoints, add ocular findings, add additional clinical activity secondary endpoints, and revise the questionnaire in exploratory section from MDASI-MM to EORTC-QLQ-C30 and EORTC-QLQ-MY20; updated associated sections of protocol to reflect changes • Updates/revisions to the inclusion/exclusion criteria to incorporate changes to the standard language for belantamab mafodotin and pembrolizumab • Revised contraception language for both male and female to follow belantamab mafodotin standard language in Inclusion/Exclusion criteria and protocol sections; revisions to the pregnancy section due to change in standard language • Increased the maximum number of combination cycles from 32 to 35 to be in line with standard pembrolizumab language and to be in line with 2-year treatment; update of associated study schematic • Revision to the follow-up definition; addition of progression free survival follow-up visits • In addition to the FDA mandated DLT revisions, added clarity to DLT definition, revised wording to existing DLTs and added new DLTs • Revisions/updates to the corneal event language, supportive care, monitoring and mitigation language throughout the document, inclusive of changes to Appendix 9		

- Revision of statistical model in dose escalation from Bayesian Logistic Regression Model to modified mTPI; revision to various calculations associated with change to this model and to change in subject number; revisions to statistical sections of protocol, including revision to clinical activity analyses section
- Updates to the background/data for belantamab mafodotin from first time in human study BMA117159
- Updated background information related to pembrolizumab to be in line with changes to standard language and to address the MM study information from KEYNOTE 183 and 185; Revision of Benefit:Risk statement based on this information
- Updated Risk assessment and mitigation table
- Revisions to subject completion language and study completion language
- Revisions to Investigational Product section to be in line with standard language
- Updates to the belantamab mafodotin and pembrolizumab Dose Modification tables based on current standard language
- Revised the Table and Events section by splitting one table into multiple tables based on phase of study. Added in eGFR, Spot Urine, Skeletal survey, revisions to PK and ADA assessments; replaced MDASI-MM with EORTC questionnaires, removed INR/PTT, TBNK and CK-MB. On-treatment assessments linked to weekly schedule and/or dosing of combination treatment; addition of PFS follow-up column and clarification of OS follow-up
- Removal of Sentinel Event language from protocol
- Addition of adverse events of special interest section
- Addition of specific requirements for ocular examinations and procedures
- Removed TBNK from Biomarker sections, other wording revisions in this section
- Revision of All Evaluable Subjects population
- Addition of an Internal Safety Review Committee
- Appendices updates including revision to abbreviations, update of liver chemistry stopping criteria formatting, removal of International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma appendix, removal of appendix listing P-gp inhibitors, revisions to contraception and corneal event appendices due to updates to standard language
- Other minor clarifications/revisions were added

2016N273410_02	**26-FEB-2020**	**Amendment No. 2**

Amendment 2 applies to all global sites. The following changes were based on review and comments from global agencies, inclusion of items noted in protocol clarification letters, revisions due to discrepancies, revision of study drug related language and other clarifications noted since Amendment #1:

- Update to Author list, sponsor signatory, and sponsor contact list
- Universal update to document to clarify name of GSK2857916 as belantamab mafodotin
- Based on emerging data, removal of mandated steroid eye drops throughout protocol, inclusive of Appendix 9
- Updated timelines for requirement of contraception for females and males based on additional data collected and Investigator Brochure; added statements that use should be consistent with local regulations; inclusive of Appendix 8

- Due to emerging data, modified the timings of ocular exams after the 4th dose of belantamab mafodotin
- Removal of detailed non-clinical pharmacokinetics and addition of cross reference to revised Investigator Brochure which contains information
- Revision of effects in human section and addition of pharmacokinetics section based on updated data from single agent belantamab mafodotin studies
- Simplification of dose level reduction language for belantamab mafodotin
- Revision of Part 1 completion language to clarify belantamab mafodotin RP2D decision criteria
- Based on agency feedback, addition to benefit:risk section and Table to highlight risks/mitigations for potential risks associated with the combination of belantamab mafodotin and pembrolizumab; Update of belantamab mafodotin and pembrolizumab language based on emerging data
- Clarification of subject completion definition, with definition applying to both Part 1 and Part 2
- Based on agency feedback, addition of belantamab mafodotin administration language in applicable sections
- Based on emerging data for both study treatments, updated belantamab mafodotin and pembrolizumab dose modification Tables
- Added clarification to contact lens use based on emerging data
- Based on emerging data, revision of prohibited medication section
- Clarification of clinical stable definition of ocular signs and symptoms
- Revisions to Time and Events Table 7: clarify pregnancy test language, clarify imaging language, addition of cytogenetic tests
- Revisions to Time and Events Table 8: clarify C1D8 assessment window, clarification of AE/SAE language, clarify ocular exam window, revise ocular exam timing language, addition of hematology monitoring as per dose modification table, clarifications/additions to bone marrow footnotes, including a mandated aspirate sample for immune cell characterization/profiling
- Revisions to Time and Events Table 9: clarify C1D8 assessment window, clarification of vital sign windows, clarification of ECG window, removal of pharmacokinetics details from footnote and replaced with pharmacokinetics section reference, revision of immunogenicity footnote, revision of serum cytokine/chemokine footnote with additional samples, revision of cfDNA footnote with additional samples, addition of whole blood RNA and cryopreserved PBMC samples to increase translational research scope
- Revisions to Time and Events Table 10: clarification of AE/SAE language, update of timing for final pregnancy test (as applicable), addition to bone marrow footnotes, including a mandated EOT aspirate sample for immune cell characterization/profiling clarification of timing for exit interview
- Based on emerging data, revision to ocular examination section, with removal of some tests/eye segment review, and ocular photography
- Addition of CK and LDH isoenzyme tests, based on emerging data, revision of clinical laboratory Table
- Addition of pharmacokinetics Table in Section 7.4.1. to provide clarity, removal of select belantamab mafodotin and pembrolizumab pharmacokinetic samples;

addition of sBCMA collection at each belantamab mafodotin PK collection timepoint • Revision of biomarker wording to reflect addition of new tests and/or samples • Addition of DLT evaluable population to further define Part 1 population • Other minor clarifications/revisions were added

Amendment 3: 27-AUG-2021 (TMF-12902367)

Overall Rationale for the Amendment:

This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Section # and Name	Description of Change	Brief Rationale
Title Page	Update to medical monitor information and SAE reporting	Medical monitor list is not provided as per GSK template. Details provided in the SRM
Section 4.5.2. Pembrolizumab Dose Justification; Section 4.6. Benefit: Risk Assessment; Section 6.5.2. Dose modification and toxicity management for immune-related AEs associated with pembrolizumab	Update to pembrolizumab safety language Update to pembrolizumab ECI-overdose language Update to standard text based on pembrolizumab and belantamab mafadotin Investigator Brochures, as appropriate	Updated information as per Latest IB Update for pembrolizumab (2021) and belantamab (2021)
Section 1. Synopsis; Section 9. Statistical Considerations And Data Analyses, Section 9.6 Primary Analysis,	Addition of Primary Analysis at approximately 15 months follow-up from LSFV	To test the hypothesis that a meaningful response rate (ORR) can be achieved of the combination
Section 7.4.1. Blood Sample Collection for Pharmacokinetics, Section 9.8.3.2. Derived Pharmacokinetic Parameters, Section 9.8.4. Pharmacokinetic/ Pharmacodynamic Analyses	Update on planned derived pharmacokinetic parameters and pharmacokinetic/ pharmacodynamic analyses	PK parameters will be determined for belantamab mafodotin, total mAb, and pembrolizumab (if measured) for each participant after each dose of belantamab mafodotin or of pembrolizumab.
Section 12.13. 12.13.Appendix 13:	Updates to data monitoring wording	Source Data Verification/Source Document Review, eCRF/CRF Final or

Section # and Name	Description of Change	Brief Rationale
Data Management/Monitoring		Interim Sign off Process and Essential Document Sign Off Process details added

Amendment 01

Where the Amendment Applies:

Protocol Amendment 01 applies to all sites and countries.

Amendment Changes with Rationale:

The original protocol dated 11 May 2017 is replaced by Amendment 01 dated 26 SEP 2018.

The following protocol changes have been implemented as a result of comments received from the US Food and Drug Administration, which included removal of lower dose level as starting dose, revision of DLT definitions, population move to later line of therapy, adjustment of subject numbers and addition of Part 2 stopping criteria. The revisions also include language updates from Merck to pembrolizumab indications, dose rationale, and dose modifications. Additional revisions include revisions to background/rationale wording for GSK2857916, update to objective/endpoint wording, inclusion/exclusion criteria based on GSK/Merck updated wording, adjustment of contraception language, adjustment to maximum study treatment cycles, revisions to corneal event sections, updated statistical design wording, non FDA related update of DLT definitions, revisions of safety language and monitoring/management language, removal of IMWG response Appendix and associated links, removal of P-gp inhibitor appendix with addition of SRM for additional information, addition of MRD testing, addition of AE of special interest section, removal of sentinel event, update to benefit:risk information, replacement of questionnaire in Part 2 and updated Table of Events. Additionally, administrative corrections of minor typographical, and/or inconsistent language throughout the protocol were made as well as an update to the Reference section.

Original text is displayed as strikethrough indicates replaced or removed text. New text is displayed as underline. If applicable, revisions within the tables will be displayed as text or if same revision affects multiple tables, the changes will be summarized; revisions to figures will be displayed first by the old figure, and then followed by the new figure. Administrative changes will not be displayed in the summary of changes.

Summary of Changes:

1. Medical Monitor/SAE Contact Information

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Site Address
Primary Medical Monitor	PPD , MD, PhD PPD ~~MD, PhD~~	PPD	PPD	GlaxoSmithKline 1250 South Collegeville Road Mailstop UP4300 Collegeville, PA 19426, USA PPD
Secondary Medical Monitor	PPD , MD, PhD PPD ~~MD, PhD~~	PPD	PPD	GlaxoSmithKline1250 South Collegeville Road Mailstop UP4300 Collegeville, PA 19426, USA PPD
SAE Reporting	PPD PPD ~~, MD, PhD~~	OAX37649@gsk.com		

Reason for change: Update to the GSK personnel assigned to the study.

2. Section 1 – Protocol Synopsis Rationale

B-cell maturation antigen expression is restricted to B cells at later stages of differentiation [Darce, 2007] and according to GSK internal data all patients with MM express various levels of BCMA on the surface of the tumor cells. In addition, GSK2857916 was shown to induce immunogenic cell death (ICD) characterized by expression of ecto-Calreticulin, release of adenosine tri phosphate (ATP), and secretion of HMGB1 in BCMA expressing multiple myeloma cell line (GSK unpublished data). Treatment of mice harbouring syngeneic tumors derived from the EL4 lymphoma cell line expressing human BCMA (EL4-hBCMA) with GSK2857916 delays tumor growth and promotes durable regressions. Mice which responded remained immune to re-challenge suggesting an engagement of the host immune system and immunologic memory, providing a strong rationale for clinical combinations with immuno-modulatory agents (GSK unpublished data). Exposure of dendritic cells to tumor cells undergoing ICD evokes an inflammatory phenotype (innate response), where mature dendritic cells (DCs) are ~~undergoing~~ activated~~ion~~ and may induce an antigen-specific T cell response. It is ~~We~~ hypothesized ~~ise~~ that the T cell dependent anti-tumor response induced by GSK2857916 can be further augmented by PD-1 inhibitor, pembrolizumab when both drugs are used in combination.

Reason for change: Provision of additional data obtained to support rationale for combination with pembrolizumab.

3. Section 1 – Objective(s)/Endpoint(s)

Part 1: Dose Escalation

Objectives	Endpoints
Primary	
• To determine safety, tolerability and to establish the recommended Phase 2 dose (RP2D) of the combination of GSK2857916 and pembrolizumab in subjects with relapsed/refractory ~~(rel/ref)~~ RRMM	• Percent of subjects with adverse events (AEs), changes in clinical signs and laboratory parameters • Number of subjects with dose limiting toxicities (DLTs)
Secondary	
• To evaluate clinical activity of the combination of GSK2857916 and pembrolizumab in subjects with RRMM	• Overall Response Rate (ORR), defined as the percentage of subjects with a confirmed partial response (PR) or better (i.e., PR, very good partial response [VGPR], complete response [CR] and stringent complete response [sCR]), according to the International Myeloma Working Group (IMWG) Response Criteria [Kumar, 2016]
• To evaluate the pharmacokinetic profile of GSK2857916 when administered intravenously in combination with pembrolizumab[1)]	• ~~GSK2857916~~ Pharmacokinetic (PK) parameters following IV administration as data permit (e.g., area under the curve [AUCs], mean maximum concentration [Cmax], time of Cmax [tmax], terminal phase half-life [t½]) after the first dose; ~~and~~ concentration at trough (Ctrough), and end of infusion concentration in subsequent cycles, when measured
• To assess anti-drug antibodies (ADAs) against GSK2857916[1)].	• Incidence and titers of ADAs against GSK2857916
Exploratory	
~~• To evaluate clinical activity of the combination of GSK2857916 and pembrolizumab in subjects with rel/ref MM~~	~~• Overall Response Rate (ORR) defined as % of patients achieving ≥ PR~~ ~~• Clinical Benefit Rate (CBR) defined as % of patients achieving ≥ MR~~ ~~• Duration of Response (DOR) data permitting~~ ~~• Progression Free Survival (PFS) data permitting~~ ~~• Overall survival (OS) data permitting~~ ~~• Time to Response (TTR) data permitting~~

Objectives	Endpoints
• To assess Minimal Residual Disease (MRD) in participants who achieve ≥VGPR or better	• Minimal Residual Disease (MRD) negativity rate, defined as: the percentage of subjects who are MRD negative in subjects who achieve VGPR or CR
• To characterize the relationship between clinical response and other biologic ~~intra-tumor or microenvironment~~ characteristics ~~(DNA, protein analysis)~~	• BCMA expression levels on malignant cells, ~~and other markers in tumor tissue,~~ serum sBCMA levels, serum cytokines, ~~baseline immune status~~ and immune cell characterization and their relationship to clinical response (Protein, RNA, DNA analysis)
• To investigate the relationship between genetic variants in the host and response to GSK2857916 in combination with pembrolizumab	• Possible relationship between host genetic variation and response to GSK2857916 in combination with pembrolizumab
• To evaluate the tolerability of GSK2857916 in combination with pembrolizumab based on patient self-report of symptomatic adverse effects	• Symptomatic adverse effects as measured by the Patient-reported outcome version of the Common Term Criteria for Adverse Events (PRO-CTCAE) • Impact of ocular adverse effects on quality of life as measured by the Visual Function questionnaire(s): National Eye Institute 25-item Visual Function Questionnaire (NEI-VFQ-25) and Ocular Surface Disease Index (OSDI)
• To evaluate disease and treatment related symptoms and associated impacts on function and health-related quality of life	• Exit Interview

1. PK and ADA samples for pembrolizumab will be collected and stored during the trial. The analysis will be triggered only in case of unexpected clinical findings.

Part 2: Expansion

Objectives	Endpoints
Primary	
• To assess the clinical activity of the combination treatment with GSK2857916 and pembrolizumab in subjects with ~~rel/ref~~ RRMM	• Overall Response Rate (ORR), defined as the percentage of participants with a confirmed PR or better (i.e., PR, VGPR, CR and sCR), according to the IMWG Response Criteria [Kumar, 2016] ~~Overall Response Rate (ORR) defined as % of patients achieving ≥ PR~~
Secondary	
• To further evaluate ~~confirm~~ safety of GSK2857916 administered in combination with pembrolizumab in subjects with RR ~~rel/ref~~ MM	• Number of subjects with AEs, changes in clinical signs and laboratory parameters • Ocular findings on ophthalmic exam

Objectives	Endpoints
• To further characterize the clinical activity of the combination treatment with GSK2857916 and pembrolizumab in subjects with ~~rel/ref~~ RRMM	• ~~Clinical Benefit Rate (CBR) defined as % of patients achieving ≥ MR~~ • ~~Duration of Response (DOR) data permitting~~ • ~~Progression Free Survival (PFS) data permitting~~ • ~~Overall Survival (OS) data permitting~~ • ~~Time to Response (TTR) data permitting~~ • Clinical benefit rate (CBR), defined as the percentage of participants with a confirmed minimal response (MR) or better per IMWG • Duration of response (DoR), defined as: the time from first documented evidence of PR or better to the time when disease progression (PD) is documented per IMWG, or death due to PD among subjects who achieve an overall response, i.e. confirmed PR or better. • Time to response (TTR), defined as: the time between the date of first dose and the first documented evidence of response (PR or better) among subjects who achieved a confirmed response of PR or better. • Time to best response, defined as the time between the date of first dose and the first best documented response (PR or better) among subjects who achieve a confirmed response of PR or better. • Progression-free survival (PFS), defined as: the time from first dose to the earliest date of PD per IMWG, or death due to any cause. • Time to disease progression (TTP), defined as: the time from first dose until the earliest date of PD per IMWG, or death due to PD. • Overall Survival (OS), defined as the time from first dose to death due to any cause
• To evaluate the pharmacokinetic profile of GSK2857916 when administered intravenously in combination with pembrolizumab[1]	• Pharmacokinetic (PK) parameters following IV administration as data permit (e.g., area under the curve [AUCs], mean maximum concentration [Cmax], time of Cmax [tmax], terminal phase half-life [t½]) after the first dose; concentration at trough (Ctrough), and end of infusion concentration in subsequent cycles, when measured
• To assess anti-drug antibodies (ADAs) against GSK2857916[1]	• Incidence and titers of ADA to GSK2857916
Exploratory	
• To assess Minimal Residual Disease (MRD) in participants who achieve ≥VGPR or better	• Minimal Residual Disease (MRD) negativity rate, defined as: the percentage of subjects who are MRD negative in subjects who achieve VGPR or CR

Objectives	Endpoints
• To characterize the relationship between clinical response and other biologic ~~intra-tumor or microenvironment~~ characteristics ~~(DNA, protein analysis)~~	• BCMA expression levels on malignant cells ~~and other markets in tumor tissue~~, serum sBCMA levels ~~baseline immune status~~, serum cytokines, and immune cell characterization and their relationship to clinical response (Protein, RNA, DNA analysis)
• To investigate the relationship between genetic variants in the host and response to GSK2857916 in combination with pembrolizumab	• Possible relationship between host genetic variation and response to GSK2857916 in combination with pembrolizumab
~~• Plasma concentrations of GSK2857916 when administered intravenously in combination with pembrolizumab[1)]~~	~~• GSK2857916 end of infusion concentration and concentration at trough~~
• To explore the effect of the combination therapy of GSK2857916 with pembrolizumab on symptoms and health-related quality of life ~~HRQoL~~ in subjects with ~~rel/ref~~ RR-MM	• Changes from baseline in symptoms and health-related quality of life as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module (EORTC-QLQ-C30) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma Module (EORTC-QLQ-MY20) ~~MD Anderson Symptom Inventory Multiple Myeloma (MDSI MM) module~~
• To evaluate the tolerability of GSK2857916 in combination with pembrolizumab based on patient self-report of symptomatic adverse effects	• Symptomatic adverse effects as measured by the PRO-CTCAE • Impact of ocular adverse effects on quality of life as measured by the Visual Function questionnaire(s): NEI-VFQ-25 and OSDI
• To evaluate disease and treatment related symptoms and associated impacts on function and health-related quality of life	• Exit Interview

1. PK and ADA samples for pembrolizumab will be collected and stored during the trial. The analysis will be triggered if unexpected clinical findings have been identified.

Reason for change: Revision of Objective/Endpoints to revise secondary endpoint for dose escalation, add MRD for response endpoints, replace MDASI-MM with EORTC questionnaires, add clarity to primary and secondary endpoints for dose expansion, and revise biomarker wording.

4. Section 1 – Type and Number of Subjects

The study will enroll adult subjects with RR ~~rel/ref~~ MM, who have undergone stem cell transplant~~,~~ or who are considered transplant ineligible. Subjects must have been~~, and who have been~~ previously treated with at least 3~~2~~ prior lines that include the following: ~~,~~ ~~containing 3 classess of anti-myeloma drugs: an alkylating agent, AND~~ an immunomodulatory imide drug -IMiD (eg ~~i.e.~~ lenalidomide or pomalidomide)~~,~~ ~~AND a~~

proteasome inhibitor -PI (eg ~~i.e.~~ bortezomib, ixazomib or carfilzomib) and an anti-CD38 antibody alone or in combination. Line of therapy are defined by consensus panel of the International Myeloma Workshop [Rajkumar, 2011]. ~~In addition, subject must be prgressing on, or within 60 days since the most recent therapy (as defined by IMWG).~~

Overall, it is estimated that up to 40~~8~~ evaluable subjects will be enrolled in this two-part study (up to 12~~8~~ in Part 1, and 28~~30~~ in Part 2).

Reason for change: Revision of the targeted population and number of subjects due to FDA comments and adjustment to proposed dose level due to FDA comments.

5. Section 1 – Key Inclusion Criteria

Subjects eligible for enrolment in the study must meet all of the following criteria:

- Provide signed written informed consent, which includes compliance with the requirements and restrictions listed in the consent form
- Male or female, 18 years or older (at the time consent is obtained)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- ~~Have confirmed diagnosis of Multiple Myeloma and have undergone stem cell transplant, or are considered transplant ineligible~~
- Histologically or cytologically confirmed diagnosis of MM as defined according to IMWG, 2014 [Rajkumar, 2014], and
    - Has undergone stem cell transplant or is ~~are~~considered transplant ineligible, and
    - Ha~~ve~~s been treated with at least 3~~2~~ prior lines of ~~prior~~ anti-myeloma treatments, including ~~3 classess of drugs: an alkylating agent, AND~~ an IMi~~I~~D (eg. lenalidomide or pomalidomide), ~~AND a~~ proteasome inhibitor (eg., bortezomib, ixazomib or carfilzomib) and an anti-CD38 antibody, alone or in combination. Line of therapy are defined by consensus panel of the International Myeloma Workshop [Rajkumar, 2011]. ~~In addition, subject must be progressing on, or within 60 days since the most recent treatment (as defined in International Myeloma Working Group Uniform Response Criteria, 2011 [Rajkumar, 2011]~~
- ~~In addition to the criteria above, subjects in **Part 2** must have~~ Has measurable disease defined as 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 (≥100 mg/L) and an abnormal serum free light chain ratio (<0.26 or >1.65)
    ~~d) Biopsy proven plasmacytoma (should be measured within 28 days of Screening Visit)~~
- Subjects with a history of autologous stem cell transplant (SCT) are eligible for study participation provided the following eligibility criteria are met:
    a) Transplant was > 100 days prior to study enrolment.
    b) No active infection (s).
    c) Subject meets the other eligibility criteria outlined in this protocol.

- ~~Subjects after prior allo SCT are allowed if the allo transplant was performed ≥ 5 years ago, and if subject has no active graft versus host disease requiring treatment.~~
- Subject has adequate organ system functions defined in the Table below:

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)[1]	≥ 1.0 X 10^9/L
Hemoglobin	≥ 8.0 g/dL
Platelets	≥ 75 ~~50~~ X 10^9/L
~~**Coagulation**~~	
~~INR~~	~~≤1.5 ULN~~
~~aPTT~~	~~≤1.5 x ULN~~
Hepatic	
Total bilirubin	≤1.~~2~~5X ULN (Isolated bilirubin >1.~~2~~5xULN ~~and ≤ 3xULN~~ is acceptable if bilirubin is fractionated and direct bilirubin <35%)
AST and ALT	≤~~1~~ 2.5 X ULN
Renal	
eGFR[2] ~~Albuminuria~~ Spot urine (albumin creatinine ratio)	≥~~45~~0 mL/min ≤500mg/g (56 mg/mmol)~~24hr~~
Cardiac	
LVEF (Echo)	≥50%
QTcF interval[3]	< 470 msecs

1. Without Growth factor support for the past 14 days, excluding erythropoietin
2. As calculated by Modified Diet in Renal Disease (MDRD) formula
3. The QT interval should be corrected for heart rate by Fridericia's formula (QTcF)

- All prior treatment-related toxicities (defined by National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.03, 2010) [NCI, 2010] must be ≤ Grade 1 at the time of enrollment except for alopecia, and Grade 2 neuropathy.
- A female subject is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP)

    OR
  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 8 during the intervention period and for at least 120 days 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.

Additional requirements for pregnancy testing during and after study intervention are located in Appendix 8.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

- Male Subjects:
  - Male subjects are eligible to participate if they agree to the following during the intervention period and for at least 140 days after the last dose of study intervention:
    - 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 as detailed below
    - Agree to use a male condom and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Appendix 8 when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

~~A female subject is of non-childbearing potential or women of childbearing potential must have a negative serum pregnancy test within 72 hours prior to the first dose of study treatment and agree to use effective contraception during the study and for 120 days following the last dose of study treatment.~~

~~Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception from the time of first dose of study treatment until 140 days after the last dose of study treatment to allow for clearance of any altered sperm.~~

Reason for change: Revision of Inclusion Criteria due to update in line of therapy and update of contraception language.

6. Section 1 – Key Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

- Systemic anti-myeloma therapy or an investigational drug ~~within~~ ≤14 days or five half-lives, whichever is shorter, preceding ~~prior to~~ the first dose of study drug ~~or~~
- ~~p~~Plasmapheresis within 7 days prior to the first dose of study drug

- Prior treatment with a monoclonal antibody within 30 days of receiving the first dose of study drugs
- Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137) and was discontinued from that treatment due to a Grade 3 or higher immune related adverse event (irAE)
- Current corneal epithelial disease except mild punctate keratopathy
- ~~Use of an investigational drug within 14 days or five half-lives, whichever is shorter, preceding the first dose of study drug~~
- ~~History of an allogeneic stem cell transplant within last 5 years~~
- ~~Evidence of active mucosal or internal bleeding~~
- Any major surgery within the last four weeks prior to the first dose of study therapy
- Presence of active renal condition (infection, requirement for dialysis or any other condition that could affect subject's safety). Subjects with isolated proteinuria resulting from MM are eligible, provided they fulfil criteria for ~~the~~ adequate renal function~~s~~ defined in the inclusion criteria
- Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions (including lab abnormalities)
- Has received prior radiotherapy within 2 weeks of start of study therapy. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-central nervous system (CNS) disease
- History of (non-infectious) pneumonitis that required steroids or current pneumonitis
- Current active 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 chronic liver disease (~~with the exception of~~ Gilbert's syndrome or asymptomatic gallstones ~~or otherwise stable chronic liver disease per investigator's assessment~~) or hepatobiliary involvement of malignancy is acceptable if subject otherwise meets entry criteria
- Malignancies other than disease under study are excluded, except for any other malignancy from which the participant has been disease-free for more than 2 years and, in the opinion of the principal investigators and GSK Medical Monitor, will not affect the evaluation of the effects of this clinical trial treatment on the currently targeted malignancy (RRMM). In addition, subjects with curatively treated non-melanoma skin cancer are allowed
- Has known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study therapy ~~Subjects with previous or concurrent malignancies are allowed only if the second tumor is not contributing to the subject's illness.~~

- Evidence of any cardiovascular risk defined in the protocol
  - QTcF interval ≥470 msecs
  - Evidence of current clinically significant uncontrolled arrhythmias;
    - including clinically significant electrocardiogram (ECG) abnormalities including 2nd degree (Type II) or 3rd degree atrioventricular (AV) block.
  - History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within six months of Screening.
  - Class III or IV heart failure as defined by the New York Heart Association functional classification system ~~(Appendix 4)~~
  - Uncontrolled hypertension
  - Presence of cardiac pacemaker (or defibrillator) with a predominantly ventricular paced rhythm, limiting ECG/QTcF analysis.
  - Abnormal cardiac valve morphology (≥Grade 2) documented by echocardiogram (subjects with grade 1 abnormalities CCI [redacted] can be entered on study). Subjects with moderate valvular thickening should not be entered on study.
- Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK2857916 or pembrolizumab, or any of the components of the study treatment.
- Pregnant or lactating female
- Known active infection requiring antibiotic, antiviral, or antifungal treatment
- Known HIV infection
- 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)
- 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: Subjects with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained
  NOTE: Hepatitis RNA testing is optional and subjects with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing
- ~~Subjects with positive test for Hepatitis B surface (HBS Ag) or Hepatitis B core (HBc) antigen.~~
- ~~Subjects with positive test for hepatitis C (HCV) infection are excluded regardless of viral load (if hepatitis C antibody is positive but confirmatory PCR or RIBA test is negative, subject is eligible).~~
- ~~Current corneal epithelial disease~~
- Has received a live-virus vaccination within 30 days of planned start of study therapy.
- Active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
- Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other

form of immunosuppressive therapy within 7 days prior the first dose of study therapy

- Has known psychiatric or substance abuse disorders that would interfere with the subject's ability to cooperate with the requirements of the study
- Has had an allogenic tissue/solid organ transplant

Reason for change: Revision of Exclusion Criteria due to updates to the GSK and Merck standard language.

7. Section 1 – Study Treatment and Duration

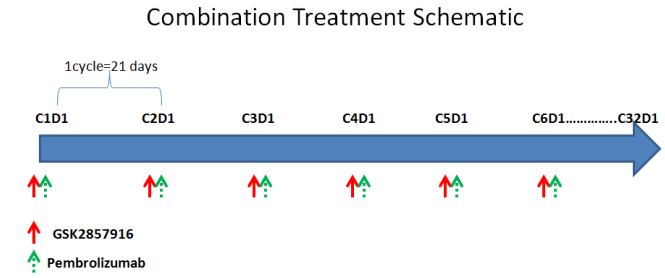
Study Treatment and Duration

Product name:	GSK2857916	Pembrolizumab
[Formulation description:]	20mg/mL, 1.5 mL/vial	100 mg/4mL
Route of Administration	Delivered as ~~30 min~~ IV infusion. Refer to Study Reference Manual (SRM) for details.	Delivered as 30 min IV infusion

Treatment Duration

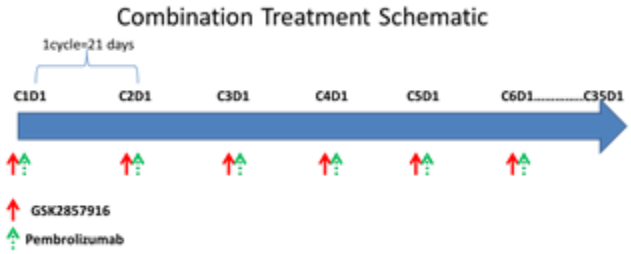
GSK2857916 and pembrolizumab will be administered via intravenous (IV) infusion on day 1 of each 21-day cycle (once every 3 week ~~Q3W~~ dosing schedule). Subjects enrolled in Part 1 and 2 will be treated until disease progression, intolerable toxicity, informed consent withdrawal, or for a maximum of ~~32~~ 35 cycles (approximately 2 years, See Combination Treatment Schematic below).

Old Figure:



Dosing:
-GSK2857916 and pembrolizumab on D1 of each cycle
-GSK2857916 first, Pembrolizumab as second iv infusion (1hr apart)
-If IRR related to GSK2857916, the pembrolizumab dosing will be delayed (up to 48 hrs)
-Max treatment duration: 32 cycles

New Figure:



Dosing:
-GSK2857916 and pembrolizumab on D1 of each cycle
-GSK2857916 first, Pembrolizumab as second iv infusion (1hr apart)
-If IRR related to GSK2857916, the PD1 dosing will be delayed
-Max treatment duration: 35 cycles combination treatment

~~Subjects who achieve complete response (CR/sCR) are allowed to have early treatment discontinuation under following conditions: subjects have attained a CR/sCR and have been treated for at least 8 cycles with the combination of GSK2857916 and pembrolizumab and had at least 2 treatment cycles with both study drugs beyond the date when the initial CR is declared.~~

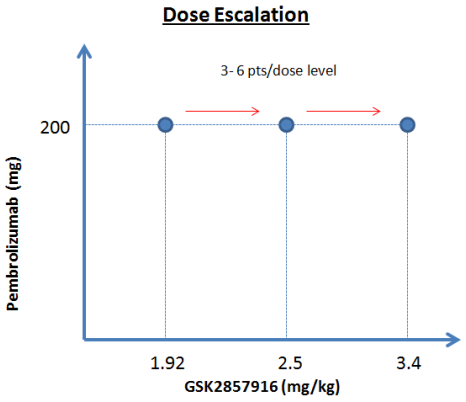
~~The subjects who have early treatment discontinuation will not be allowed to re-enter the study treatment at later time.~~

~~After treatment discontinuations all subjects will be followed up every 3 months for 12 months for PFS and OS.~~ Subjects who discontinued treatment for reasons other than PD will be followed up every 3 weeks until confirmed PD, initiation of a new anticancer therapy or death. All subjects with confirmed PD will be followed for OS every 3 months until the end of study. End of study is defined as when all subjects have been followed for 36 months from first dose of study treatment or died or withdrew consent or are lost to follow-up. The next subsequent therapy will be collected for all subjects who have confirmed PD before initiation of new anticancer therapy.

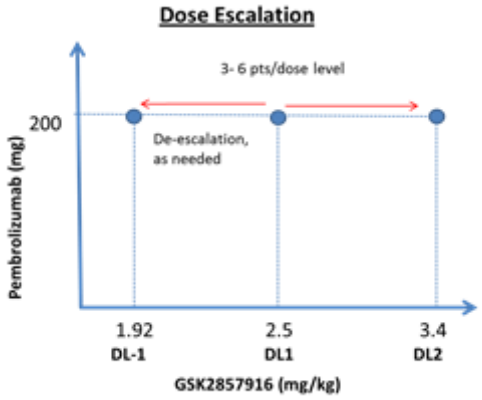
Part 1: Dose Escalation

Part 1 dose escalation will characterize the safety and tolerability of escalating doses of GSK2857916 in combination with 200 mg pembrolizumab to establish the RP2D. The following dose levels of GSK2857916 in combination with 200 mg pembrolizumab are planned to be studied: ~~1.92 mg/kg,~~ 2.5 mg/kg (dose level [DL] 1) and 3.4 mg/kg (DL2) (as outlined in Dose Escalation Schematic for Part 1 below). Additionally, other ~~intermediate~~ dose levels may also be explored. Dose level 1.92 mg/kg may be tested if dose level 2.5 mg/kg is not cleared. During the dose escalation, at least 3 evaluable subjects will be studied per dose level. In Part 1, any subject who received at least one treatment cycle of the combination will be evaluated for DLTs. Subjects who have received only GSK2857916 or have been withdrawn from the study for reasons other than toxicity but prior to completion of DLT observation period will be replaced.

Old Dose Escalation Schematic for Part 1


Dose Escalation
3- 6 pts/dose level
200
Pembrolizumab (mg)
1.92
2.5
3.4
GSK2857916 (mg/kg)

New Dose Escalation Schematic for Part 1



Reason for change: Update to number of total cycles based on actual 24 month calendar and in line with maximum dosing from Merck language. Revisions of schematics to match revised plan. Revision of starting dose based on guidance from FDA. Removal of option to discontinue treatment if CR/sCR achieved based on program language.

8. Section 1 – Dose Limiting Toxicity Criteria (Part 1 only)

The DLT observation window will be 21 days (=1 cycle). Any subject in Part 1 who received at least one treatment cycle of the combination of GSK2857916 and pembrolizumab will be evaluated for DLTs using National Cancer Institute (NCI) CTCAE Version 4.03 [NCI, 2010]. In addition, for GSK2857916 treatment related corneal events, the GSK grading scale for corneal events (Appendix 9) should be used for evaluation of DLT.

A DLT is defined as an AE that meets at least one of the criteria defined below and is considered by the investigator to be clinically relevant and attributed (definitely, probably, or possibly) to the study therapy during the 21 day DLT observation period.

~~An event will be considered a DLT if its relationship to the investigational agents cannot be ruled out, occurs within the DLT reporting period, and meets one of the following criteria:~~

1. Any Grade 4 non-hematologic toxicity
2. Any Grade 3 ~~or greater~~ non-hematologic toxicity, with the following exceptiosn (i.e., the following will not be considered a DLT): Grade 3 diarrhea, nausea, or vomiting that responds to standard of care within 72 hours; Grade 3 hypertension (controlled following addition of 1 antihypertensive medication); and Grade 3 tumor lysis syndrome ~~not resolving with appropriate supportive treatment within 48 hours, or resulting in a delay in initiating cycle 2 by 14 days or more~~
3. Any Grade 3 or greater non-hematologic laboratory value if either:
   - The laboratory abnormality persists for >48 hrs despite supportive treatment, or
   - The abnormality leads to hospitalization
4. Hematologic toxicity:
   - Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia:
     - Grade 4 thrombocytopenia of any duration

- Grade 3 thrombocytopenia associated with clinically significant bleeding
- Grade 3 or greater febrile neutropenia lasting >48 hours despite adequate treatment:

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

- ~~Grade 4 Thrombocytopenia <25,000/mm^3 if platelet transfusion is required.~~

5. Nephrotoxicity requiring dialysis, and not considered to be ~~related~~ due to disease under study (ie. myeloma) ~~progression~~ based on investigator's assessment.
6. Liver toxicity meeting pre-specified GSK liver stopping criteria
7. Prolonged delay (>14 days) in initiating Cycle 2 due to any treatment (pembrolizumab or GSK2857916) related toxicity, with the exception of Grade 1-2 corneal events (GSKgrading scale for GSK2857916 treatment related corneal events)
8. Any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1.
9. Any other toxicity considered to be dose-limiting that occurs beyond 21 days will be considered in the selection of the dose to recommend for expansion cohorts.
10. Any other event which in the judgment of the investigator and GSK Medical Monitor is considered to be a DLT

A subject who develops a DLT will be allowed to continue on study treatment if the toxicity did not meet predefined stopping criteria and recovered to ≤Grade 1 within 14 days~~, or after a longer recovery period~~ if the investigator and medical monitor agree that for a given subject the potential benefits may outweigh the risks.

Reason for change: Update to DLT language based on FDA comments and revisions to the GSK and Merck standard language.

9. Section 1 – Recommended Phase 2 Dose and Part 2: Expansion

All available data from Part 1 will be analyzed after the last cohort of subjects complete the 21-day DLT observation period.~~all evaluable subjects in the last cohort have completed at least pre-specified cycle of treatment, or have been withdrawn from the study due to disease progression, or toxicity~~. Data considered for RP2D selection will include, but not be limited to: safety, available PK profile, and observed signs of clinical activity. A dose level below maximum pre-specified dose (3.4mg/kg) may be selected as RP2D if compelling safety and encouraging clinical activity can be demonstrated at dose levels below 3.4 mg/kg.

Part 2: Expansion

Once the RP2D has been identified, an expansion cohort (Part 2) will open for enrollment of up to 28~~30~~ subjects with ~~rel/ref~~ RRMM in order to confirm the safety profile and to evaluate the clinical activity of the combination.

~~During an ongoing enrolment in Part 2, futility analysis will be performed once approximately 15 subjects in Part 2 are evaluable for futility. Subjects are considered evaluable if they are in the all treated population, have received at least 2 doses of combination treatment, and have had at least one disease assessment post 2nd dose. Subjects are also considered evaluable if they are in the all treated population and have progressed or died or have permanently discontinued the study treatment.~~

Reason for change: Update to language to clarify analysis population and update to subject number due to removal of lowest dose level. Removed analysis information from this section as should be in analysis section.

10. Section 1 – Corneal Supportive Guidelines ~~for Corneal Toxicity~~ (GSK2857916)

Corneal events ~~toxicity~~, which commonly manifest~~s~~ as a superficial microcystic keratopathy, ha~~ve~~s previously been observed with antibody drug conjugates, including those conjugated to MMAF. It is required that sites establish a close collaboration with an ophthalmologist (or optometrist, if ophthalmologist is not available) who will be responsible for assessing subjects on study and managing subjects who develop a corneal event~~toxicity~~ in close communication with the GSK Medical Monitor and ~~the~~ possibly a GSK~~coordinating~~ ophthalmologist.

Subjects will be assessed by ophthalmologists (or ~~/~~optometrist~~s~~, if ophthalmologist is not available) at baseline, and then every three weeks. If there is no change in vision and no corneal signs consistent with toxicity at time of the cycle 4 exam, subjects may have their ophthalmologic exams decreased to once every 3 months. If a subject subsequently develops a change in visual acuity or other ocular symptoms, the subject should be evaluated by an eye care professional. Intraocular pressure must be monitored if steroid eye drops are used for more than 7 days. ~~prior to each dose of cycles 1-4. If asymptomatic and without signs consistent with corneal toxicity at time of the cycle 4 exam, subjects may have their ophthalmologic exams decreased to once every 4 cycles. If a subject subsequently develops signs / symptoms, or they require additional treatment, e.g. topical steroid for more than 7 days, additional assessment by an ophthalmologist / optometrist will be implemented.~~

Further information regarding corneal event associated with GSK2857916, including a grading scale and prophylactic measures are in Appendix 9.

Reason for change: Update to language regarding corneal events.

11. Section 1 – Clinical Activity Assessment

Standard disease assessments for MM will include laboratory tests (serum and urine M protein test, sFLC, and corrected calcium), bone marrow core biopsy and aspirate (in case of suspected CR or to demonstrate progression), immunohistochemistry (IHC) of bone marrow samples to confirm stringent CR) or imaging, and minimal residual disease by Next Generation Sequencing (NGS; in subjects with achieve confirmed VGPR or CR). Response evaluation will be performed according to the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma 2016~~1~~ [Kumar, 2016 ~~Rajkumar,~~

~~2011~~]. ~~Clinical activity measured as Overall Response Rate (ORR) is defined as the percentage of subjects with confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR). Other assessments of interest like clinical benefit rate (CBR), PFS, TTR, DOR, and OS will also be analyzed.~~ Minimal residual disease negative rate will be assessed in those subjects who achieve a VGPR or CR.

Reason for change: Update to language due to change in response criteria and deletion of clinical activity as information is in other section of synopsis.

12. Section 1 – Pharmacokinetic assessments

Blood PK samples will be collected during the trial and analysed for GSK2857916 (ADC and total antibody) and cyc-mcMMAF concentration. Blood samples for pembrolizumab measurements will be collected and stored, but will only be analyzed in case of unexpected clinical findings.

Reason for change: Clarification of analytes.

13. Section 1 – Value Evidence and Outcome

Subjects enrolled in Part 2 only will self-complete additional questionnaires to assess the ~~The~~ symptoms related to multiple myeloma and its treatment, and the impact of these symptoms on daily functioning. Symptoms will be assessed using two questionnaires: EORTC-QLQ-C30 and EORTC-QLQ-MY20 ~~the MD Anderson Symptom Inventory – Multiple Myeloma (MDASI-MM) module. Subjects enrolled in Part 2 only will self-complete the MDASI-MM module at the specified visits.~~

Reason for change: Change in the questionnaire used for this analysis.

14. Section 1 – Statistical Analysis

For part 1, n~~N~~o formal statistical hypotheses are being tested. In Part 1, ~~after each dose level, the Bayesian Logistic Regression Model (BLRM) with overdose control will be used to predict probability of toxicity of the next planned dose based on observed dose-limiting toxities (DLTs) in previous cohorts. t~~The dose escalation decisions will be guided by the Modified Toxicity Probability Interval (mTPI) approach, ~~made based on this recommendation,~~ as well as the totality of the safety data. After the last cohort of subjects in Part 1 completes the 21-day DLT observation period, a formal interim analysis will be performed to support the RP2D decision, except for scenarios where RP2D is clearly defined by the toxicity profile.

The primary goal of Part 2 is to confirm safety and to characterize clinical activity of the combination and to detect if meaningful overall response rate (ORR) can be achieved. ~~Based on historical information [Lokhorst, 2015] and clinical judgement, the null hypothesis has been defined as ORR ≤ 40% for the purpose of this study. The alternative hypothesis has been defined as ORR ≥ 60%. A decision will be made using the specified stopping rules in the protocol. Descriptive statistics will be used to report the observed~~

~~ORR in the expanded cohort. Overall response rate will be defined as percentage of subjects achieving sCR+CR+VGPR+PR per IMWG Uniform Response Criteria [Kumar, 2011].~~

~~A Bayesian predictive adaptive design [Lee, 2008] allowing the trial to be monitored more frequently at multiple stages will be used. For Part 2 expansion cohort, starting with 13 subjects and allowing for a maximum sample size of 30, this design will have a type I error rate α of 0.092 and 80.9% power when the true response rate is 60%. The trial is designed to stop early for futility if the predictive probability of success is about 3.0% or less. Futility analysis will be performed once approximately 15 subjects in Part 2 are evaluable. Futility will be determined by comparing numbers of responses (defined as PR or greater) and evaluable subjects with the stopping rules specified in the protocol.~~

During part 2 of the study, treatment-rated Grade 4 or higher AEs will be continuously monitored starting from when 5 subjects are dosed. If observed toxicity level is significantly higher than 12% at 1-sided alpha of 0.025, the study may be terminated early based on totality of safety data. The 12% threshold is chosen based on 11% Grade 4 or higher AE observed in study BMA117159.

For Part 2, futility analyses for ORR will start when 10 subjects are evaluable. Enrollment may stop if the stopping rule is met based on totality of data.

Final analysis of the data captured in Part 1 and Part 2 will be undertaken after all subjects meet at least one of the following criteria: have reached the end of study or died. End of study is defined as when all subjects have been followed for 36 months from first dose of study treatment or died or withdrew consent or are lost to follow-up or the safety stopping criteria is met, whichever occurs first. ~~have received all prespecified treatments (32 cycles) or have progressed; or has died; or has been permanently withdrawn from the study for toxicity or other resons.~~

Reason for change: Revisions to statistical calculations and wording based on change to subject number, switch to mTPI design and clarification of end of study definition.

15. Section 2.1 Study 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 U.S. in 2016 [Siegel, 2016]. ~~Approximately 20,000 people will be diagnosed with MM each year in the United States [Rajkumar, 2011].~~ Despite significant advances with current novel therapies and hematopoietic stem cell transplantation (HSCT), novel therapies like second- and third-generation proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and recent addition of monoclonal antibodies (mAbs), ~~cannot achieve cure, and most~~ MM patients will relapse and ultimately develop resistance to existing therapies ~~will die of relapse~~ [Laubach, 2014]. Thus, there is a need to develop treatments with novel mode of action (MOA) which could potentially prevent the cross resistance to existing therapies. ~~new treatments are urgently needed.~~

Before the introduction of daratumumab, patients with disease refractory to both IMiDs and PIs had a median overall survival (OS) ranging from 9 months [Kumar, 2012] to 12 months [San Miguel, 2013].

Daratumumab [DARZALEX, 2017], is a human IgGk monoclonal antibody that was granted accelerated approval as monotherapy for the treatment of relapsed/refractory multiple myeloma (RRMM) in the US in November 2015 based on the results from a Phase II monotherapy study (n=106) which reported 29.2% overall response rate (ORR) and median progression free survival (mPFS) of 3.7 months in patients with RRMM [Lonial, 2016]. The median number of prior lines of treatment reported in this study was 5.

Daratumumab has also been approved in combination with lenalidomide/ dexamethasone or bortezomib/dexamethasone for patients who were previously treated with at least one prior line of therapy, and in combination with pomalidomide and dexamethasone for patients previously treated with at least 2 prior lines of therapy based on improvement in mPFS and ORR [DARZALEX, 2017; Janssen-Cilag International NV, 2016].

While the data with daratumumab indicates that prolongation of PFS can been achieved, patients continue to relapse after treatment with daratumumab; additional treatment options to control the disease are needed. Patients with RRMM who relapse after daratumumab, IMiD, and PI based therapies, have few treatment options available.

B cell maturation antigen (BCMA also referred to as TNFRSF17 or CD269) 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 influence B cell survival and proliferation. Mice deficient for BCMA are viable, have normal B cell development, and exhibit normal humoral responses [Xu, 2001]. BCMA is widely expressed on malignant plasma cells in MM and to a lesser degree in other B cell malignancies [Tai, 2006]. A soluble form of BCMA has been identified in serum from MM patients and shown to correlate with progressive disease [Sanchez, 2016]. Since all malignant plasma cells express various levels of BCMA, MM has a biologically based rationale as a key indication for anti-BCMA therapy. ~~All patients with MM are expressing various levels of BCMA on the surface of the tumor cells, therefore MM is a good target disease for anti-BCMA therapy.~~

GSK2857916 is a humanized immunoglobulin G1 (IgG1) antibody-drug conjugate (ADC) that binds specifically to B cell maturation antigen (BCMA). The parent antibody (GSK2857914) competes with the BCMA ligands APRIL and BAFF and is conjugated to the microtubule inhibitor monomethyl auristatin-F (MMAF), resulting in an ADC molecule. The conjugate is produced in an afucosylated form to generate enhanced antibody-dependent cellular cytotoxicity (ADCC). In addition, when MM cells expressing BCMA are exposed to GSK2857916, immunogenic cell death (ICD) markers are induced. Exposure of dendritic cells to tumor cells undergoing ICD may result in antigen-specific T-cell response, enabling the patient's own immune response against the MM tumor.

Of the four proposed mechanisms of action (MOA) for GSK2857916, the ADC and ADCC MOAs have been linked to efficacy in non-clinical models: in vitro and in vivo against multiple myeloma cell lines, and ex vivo against primary patient myeloma samples. Inhibition of BCMA signaling has been demonstrated biochemically; however, functional effects on myeloma cells have not been demonstrated. ICD markers on cells are induced by GSK2857916 both in vivo and in vitro, but effects on efficacy have not been established in non-clinical models. These different mechanisms may enable GSK2857916 to deliver anti-tumour activities targeting both dividing and nondividing tumour cells and associate the cell kill with an adaptive immune response; these MoA characteristics clearly differentiate GSK2857916 from existing approved treatments [GlaxoSmithKline Document Number 2013N175128_05.

~~GSK2857916 is a humanized (IgG_1) antibody drug conjugate (ADC) which binds specifically to BCMA. The parent anti-BCMA antibody (J6M0) is conjugated to the microtubule inhibitor monomethyl auristatin F (MMAF) via a protease resistant maleimidocaproyl (mc) linker to produce the GSK2857916 ADC molecule. Upon binding to the cell surface, GSK2857916 is rapidly internalized and active drug (cys-mcMMAF) is released inside the cell. GSK2857916 has also been produced in an afucosylated form to generate an enhanced antibody dependent cellular cytotoxicity (ADCC) response upon binding to FcγRIIIa receptors on the surface of human effector cells. This dual mechanism of action may improve efficacy by targeting dividing (ADC) and non-dividing tumor cells (ADCC). All patients with MM are expressing various levels of BCMA on the surface of the tumor cells, therefore MM is a good target disease for anti-BCMA therapy. GSK2857916 is currently being tested in First Time in Human Trial (FTIH), and doses from 0.03 mg/kg up to 4.6 mg/kg have been tested, with no DLTs reported. Signals of clinical activity have been observed in patients.~~

Many tumors, including MM ~~are using~~use various escape mechanisms to evade the immune control and to promote tumor growth and clonal tides [McLaughlin, 2016]. One of those mechanisms is the expression of PD-1 ligands (PD-L1). Recent advances in cancer treatment include successful checkpoint blockade by using antibodies binding to PD-1 or PD-L1 (e.g., pembrolizumab, nivolumab). The anti-PD-1 and anti-PD-L1 antibodies have a ~~good~~ favorable safety profile ~~in the clinic~~ and have resulted in durable responses in a variety of cancers, including melanoma, kidney cancer, lung cancer, and Hodgkin lymphoma. The agents continue to be evaluated in various solid tumors and hematological malignancies, alone or in combination with other therapies [Dolan, 2014]. There is also growing body of data demonstrating broad expression of PD-1 and its ligands in the microenvironment of ~~multiple myeloma~~MM, and indicating an important role of the PD-1 pathway~~in the immune evasion by MM~~. [Liu, 2011; Kuranda, 2010; Atanackovic, 2014; Benson, 2010]. Although, so far, anti-PD-1 treatment alone has not been effective in MM [Lesokhin, 2014; Suen, 2006].

The KEYNOTE-023 study examined whether an anti-PD-1 treatment (Keytruda [pembrolizumab]) in combination with immunomodulatory agents may create synergism, in this case lenalidomide and dexamethasone. Lenalidomide doses of 10 mg and 25 mg were examined, with the 25 mg dose further explored. Of the subject's evaluable for efficacy (N=40), 88% of subjects had a decrease in M protein. The ORR for this population was 50%, including a 38% ORR for subjects who were lenalidomide

refractory [Mateos, 2016]. Based on these findings, the KEYNOTE-183 and KEYNOTE-185 studies were initiated, exploring combinations of pembrolizumab with IMiDs.

Following review of both studies by data monitoring committees, KEYNOTE-183 and KEYNOTE-185 were placed on full clinical hold. In both studies, it was determined that the benefit-risk was unfavorable for the combination of pembrolizumab with IMiDs. The US FDA also placed Cohort 1 (combination with lenalidomide and dexamethasone) of KEYNOTE-023 on full clinical hold as a result of the data from KEYNOTE-183 and KEYNOTE-185.

This study will evaluate the safety and anti-myeloma activity of GSK2857916 in combination with pembrolizumab. Safety will be closely monitored with dose modification guidelines in Section 6.5. GSK will also use an internal Safety Review Committee (iSRC) as described in Section 10.9.1 for review of safety. We hypothesize that given the immunogenic properties of the cell death induced by GSK2857916 an augmented anti-tumor activity will be observed in MM subjects~~patients~~, when treated with combination of GSK2857916 and pembrolizumab.

Reason for change: Inclusion of background information for revision to later line of therapy based on FDA comments and update to standard Merck language.

16. Previous Section 2.2 Brief Background

Removal of section

~~Currently, blockade of PD-1/PD-L1 signalling pathway has been proven one of the most promising immunotherapeutic strategies against cancer. Pembrolizumab (one of the PD-1 inhibitors) has gained regulatory approval by FDA and EMA and is successfully used for treatment of selected solid tumors.~~

~~Given the immunogenic properties of the cell death induced by GSK2857916 (internal GSK data) we hypothesize that anti-myeloma activity of GSK2857916 can be further enhanced by combining it with a PD-1 inhibitor, pembrolizumab. The aim of this approach is to achieve additive, or possibly synergistic anti-MM activity in patients which may transform into a long lasting benefit.~~

Reason for change: Consolidation of language.

17. Section 2.2~~3~~.1 – Nonclinical Pharmacology

~~GSK2857916 is an antibody drug conjugate (ADC) consisting of an Fc-enhanced, humanized anti-BCMA monoclonal antibody (mAb) that is conjugated to monomethyl auristatin F (MMAF). Upon binding to the cell surface, GSK2857916 is rapidly internalized and active cytotoxic drug (cys-mcMMAF) is released inside the cell. Additionally, the antibody is afucosylated which increases binding to FcγRIIIa receptors and enhances recruitment and activation of immune effector cells, which can kill tumor cells by antibody dependent cellular cytotoxicity (ADCC). The dual mechanism of action~~

~~of GSK2857916 is designed to enable anti-tumor activity of cells by ADCC activity (non-dividing), as well as ADC activity (dividing cells).~~

Reason for change: Consolidation of language.

18. Section 2.2~~3~~.5 – Effects in Humans (GSK2857916)

GlaxoSmithKline (GSK) initiated the clinical development of GSK2857916 in July 2014, with the FTIH study (BMA117159) in subjects with RR~~rel/ref~~ MM and other advanced hematologic malignancies expressing BCMA (ClinicalTrials.gov Identifier: NCT02064387). As of the data cut from 26 June 2017, a total of 73 subjects with RRMM have been treated with at least one dose of GSK2857916.~~October 14, 2016, 51 subjects have received at least one dose of GSK2857916.~~ Thirty eight subjects ~~patients~~ were treated in Part 1 (dose escalation): 0.03 mg/kg (n=1), 0.06 mg/kg (n=1), 0.12 mg/kg (n=4), 0.24 mg/kg (n=4), 0.48 mg/kg (n=4), 0.96 mg/kg (n=3), 1.92 mg/kg (n=4), 2.5 mg/kg (n=8), 3.4mg/kg (n=3), and 4.6mg/kg (n=6). Since the RP2D (3.4 mg/kg) selection (August 11, 2016), an additional 35~~21~~ subjects have been enrolled into Part 2 (expansion cohort). Of these 35 subjects,40% had receive prior daratumumab. The ORR for this sub-population was 43% [Trudel, 2017].

The most frequently-reported AEs (≥15.0%) in the All Treated Population included: vision blurred (37%), nausea (36%), fatigue (33%), anemia (29%), dry eye (29%), thrombocytopenia (26%), aspartate aminotransferase increased (25%), chills (23%), platelet count decreased (23%) pyrexia (22%), cough (18%), photophobia (16%), back pain (15%), headache (15%), and upper respiratory tract infection (15%).

In the Part 2 population, 59% (20/35) of subjects had 5 or more prior treatment lines. Among the subjects in Part 2 (N=35), the most frequently reported AEs ~~Overall, the most common AEs~~ (≥15.0%) included: ~~were as follows:~~ vision blurred (46%), platelet count decreased (37%), dry eye (34%), anemia (29%), aspartate aminotransferase increased (29%), increased cough (26%), chills (23%), nausea (23%), photophobia (23%), pyrexia (23%), fatigue (20%), thrombocytopenia ~~ic events~~ (~~47~~20%), back pain (17%), and diarrhea (17%). ~~ocular toxicity related events (43%), nausea (37%), fatigue (33%), pyrexia (27%), anemia (25%), chills (24%), and AST increased (24%). The most frequent Grade 3 or 4 AEs occurring in >10% of subjects were thrombocytopenia (37%) and anemia (14%). Most of reported adverse events are reversible without sequelae~~. As of 26 June 2017, a total of 14 (40%) patients in Part 2 had an SAE and there were no fatal SAEs. The related SAEs are described below.

- **Infusion-Related Reaction (IRR):** Two patients experienced serious, Grade 3 infusion-related reactions during the first infusion that were characterized by tachycardia, hypertension and pyrexia. These subjects subsequently received pre-medication and IRRs did not recur.
- **Intracranial Hemorrhage:** A patient with a history of intracranial bleeding experienced a Grade 2 intracranial hemorrhage with concomitant Grade 4, thrombocytopenia. At the same time, the patient's disease was starting to progress; the patient was taken off study and salvage chemotherapy was started.

- **Pericardial Effusion:** A Grade 4 pericardial effusion consistent with tamponade was found prior to Cycle 9 during a routine study echocardiogram in an asymptomatic patient who had a concurrent upper respiratory tract infection. The fluid was evacuated, and the effusion was resolving at the time of data cut-off. The patient received three more cycles of treatment after this event. This SAE is listed as "not resolved" at the time of data cut, however a subsequent echocardiogram has confirmed no evidence of a pericardial effusion.
- **Lung Infection and Pyrexia:** A patient experienced a Grade 2 lung infection resulting in a dose delay. Approximately three months later, the patient developed a Grade 2 fever resulting in hospitalization. The fever resolved the same day; the patient was not neutropenic.

~~To date, GSK28579165 was well tolerated in humans with no Grade 5 events.~~ Overall, GSK2857916 has a manageable safety profile with thrombocytopenia / platelet count decreased and corneal events as the most commonly reported events, as described in the following subsections.

2.2.5.1 Thrombocytopenia

A total of 36 patients (49%) in the All treated population, and 20 patients (57%) in Part 2 have experienced thrombocytopenia/platelet count decreased. GSK2857916 may cause transient worsening of thrombocytopenia in some patients, but in most cases these events are resolved during between-dosing intervals. In the Part 2 MM population, two serious bleeding events were reported: intracranial hemorrhage in a patient with a history of an intracranial bleeding and in the setting of disease progression, and hematuria in a patient with a large bladder mass in the setting of progressive disease.

2.2.5.2. Corneal Events

Corneal AEs have been observed with various ADC drugs and represent the most commonly reported types of AEs associated with GSK2857916. As there is no single term which appropriately captures these events, the term 'corneal events' includes reported preferred terms describing events associated with the corneal toxicity related to GSK2857916. The most commonly reported corneal events include vision blurred, dry eye, photophobia, and lacrimation increased. A total of 42 patients (58%) in the all treated population, and 22 patients (63%) in Part 2 have experienced corneal events which were predominantly low-grade.

In Part 2, there were three patients with ≥ Grade 3 corneal events: one with Grade 3 keratitis resulting in a delay and a dose reduction, one with Grade 3 eye pain resulting in a delay; and one Grade 3 dry eye resulting in a dose delay. In Part 2, there were no serious corneal events and no patients permanently discontinued study treatment due to a corneal event.

In Part 1, there was one SAE of Grade 3 limbal stem cell deficiency (in a patient at the 1.92 mg/kg dose) that was characterized by blurred vision and dry eyes. The events resolved after treatment was discontinued, and the patient's vision returned to baseline. Another patient in Part 1 (4.6 mg/kg) discontinued treatment due to the feeling of a foreign object in the eye (Grade 2).

In addition to the AEs describing corneal events, 89% of patients 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 patients experiencing these clinical findings, but improved on average to near baseline in patients completing end of study treatment visits (n=13). Eleven of these 13 patients (84.6%) had corneal clinical signs at the end of study treatment visit, with most cases (9/11 or 81.8%) considered as having "mild" changes.

Reason for change: Updated language based on updated information from First Time in Human study.

19. Section 2.34.1 – Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [Disis, 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies ~~[Mei , 2014; Salgado, 2015; Schatton, 2014; Gooden, 2011; Schreiber, 2011; Bremnes, 2011; Talmadge, 2011; Shirabe 2010; Nosho, 2010; Bellati, 2009; Oble, 2009; Uppaluri, 2008; Dunn, 2007]~~. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells (T-regs) ~~seem to~~ correlates with improved prognosis and long-term survival in ~~many~~ solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, including durable objective tumor responses in cancers such as melanoma ~~tumors [Nosho,2010; Chang, 2014; Preston, 2013; Yoon, 2012; Kim, 2013; Mathai, 2012; Liu, 2011; Kirk, 2010].~~ [Dudley, 2005; Hunder, 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control ~~[Pedoeem, 2014]~~. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and CTLA-4, which has been shown to negatively regulate antigen receptor signalling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, 2005; Okazaki, 2001].

The structures of murine PD-1 has been resolved ~~alone~~ [Zhang, 2004]. ~~and in complex with its ligands were first resolved [Lazar-Molnar, 2008; Lin, 2008], and more recently the NMR-based structure of the human PD-1 extracellular region and analyses of its interactions with its ligands were also reported [Cheng, 2013].~~ PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase

(ZAP70), which are involved in the CD3 T cell signaling cascade [Okazaki, 2001; Chemnitz, 2004; Sheppard, 2004; Riley, 2009]. The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from that of CTLA-4, because both molecules regulate an overlapping set of signalling proteins [Parry, 2005; Francisco, 2010 ~~Ott, 2013~~]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in RRMM.

~~PD-1 was shown to be expressed on activated lymphocytes, including peripheral CD4+ and CD8+ T cells, B cells, T regs and Natural Killer cells [Yao, 2014]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells [Nishimura, 1996], as well as subsets of macrophages [Huang, 2009] and dendritic cells [Pena Cruz, 2010]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types [Keir, 2008]. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments [Keir, 2008]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T cell activation triggered through the T cell receptor. PD-L2 is thought to control immune T cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T cell inhibitor [Karim, 2009; Taube, 2012], which, via its interaction with the PD-1 receptor on tumor-specific T cells, plays a critical role in immune evasion by tumors [Sanmamed, 2014]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer [Topalian, 2012]~~

Reason for change: Revisions to the standard Merck language.

20. Section 2.34.3 – Pembrolizumab Background and Clinical Trials

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator brochure.

Keynote-183 was a randomized trial which evaluated pomalidomide and low-dose dexamethasone with or without pembrolizumab in subjects with relapsed and refractory multiple myeloma. The ORR was 34% in the pembrolizumab containing arm versus 40% in the control arm without pembrolizumab; however, there was no difference in time-to-progression between arms. There were 29 deaths in the pembrolizmab arm compared to 21 in the control arm, reflecting an overall survival hazard ratio of 1.61 (95% CI: 0.91, 2.85) [Krauss, 2018]. An analysis conducted with the removal of subjects with high-risk

disease characteristics (high-risk cytogenetics, plasmacytoma and quadruple refractory status) resulted in a similar number of deaths (n=13) in both arms [Mateos, 2018].

Keynote-185 was a randomized trial which evaluated lenalidomide and dexamethasone with or without pembrolizumab in subjects with newly diagnosed multiple myeloma. The ORR was 64% in the pembrolizumab containing arm versus 62% in the control arm without pembrolizumab; however, there was no difference in time-to-progression between arms. There were 19 deaths in the pembrolizmab arm compared to 9 in the control arm, reflecting an overall survival hazard ratio of 2.06 (95% CI: 0.93, 4.55) [Krauss, 2018].

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475 [KEYTRUDA Product Information].

~~Pharmacokinetics of Pembrolizumab~~

~~The pharmacokinetics of pembrolizumab was studied in 2195 patients who received doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Based on population pharmacokinetic analyses in patients with solid tumors, the geometric mean [% coefficient of variation (CV%)] for clearance, steady state volume of distribution, and terminal half-life were 202 mL/day (37%), 7.38 L (19%) and 27 days (38%), respectively. Steady-state concentrations of pembrolizumab were reached by 19 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.2-fold. The peak concentration (Cmax), trough concentration (Cmin), and area under the plasma concentration versus time curve at steady state (AUCs) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.~~

~~Pharmacokinetic drug interactions~~

~~No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab.~~

~~Toxicity of Pembrolizumab~~

~~The principal nonclinical toxicology findings in monkeys associated with pembrolizumab consisted of generalized lymphocytic infiltration consistent with its pharmacologic activity, which was not associated with clinical toxicities. In a human PBMC cytokine release assay, pembrolizumab did not cause cytokine release in nonstimulated cultures but did cause increases in IL-2, TNF-α, IFN γ, IL-6 and IL-17 in staphylococcal enterotoxin B (SEB)-stimulated cells, suggesting the potential for inappropriate cytokine release under stimulated conditions [FDA Pharmacology Toxicology Review, 2014]. The most commonly reported adverse events (AEs) in clinical trials with pembrolizumab include fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia and diarrhea [KEYTRUDA Package Insert, 2017]. Serious and fatal AEs associated with treatment include immune-mediated adverse reactions, which consisted of pneumonitis, colitis, hepatitis, hypophysitis, and renal failure due to nephritis and thyroid disorders.~~

~~Genotoxicity, Reproductive Toxicity and Carcinogenicity of pembrolizumab~~

~~No studies have been performed to test the potential of pembrolizumab for carcinogenicity or genotoxicity. Fertility studies have not been conducted with pembrolizumab. In 1-month and 6-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.~~

~~Based on its mechanism of action, pembrolizumab may cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PDL-1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment with Keytruda and for 4 months after the last dose of pembrolizumab *[see PI Use in Specific Populations (8.1, 8.8)]*[KEYTRUDA Package Insert, 2017]~~

Reason for change: Revisions to the standard Merck language. Summaries added for analysis of KEYNOTE-183 and KEYNOTE-185 to provide context and top level data from the interim analyses.

21. Section 2.4~~5~~ – Assessment of Nonclinical Data for GSK2857916 when Co-Administered with Pembrolizumab

In addition, the starting dose of GSK2857916 in this combination regimen has been selected to be ~~2~~1 dose level~~s~~ below a dose that has been shown to be well tolerated during the GSK2857916 monotherapy dose escalation. The determination of the starting dose is based on an assumption that less than 25~~50~~% of the declared safe dose of GSK2857916 should provide a sufficient safety margin when pembrolizumab is added at 200 mg. In addition, close clinical monitoring will be implemented

Reason for change: Update of the number of doses and percentage decrease of starting dose based on comments from FDA.

22. Section 3 – Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine safety, tolerability and to establish the ~~recommended Phase 2 dose (~~RP2D~~)~~ of the combination of GSK2857916 and pembrolizumab in subjects with ~~relapsed/refractory (rel/ref)~~ RRMM	• Percent of subjects with ~~adverse events (~~AEs~~)~~, changes in clinical signs and laboratory parameters • Number of subjects with dose limiting toxicities (DLTs)
Secondary	
• To evaluate clinical activity of the combination of GSK2857916 and pembrolizumab in subjects with RRMM	• Overall Response Rate (ORR), defined as the percentage of subjects with a confirmed partial response (PR) or better (i.e., PR, very good partial response [VGPR], complete response [CR] and stringent complete response [sCR]), according to the

Objectives	Endpoints
	International Myeloma Working Group (IMWG) Response Criteria [Kumar, 2016].
• To evaluate the pharmacokinetic profile of GSK2857916 when administered intravenously in combination with pembrolizumab[1]	• ~~GSK2857916~~ Pharmacokinetic (PK) parameters following IV administration as data permit (e.g., area under the curve [AUCs], mean maximum concentration [Cmax], time of Cmax [tmax], terminal phase half-life [t½]) after the first dose; ~~and~~ concentration at trough (Ctrough), and end of infusion concentration in subsequent cycles, when measured
• To assess anti-drug antibodies (ADAs) against GSK2857916[1]~~.~~	• Incidence and titers of ADAs against GSK2857916
Exploratory	
~~• To evaluate clinical activity of the combination of GSK2857916 and pembrolizumab in subjects with rel/ref MM~~	~~• Overall Response Rate (ORR) defined as % of patients achieving ≥ PR~~ ~~• Clinical Benefit Rate (CBR) defined as % of patients achieving ≥ MR~~ ~~• Duration of Response (DOR) data permitting~~ ~~• Progression Free Survival (PFS) data permitting~~ ~~• Overall survival (OS) data permitting~~ ~~• Time to Response (TTR) data permitting~~
• To assess Minimal Residual Disease (MRD) in participants who achieve ≥VGPR or better	• Minimal Residual Disease (MRD) negativity rate, defined as: the percentage of subjects who are MRD negative in subjects who achieve VGPR or CR
• To characterize the relationship between clinical response and other biologic ~~intra-tumor or microenvironment~~ characteristics ~~(DNA, protein analysis)~~	• BCMA expression levels on malignant cells, ~~and other markers in tumor tissue,~~ serum sBCMA levels, serum cytokines, ~~baseline immune status~~ and immune cell characterization and their relationship to clinical response (Protein, RNA, DNA analysis)
• To investigate the relationship between genetic variants in the host and response to GSK2857916 in combination with pembrolizumab	• Possible relationship between host genetic variation and response to GSK2857916 in combination with pembrolizumab
• To evaluate the tolerability of GSK2857916 in combination with pembrolizumab based on patient self-report of symptomatic adverse effects	• Symptomatic adverse effects as measured by the Patient-reported outcome version of the Common Term Criteria for Adverse Events (PRO-CTCAE) • Impact of ocular adverse effects on quality of life as measured by the Visual Function

Objectives	Endpoints
	questionnaire(s): National Eye Institute 25-item Visual Function Questionnaire (NEI-VFQ-25) and Ocular Surface Disease Index (OSDI)
• To evaluate disease and treatment related symptoms and associated impacts on function and health-related quality of life	• Exit Interview

1. PK and ADA samples for pembrolizumab will be collected and stored during the trial. The analysis will be triggered only in case of unexpected clinical findings.

Part 2: Expansion

Objectives	Endpoints
Primary	
• To assess the clinical activity of the combination treatment with GSK2857916 and pembrolizumab in subjects with ~~rel/ref~~ RRMM	• Overall Response Rate (ORR), defined as the percentage of participants with a confirmed PR or better (i.e., PR, VGPR, CR and sCR), according to the IMWG Response Criteria [Kumar, 2016]. ~~Overall Response Rate (ORR) defined as % of patients achieving ≥ PR~~
Secondary	
• To further evaluate ~~confirm~~ safety of GSK2857916 administered in combination with pembrolizumab in subjects with RR ~~rel/ref~~ MM	• Number of subjects with AEs, changes in clinical signs and laboratory parameters • Ocular findings on ophthalmic exam
• To further assess the clinical activity of the combination treatment with GSK2857916 and pembrolizumab in subjects with ~~rel/ref~~ RRMM	~~• Clinical Benefit Rate (CBR) defined as % of patients achieving ≥ MR~~ ~~• Duration of Response (DOR) data permitting~~ ~~• Progression Free Survival (PFS) data permitting~~ ~~• Overall Survival (OS) data permitting~~ ~~• Time to Response (TTR) data permitting~~ • Clinical benefit rate (CBR), defined as the percentage of participants with a confirmed minimal response (MR) or better per IMWG. • Duration of response (DoR), defined as: the time from first documented evidence of PR or better to the time when disease progression (PD) is documented per IMWG, or death due to PD among subjects who achieve an overall response, i.e. confirmed PR or better. • Time to response (TTR), defined as: the time between the date of first dose and the first documented evidence of response (PR or better) among subjects who achieved a confirmed response of PR or better. • Time to best response, defined as the time between the date of first dose and the first best documented response (PR or better) among subjects who achieve a confirmed response of PR or better.

Objectives	Endpoints
	• Progression-free survival (PFS), defined as: the time from first dose to the earliest date of PD per IMWG, or death due to any cause. • Time to disease progression (TTP), defined as: the time from first dose until the earliest date of PD per IMWG, or death due to PD. • Overall Survival (OS), defined as the time from first dose to death due to any cause
• To evaluate the pharmacokinetic profile of GSK2857916 when administered intravenously in combination with pembrolizumab[1]	• Pharmacokinetic parameters following IV administration as data permit (e.g., AUCs, Cmax, time of Cmax [tmax], terminal phase half-life [t½]) after the first dose; concentration at trough (Ctrough), and end of infusion concentration in the subsequent cycles when measured.
• To assess ~~anti-drug antibodies (~~ADAs~~)~~ against GSK2857916[1)]	• Incidence and titer of ADA to GSK2857916[1)]
Exploratory	
• To assess Minimal Residual Disease (MRD) in participants who achieve ≥VGPR or better	• Minimal Residual Disease (MRD) negativity rate, defined as: the percentage of subjects who are MRD negative in subjects who achieve VGPR or CR
• To characterize the relationship between clinical response and other biologic ~~intra-tumor or microenvironment~~ characteristics ~~(DNA, protein analysis)~~	• BCMA expression levels on malignant cells~~ and other markets in tumor tissue~~, serum sBCMA levels~~ baseline immune status~~, serum cytokines, and immune cell characterization and their relationship to clinical response (Protein, RNA, DNA analysis)
• To investigate the relationship between genetic variants in the host and response to GSK2857916 in combination with pembrolizumab	• Possible relationship between host genetic variation and response to GSK2857916 in combination with pembrolizumab
~~• Plasma concentrations of GSK2857916 when administered intravenously in combination with pembrolizumab[1)]~~	~~• GSK2857916 end of infusion concentration and concentration at trough~~
• To explore the effect of the combination therapy of GSK2857916 with pembrolizumab on symptoms and health-related quality of life ~~HRQoL~~ in subjects with ~~rel/ref~~ RR-MM	• Changes from baseline in symptoms and health-related quality of life as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module (EORTC-QLQ-C30) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma Module (EORTC-QLQ-MY20) ~~MD Anderson Symptom Inventory Multiple Myeloma (MDSI-MM) module~~

Objectives	Endpoints
• To evaluate the tolerability of GSK2857916 in combination with pembrolizumab based on patient self-report of symptomatic adverse effects	• Symptomatic adverse effects as measured by the PRO-CTCAE • Impact of ocular adverse effects on quality of life as measured by the Visual Function questionnaire(s): NEI-VFQ-25 and OSDI
• To evaluate disease and treatment related symptoms and associated impacts on function and health-related quality of life	• Exit Interview

1. PK and ADA samples for pembrolizumab will be collected and stored during the trial. The analysis will be triggered if unexpected clinical findings have been identified.

Reason for change: Revision of Objective/Endpoints to revise secondary endpoint for dose escalation, add MRD for response endpoints, replace MDASI-MM with EORTC questionnaires, add clarity to primary and secondary endpoints for dose expansion, and revise biomarker wording.

23. Section 4.1 – Overall Design

This is a phase I/II, single arm, open label, two-part study to determine the RP2D of GSK2857916 administered in combination with 200 mg of pembrolizumab, and to evaluate safety and clinical activity of the combination in subjects with ~~rel/ref~~RRMM. The study will be conducted in two parts: Part 1: dose escalation of GSK2857916 with a constant dose of pembrolizumab at 200 mg, and Part 2: expansion cohort at RP2D of GSK2857916 in combination with 200 mg pembrolizumab. A total of up to 40~~8~~ evaluable subjects with ~~rel/ref~~ RRMM will be enrolled into this study (up to 12~~8~~ in Part 1, and 28~~30~~ in Part 2).

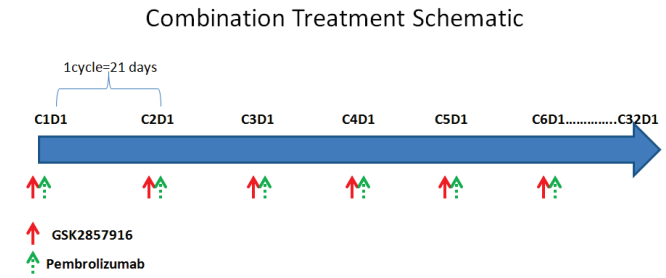
Reason for change: Update to overall subject numbers due to removal of lower first dose level per FDA comments.

24. Section 4.2.1 – Study Treatment

This is a single arm, open label study. Subjects in Part 1 and in Part 2 will receive GSK2857916 and pembrolizumab via IV infusion on day 1 of each 21-day cycle. GSK2857916 will be administered first, as ~~approximately 30 min~~ an IV infusion, followed by at least 1 hour rest. Refer to the SRM for details on GSK2857916 infusion. Provided there is no infusion related reaction (IRR) warranting a prolonged interval between dosing, pembrolizumab will be administered as second drug over approximately 30 min via IV infusion. If a subject develops IRR during or after GSK2857916 infusion, he or she will be treated according to institutional guidelines. In such cases the infusion of pembrolizumab may have to be delayed until IRR has recovered to Grade 1 or less, and investigator considers it safe to continue with infusion with pembrolizumab. The infusion of pembrolizumab may be delayed for up to the +3 day window from scheduled visit~~48 hours~~ to allow for recovery of IRR, and to accommodate scheduling conflicts. If a subject does not recover from IRR to Grade 1 or less within the +3 day window~~48 hours~~,

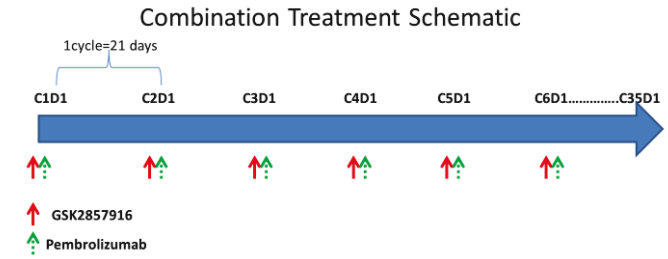
the dosing of pembrolizumab will be skipped in a given cycle, and may be resumed in the next cycle.

Old Figure:



Dosing:
-GSK2857916 and pembrolizumab on D1 of each cycle
-GSK2857916 first, Pembrolizumab as second iv infusion (1hr apart)
-If IRR related to GSK2857916, the pembrolizumab dosing will be delayed (up to 48 hrs)
-Max treatment duration: 32 cycles

New Figure:



Dosing:
-GSK2857916 and pembrolizumab on D1 of each cycle
-GSK2857916 first, Pembrolizumab as second iv infusion (1hr apart)
-If IRR related to GSK2857916, the PD1 dosing will be delayed
-Max treatment duration: 35 cycles combination treatment

Reason for change: Removal of specific 30 min GSK2857916 wording and added reference to SRM for instructions. Revision to allowed window for pembrolizumab if dose delay required after GSK2857916 dosing. Revisions of schematics to match revised plan.

25. Section 4.2.2 – Duration of Treatment

Subjects will be treated until disease progression, intolerable toxicity, informed consent withdrawal, or for a maximum of 35~~2~~ cycles (approximately 2 years).

~~In case subject achieves complete response (CR), the assessment of stringency should be performed. Subjects with CR/sCR are allowed to end the study treatment sooner if they fulfil the criteria outlined in Section 5.4.1..~~

After the study treatment discontinuation, subjects will undergo end of ~~study~~treatment assessments 30 days (±7 days) after the last dosing, or prior to the start of new anti-cancer treatment (whichever occurs first). Subjects who discontinued treatment for reasons other than PD, will be followed up every 3 weeks until confirmed PD, until initiation of a new anticancer therapy or death. All subjects with confirmed PD will be

followed for OS and subsequent anti-cancer therapy every 3 months until the end of study. End of study is defined in Section 5.5.2.

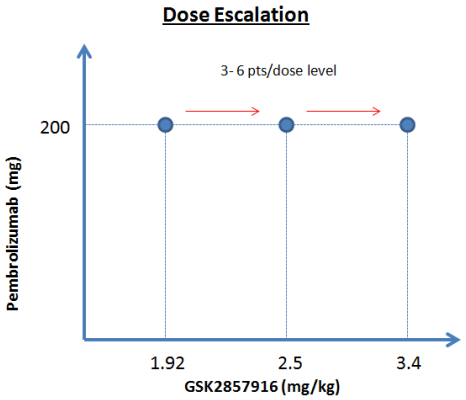
~~After the study treatment discontinuation, subjects will undergo end of study assessments 30 days (±7 days) after the last dosing, or prior to the start of new anti-cancer treatment (whichever occurs first). All subjects will continue to be followed-up every 3 months to collect data on PFS, OS, and next treatment for the duration of 1 year after the last dose of study treatment.~~
~~All subjects will continue to be followed-up every 3 months to collect data on PFS, OS, and next treatment for the duration of 1 year after the last dose of study treatment.~~
~~All subjects who permanently discontinue all study treatments without disease progression will be followed for progression according to the Time and Events Table 6. Follow-up will continue until disease progression, death, start of new anti-cancer therapy or withdrawal of consent, whichever is documented first.~~

Reason for change: Update to number of total cycles based on actual 24 month calendar and in line with maximum dosing from Merck language. Removal of language allowing treatment discontinuation if subject achieves CR/sCR. Addition of option for re-treatment if subject meets certain criteria. Adjustment of discontinuation language.

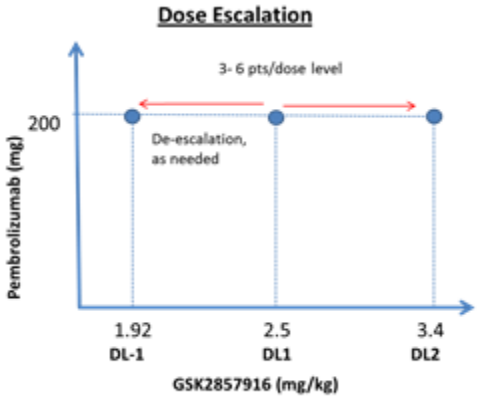
26. Section 4.2.3 – Part 1: Dose-Escalation

Part 1 dose escalation will characterize the safety and tolerability of escalating doses of GSK2857916 in combination with 200 mg pembrolizumab to establish the RP2D. In the currently ongoing FTIH study (ClinicalTrials.gov Identifier: NCT02064387), no DLTs were observed up to the highest~~recently~~ tested dose level of 4.6 mg/kg of GSK2857916 and 3.4 mg/kg was selected as RP2D dose. The following dose levels of GSK2857916 in combination with 200 mg pembrolizumab are to be tested in this study: ~~1.92 mg/kg,~~ 2.5 mg/kg and 3.4 mg/kg (as outlined in Figure 2). Additionally, ~~intermediate~~ other dose levels may also be tested if emerging data suggests a beneficial risk/benefit profile at those dose levels. The RP2D from the monotherapy FTIH study (3.4 mg/kg (ClinicalTrials.gov Identifier: NCT02064387)) will not be exceeded in this combination study. During the dose escalation, at least 3 evaluable subjects will be tested per dose level, and escalation will be guided by the modified Toxicity Probability Interval (mTPI) approach~~follow the Bayesian Logistic Regression Model (BLRM) with overdose control as outlined in Section 9.5.1.~~

Old Dose Escalation Schematic for Part 1



New Dose Escalation Schematic for Part 1



The mTPI design assumes the true underlying toxicity rate for maximum tolerated dose (MTD) of GSK2857916 falls within the range from 25% to 35% and centered at 30%. The monitoring rules for guiding dose escalations are provided in Table 1. Columns provide the numbers of subjects treated at the current dose level, and rows provide the corresponding numbers of subjects experiencing toxicity. The entries of the table are dose-finding decisions (i.e., E, S, and D) representing escalating the dose, staying at the same dose, and de-escalating the dose. In addition, decision U means that the current dose level is unacceptable because of high toxicity; the current dose level and any higher dose level should be excluded from the trial. For example, when one of three subjects experiences toxicity, the decision can be located at row 1 and column 3, which is S – to stay at the current dose level. Consequently, the next cohort of subjects will be treated at the same dose level currently being used. If 0 of 3 subjects experiences toxicity, the decision is at row 0 and column 3, which is E – to escalate. Thus, the next cohort of subjects will be treated at the next-higher dose level. If three of three subjects experiences toxicity, the decision is DU – to de-escalate to the next-lower dose level, and exclude the current dose and any higher dose from the trial, because the high toxicity level is unacceptable. In dose escalation (E)/de-escalation (D), no dose skipping is allowed.

New Table 1 Dose-Escalation Monitoring Rules for Part 1 Using the mTPI Method
Dose finding Criteria for the Modified Toxicity Probability Interval Dose Finding

Number of DLTs ~~Toxicities~~	Number of Subjects treated at current dose					
	1	2	3	4	5	6
0	E	E	E	E	E	E
1	D	S	S	S	S	E
2		DU	D	S	S	S
3			DU	DU	D	S
4				DU	DU	DU
5					DU	DU
6						DU

The table was generated based on a beta/binomial model and precalculated before trial initiation. The letters in different colors are computed based on the decision rules under the mTPI method and represent different dose-finding actions. In addition to actions de-escalate the dose (D), stay at the same dose (S), and escalate the dose (E), the table includes action unacceptable toxicity (DU), which is defined as the execution of the dose-exclusion rule in mTPI. Excerpted from Ji et al . [Ji, 2010]

~~After each cohort, the BLRM will be used to calculate the posterior probabilities of DLT rate for all potential doses of GSK2857916 in combination with pembrolizumab lying within four toxicity intervals (under dosing, target dose range, excessive toxicity, and unacceptable toxicity). The four DLT toxicity intervals are defined as follows:~~
~~[0%, 16%) Underdosing~~
~~[16%, 33%) Target toxicity~~
~~[33%, 60%) Excessive toxicity~~
~~[60%, 100%] Unacceptable toxicity~~
~~The recommended dose for next cohort will be based on the following criteria: dose with the highest posterior probability of DLT rate lying in the target toxicity interval with the additional requirement that the sum of the posterior probabilities of the DLT rate lying in the excessive toxicity or unacceptable toxicity range is less than 25%. Selection of the next dose cohort to be enrolled is also subject to the constraint that the next dose level can be no more than two times that of the current dose level. Note that de-escalation as well as escalation is possible using this method.~~

The DLT observation period for subjects in Part 1 is 21 days after the first dose of the study treatment. The complete safety data from DLT observation period of at least 3 subjects are needed for dose escalation decisions. Subjects who have only received GSK2857916 or have been withdrawn from the study for reasons other than toxicity but prior to completion of DLT observation period will be replaced.

In Part 1, dose escalation/de-escalation decisions will take into account all available safety and tolerability data. The decisions will be informed by ~~the BLRM model~~ the mTPI approach~~with overdose control~~ and will occur following review of these data and joint discussion by the GSK Study Team and investigators.

~~Although the BLRM will be used to recommend the next dose level, clinical judgment by the Medical Monitor and GSK study team in consultation with the investigators can influence the decision about the next dose as deemed appropriate by the emerging clinical data as long as adherence to the outlined restrictions is assured: the next dose level cannot~~

~~be greater than 100% increment of previously tested dose AND the selected dose at any time of the trial cannot exceed the RP2D from the FTIH trial.~~

The dosing may be adjusted to expand any cohort to further evaluate safety at a given dose level, or to add cohorts to evaluate additional, intermediate dose levels of GSK2858916 after discussion between GSK study team and investigators. The study procedures for these additional subject(s) or cohort(s) will be the same as that described in Section 5 and Section 7. The dose of pembrolizumab will be kept constant at 200 mg throughout the study.

Reason for change: Revision of starting dose based on guidance from FDA. Revisions to statistical calculations and wording based on change to subject number, switch to mTPI design and clarification of end of study definition.

27. Section 4.2.3.1 – Dose-Limiting Toxicity Criteria (Part 1 only)

~~The DLT observation window will be 21 days (=1 cycle).~~ Any subject in Part 1 who received at least one treatment cycle of GSK2857916 in combination with pembrolizumab will be evaluated for DLTs. ~~Subjects who have only received GSK2857916 or have been withdrawn from the study for reasons other than toxicity but prior to completion of DLT observation period will be replaced.~~

All toxicities will be graded using National Cancer Institute (NCI) CTCAE Version 4.03 [NCI, 2010]. In addition, for GSK2857916 treatment related corneal events, the GSK Grading Scale (Appendix 9) should be used for evaluation of DLT.

A DLT is defined as an AE that meets at least one of the criteria defined below and is considered by the investigator to be clinically relevant and attributed (definitely, probably, or possibly) to the study therapy during the 21 day DLT observation period. ~~An event will be considered a DLT if its relationship to the investigational agents cannot be ruled out, occurs within the DLT reporting period, and meets one of the following criteria:~~

- Any Grade 4 non-hematologic toxicity
- Any Grade 3 ~~or greater~~ non-hematologic toxicity, with the following exceptions (i.e., the following will not be considered a DLT): Grade 3 diarrhea, nausea or vomiting that responds to standard of care within 72 hours; Grade 3 hypertension (controlled following addition of 1 antihypertensive medication); and Grade 3 tumor lysis syndrome ~~not resolving with appropriate supportive treatment within 48 hours or resulting in a delay in initiating cycle 2 by 14 days or more~~
- Any Grade 3 or greater non-hematologic laboratory value if either:
  - The laboratory abnormality persists for >48 hrs despite supportive treatment or
  - The abnormality leads to hospitalization
- Hematologic toxicity:
  - Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia:
    - Grade 4 thrombocytopenia of any duration
    - Grade 3 thrombocytopenia associated with clinically significant bleeding

- Grade 3 or greater febrile neutropenia lasting >48 hours despite adequate treatment:

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

- ~~Grade 4 Thrombocytopenia <25,000/mm^3 if platelet transfusion is required.~~
- Nephrotoxicity requiring dialysis, and is not considered to be related due to disease under study (i.e., myeloma)~~progression~~ based on investigator's assessment
- Liver toxicity meeting pre-specified GSK liver stopping criteria (see Section 5.4.1.1~~5.4.2.1~~)
- Prolonged delay (>14 days) in initiating Cycle 2 due to any treatment (pembrolizumab or GSK2857916) related toxicity, with the exception of Grade 1-2 corneal events (GSK grading scale for GSK2857916 treatment related corneal events; Table 16)
- ~~Tumor lysis syndrome does NOT constitute a DLT (Section 6.12.2).~~
- Any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1.
- Any other toxicity considered to be dose-limiting that occurs beyond 21 days will be considered in the selection of the dose to recommend for expansion cohorts.
- Any other event which in the judgment of the investigator and GSK Medical Monitor is considered to be a DLT

A subject who develops a DLT will be allowed to continue on study treatment if the toxicity did not meet predefined stopping criteria (Section 5.4) and recovered to ≤ Grade 1 within 14 days~~, or after a longer recovery~~ period if the investigator and medical monitor agree that for a given subject the potential benefits may outweigh the risks.

Reason for change: Update to DLT language based on FDA comments and revisions to the GSK and Merck standard language

28. Section 4.2.3.2 – Completion of Dose Escalation and the Recommended Phase 2 Dose (RP2D)

The dose escalation will complete when RP2D is determined. A dose level at or below the pre-specified max dose of 3.4 mg/kg may be selected as RP2D in combination with the fixed dose of 200 mg pembrolizumab. ~~The RP2D will be the pre-specified max dose of 3.4 mg/kg, or a lower dose that provides adequate PK exposure and clinical activity with superior tolerability. If necessary, alternative doses and schedules can be explored to determine additional biologically active doses.~~

~~Recommended Phase 2 Dose (RP2D)~~

All available data from Part 1 will be analyzed. Data considered for RP2D selection will include, but not be limited to: safety, available PK profile, and observed signs of clinical

activity. If necessary, alternative doses and schedules can be explored to determine additional clinically active regimens. ~~A dose level below the pre-specified max dose of 3.4 mg/kg may be selected as RP2D compelling safety and encouraging clinical activity can be demonstrated at dose levels below pre-specified max dose of 3.4 mg/kg.~~

~~Part 2: Expansion~~

Once the RP2D has been identified, an expansion cohort (Part 2) will open for enrollment of up to 28~~30~~ subjects with ~~rel/ref~~RRMM in order to confirm the safety profile and to evaluate the clinical activity of the combination.

~~During an ongoing enrolment, futility analysis will be once approximately 15 subjects in Part 2 are evaluable for futility analysis. The details for defining a subject to be evaluable for futility analysis is provided in Section 9.4.1.~~

Reason for change: Revision of language to allow flexibility and revision of subject numbers. Consolidation of language.

29. Section 4.3 – Type and Number of Subjects

The study will enroll adult subjects with ~~rel/ref~~RRMM, who have undergone stem cell transplant, or are considered transplant ineligible, and who have been previously treated with at least 3~~2~~ prior lines that include the following: ~~, containing 3 classes of anti-myeloma drugs: an alkylating agent, AND~~ an IMiD (i.e. lenalidomide or pomalidomide), AND a proteasome inhibitor (i.e. bortezomib, ixazomib or carfilzomib) and an anti-CD38 antibody alone or in combination. Line of therapy are defined by consensus panel of the International Myeloma Workshop [Rajkumar, 2011]. ~~In addition, subject must be progressing on, or within 60 days since the most recent therapy (as defined by IMWG).~~

Overall, it is estimated that up to 4~~0~~8 evaluable subjects will be enrolled in this two-part study (up to 12~~8~~ in Part 1, and 28~~30~~ in Part 2).

Reason for change: Revision to target treatment line and number of subjects based on FDA comments.

30. Section 4.3 – Design Justification

This is the first clinical study in which GSK2857916 will be administered in combination with pembrolizumab. Therefore, a two-part study design is implemented to allow for careful safety assessments during dose escalation. Part 1 will consist of dose escalation to establish the RP2D of GSK2857916 in combination with 200 mg of pembrolizumab. Once RP2D has been established, Part 2 will enroll an additional 28~~30~~ subjects with ~~rel/ref~~RRMM to further confirm safety and to assess the clinical activity of the combination at the RP2D of GSK2857916. F~~A f~~utility analyse~~i~~s will be conducted from ~~after~~when response data is available from 10~~5~~ subjects. Details of the futility analysis ~~have been~~are described in Section 9.5.2.

Reason for change: Consistency of language throughout protocol to address subject number change.

31. Section 4.5.1. – GSK2857916 Starting Dose Justification

The starting dose for GSK2857916 will be 2.5~~1.92~~ mg/kg administered intravenously ~~once every 3 weeks (~~Q3W~~)~~ on Day 1 of each 21-day Cycle. Careful dose escalation and monitoring will be implemented to protect subjects' safety throughout the study.

The 2.5~~1.92~~ mg/kg dose is considered to be appropriate starting dose for combination with a fixed dose of 200 mg pembrolizumab~~with following justification~~:

- The starting dose of 2.5 mg/kg is one dose level below the 3.4 mg/kg, which had an acceptable safety profile in FTIH trial;
- ~~Based on the non-specific clearance mechanism with large capacity of both: GSK2857916 and pembrolizumab, the likelihood for drug-drug interactions from combining GSK2857916 with pembrolizumab is considered to be low.~~
- ~~According to~~Per currently available data, it is anticipated that the starting dose of 2.5~~1.92~~ mg/kg will be well tolerated and is not expected to result in an excessive toxicity~~, while allowing to derive anti-tumor activity;~~
- Based on the non-specific clearance mechanism with large capacity of both: GSK2857916 and pembrolizumab, the likelihood for drug-drug interactions from combining GSK2857916 with pembrolizumab is low.
- ~~Doses up to 4.6 mg/kg have been tested and 3.4 mg/kg was selected as the RP2D in the ongoing FTIH trial, and did not result in excessive toxicity. The starting dose of 1.92 mg/kg is two dose levels below the 3.4 mg/kg which was declared safe in FTIH trial. In addition it is less than 25% of the highest tested dose of 4.6 mg/kg, which did not result in excessive toxicity in humans.~~
- ~~Careful dose escalation and monitoring will be implemented to protect subjects' safety throughout the study.~~

Reason for change: Revision to starting dose and justification based on changes suggested by FDA comments.

32. Section 4.5.2. – Pembrolizumab Dose Justification

The dose of pembrolizumab for this study~~in this trial~~ is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications regardless of tumor type. As outlined below, this dose is justified by: ~~administered intravenously once every 3 weeks (Q3W) on Day 1 of each 21-day Cycle.~~

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and

- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

~~The dose recently approved in the United States and several other countries for treatment of melanoma subjects is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.~~

~~In KEYNOTE-001, an open-label Phase I study conducted to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD), and anti-tumor activity of pembrolizumab when administered as monotherapy. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg and 10 mg/kg, administered every 2 weeks (Q2W) and dose expansion cohorts evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated and no dose-limiting toxicities were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No maximum tolerated dose (MTD) has been identified. In addition, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose~~

~~of 2 mg/kg versus 10 mg/kg Q3W have been completed, and one randomized cohort evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of important differences in efficacy or safety profile across doses.~~

~~An integrated body of evidence suggests that 200 mg every 3 weeks (Q3W) is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose.~~

~~A population pharmacokinetic (PK) model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. Pharmacokinetic properties of pembrolizumab, and specifically the weight-dependency in clearance and volume of distribution are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.~~

~~In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at tested doses among tumor types. Thus the 200 mg Q3W fixed dose regimen is considered an appropriate fixed dose for other tumor indications as well.~~

~~A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg Q3W as the appropriate dose for pembrolizumab.~~

Reason for change: Revisions to the Merck standard language.

33. Section 4.6.1. – Risk Assessment

The risk assessment and risk mitigation plan for GSK2857916 and~~the~~ study procedures are summarized in Table 2. Refer to Table 5 for pembrolizumab guidance.

New Table 21 revisions: Below will highlight major changes per applicable row

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (GSK2857916)		
Corneal events ~~toxicity~~	Reversible corneal toxicity has been observed with various antibody drug conjugates (specific corneal changes with ADCs conjugated to MMAF). Corneal related AEs (blurred vision, dry / watery eyes, decreased visual acuity, photophobia) are among the most common AEs associated with GSK2857916 in the clinic. The majority of events have been non-serious and transient, some requiring dose delays and/or reductions. Time to recovery is variable and in some instances the resolution may take several weeks.	Active monitoring for corneal events ~~toxicity~~ according to Table 4. Prophylactic~~Preventive~~ use of steroid eye drops as outlined in Section 6.12.3 and Appendix 9. Timely evaluation and management by an eye care professional ~~ophthalmologist~~ upon developing corneal related events (see Section 6.5.1 and Appendix 9. Recommendations for dose delays / reductions are provided in Section 6.5.1.
Infusion related reaction	The majority of IRRs observed in the clinic without any premedication to date have been G1-2 and non-serious; however, there have also been serious IRRs. Overall, subjects who experienced an IRR during the initial infusion were pre-medicated prior to subsequent infusions and IRRs did not recur.	Subjects will be closely monitored for signs of IRR. Premedication prior to first infusion of GSK2857916 is not mandatory but may be considered based on investigator judgement. If an infusion-related reaction occurs during administration of GSK2857916 the management ~~will~~ may follow ~~according to~~ guidance in Table 4 ~~3~~ or local standard of care.
Hepatotoxicity	Non-clinical safety experiments demonstrated increased liver weight and elevated liver enzymes in rats. Elevations in liver enzymes and increased mitotic figures in Kupffer cells were observed in monkeys. All of these changes were dose dependent and reversible. Non-serious elevations in ALT, AST have been observed in the clinic.	Only subjects with well-preserved liver function will be allowed on study. Subjects with Hepatitis B (HBV) and C will be excluded from the trial. Liver function tests will be frequently monitored in all subjects on study and in case of liver abnormalities management will be implemented according to clinical practice. Subjects that meet liver stopping criteria (Section 5.4.1.1) will be withdrawn from the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Nephrotoxicity	Non clinical safety experiments have demonstrated primary glomerular injury and tubular degeneration (in rat and monkey). The morphologic changes were accompanied by large molecular proteinuria (albuminuria). The renal changes were dose dependent and reversible. No kidney failure has been reported in the clinic ~~so far~~ to date.	Only subjects with well-preserved kidney function will be allowed on study. During the study subjects will be monitored for kidney function by assessing creatinine/eGFR, electrolytes, protein ~~and albumin~~ excretion in 24 hr urine collection and albumin / creatinine ratios (spot urine). Subjects will be educated about the need of maintaining adequate urinary output. Management will be implemented according to clinical practice. Dose reductions and treatment stopping criteria will be applied according to Section 6.5.
Pulmonary toxicity (pneumonitis)	Preliminary non clinical safety experiments have demonstrated the presence of microscopic changes in the lungs (prominent alveolar macrophages associated with flocculent eosinophilic material; mixed perivascular inflammation) in rats at all doses tested. As of to date no pulmonary toxicity / cases of pneumonitis have~~has~~ been observed in the clinic.	Monitoring for clinical signs and symptoms potentially related to pulmonary toxicity. Further diagnostic tests and management will be implemented immediately according to recommendations provided in Section 6.5.1.
Immunosuppression	In non-clinical studies GSK2857916 has been associated with decrease in immunoglobulins in monkeys. An increase in immunoglobulins was seen in rats (rats are not an antigen specific species for GSK2857916). ~~As of the data cut off, there have been no serious infections observed in the clinic.~~	Immunoglobulin levels will be assessed throughout the study. Active monitoring for infections, especially opportunistic infections will be performed. Subjects~~Patients~~ will receive immediate treatment according to standard practice.
~~**Investigational drug: Pembrolizumab**~~		
~~**Immune-mediated pneumonitis**~~	~~Immune-mediated pneumonitis, including fatal cases, occurred in patients receiving pembrolizumab.~~	~~Patients will be monitored for signs and symptoms of pneumonitis, and in case of symptoms will be evaluated with radiographic imaging and treated accordingly. Stopping rules are provided in the protocol.~~
~~**Infusion-related reactions**~~	~~Severe and life-threatening infusion-related reactions have been reported in 3~~	~~Patients will be monitored for signs and symptoms of infusion-related reactions including rigors, chills,~~

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	~~(0.1%) of 2117 patients receiving pembrolizumab in clinical trials.~~	~~wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, infusion of pembrolizumab will be stopped and pembrolizumab will be permanently discontinued.~~
Study Procedures		
Incidental findings during imaging data acquisition	During the acquisition of imaging data (e.g., MRI, CT, PET, ECHO), non-MM disease or drug related clinical abnormalities could be found by the radiographer or echocardiographer performing the exams.	All imaging scans will be reported to the site by an appropriate imaging clinician (non-anonymized) for non- MM Disease or drug related clinical abnormalities.

Reason for change: Revisions to the GSK2857916 language, update of links based on other revisions. Per Merck guidance removed risk mitigation language from this table and refer to Table 5 for all pembrolizumab guidance.

34. Section 4.6.3. – Overall Benefit: Risk Conclusion

Although there is limited human experience with GSK2857916, and no clinical experience with the combination of GSK2857916 with pembrolizumab, given the currently available safety data and the low likelihood of drug-drug interaction between GSK2857916 and pembrolizumab, ~~it~~ combination therapy ~~is reasonable to assume that the combination will be prove safe~~ may have an acceptable safety profile, and may provide anti-tumor effect in subjects with MM; but this is unknown.

Of note, excess deaths were noted with pembrolizumab in combination with lenalidomide and dexamethasone (Keynote-185) or in combination with pomalidomide and dexamethasone (Keynote-183) leading the FDA to suspend these phase 3 trials, in addition to other trials of anti-PD[L] therapies in combination with ImiDs in myeloma or non Hodgkin lymphoma were suspended . This statement does not apply to patients taking KEYTRUDA® (pembrolizumab) for an approved indication. The safety and efficacy of using KEYTRUDA® (pembrolizumab) for approved, on-label uses have been proven. (https://www.fda.gov/Drugs/DrugSafety/ucm574305.htm). Considering the measures taken to minimize risk to ~~participants~~subjects, the potential risks associated with GSK2857916 in combination with pembrolizumab are justified by the anticipated benefits that may be afforded to ~~participants~~subjects with MM.

Reason for change: Updated section based on currently pembrolizumab study history in Multiple Myeloma. Revisions to the GSK and Merck standard language

35. Section 5.1 – Inclusion Criteria

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. Provide signed written informed consent, which includes compliance with the requirements and restrictions listed in the consent form
2. Male or female, 18 years or older (at the time consent is obtained)
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix 2)
4. Subjects must:
   - Histologically or cytologically confirmed diagnosis of MM as defined according to IMWG, 2014 [Rajkumar, 2014], and ~~have confirmed diagnosis of Multiple Myeloma~~
   - H~~ha~~s~~ve~~ undergone stem cell transplant or is ~~to be~~ considered transplant ineligible, and
   - Ha~~ve~~s been treated with at least 3~~2~~ prior lines of ~~prior~~ anti-myeloma treatments, including ~~3 classess of drugs: an alkylating agent, AND~~ an IMi~~I~~D (eg.~~i.e.,~~ lenalidomide or pomalidomide), ~~AND~~ a proteasome inhibitor (eg., bortezomib, ixazomib or carfilzomib) and an anti-CD38 antibody, alone or in combination. Line of therapy are defined by consensus panel of the International Myeloma Workshop [Rajkumar, 2011]. ~~In addition, subject must be progressing on, or within 60 days since the most recent treatment (as defined be IMWG)~~
   - ~~In addition to the criteria above, subjects in **Part 2** must have~~ Has measurable disease defined as 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 (≥100 mg/L) and an abnormal serum free light chain ratio (<0.26 or >1.65)
     d) ~~Biopsy proven plasmacytoma (should be measured within 28 days of Screening Visit)~~
5. Subjects with a history of autologous stem cell transplant (SCT) are eligible for study participation provided the following eligibility criteria are met:
   a) Transplant was > 100 days prior to study enrolment.
   b) No active infection (s).
   c) Subject meets the other eligibility criteria outlined in this protocol.

   ~~6. Subjects after prior allo SCT are allowed if the allo transplant was performed ≥ 5 years ago, and if subject has no active GVHD requiring treatment.~~
6. Subject has adequate organ system functions as defined in the Table 3~~2~~

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)[1]	≥ 1.0 X 10^9/L
Hemoglobin	≥ 8.0 g/dL
Platelets	≥ 75 ~~50~~ X 10^9/L
~~**Coagulation**~~	
~~INR~~	~~≤1.5 ULN~~
~~aPTT~~	~~≤1.5 x ULN~~
Hepatic	
Total bilirubin	≤1.~~2~~5X ULN (Isolated bilirubin >1.~~2~~5xULN ~~and ≤ 3xULN~~ is acceptable if bilirubin is fractionated and direct bilirubin <35%)
AST and ALT	≤~~1~~ 2.5 X ULN
Renal	
eGFR[2] ~~Albuminuria~~ Spot urine (albumin creatinine ratio)	≥~~4~~50 mL/min ≤500mg/g (56 mg/mmol)~~24hr~~
Cardiac	
LVEF (Echo)	≥50%
QTcF interval[3]	< 470 msecs

1. Without Growth factor support for the past 14 days, excluding erythropoietin
2. As calculated by Modified Diet in Renal Disease (MDRD) formula
3. The QT interval should be corrected for heart rate by Fridericia's formula (QTcF)

NOTE: Laboratory results obtained during Screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the investigator may retest the subject and the subsequent within range screening result may be used to confirm eligibility.

7. All prior treatment-related toxicities (defined by National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.03, 2010) [NCI, 2010] must be ≤ Grade 1 at the time of enrollment except for alopecia, and Grade 2 neuropathy

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

   - Is not a woman of childbearing potential (WOCBP)

     OR

   - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 8 during the intervention period and for at least 120 days 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.

Additional requirements for pregnancy testing during and after study intervention are located in Appendix 8.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

9. Male Subjects:
   - Male subjects are eligible to participate if they agree to the following during the intervention period and for at least 140 days after the last dose of study intervention:
     - 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 as detailed below
     - Agree to use a male condom and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Appendix 8 when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

~~A female subject is of non-childbearing potential or women of childbearing potential must have a negative serum pregnancy test within 72 hours prior to the first dose of study treatment and agree to use effective contraception during the study and for 120 days following the last dose of study treatment.~~

~~Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception from the time of first dose of study treatment until 140 days after the last dose of study treatment to allow for clearance of any altered sperm.~~

Reason for change: Revision of Inclusion Criteria due to update in line of therapy and update of contraception language.

36. Section 5.2 – Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Systemic anti-myeloma therapy or an investigational drug ~~within~~ ≤14 days or five half-lives, whichever is shorter, preceding ~~prior to~~ the first dose of study drug ~~or~~
2. ~~p~~Plasmapheresis within 7 days prior to the first dose of study drug
3. Prior treatment with a monoclonal antibody within 30 days of receiving the first dose of study drugs

4. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137) and was discontinued from that treatment due to a Grade 3 or higher immune related adverse event (irAE)
5. Current corneal epithelial disease except mild punctate keratopathy
   ~~Use of an investigational drug within 14 days or five half lives, whichever is shorter, preceding the first dose of study drug~~
   ~~Any toxicity from previous treatments which has not recovered to ≤ Grade 1 or to baseline~~
   ~~History of an allogeneic stem cell transplant within last 5 years. Subjects with a history of an autologous stem cell transplant are NOT excluded if they meet Inclusion Criterion #5.~~
   ~~Evidence of active mucosal or internal bleeding~~
6. Any major surgery within the last four weeks prior to the first dose of study therapy
7. Presence of active renal condition (infection, requirement for dialysis or any other condition that could affect subject's safety). Subjects with isolated proteinuria resulting from MM are eligible, provided they fulfil criteria given in Table 3~~2~~
8. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions (including lab abnormalities) that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures.
9. Has received prior radiotherapy within 2 weeks of start of study therapy. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease
10. History of (non-infectious) pneumonitis that required steroids or current pneumonitis
11. Current active 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 chronic liver disease (~~with the exception of~~ including Gilbert's syndrome or asymptomatic gallstones ~~or otherwise stable chronic liver disease per investigator's assessment~~) or hepatobiliary involvement of malignancy is acceptable if subject otherwise meets entry criteria
12. Malignancies other than disease under study are excluded, except for any other malignancy from which the participant has been disease-free for more than 2 years and, in the opinion of the principal investigators and GSK Medical Monitor, will not affect the evaluation of the effects of this clinical trial treatment on the currently targeted malignancy (RRMM). In addition, subjects with curatively treated non-melanoma skin cancer are allowed.
13. Has known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study therapy ~~Subjects with previous or concurrent malignancies are allowed only if the second tumor is not contributing to the subject's illness. The subject must not be receiving active therapy, other~~

~~than hormonal therapy for this disease and the disease must be considered medically stable for at least 2 years.~~

14. Evidence of any cardiovascular risk defined in the protocol
    a. QTcF interval ≥470 msecs
    b. Evidence of current clinically significant uncontrolled arrhythmias;
        i. including clinically significant electrocardiogram (ECG) abnormalities including 2nd degree (Type II) or 3rd degree atrioventricular (AV) block.
    c. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within six months of Screening.
    d. Class III or IV heart failure as defined by the New York Heart Association functional classification system (Appendix 4)
    e. Uncontrolled hypertension
    f. Presence of cardiac pacemaker (or defibrillator) with a predominantly ventricular paced rhythm, limiting ECG/QTcF analysis.
    g. Abnormal cardiac valve morphology (≥Grade 2) documented by echocardiogram (subjects with grade 1 abnormalities CCI [redacted] can be entered on study). Subjects with moderate valvular thickening should not be entered on study.
15. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK2857916 or pembrolizumab, or any of the components of the study treatment.
16. Pregnant or lactating female
17. Known active infection requiring antibiotic, antiviral, or antifungal treatment
18. Known HIV infection
19. 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)
20. 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: Subjects with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained

    NOTE: Hepatitis RNA testing is optional and subjects with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing

~~Subjects with positive test for Hepatitis B surface (HBS Ag) or Hepatitis B core (HBc) antigen.~~

~~Subjects with positive test for hepatitis C (HCV) infection are excluded regardless of viral load (if hepatitis C antibody is positive but confirmatory PCR or RIBA test is negative, subject is eligible).~~

~~Current corneal epithelial disease~~

21. Has received a live-virus vaccination within 30 days of planned start of study therapy. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist) are live attenuated vaccines, and are not allowed.
22. Active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid

replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

23. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other chronic form of immunosuppressive therapy within 7 days prior the first dose of study therapy
24. Has known psychiatric or substance abuse disorders that would interfere with the subject's ability to cooperate with the requirements of the study
25. Has had an allogenic tissue/solid organ transplant

Reason for change: Revision of Exclusion Criteria due to updates to the GSK and Merck standard language.

37. Section 5.3 – Screening Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria. ~~Data for screen failures will be collected in source documentation at the site but will not be transmitted to GSK.~~

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened subjects must be assigned a new unique subject number that is different from the initial number.

Reason for change: Revision language due to update of GSK standard.

38. Section 5.4 – Withdrawal/Stopping Criteria

Subjects will receive study treatment until disease progression, death or unacceptable toxicity (including but not restricted to meeting stopping criteria for significant toxicity as outlined in Section 1), or completion of pre-assigned treatment by reaching a maximum of 3~~2~~5 treatment cycles. In addition, study treatment may be permanently discontinued for any of the following reasons:

- ~~subjects with CR are allowed to end the treatment sooner if they fulfil the criteria outlined in Section 5.4.1.~~.
- Recurrent Grade 2 pneumonitis
- subject has met any of the protocol defined safety stopping criteria (Section 5.4.1.)
- deviation(s) from the protocol
- request of the subject or proxy (withdrawal of consent by subject or proxy)
- investigator's discretion
- concurrent illness that prevents further administration of study treatment(s)
- study treatment must be permanently discontinued in case of pregnancy
- subject is lost to follow-up
- study is closed or terminated

The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and electronic case report form (eCRF)

If the subject withdraws the consent and discontinues from treatment due to toxicity, 'adverse event (AE)' will be recorded as the primary reason for permanently discontinuation on the ~~electronic case report form (~~eCRF~~)~~.

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be re-entered the study.

After the study treatment discontinuation, subjects will undergo end of treatment assessments 30 days (±7 days) after the last dosing, or prior to the start of new anti-cancer treatment (whichever occurs first). Subjects who discontinued treatment for reasons other than PD will be followed up every 3 weeks until confirmed PD, until initiation of a new anticancer therapy or death. All subjects with confirmed PD will be followed for OS and next subsequent anti-cancer therapy every 3 months until the end of study. End of study is defined in Section 5.5.2.

~~All subjects who discontinue from study treatment will complete safety assessments, and will be followed up for PFS, OS, and treatment after study as specified in Time and Events Tables (Table 7).~~

The following actions must be taken ~~in relation to~~ for~~a~~ subject~~s~~ who fails to attend the clinic for a required study visit:

Reason for change: Removal of wording related to discontinuation for achieving CR due to update in program language, addition of pneumonitis, addition of statement related to pregnancy. Revision of study discontinuation language

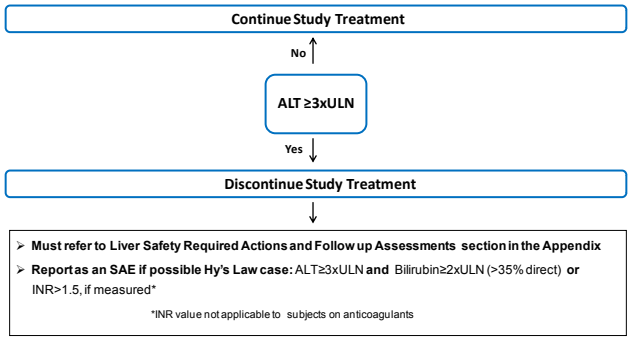
39. Section 5.4.1 – Early Discontinuation of Study Treatment after Achieving a Complete Response (CR)

~~Early discontinuation of treatment may be considered for subjects who have attained a complete response (CR) and who have been treated for at least 8 cycles with the combination of GSK2857916 and pembrolizumab and had at least 2 treatments with both study drugs beyond the date when the initial CR is declared. The assessment for stringency will be performed in all subjects achieving CR. For subjects discontinuing early due to achieving CR, the reason for treatment discontinuation will be recorded in eCRF as: achieving CR, and subject will complete the end of treatment visit, and enter the follow up period. Subject will not be allowed to re-enter the study at later time~~

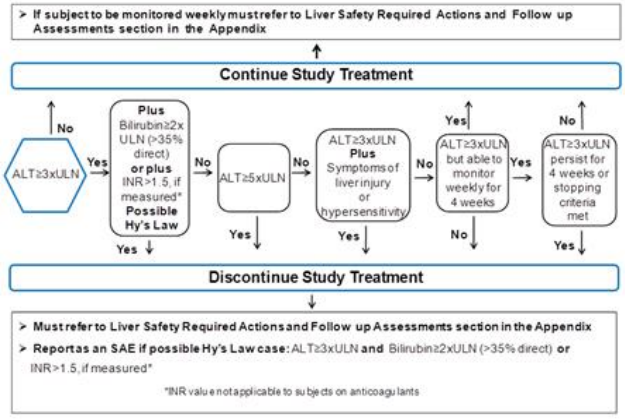
Reason for change: Deletion of section due to removal of ability to discontinue treatment if achieving CR due to program updates.

40. Section 5.4.1 – Safety stopping criteria

Section 5.4.2.1 Old Figure



Section 5.4.2.1 New Figure



Addition of Section 5.4.2.2; Renumbered the remainder of the section

5.4.2.2 Study Treatment Restart or Rechallenge

If subject meets liver chemistry stopping criteria do not restart/rechallenge subject with study treatment unless:

- GSK Medical Governance approval is granted (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

If GSK Medical Governance approval to restart/rechallenge subject with study treatment is not granted, then subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments.

Reason for change: Update of the GSK standard language.

41. Section 5.4.2.8.1 – Infusion-Related Reactions Associated with GSK2857916

Premedication is not required prior to infusion of GSK2857916 unless deemed medically appropriate by the investigator following evaluation of infusion related reactions. Premedication should be considered in any subject who experienced an infusion related reaction at first or any subsequent infusion with GSK2857916

~~If an i~~Infusion-related reactions should be managed by guidelines provided in Table 4. A subject that experiences a Grade 4 IRR after GSK2857916, should be permanently withdrawn from the study. ~~occurs during administration of GSK2857916, the infusion rate may be reduced or halted at the discretion of the investigator and/or GSK medical monitor depending on the severity of the symptoms. The subject will receive appropriate medical treatment. When the subject's condition is stable, the infusion may be restarted according to the judgment of the investigator. For details on re-start guidance and stopping criteria please see Table 3. Upon restart, the infusion rate should be half of the infusion rate at the time the infusion was paused. If the IRR occurred during, or immediately post GSK2857916 infusion, the pembrolizumab infusion must be delayed to allow recovery to G1 or less. The infusion of pembrolizumab may be delayed for up to 48 hours to allow for recovery of IRR caused by GSK2857916, and to accommodate scheduling conflicts. If a subject does not recover from IRR to G1 or less within 48 hours, the dosing of pembrolizumab will be skipped in a given cycle, and may be resumed in the next cycle.~~

~~Blood for serum cytokines should be collected in each subject who developed IRR regardless whether the infusion has been completed or not.~~

Reason for change: Update of the GSK and Merck standard language.

43. Section 5.5 – Subject and study Completion

5.5.1 Subject completion

For Part 1: A subject is considered to have completed the study if the subject is treated through the DLT determinative period or has a DLT during the DLT determinative period, i.e., a completed subject is one who is evaluable for the determination of DLT rate.

For Part 2, a subject is considered to have completed the study if they received at least 1 cycle of combination study treatment, and:

- The subject is followed until death, or
- The subject is followed until the end of study

~~A completed subject in Part 1 is a subject who has received at least one dose of study treatment, and has completed the End of Study visit.~~

~~A completed subject in Part 2 is one who has completed all pre-assigned 32 treatment cycles, or has stopped study treatment early due to achieving CR, and has completed the End of Study Visit~~.

The end of study is defined in Section 5.5.2. The end of study analyses will be performed at that time.

The eCRF should continue to be completed during the follow up period (every 3 months (±7 days) until the ~~, up to~~ end of study. Please refer to Table 10 for assessments to be completed during PFS follow-up visits or OS follow-up. OS follow-up~~12 months) with survival/progression~~ data can be based on contacting patients via phone calls/e-mails/or, other means of communication. Subjects who cannot be contacted will be considered lost to follow up. Follow-up data will be entered into the eCRF.

5.5.2. Study Completion

The ~~A~~ end of study is defined as ~~will be considered completed~~ when all subjects have been followed for 36 months from first dose of study treatment or died or withdrew consent or are lost to follow-up or the safety stopping criteria is met, whichever occurs first. ~~having met the study objectives, when the last subject has received their last dose of study medication and completed the End of Study visit.~~

Per the EU Clinical Trial Directive, the end of the study is defined as the last subject's last visit.

~~The follow up contact will occur via phone calls/e-mails, or any other means of communication, no visit in the clinic is required. The survival/progression data gathered during the contact will be entered into eCRF.~~

5.5.3 Treatment after the End of Study

The investigator is responsible for ensuring that consideration has been given for the post-study care of the subject's medical condition whether or not GSK is providing specific post-study treatment. If a subject remains on treatment at the time end of study is achieved they may be offered an option to extend treatment.

~~Subjects' survival and status of post-study treatment will be documented via phone calls, and/or medical charts analysis every 3 months (±7 days) for the duration of 1 year (12 months) after the last dose of study treatment~~

Reason for change: Revision of the definition of subject completion, end of treatment and other language.

44. Section 6.1 – Investigational Products

Product name:	GSK2857916	Pembrolizumab
Dosage form:	20 mg/mL solution for infusion Supplied as frozen liquid. ~~Recommended storage condition is (minus 50°C to minus 15°C).~~ Protect from light.	100 mg/4mL solution that should be stored under refrigeration at 2-8°C (36-46°F). Protect from light. Do not freeze. Do Not Shake.
Route of Administration	Delivered as ~~30 min~~ IV infusion. Refer to SRM for details.	Delivered as 30 min IV infusion
Manufacturer/ Source of Procurement:	GSK/Baxter	Merck

Reason for change: Additions of GSK and Merck standard language.

45. Section 6.3.1. – Study Treatment Administration

For GSK2857916, please refer to the SRM for additional details on administration. For pembrolizumab, the ~~both study drugs the~~ study medical staff should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes -5 min/+10 min).

Reason for change: Revision of GSK2857916 language to refer to SRM for infusion instructions.

46. Section 6.3.1.1 – GSK2857916 Administration

GSK2857916 will be administered on Day 1 of each cycle at the assigned dose. ~~as approximately 30 min infusion.~~ Premedication is not required prior to infusion unless deemed medically necessary by the investigator, in which case it should be administered according to institutional recommendations. In case of infusion related reactions related to GSK2857916 the rules outlined~~s~~ in Section 5.4.1.8.1 ~~5.4.2.8.1~~ and in Table 6 should be followed.

~~Blood for serum cytokines should be collected in each subject who developed IRR regardless whether the infusion has been completed or not. The time of serum collection will be documented in eCRF.~~

Reason for change: Removal of GSK2857916 infusion timing with move to SRM for instructions. Removal of serum cytokine language.

47. Section 6.3.1.2. – Pembrolizumab administration

Pembrolizumab will be administered using IV infusion on Day 1 of each 3-week treatment cycle after all procedures and assessments have been completed.

Pembrolizumab will be administered as a dose of ~~at the flat dose of~~ 200 mg using ~~via approximately~~ a 30 min IV infusion after at least approximately 1 hour rest period after completion of GSK2857916 infusion. Premedication is not required prior to infusion unless deemed medically necessary, in which case it should be administered according to institutional recommendations.

In case of IRR during or after preceding GSK2857916 infusion, the administration of pembrolizumab will be delayed to allow for recovery to Grade 1 or less. In total, the infusion of pembrolizumab may be delayed for up to the allowed +3 day window from the scheduled dose date~~48 hours~~ to allow for recovery, and to accommodate scheduling conflicts in a given cycle. If the subject does not recover from IRR to Grade 1 or less within the +3 day window~~48 hours~~, the dosing of pembrolizumab will be skipped in a given cycle, and may be resumed in the next cycle.

All subjects are required to remain under observation at the study site for at least three hours post-infusion of the last study drug administered for the first two study treatment dosing visits. At subsequent study treatment dosing visits, for subjects who experience infusion-related reactions, the post-infusion observation time should remain as at least three hours; for subjects who do not experience infusion reactions, these subjects should remain under observation for at least one hour or per the judgement of the investigator or as per institutional guidelines.

Reason for change: Revision of Merck standard language and addition of subject observation post all infusions.

48. Section 6.5. – Subject Specific Dose Adjustment Criteria

Revisions in this section will be highlighted and full tables may not be reproduced.

Section 6.5.1. – Dose modifications and management~~reductions~~ for GSK2857916-related toxicity

In individual cases where, in the judgement of an investigator, waiting a full planned Cycle (21 days) to resume treatment after delays due to toxicities would be detrimental to the subjects' health, the Medical Monitor should be contacted to discuss an earlier re-start. An earlier re-start may be considered only for subjects who have recovered from toxicity to Grade 1 or less. Dosing cannot occur more frequently than every 21 days (±3 days). In such cases, efficacy and safety assessments must remain every 3 weeks from the initial efficacy and safety assessments (Cycle 1 Day 1), which may result in 2 separate visits (1 for disease assessment [Table 8] and 1 for dosing [Table 9]).

If GSK2857916 is held or discontinued for any toxicity, pembrolizumab is to be held or discontinued.

Table 4 – Dose Modification Guidelines for GSK2857916-related AEs

Toxicity	Grade	Recommendations to GSK2857916	Recommendations to pembrolizumab
Serum creatinine elevation or decrease in eGFR which cannot be explained by concomitant sepsis, TLS, other severe infection with fever or dehydration	~~2~~ If absolute serum creatinine increase from baseline of >0. 5 mg/dL	• Repeat within 48 hours • If confirmed: withhold therapy, institute treatment and monitoring as clinically indicated, and follow for resolution • Discuss any further dosing with Medical Monitor[a] • ~~When recovered to ≤G1 continue GSK2857916, consider 25% dose reduction (after discussion with Medical Monitor)~~	See Table 5~~4~~ for guidance on pembrolizumab
Serum creatinine>Grade 3 (acute kidney injury) ~~Elevated serum creatinine or decrease in eGFR which cannot be explained by concomitant sepsis, TLS, other severe infection with fever or dehydration~~	>4~~3~~.0 mg/dL Or >3.0x baseline or hospitalization indicated	• Provide appropriate medical treatment. • Provide appropriate medical treatment. • Permanently discontinue treatment with GSK2857916 • ~~Withhold the dosing. Only resume treatment with GSK2857916 at reduced dose (25-50%) when creatinine returns to G1 or less~~	Resume treatment with pembrolizumab only if treatment with GSK2857916 may be continued
Spot urine (albumin / creatinine ratios)	>2000mg/g (or 224 mg/mmol)	• Re-test (at least 7 days apart). • If not confirmed, continue GSK2857916 at 100% dose • If confirmed on re-test and no clear evidence of disease progression[c] 1. Interrupt treatment with GSK2857916 2. Repeat testing within 4 weeks 1. If spot urine <2000mg/g (224/mg/mmol) may restart GSK2857916 with 25% dose reduction 2. If spot urine remains >2000mg/g (224/mg/mmol) after 4weeks; Permanently discontinue GSK2857916 and withdraw subject from study; provide treatment as clinically indicated and follow for resolution	Resume treatment with pembrolizumab only if treatment with GSK2857916 may be continued

Toxicity	Grade	Recommendations to GSK2857916	Recommendations to pembrolizumab
GSK2857916 Treatment Related Corneal events ~~toxicity~~[b]	Corneal Management Care Regardless of Grade	**Steroid Eye Drops:** • If symptoms occur within the 7-day steroid eye drop prophylaxis window, increase the frequency to 1 drop every 2-4 hours (6-12 times daily) and continue until symptom resolution. • If symptoms occur after the 7-day prophylaxis window is complete, re-start ocular steroid drops at 4x daily until symptom resolution. **Preservative-free artificial tears**: • Increase to 1 drop as frequently as every 2 hours, as needed	
	Grade 1 per GSK Scale	• Continue treatment with current dose of GSK2857916 ~~• Consider ophthalmology consult~~ ~~• If symptoms occur after the mandatory 7 day prophylactic treatment with steroid eye drops is complete, consider re-starting ocular steroid drops at four times daily until resolution. If topical steroid use is prolonged, i.e. > 7 days, consult ophthalmology.~~ ~~• If symptoms occur within the 7 day prophylaxis window with steroid eye drops, consider increased frequency of steroid eye drops to 1 drop every 2-4 hours and continue until resolution. If topical steroid use is prolonged, i.e. > 7 days, consult ophthalmology.~~ • ~~Use of preservative-free artificial tears may be increased up to every 2 hours.~~	• None
	Grade 2 per GSK Scale	• If **either** ophthalmic exam finding **or** visual acuity findings are **Grade 1,** continue dosing with GSK2857916 at current dose • If visual acuity **and** exam findings are **both** Grade 2, **HOLD** GSK2857916 • Upon improvement of either visual acuity or ophthalmic exam findings to Grade 1 or baseline, resume with current dose ~~• Continue treatment with current dose of GSK2857916 consult ophthalmology as soon as possible~~ ~~• If symptoms occur after the mandatory 7 day prophylactic treatment with steroid eye drops is complete, re-start ocular steroid drops at four times daily until resolution.~~	• Hold/Delay treatment until the next GSK2857916 dose ~~None~~

Toxicity	Grade	Recommendations to GSK2857916	Recommendations to pembrolizumab
		~~• If symptoms occur within the 7 day prophylaxis window with steroid eye drops, consider increased frequency of steroid eye drops to 1 drop every 2-4 hours and continue until resolution~~ ~~• Use of preservative free artificial tears may be increased up to every 2 hours, as needed~~ ~~In case of recurring ≥ Grade 2 events, consult the MM~~	
	Grade 3 per GSK Scale	• Hold GSK2857916 ~~and consult ophthalmology as soon as possible~~ • Upon improvement of either visual acuity or ophthalmic exam findings to Grade 1 or baseline, resume with 25% dose reduction (for subjects receive 1.92 mg/kg dose, continue at 1.92 mg/kg) • In case of recurring ≥Grade 3 events, consult GSK Medical Monitor ~~• Hold GSK2857916 and consult ophthalmology as soon as possible~~ ~~• If symptoms occur after the mandatory 7 day prophylactic treatment with steroid eye drops is complete, re-start ocular steroid drops at four times daily until resolution~~ ~~• If symptoms occur within the 7 day prophylaxis window with steroid eye drops, consider increased frequency of steroid eye drops to 1 drop every 2-4 hours and continue until resolution~~ ~~• Use of preservative free artificial tears may be increased up to every 2 hours, as needed~~ ~~• If resolved to ≤ Grade 2 within 14 days discuss with MM prior to continuing at pre-hold dose.~~ ~~• If resolved to ≤ Grade 2 after 14 days, consider 25% dose reduction.~~ • ~~In case of recurring ≥ Grade 3 events, hold GSK2857916 and consult MM~~	• Hold/Delay treatment until the next GSK2857916 dose ~~None~~
	Grade 4 per GSK Scale	• Stop treatment with GSK2857916 ~~• Consult ophthalmology immediately~~ ~~• If symptoms occur after the mandatory 7 day prophylactic treatment with steroid eye drops is complete, re-start~~	• Stop treatment with pembrolizumab. • Further treatment only possible if

Toxicity	Grade	Recommendations to GSK2857916	Recommendations to pembrolizumab
		~~ocular steroid drops at four times daily until resolution~~ • ~~If symptoms occur within the 7 day prophylaxis window with steroid eye drops, consider increased frequency of steroid eye drops to 1 drop every 2-4 hours and continue until resolution Additional topical treatment as recommended by ophthalmologist~~ • ~~Use of preservative free artificial tears may be increased up to every 2 hours, as needed~~ • Additional topical treatment may be prescribed, as ~~if~~ recommended by ophthalmologist • Treatment re-start may be possible after discussion and agreement between ophthalmologist (or optometrist if an ophthalmologist is not available), treating physician, GSK Medical Monitor and possibly a GSK ophthalmologist ~~at the reduced dose in only possible after discussion and agreement between the treating ophthalmologist, the GSK MM and possibly a GSK ophthalmologist with subject's re-consent~~	GSK2857916 is allowed to restart
Infusion Reaction~~a~~[c]	2	Stop the infusion, provide medical treatment and continue at slower pace after resolution to Grade 0-1	See Table ~~5~~6 for guidance on pembrolizumab
	3	Further treatment with GSK2857916 needs to be discussed with Medical Monitor. Continuation only allowed after recovery to ≤ Grade 1 and with pre-medication, and extension of infusion time to 2-4 hours. Any future infusion needs to be pre-medicated	
	4	Permanently discontinue	Permanently discontinue

a. Medical Monitor may consult GSK's nephrotoxicity panel about plans to continue therapy
b. Corneal toxicity should be graded according to GSK scale for GSK2857916 treatment related Corneal Events (Appendix 9)
c. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose

Section 6.5.2. – Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

Table 5 – Dose Modification Guidelines for Pembrolizumab-Related AEs

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	~~Grade 3, or i~~ Intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

New Section 6.5.3. – Dose modification and toxicity management for infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are in Table 6.

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Reason for change: Revision of language and Table based on update to guidelines for Merck standard language. Move of Table from Section 6.12.4.

49. Section 6.10. – Treatment of Investigational Product Overdose

For this study,~~trial using a fixed dose regimen of pembrolizumab,~~ an overdose of pembrolizumab will be~~is~~ defined as ≥1000 mg or ≥~~(~~5 times the indicated dose. ~~) of pembrolizumab.~~

No ~~There is no~~ specific information on the treatment of overdose~~age~~ of pembrolizumab and GSK2857916.

Reason for change: Revision of Merck standard language.

50. Section 6.11. – Lifestyle and/or Dietary Restrictions

6.11.1. - Contraception

GSK2857916 and pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study.

6.11.1.1. – Female Subjects

In order to participate in the study, WOCBP must adhere to the contraception requirement (from the day of study medication initiation) throughout the study period up to 120 days after the last dose of study treatment. If there is any question that a WOCBP will not reliably comply with the requirements for contraception, that subject should not be entered into the study. Full details are in Appendix 8.

~~A female of non-childbearing potential (FNRP):~~

- ~~Females with one of the following procedures documented and no plans to utilise assisted reproductive techniques~~

- Bilateral tubal ligation or salpingectomy
- Hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
- Hysterectomy
- Bilateral oophorectomy

- Post-menopause
  - Female 60 years of age or older
  - Menopause is the phase associated with complete cessation of menstrual cycles and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile, e.g., age appropriate, >45 years in the absence of hormone replacement therapy (HRT) or medical suppression of the menstrual cycle (e.g., leuprolide treatment). In questionable cases for women under 60 years of age, a blood sample with simultaneous follicle stimulating hormone and estradiol falling into the central laboratory's post-menopausal reference range is confirmatory (these levels need to be adjusted for specific laboratories/assays).
  - Females under 60 years of age, who are on HRT and wish to continue, and whose menopausal status is in doubt, are required to use highly effective method to avoid pregnancy, as outlined below

A female of reproductive potential (FRP):

- Females with functioning ovaries
- This category include females with oligomenorrhea, females who are peri-menopausal and young female who have begun to menstruate
- Also note that FRP includes females who are pregnant or nursing.

Female subjects of reproductive potential must not become pregnant for 14 days prior to first dose of study treatment, through the dosing period, and for at 120 days after the last dose of study treatment. and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of <1% (See below).

Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Complete abstinence from sexual intercourse for 14 days prior to first dose of study treatment, through the dosing period, and for at 120 days after the last dose of study treatment.

The following is the all inclusive list of the highly effective methods with a Failure Rate of <1%.

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term or persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence and withdrawal are not acceptable methods of contraception.

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
- Injectable progestogen [Hatcher, 2011]

- ~~Contraceptive vaginal ring [Hatcher, 2011]~~
- ~~Percutaneous contraceptive patches [Hatcher, 2011]~~
- ~~Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this make is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's review of subject's medical records, medical examination and/or semen analysis or medical history interview provided by her or her partner.~~

~~These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception~~.

6.11.1.2. – Male Subjects

Male subjects with female partners of child bearing potential must comply with the ~~following~~contraception requirements highlighted in Section 5.1 from the time of first dose of study medication until 140 days after the last dose of GSK2857916. Details on contraceptive options for subjects with a partner of childbearing potential are in Appendix 8.

- ~~Vasectomy with documentation of azoospermia. The documentation on male sterility can come from the site personnel's review of subject's medical records, medical examination and/or semen analysis or medical history interview.~~
- ~~Male condom plus partner use of one of the contraceptive options below that meets the SOP effectiveness criteria including a <1% rate of falture per year, as tated in the product label:~~
  - ~~Contraceptive subdermal implant~~
  - ~~Intrauterine device or intrauterine system~~
  - ~~Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]~~
  - ~~Injectable progestogen [Hatcher, 2011]~~
  - ~~Contraceptive vaginal ring [Hatcher, 2011]~~
  - ~~Percutaneous contraceptive patches [Hatcher, 2011]~~

~~Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.~~

Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration from the time of first dose of study until 140 days after the last dose of study treatment to allow for clearance of any altered sperm.

6.11.2. – Subjects with Contact Lenses

~~Subjects should avoid use of~~ Ceontact lenses are prohibited while on the study treatment (from first dosing to the end of study treatment).

Reason for change: Revision of contraception language and contract lenses language based on updated data from GSK2857916 data.

51. Section 6.12. – Concomitant Medications/Vaccinations and Non-Drug Therapies

Subjects will be instructed to inform the investigator prior to starting any new medications from the time of first dose of study treatment until the end of the treatment visit~~study (Final Study Visit)~~. Any concomitant medication(s), including non-prescription medication(s) and herbal product(s), taken during the study will be recorded in the ~~electronic case report form (~~eCRF~~)~~. Additionally, a complete list of all prior anti-cancer therapies will be recorded in the eCRF.

Concomitant dosing of GSK2857916 with P-gp inhibitors should be avoided if possible, unless considered medically necessary and with appropriate clinical monitoring. Please refer to the SRM for a list of relevant P-gp inhibitors. .

Elimination pathways for GSK2857916 or cys-mcMMAF in humans have not been characterized, and care should be exercised when combined with potent cytochrome P450 (CYP) inhibitors, CYP inducers, and transporter modulators. Please refer to the SRM for further information.

Reason for change: Revision of P-gp inhibitors to refer to SRM and removal of Appendix, addition of CYP restrictions introduced in program with refer to the SRM.

52. Section 6.12.1. – Permitted Medication(s)

Subjects should receive full supportive care during the study, including transfusion of blood products, growth factors, and treatment with antibiotics, anti-emetics, antidiarrheals, and analgesics, as appropriate.

~~Chronic treatment with oral steroids is prohibited while the subject is on study, unless used as a short course for treatment of acute complications related to study treatment, or pre-medication prior to GSK2857916, or pembrolizumab infusion. Steroids may be used to treat infusion related reactions. Inhaled steroids are allowed for management of asthma, or COPD exacerbations.~~

Concomitant therapy with ~~biphosphonates~~bisphosphonates and RANKL inhibitors are~~is~~ allowed.

Subjects may receive local irradiation or elective surgery, eg. for pain control after discussion with the medical monitor. ~~or stability control~~

Reason for change: Revision of GSK standard language and to reduce duplication.

53. Section 6.12.3. – Supportive Care Guidelines for Corneal Events~~Toxicity~~

Corneal events~~toxicity~~, which commonly manifests as a superficial microcystic keratopathy, has previously been reported with antibody drug conjugates, including those conjugated to MMAF [Tannir, 2014; Eaton, 2012; Younes, 2012]. It is required that the sites establish a close collaboration with an ophthalmologist (or optometrist, if ophthalmologist is not available) who will be responsible for assessing subjects on study and managing subjects who develop corneal toxicity in close communication with GSK Medical Monitor and possibly a GSK ophthalmologist.

Subjects will be assessed by ophthalmologists (or ~~/~~optometrist, if an ophthalmologist is not available) at baseline, and then every three weeks. If there is no change in vision and no corneal signs consistent with toxicity at time of the cycle 4 exam, subjects may have their ophthalmologic exams decreased to once every 3 months. If a subject subsequently develops a change in visual acuity or other ocular symptoms, the subject should be evaluated by an eye care professional. Intraocular pressure must be monitored if steroid eye drops are used more than 7 days. ~~prior to each dose of cycles 1-4. If asymptomatic and without signs consistent with corneal toxicity at time of the cycle 4 exam, subjects may have their ophthalmologic exams decreased to once every 4 cycles. If a subject subsequently develops signs / symptoms, or they require additional treatment, e.g. topical steroid for more than 7 days, additional assessment by an ophthalmologist/optometrist will be implemented.~~

Subjects who have signs or symptoms of corneal toxicity present at end of study will continue to be followed monthly for up to 12 months, or until deemed clinically stable by an ophthalmologist (or optometrist, if ophthalmologist is not available), whichever comes first.

Reason for change: Update to GSK language related to treatment of corneal guidelines.

54. Section 6.12.4. – Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs~~adverse events~~ with potential immunologic etiology are outlined along with the dose modification guidelines in 6.5.2. ~~below.~~, Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance. ~~(as outlined below).~~ Refer to ~~for dose modification.~~4 Table 5 for guidelines regarding dose modification and supportive care. ~~below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.~~

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

~~Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.~~

Reason for change: Update to Merck standard language.

55. Section 6.12.5. – Prohibited Medication(s)

Other Prohibited Therapies:

- Plasmapheresis is prohibited from 7 days prior to study entry through the end of study.
- ~~Immunotherapy not specified in this protocol~~
- Anticancer therapies other than those referred to as Study Treatment that include but are not limited to chemotherapy, immunotherapy, biologic therapy, hormonal therapy (other than physiologic replacement), surgery, and radiation therapy (other than palliative intervention as described in Section 6.12.1). Radiation therapy or surgery may be permitted after mutual agreement of the investigator, the sponsor and the subject.
- ~~Chemotherapy not specified in this protocol~~

Reason for change: Update to GSK standard language and to reduce duplicate language.

56. Section 7 – Study Assessments and Procedures

Overall revision from one Table and Events Table into four Table and Events Tables: Screening Assessments, On Study Assessments Independent of Dosing, On Study Assessments with Dosing, End of Treatment and Follow-up Assessments. New tables are presented.

Table 7 Time and Events Table: Part 1 and Part 2 – Screening Assessments

Study Assessments[1]	Screen[2]	Notes
Informed Consent	X	1. All assessments will apply to Part 1 and 2 unless stated otherwise. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. 2. All Screening assessments must be performed within 28 days prior to first dose unless otherwise specified. Informed Consent must be signed before any study-specific assessments are performed. Screening Assessment do not need to be repeated on C1D1 unless otherwise specified. 3. Screening ocular examination to be performed by an ophthalmologist (or an optometrist if an ophthalmologist is not available) within 28 days prior to the first dosing. See Section 7.3.5. for list of ophthalmic exam procedures. 4. Perform only in women of child-bearing potential. A serum pregnancy test must be performed. 5. eGFR as calculated by Modified Diet in Renal Disease (MDRD) formula (Appendix 3) 6. Albumin / creatinine ratios (spot urine from first void). 7. Troponin will be measured at the local lab (troponin I or T) and a central lab (troponin I). 8. BNP to be measured locally at screening; if cardiac workup is required due to safety concerns during the study, BNP should be measured. 9. Triplicate ECG measurement.
Baseline Demographics	X	
Medical History	X	
Physical Exam	X	
Concomitant Medications	X	
ECOG Performance Status	X	
	Safety	
Ocular Exam	X[3]	
Vital Signs (BP, HR, Body Temperature)	X	
Weight and Height	X	
Pregnancy Test	X[4]	
Hematology	X	
Clinical chemistry (with corrected calcium)	X	
eGFR	X[5]	
Urine Dipstick	X	
Spot Urine (albumin / creatinine ratio)	X[6]	
~~INR, PTT~~	~~X~~	
CRP	X	
HBsAg, HBcAb, HCV tests	X	

Study Assessments[1]	Screen[2]	Notes
Troponin	X[7]	10. LVEF may be performed within 28 days prior to first dose. To be sent for central imaging storage. 11. Skeletal Survey: Imaging of bones for lytic lesions by a method aligned with the institutional guidance (X-ray, CT, or MRI). Skeletal survey results within 28 days prior to C1D1 may be used for screening. Same modality used at Screening must be used throughout study.
BNP	X[8]	
12-lead ECG	X[9]	
LVEF and valves assessment (ECHO)	X[10]	
	Disease Evaluation	
Beta2 microglobulin	X	
Skeletal Survey	X[11]	
UPEP 24 hr urine collection	X	
Urine immunofixation	X	
SPEP	X	
Serum Immunofixation	X	
Extramedullary Plasmacytoma Assessment (by whole body CT or whole body MRI or CT/PET)	X[12]	12. May be performed up to 28 days prior to C1D1 as screening value. Needs to be performed by the same method throughout the study as was done at baseline (i.e. if CT/PET scan was used as baseline, subject needs to be followed by CT/PET scans). Selected target lesion needs to be measured and followed over time. For sites in Germany, only MRI is allowed as imaging modality. 13. Only required for subjects with IgD/E myeloma If patient has IgD or IgE myeloma, then IgG/A/M testing is not required. 14. FISH testing at least for: t(4;14), t(14;16), 17p13del. FISH results from samples taken within 60 days prior to first dose are acceptable. 15. Samples from within 28 days prior to first dose are acceptable. Portion of the aspirate collected for disease assessment will be used for biomarker research, for FISH testing, and MRD testing MRD testing will be performed by a central lab.
Serum Kappa, Lambda free Light chain, FLC ratio	X	
Calcium corrected for albumin (serum)	X	
IgG, IgM, IgA	X	
IgD/E	X[13]	
	Bone Marrow (BM) Aspiration/Biopsy	
BM aspirate for FISH testing	X[14]	
BM aspirate for BCMA expression and immune cell characterization	X[15]	
MRD testing bone marrow aspirate	X[15]	
BM aspirate/biopsy for Percent malignant plasma cell	X[15]	
	Health Outcomes	
PRO-CTCAE	X	
NEI-VFQ-25 and OSDI	X	

Abbreviations:
BP = Blood pressure; BNP = B-type natriuretic peptide; CRP = C-reactive protein; CT = Computed tomography; eGFR = Estimated glomerular filtration rate; ECG = Electrocardiogram; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; FISH = Fluorescence in situ hybridization; FLC = Free light chain; HBsAg = surface antigen of Hepatitis B virus; HBcAb = Hepatitis B core antibody; HCV = Hepatitis C virus; HR = Heart rate; Ig = Immunoglobulin; LVEF = Left Ventricular Ejection Fraction; MRD = Minimal residual disease; MRI = Magnetic resonance imaging; NEI-VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; OSDI = Ocular Surface Disease Index; PET = Positron emission tomography; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Term Criteria for Adverse Events; SPEP = Serum protein electrophoresis; UPEP = Urine protein electrophoresis;

Table 8 Time and Events Table: Part 1 and Part 2 – On Study Assessments Completed Independent of Dosing

Study Assessments[1]	C1 Day 1 (Week 1)	C1 Day 8 (Week 2)	Treatment Period: Q3W from Wk4 until EOT
Physical Exam	X		X
Vital Signs (BP, HR, Body Temperature)	X[2]	X	X[2]
Adverse Events[3]	Ongoing		
Concomitant Medications	Ongoing		
Genetics[4]	X		
ECOG Performance Status			X
			Safety
Ocular Exam			X[5]
Hematology	X[6]	X	X
Clinical chemistry (with corrected calcium)	X[6]	X	X
eGFR[7]	X[6]	X	X
Urine Dipstick	X[6]		X
~~INR, PTT~~	~~X[6]~~	~~X~~	~~X~~
CRP			X
Free T3, Free T4 and TSH	X		X[8]
LVEF and valves assessment (ECHO)[9]			X[9]
			Disease Evaluation
Skeletal Survey			X[10]
UPEP 24 hr urine collection	X[6]		X
Urine immunofixation	X[6]		X[11]
SPEP	X[6]		X
Serum Immunofixation	X[6]		X[11]

Notes

1. All assessments will apply to Part 1 and 2 unless stated otherwise. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. All assessments from Cycle 2 can be performed +/-3 days prior to the scheduled date unless otherwise specified.
2. Single vital sign assessment required if dosing is held. Refer to Table 9 for additional vital sign assessments to be completed if dosing.
3. AEs/SAEs will be assessed from first study dose.
4. Informed consent for optional sub studies (e.g. genetic research) must be obtained before collecting a sample. The sample will be collected on C1D1 prior to infusion.
5. On-study ocular exams to be performed by an ophthalmologist (or an optometrist if an ophthalmologist is not available) every three weeks. See Section 7.3.5 for list of ophthalmic exam procedures. If there is no change in vision and no corneal signs consistent with toxicity at time of the cycle 4 exam, subjects may have their ophthalmologic exams decreased to once every 3 months. Additional exams may be performed by the eye care professional, as clinically indicated. If a subject subsequently develops a change in visual acuity or other ocular symptoms, the subject should be evaluated by an eye care professional. Intraocular pressure must be monitored if steroid eye drops are used more than 7 days.
6. If completed within 72 hrs prior to the first dose, this assessment does not need to be repeated on Day 1 of Cycle 1. Refer to Table 11 for comprehensive list of lab tests.
7. eGFR as calculated by Modified Diet in Renal Disease (MDRD) formula (Appendix 3)
8. Every 6 weeks from first dose while on study.
9. ECHOs to be done locally up to 7 days prior to scheduled visit. On treatment ECHOs will occur every 12 weeks from first dose and will continue regardless of dose delays. All EHCOs will be sent for central imaging storage.
10. At the time of suspected disease progression or as clinically indicated. Same modality used at Screening must be used throughout study.
11. At time of first achieving SPEP or Urine M protein ~ 0g/dl (suspected CR) and until suspected PD after CR or sCR.

Study Assessments[1]	C1 Day 1 (Week 1)	C1 Day 8 (Week 2)	Treatment Period: Q3W from Wk4 until EOT	Notes
Extramedullary Plasmacytoma Assessment (by whole body CT or whole body MRI or CT/PET)			X[12]	12. **Q12 weeks (± 3 weeks) through 1 year and then as clinically indicated.** To be performed by the same method throughout the study as was done at baseline (i.e. if CT/PET scan was used as baseline, subject needs to be followed by CT/PET scans). Selected target lesion needs to be measured and followed over time. For sites in Germany, only MRI is allowed as imaging modality. 13. Only required for subjects with IgD/E myeloma. If patient has IgD or IgE myeloma, then IgG/A/M testing is not required. 14. Optional Collection at time of Progressive Disease. 15. Additional bone marrow aspirate samples may be collected at C1D8 or during every 3 week period for biomarker assessments 16. MRD assessment to be performed by a central lab at the time of first achieving VGPR or CR, repeat MRD testing every 6 and 12 months after achieving VGPR or CR (provided VGPR/CR is maintained). 17. At the time of suspected CR for confirmation of PC% <5% (always) or at time of suspected PD (only if not evident otherwise). Bone marrow core biopsy is preferred. 18. IHC only to confirm sCR at the time of confirmation of CR bone marrow bx/aspirate is performed. 19. Additional assessments may be conducted for those subjects who are experience a worsening in visual function. 20. Collected pre-dose <u>every **Q6 weeks**</u> from C1 until EOT
Serum Kappa, Lambda free Light chain, FLC ratio	X[6]		X	
Calcium corrected for albumin (serum)	X[6]		X	
IgG, IgM, IgA	X[6]		X	
IgD/E[13]	X[6]		X	
			Bone Marrow (BM) Aspiration/Biopsy	
BM aspirate for BCMA expression and immune cell characterization		X[15]	X[14,15]	
MRD testing bone marrow aspirate			X[16]	
BM aspirate/biopsy for Disease assessment			X[17]	
BM biopsy to assess sCR			X[18]	
			Health Outcomes	
PRO-CTCAE	X	X	X	
NEI-VFQ-25 and OSDI	X	X	X[19]	
EORTC-QLQ-C30 and EORTC-QLQ-MY20 **(Part 2 only)**	X[20]		X[20]	

Abbreviations:
AE = Adverse Event; BP = Blood pressure; CR = Complete response; CRP = C-reactive protein; CT = Computed tomography; eGFR = Estimated glomerular filtration rate; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module; EORTC-QLQ-MY20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma Module; FLC = Free light chain; HR = Heart rate; Ig = Immunoglobulin; IHC = Immunohistochemistry; MRD = Minimal residual disease; MRI = Magnetic resonance imaging; NEI-VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; OSDI = Ocular Surface Disease Index; PC = clonal plasma cells; PD = Progressive disease; PET = Positron emission tomography; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Term Criteria for Adverse Events; Q3W = Every 3 weeks; sCR =

Stringent complete response; SAE = Serious adverse event; SPEP = Serum protein electrophoresis; T3 = Triiodothyronine 3; T4 = Triiodothyronine 4; TSH = Thyroid Stimulating Hormone; UPEP = Urine protein electrophoresis; VGPR = Very good partial response

Table 9 Time and Events Table: Part 1 and Part 2 – On Study Assessments with Dosing Days (Cycles)

Study Assessments[1]	C1 Day 1 (Week 1)	C1 Day 8 (Week 2)	Day 1 of C2 – C35, (IF DOSING) Cycles = 21 days	Notes
			Safety	1. All assessments will apply to Part 1 and 2 unless stated otherwise. Assessments should be done prior to drug administration, unless otherwise specified. From Cycle 2, assessments can be performed +/-3 days prior to the scheduled date unless otherwise specified. 2. Infusion vital signs must be assessed for each infusion (GSK2857916 and pembrolizumab) at: pre-dose (within 30 minutes prior to SOI); post each infusion (EOI); and 1 hour post EOI. **On dosing days with PK sampling time points, vital signs should be assessed prior to PK samples being drawn.** 3. Perform only in women of child-bearing potential. Pregnancy tests may be either pre-dose serum or urine and should be performed within 72 hours prior to dosing. 4. Pre-dose. Troponin will be measured at the local lab (troponin I or T) and a central lab (troponin I). 5. Albumin / creatinine ratios (spot urine from first void). 6. If completed within 72 hrs prior to the first dose, this assessment does not need to be repeated on Day 1 of Cycle 1. Refer to Table 11 for comprehensive list of lab tests. 7. Triplicate ECGs to be performed at pre-dose (within 30 minutes prior to SOI GSK2857916) and at EOI GSK2857916 (withing 5 min prior to GSK2857916 EOI) at each cycle. ECG recordings should be made after at least 10 min rest and collected 2 min apart. On days with PK sampling time points, ECGs should be performed prior to PK samples being drawn. 8. PK samples to be taken (in all subjects) for both GSK2857916 and pembrolizumab measurement: C1D1: pre-dose (within 30 mins prior to SOI GSK2857916), EOI GSK2857916 (±5 min), pre-dose pembrolizumab (within 10 min prior to SOI pembrolizumab), EOI pembrolizumab (±5 min), 4 h after GSK2857916 SOI (±15 min), 9 h OR 24 h after GSK2857916 SOI (±1 h) according to the subject's preference; C1D4: one sample anytime; C1D8 to C1D15: one sample anytime; C2D1 and C5D1: pre-dose (within 30 min prior to SOI GSK2857916) and EOI GSK2857916 (±5 min), pre-dose pembrolizumab (within 10 min prior to SOI pembrolizumab)), EOI pembrolizumab (±5 min); C8D1 and C11D1: pre-dose (within 30 min prior to SOI
Infusion Related Vital Signs (BP, HR, Body Temperature)			X[2]	
Weight	X		X	
Pregnancy Test			X[3]	
~~CK-MB,~~ Troponin		X	X[4]	
Spot Urine (albumin / creatinine ratio)	X[5, 6]		X[5]	
Triplicate 12-lead ECG	X[7]	X	X[7]	
			PK and ADA	
Pharmacokinetics[8] for GSK2857916 and pembrolizumab	X	X	X[8]	
Immunogenicity (ADA)	X		X[9]	
			Biomarker	
Soluble BCMA	X[10]		X[10]	
Serum (cytokines/ chemokines)[11]	X	X		

Study Assessments[1]	C1 Day 1 (Week 1)	C1 Day 8 (Week 2)	Day 1 of C2 – C35, (IF DOSING) Cycles = 21 days	Notes
Plasma-cfDNA	X			GSK2857916; EOI GSK2857916 (±5 min); C14D1 and every 3 cycles thereafter (i.e., C17, 20, until EOT): pre-dose (within 30 min prior to SOI GSK2857916). In Cycle 1, in the event the pembrolizumab infusion is delayed by at least 24 h samples should also be taken prior to SOI pembrolizumab dose, at EOI pembrolizumab and at 2.5 h and 7 h post pembrolizumab SOI in addition to the time points listed above. 9. Pre-dose GSK2857916 C1 Day1 (week 1), C2, C5 and every 3 cycles thereafter (i.e., C8, C11,..) until EOT. 10. Serum sBCMA samples will be collected each cycle at pre-dose (within 30 minutes prior to SOI) and at each PK timepoint in cycle 1. 11. Collect cytokine serum sample at C1D1 at pre-dose (within 30 minutes prior to SOI), EOI of pembrolizumab (±5 min) (even when infusion is interrupted or halted), 4h after GSK2857916 SOI, 9h ***OR*** 24h after GSK2857916 SOI (±1 hr) according to the subject's preference; and at C1D8.
			Treatment	
Administration of GSK2857916[12]	X		Day 1 of each cycle	12. A window of ± 3 days is acceptable for administration of study treatment after C1. GSK2857916 will be administered first as IV infusion, followed by 1 hr rest period. Refer to SRM for details. Pembrolizumab will be administered as second, in a 30min infusion, 1 hr after GSK287916 EOI, provided subject did not develop IRR requiring intervention. If planned Cycle treatment is delayed due to toxicities which have resolved, if in the judgement of the investigator, treatment needs to be initiated prior to next planned Cycle, this can be discussed with the medical monitor. Dosing cannot occur more frequently than every 21 days (±3 days). 13. Premedication should be considered in any subject who experienced an infusion related reaction at first or any subsequent infusion with GSK2857916 and pembrolizumab. 14. Corneal management information: - Prophylaxis with steroid eye drops (such as prednisolone phosphate 1% or dexamethasone 0.1%) 1 drop QID starting from 1 day prior to infusion and continuing for a total of 7 consecutive days. If dosing delayed for a non-corneal event, the prophylactic steroid drops can be stopped. - Prophylactic preservative-free artificial tears must be administered in each eye at least 4-8 times daily beginning on Cycle 1 Day 1 until end of treatment. - At the start of each infusion, subjects may apply cooling eye masks to their eyes for approximately 1 hour as long as tolerated.
Administration of pembrolizumab[12]	X		Day 1 of each cycle	
Premedication if needed[13]	X		X (at the start of each cycle)	
Corneal events management: Steroid eye drops, preservative-free artificial tears and cooling masks[14]	X[14]		X[14]	

Abbreviations:
ADA = Antibody Drug Antibody; BP = Blood pressure; cfDNA = Circulating free DNA; ECG = Electrocardiogram; EOI = End of Infusion; HR = Heart rate; IRR = Infusion related reaction; PK = Pharmacokinetics; QID = 4 times a day; SOI = start of infusion;

Table 10 Time and Events Table: Part 1 and Part 2 – End of Treatment and Follow-up Assessments

Study Assessments[1]	End of Treatment Visit[2]	PFS Follow-up[3]	OS Follow-up[4]
Physical Exam	X	X	
Vital Signs (BP, HR, Body Temperature)	X		
Adverse Events[5]	X	Related SAEs only	Related SAEs only
Concomitant Medications	X	X	
	Safety		
Ocular Exam	X[6,7]	X[7]	X[7]
ECOG Performance Status	X		
Hematology	X		
Clinical chemistry (with corrected calcium)	X	X	
Pregnancy Test	X[8]	X[9]	X[9]
eGFR[10]	X		
Urine Dipstick	X		
~~INR, PTT~~	~~X~~		
CRP	X		
Spot Urine (albumin / creatinine ratio)[11]	X		
Troponin[12]	X		
Free T3, Free T4 and TSH	X		
12-lead ECG	X[13]		
LVEF and valves assessment (ECHO)	X[14]		
	Disease Evaluation		
Skeletal survey	X[15]	X[15]	
UPEP 24 hr urine collection	X	X	
Urine immunofixation	X[16]	X[16]	
SPEP	X	X	
Serum Immunofixation	X[16]	X[16]	

Notes

1. All assessments will apply to Part 1 and 2 unless stated otherwise.
2. Safety follow up to occur within 30 days from the last dose, or prior to the new anti-MM treatment (whichever occurs first).
3. PFS follow-up every 21 days (±7 days) for subjects who discontinue IP for a reason other than PD. Disease evaluations will continue until confirmed PD, death, start of a new anticancer treatment, withdrawal of consent, or end of the study whichever occurs first. Once subject progresses, move to OS Follow-up.
4. The survival for MM will be documented in medical charts. No visit necessary. Contacts will be made via phone calls, emails or other means of communications every 12 weeks (± 14 days) until end of study (Section 5.5.2). Subject does not need to come in for visit unless they are being followed for corneal signs that are present at the end of study treatment.
5. AEs will be assessed up to sa post the last dose. SAEs will be assessed up to 90 days post last dose, or 45 days post last dose if the subject initiates a new anticancer therapy (whichever is shorter), All related SAEs are to be collected from first dose through OS follow-up.
6. If a subject develops signs / symptoms, or they require additional treatment, e.g. topical steroid for more than 7 days, additional assessment by an ophthalmologist (or optometrist, if ophthalmologist is not available) will be implemented. Intraocular pressure should be monitored if steroid eye drops are used more than 7 days. See Section 7.3.5 for list of exams.
7. Subjects with decreased visual acuity or corneal signs or symptoms at the end of study treatment visit will have follow-up ophthalmic exams at 3 and 6 weeks from the last dose of study treatment and then every 6 weeks (±7 days) until deemed clinically stable by an eye care professional, or up until 1 year (whichever comes first). See Section 7.3.5 for list of exams.
8. Perform only in women of child-bearing potential. May be either serum or urine.
9. Final pregnancy test (serum or urine) must be performed in women of childbearing potential 80 days (±7 days) after last study treatment.
10. eGFR as calculated by Modified Diet in Renal Disease (MDRD) formula (Appendix 3)
11. Albumin / creatinine ratios (spot urine from first void). .
12. Troponin will be measured at the local lab (troponin I or T) and a central lab (troponin I).

Study Assessments[1]	End of Treatment Visit[2]	PFS Follow-up[3]	OS Follow-up[4]	Notes
Extramedullary Plasmacytoma Assessment (by whole body CT or whole body MRI or CT/PET	X[17]	X[18]		13. Obtain a triplicate ECG measurement. 14. Sent for central imaging storage. 15. At the time of suspected disease progression or as clinically indicated. Same modality used at Screening must be used throughout study. 16. At time of first achieving SPEP or Urine M protein ~ 0g/dl (suspected CR) and until suspected PD after CR or sCR 17. In subjects with extramedullary MM, if the last radiographic assessment occurred ≥8 weeks prior withdrawal from study treatment, and PD has NOT been documented otherwise, a new assessment should be obtained at the time the subject withdrew from study treatment. To be performed by the same method throughout the study as was done at baseline (i.e. if CT/PET scan was used as baseline, subject needs to be followed by CT/PET scans). Selected target lesion needs to be measured and followed over time. For sites in Germany, only MRI is allowed as imaging modality. 18. As clinically indicated with same method as was done at baseline.
Serum Kappa, Lambda free Light chain, FLC ratio	X	X		19. Only required for subjects with IgD/E myeloma. If patient has IgD or IgE myeloma, then IgG/A/M testing is not required. 20. One PK sample for GSK2857916 and pembrolizumab should be collected at the end of treatment visit. 21. Collect one ADA at least 8 weeks post last dose. 22. MRD assessment to be performed by a central lab at the time of first achieving VGPR or CR, repeat testing at 6 and 12 months after achieving VGPR or CR (provided VGPR/CR is maintained). . 23. Only to confirm CR or suspected PD at this visit. 24. Subjects who discontinue participation in the study will continue to be assessed during follow-up until resolution of visual symptoms. Continue to follow-up with subjects via telephone who are still experiencing visual symptoms even after study discontinuation. 25. Exit Interview to be performed within 21 days of last dose of study treatment.
Calcium corrected for albumin (serum)	X	X		
IgG, IgM, IgA	X	X		
IgD/E[19]	X	X		
Subsequent anti-MM Treatment		X	X	
	PK and ADA			
Pharmacokinetics for GSK2857916 and pembrolizumab	X[20]			
Immunogenicity (ADA)	X	X[21]		
	Biomarkers			
Soluble BCMA	X			
Plasma-cfDNA	X			
	Bone Marrow (BM) Aspiration/Biopsy			
MRD testing bone marrow aspirate	X[22]	X[22]		

Study Assessments[1]	End of Treatment Visit[2]	PFS Follow-up[3]	OS Follow-up[4]	Notes
BM aspirate/biopsy for Disease assessment	X[23]	X[23]		
BM biopsy to assess sCR	X[23]	X[23]		
BM aspirate for BCMA expression and immune cell characterization	X[22]	X[22]		
	Health Outcomes			
PRO-CTCAE	X			
NEI-VFQ-25 and OSDI	X	X[24]	X[24]	
EORTC-QLQ-C30 and EORTC-QLQ-MY20 **(Part 2 only)**	X			
Exit Interview	X[25]			

Abbreviations:
AE = Adverse Event; ADA = Antibody Drug Antibody; BP = Blood pressure; BCVA = Best corrected visual acuity; BNP = B-type natriuretic peptide; cfDNA = Circulating free DNA; CR = Complete response; CRP = C-reactive protein; CT = Computed tomography; eGFR = Estimated glomerular filtration rate; ECG = Electrocardiogram; ECHO = Echocardiogram; EOI = End of Infusion; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module; EORTC-QLQ-MY20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma Module; FLC = Free light chain; HR = Heart rate; Ig = Immunoglobulin; IHC = Immunohistochemistry; INR = International normalized ratio; HR = Heart rate; MRD = Minimal residual disease; MRI = Magnetic resonance imaging; NEI-VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; OS = Overall survival; OSDI = Ocular Surface Disease Index; PD = Progressive disease; PET = Positron emission tomography; PFS = Progression free survival; PK = Pharmacokinetics; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Term Criteria for Adverse Events; PTT = Partial Thromboplastin Time; QID = 4 times a day; sCR = Stringent complete response; SAE = Serious Adverse Event; SOI = start of infusion; SPEP = Serum protein electrophoresis; T3 = Triiodothyronine 3; T4 = Triiodothyronine 4; TSH = Thyroid Stimulating Hormone; UPEP = Urine protein electrophoresis; VGPR = Very good partial response

Reason for change: Increase ease of use of the Tables by moving notes from end of the Table to be in line with the associated assessments.

57. Section 7.2 – Efficacy

Standard disease assessments for MM will include ~~laboratory tests (serum and urine M protein test, FLC), bone marrow aspirate (in case of CR), flow cytometry, or IHC to confirm stringent CR.~~ the following assessments:

- UPEP (24 hour), with M protein
- Urine Immunofixation,
- SPEP, with M protein
- Serum immunofixation,
- Corrected Calcium,

- Quantitative Immunoglobulins (IgG, IgA, and IgM and for subjects with IgD or IgE myeloma, quantitative IgD or IgE),
- Serum kappa and lambda free light chains and FLC ratio,
- Bone marrow aspirate and/or core biopsy at screening for baseline PC percentage and FISH analysis; and for disease response assessment at time of suspected CR/sCR, or PD,
- At time of VGPR or CR, MRD testing on bone marrow aspirate,
- Imaging by CT, MRI, CT/PET or X-ray to assess EMP and bone lesions. For sites in Germany, only MRI is allowed as imaging modality
- Skeletal survey (Screening and as clinically indicated). For sites in Germany, only MRI is allowed as imaging modality

Response evaluation will be performed according to the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma 2016~~1~~ [Kumar, 2016].

Clinical activity measured as ~~Overall Response Rate (~~ORR~~)~~ which is defined as follows:

The percentage of subjects with confirmed ~~stringent complete response (~~sCR~~)~~, ~~complete response (~~CR~~)~~, ~~very good partial response (~~VGPR~~)~~, and ~~partial response (~~PR~~)~~ as assessed by 201~~1~~6 recommendations of the International Myeloma Working Group (IMWG)) [Kumar, 2016]. Other assessments of interest like ~~clinical benefit rate (~~CBR~~)~~, PFS, TTR, DOR, and OS may also be considered. Minimal residual disease negative rate will be assessed in those subjects who achieve a VGPR or CR.

In subjects with extramedullary myeloma- the disease assessments have to include imaging (e.g., computed tomography [CT] scan, magnetic resonance imaging [MRI], or PET/~~et~~ CT scan) and physical examination (as indicated for palpable/superficial lesions). For participants with skin only involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the Sum of the Products of the maximal perpendicular diameters of measured lesions (SPD).

Baseline serum disease assessment will be completed during screening period (within 28~~14~~ days prior to the fist dose of study medication) and baseline imaging within 28~~21~~ days prior to the first dose of study treatment. On study serum and urine based assessments (M-protein, FLC, immunofixation) and imaging, for extramedullary disease, will be performed as required. ~~every 21 days (at the start of each cycle), or every 4 cycles (in case of imaging for extramedullary disease).~~ The final assessments will be performed during final study visit (End of treatment visit). See the Time and Events Tables (Table 7, Table 8, and Table 10) for the schedule of assessments of anti-cancer activity. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. For post-baseline assessments, a window of ±3 days is permitted to allow for flexible scheduling.

In subjects with extramedullary MM: if the last radiographic assessment was more than 8 ~~or 9 weeks~~ prior to the subject's withdrawal from study and progressive disease has not been documented, a disease assessment should be obtained at the time of withdrawal from study.

MRD negativity rate (defined as: the percentage of subjects who are MRD negative by clonoSEQ). During treatment, testing will be performed for subjects achieving VGPR or CR. In subjects who have achieved MRD negativity, the testing will be repeated after 6 and 12 months (provided CR is maintained) from time of first documented negative MRD result to assess sustained MRD negativity. MRD testing will be performed by a central lab.

Reason for change: Revision of section to clarify the efficacy measures, update IMWG to 2016 criteria and to clarify timelines for assessments.

58. Section 7.3.1.1. – Time Period and Frequency of Detecting AEs and SAEs

All AEs will be collected from the time the first dose of study treatment is administered until 4590 days following cessation of treatment~~, or 30 days following cessation~~ regardless of initiation of~~treatment if the subject initiates~~ new anticancer therapy

All SAEs will be collected from the time the first dose of study treatment is administered until 90 days following cessation of treatment, or 45 days following cessation of study treatment if the subject initiates new anticancer therapy, whichever is earlier. ~~over the same time period as stated above for AEs.~~ In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment or GSK concomitant medication must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 7.3.1.6.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. At any time after 4530 days the investigator may report any AE that they believe possibly related to study treatment.

Reason for change: Update of the GSK safety standard language and adjustment based on Merck standard language.

59. Section 7.3.1.2.~~3 Sentinel Events~~ (Removal of Section)

~~A Sentinel Event is a GSK-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. The GSK Medical Monitor is accountable for reviewing all SAEs for possible Sentinel Events which is mandated at GSK. The GSK medical monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:~~

- ~~Acquired Long QT Syndrome~~
- ~~Agranulocytosis/Severe Neutropenia~~
- ~~Anaphylaxis & Anaphylactoid Reactions~~
- ~~Hepatotoxicity~~

- ~~Acute Renal Failure~~
- ~~Seizure~~
- ~~Stevens Johnson syndrome/Toxic epidermal necrosis~~

Reason for change: Removal of section due to update of GSK standard language.

60. Section 7.3.1.6. – Adverse Events of Special Interest

Adverse events of special interest (AESI) for GSK2857916 are corneal events, thrombocytopenia and infusion related reactions. The severity of all AESI will be graded utilizing the National Cancer Institute Common Toxicity Criteria for Adverse Events. Severity of GSK2857916 treatment related corneal events will also be graded using the GSK scale for corneal events provided in Table 16. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in Table 4.

For pembrolizumab, an overdose as defined in Section 6.10 that is not associated with clinical symptoms or abnormal laboratory results is an AESI.

Reason for change: Addition of section to clarify AEs of importance for GSK2857916 and pembrolizumab.

61. Section 7.3.2. – Pregnancy ~~Testing and Reporting~~

Do not collect pregnancy information for female subjects known to be pregnant during the screening phase or before exposure to study.

The need for a screening pregnancy test depends on whether a female subject is of childbearing potential or non-childbearing potential.

If a female subject is of childbearing potential, she must have a serum β-human chorionic gonadotropin (β –HCG) pregnancy test performed within 72~~14~~ hours~~days~~ prior to the first dose of study treatment. Subjects with positive pregnancy test result must be excluded from the study. Subjects with negative pregnancy test result must agree to use an effective contraception method as described below during the study until 120 days following the last dose of study treatment.

Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of study treatment and until approximately 120 days.

If a pregnancy is reported, the investigator must inform GSK within 24 hours of learning of the pregnancy and must follow the procedures outlined in Appendix 8.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure plus an additional 30 days and correspond with the time frame for female subject contraception in Section 5.1.

Reason for change: Update to the pregnancy language for GSK2857916.

62. New Section 7.3.5. – Ocular Examinations and Procedures

A full *baseline* ophthalmic examination for all subjects must include:

1. Best corrected visual acuity
2. Documentation of manifest refraction used to obtain best corrected visual acuity
3. Current glasses prescription (if applicable)
4. Pupillary light reflex
   Extraocular muscle movements (graded from one to four with (+) sign indicating over action, (-) sign indicating under action and 0 representing normal movements
5. Intraocular pressure measurement & time checked
6. Full anterior segment examination including fluorescein staining of the cornea:
   - Anterior segment exam (slit lamp) includes: orbit/lids/adnexa, conjunctiva, sclera, cornea, anterior chamber, iris, lens and anterior vitreous
7. Anterior segment photography of a fluorescein stained cornea
8. Dilated funduscopic exam: fundus photography with interpretation

The *on treatment* and *follow-up* ophthalmic exam must include everything except the dilated funduscopic/ fundus photography, anterior segment photography, and extraocular muscle movements (all of which must be performed as clinically indicated) and current glasses prescription (if applicable). The *last follow-up visit* should also include anterior segment photography of a fluorescein stained cornea. Representative images will be collected and stored centrally.

The *end of study treatment visit* ophthalmic exam should match the *baseline (screening)* exam.

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

Reason for change: Addition of detailed ocular examination wording to clarify requirements related to corneal event management.

63. Section 7.3.8. – Electrocardiogram

Triple 12-lead ~~electrocardiogram (~~ECGs~~)~~ will be obtained at designated time points specified in the Time and Events Table (Table 7, Table 8 and Table 10) during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and ~~corrected QT (~~QTc~~)~~ intervals. At each assessment, a 12-lead ECG will be performed by qualified personnel at the site after the subject has at least a 10~~5~~ minute rest.

For triplicate ECGs, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicate ECGs should be completed in 4 minutes or less.

The QT interval should be corrected for heart rate by Fridericia's formula (QTcF). Refer to Section 5.4.1.3 for QTc withdrawal criteria. ECGs will be collected and stored centrally. Refer to the ~~Study Procedures Manual (SPM~~SRM~~)~~ for details regarding ECG procedures.

Reason for change: Additional instructions added for ECG tracing and clarification of central collection.

64. Section 7.3.9~~.~~10. – Clinical Safety Laboratory Assessments

Table 11: Addition of bicarbonate as option for Total carbon dioxide, removal of CK-MB, removal of albumin from 24-hour urine protein; addition of spot urine (albumin / creatinine ratio) with relevant footnote, addition of Hepatitis B core antibody, removal of INR and PTT, removal of peripheral blood biomarker sample.

Reason for change: Revision of Table 11 due to changes in laboratory tests.

65. Section 7.3.~~12.~~13. – Visual Function Questionnaire

The NEI-VFQ-25 and OSDI will be administered to subjects in different regions based on the availability of translated versions.

Reason for change: Clarification that Visual Function questionnaires to be administered dependent on available translated versions.

66. Section 7.4. – Pharmacokinetics

7.4.1. – Blood Sample Collection for Pharmacokinetics

Blood samples for pharmacokinetic (PK) analysis of GSK2857916 (ADC and total monoclonal antibody[mAb]), cys-mcMMAF and pembrolizumab will be collected at the time points indicated in Time and Events Table (Table 9 and Table 10). The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. Samples for pembrolizumab will be collected and stored. Pembrolizumab PK samples will only be analysed if clinical observations warrant it (e.g. to rule out or confirm suspicion of DDI).

Blood samples ~~of approximately 4 mL~~ for pharmacokinetic (PK) analysis of GSK2857916 (ADC and total mAb~~antibody~~), cys-mcMMAF, and ~~along with a further 3 mL of blood sample~~ for potential PK analysis for pembrolizumab will be collected at the time points indicated in the Time and Events Tables (Table 9). Each PK sample should be collected as close as possible to the planned time relative to the dose (i.e., time zero)

administered to the subject on PK days. The actual date and time of each blood sample collection will be recorded.

Details on PK blood sample collection including blood volumes, processing, storage and shipping procedures are provided in the ~~Study Procedures Manual (SPM~~SRM).

7.4.2. – Pharmacokinetic Sample Analysis

Plasma analysis will be performed under the control of GSK Platform Technologies and Science-Bioanalysis Immunogenicity and Biomarkers (PTS-BIB) group, the details of which will be included in the SRM. Concentrations of GSK2857916 (ADC and total mAb~~antibody~~) and cys-mcMMAF will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM~~Study Procedures Manual~~).

Once the plasma has been analysed for GSK2857916 (ADC and total mAb~~antibody~~) any remaining plasma may be analysed for other compound-related metabolites and the results reported under a separate GSK PTS-BIB~~IVIVT~~ protocol.

If analysis is warranted, concentrations of pembrolizumab in serum will be performed under the control of Merck, the details of which will be included in the SRM~~Study Procedures Manual~~. Raw data will be archived at Merck's data repository, OpenLab (detailed in the SRM~~Study Procedures Manual~~).

Reason for change: Clarification that addition of cys-mcMMAF levels in these samples, update of abbreviations and clarification of BIB group name.

67. Section 7.5. – Biomarkers

7.5.1. – sBCMA Analysis

To measure any changes in the levels of soluble BCMA (sBCMA) during the study, ~~Target engagement with soluble BCMA will be assessed. S~~serum will be collected to measure concentrations of ~~free and GSK2857916 bound~~sBCMA at the time points specified in the Time and Events Tables (refer to Table ~~6~~9 and Table 10).

Old Section ~~7.5.2 Activated TBNK cells~~

~~Whole blood will be collected and analysed for % and absolute counts of monocytes, T, B and NK cells as well as the expression of activation markers CD107 and CD69 on these cell types. In addition, baseline measurements of peripheral blood mononuclear cells and cytokines/chemokines will help inform on subject immune status. The analysis may also be conducted on bone marrow aspirates at baseline and correlation between baseline immune status and clinical outcome assessed.~~

New Section 7.5.2 – Cytokine and Chemokine Analysis

Clusters of markers Cytokines ~~circulating~~ in the blood have been found to correlate with tumor pathway activation. A broad panel of cytokines/chemokines will be evaluated at ~~various timepoints~~cycle 1 as outlined in the Time and Events Table (refer to Table 9). ~~and correlated with clinical outcome to treatment with GSK2857916. In addition to measuring total cytokine levels in serum, activated lymphocytes and monocytes producing involved in the cytokine production will be determined via intracellular cytokine assay~~

New Section 7.5.3 – Subject Stratification/Predictive Biomarkers

This is an open-label and single-arm study, no subject stratification will be performed. BCMA exhibits varied expression across haematological malignancies and therefore, BCMA expression at baseline may be an important predictor of response to GSK2857916 in combination with pembrolizumab. Though majority of MM subjects express BCMA, the intensity of expression varies. To evaluate whether BCMA expression has utility in patient stratification, malignant plasma cells at baseline will be measured for BCMA expression by IHC ~~and/or flow cytometry~~ and ~~the expression~~ correlated with clinical outcome. Because BCMA can also be detected in circulation, the soluble form (sBCMA) has the potential to serve as a surrogate for cell surface BCMA marker. This study will correlate patient sBCMA levels with cell surface expression and clinical response ~~to support future validation of sBCMA as a patient selection marker, if data warrants~~.

Any B~~b~~lood and bone marrow samples ~~will be~~collected during this study ~~and~~may be used for the purposes of measuring novel biomarkers to identify factors that may influence advanced multiple myeloma, hematological malignancies and/or medically related conditions, as well as the biological and clinical responses to GSK2857916 in combination with pembrolizumab. If relevant, this approach may be extended to include the identification of biomarkers associated with AEs

These analyses may include but not be limited to:

- Tumor/~~plasma cell~~bone marrow BCMA receptor expression by ~~flow and/or~~ IHC.
- Soluble factors, including circulating cfDNA analysis ~~of tumor tissue~~ and ~~plasma and~~ cytokine/chemokine analysis of ~~plasma~~ serum
- Additional soluble measurements to include serum levels of ~~free~~sBCMA
- ~~Activated peripheral blood mononuclear cell (PBMC) count analysis of whole blood and intracellular cytokine assessment~~
- RNA/DNA/gene and protein analysis of tumor tissue/bone marrow aspirate samples

New Section 7.5.4 – Tumor Biomarker Analysis

~~In order to~~To further characterize the subject population, biomarkers (e.g. expression of genes and proteins) related to the activity of the investigational compound ~~will~~may be assessed in malignant cells.

BCMA expression in the plasma cells of bone marrow aspirates or treph~~f~~ines will be evaluated at baseline by IHC ~~and/or flow cytometry for plasma~~for tumor cell expression

of ~~free~~BCMA~~receptors~~. Analysis of the immune context (immune cell characterization) of the bone marrow aspirate samples may also be performed to analyse the tumor microenvironment. ~~IHC and flow cytometry markers may include but not be limited to: BCMA, Blimp1, CD138, and CD38.~~ Additional bone marrow aspirate samples may be taken during the treatment period for biomarker research. All ~~Additionally,~~ bone marrow ~~tumor tissue or~~ aspirate samples collected may be evaluated for ~~any DNA /RNA changes~~ additional DNA/RNA/Protein biomarker analyses. ~~correlating with response~~

New Section 7.5.5 – Circulating Cell Free DNA (cfDNA) Analysis

~~Additionally, bone marrow tumor tissue may be evaluated for any DNA/RNA changes correlating with response.~~ Tumor specific circulating nucleic acid (cfDNA) levels detected in plasma or serum have been found to correlate with increasing tumor burden and decline following therapy. ~~Futhermore,~~ cfDNA in cancer subjects can harbour many genetic alterations (mutations, microsatellite alterations, aberrant methylation), which are generally consistent with the tumor. ~~Thus, t~~Tumor-specific circulating cfDNA has the potential to be a useful biomarker of therapeutic response as well as offering a less invasive blood based technique for identifying and selecting subjects for certain treatments. Given ~~the promise of cfDNA blood based test for subject selection,~~this promise, cfDNA~~this test~~ will be explored to determine whether mutations in cfDNA ~~correlate with that in the tumor tissue from which it is derived~~can be identified. This test will also be explored to correlate increasing cfDNA levels with increasing tumour burden.

Reason for change: Revisions of Biomarker section including removal of the TBNK section, removal of peripheral blood sample and other updates.

68. Section 7.7. – Value Evidence and Outcome

Three Health-Related Quality-of-Life (HRQoL) assessments will be performed in this study. More details about all patient questionnaires can be found in the SRM. The following assessments will be administered to subjects in different regions based on the availability of translated versions.

Section 7.7.1 - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module (EORTC QLQ-C30) ~~MD Anderson Symptom Inventory – Multiple Myeloma (MDASI-MM) Module~~

The EORTC QLQ-C30 is a 30-item questionnaire containing both single- and multi-item measures [Aaronson, 1993]. These include five functional scales (Physical, Role, Cognitive, Emotional, and Social Functioning), three symptom scales (Fatigue, Pain, and Nausea/Vomiting), a Global Health Status/QoL scale, and six single items (Constipation, Diarrhea, Insomnia, Dyspnea, Appetite Loss, and Financial Difficulties). Scores for each scale and single-item measure are averaged and transformed linearly to a score ranging from 0–100. A high score for functional scales and for Global Health Status/QoL represent better functioning ability or HRQoL, whereas a high score for symptom scales and single items represents significant symptomatology [Proskorovsky, 2014].

~~The symptoms related to multiple myeloma and its treatment, and the impact of these symptoms on daily functioning will be assessed using the MD Anderson Symptom Inventory – Multiple Myeloma (MDASI-MM) module. The MDASI is a reliable, valid *instrument that was designed for ease of administration and that asks patients to rate 13* symptoms (known as the "core" items) and 6 symptom-related interference items that are common across cancer types and treatments [Cleeland, 2000]. The MDASI is comprehensive yet brief, thus minimizing patient burden, and has a readily understood numeric scale that can be adapted for telephone, electronic, or other digital forms of administration. The developers of the original MDASI recognized that particular cancer types or treatments may require the addition of specific symptom items to the MDASI to ensure a comprehensive symptom assessment [Gning, 2009]. These MDASI "modules" include the original MDASI's 13 core symptom and interference items augmented by additional symptom items specific to certain cancers or treatments. MDASI modules have been developed and validated for patients with a variety of cancers [Gning, 2009; Armstrong, 2006; Mendoza, 2011; Rosenthal, 2007].~~

~~MD Anderson Symptom Inventory (MDASI) modules augment the 19 core MDASI symptom and interference items with additional items identified as unique to a particular patient population. MDASI modules may be disease-specific, disease-site-specific, or treatment-specific. The multiple myeloma module of the MDASI (MDASI-MM) is a site-specific module. Along with the core MDASI's 13 symptom items and 6 interference items, the MDASI-MM also assesses 7 symptoms specific to multiple myeloma [Jones, 2013]~~

~~Patients rate symptoms on a 0–10 scale ranging from "not present" to "as bad as you can imagine." Interference is rated on a 0–10 scale ranging from "did not interfere" to "interfered completely". MDASI-MM ratings can be used to derive 3 subscale scores: mean core (13 MDASI core symptom items), mean severity (13 MDASI core plus 7 MM-specific items), and mean interference (6 interference items). The interference items can be subdivided into mean activity-related (interference with work, general activity, and walking ability (WAW)) and mean mood-related (interference with relations with people, enjoyment of life, and mood (REM)) dimensions. Symptom severity can be classified as 0 CCI , 1–4 CCI , 5–6 CCI , or 7–10 CCI .~~

~~Upon availability of eDiary, subjects enrolled in Part 2 only will self-complete the MDASI-MM module at the following times:~~

- ~~Prior to dosing on Day 1 for Cycle 1–9~~
- ~~Prior to dosing on Day 1 of Cycles 12, 15, 18, 21, 24, 27 and 30~~
- ~~End/ Discontinuation Study Treatment visit~~

New Section 7.7.2 - <u>European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma module (EORTC QLQ-MY20)</u>

<u>The EORTC QLQ-MY20 is a supplement to the QLQ-C30 instrument used in patients with multiple myeloma [Aaronson, 1993; Cocks, 2007]. The module comprises 20 questions that address four myeloma-specific HRQoL domains: Disease Symptoms, Side</u>

Effects of Treatment, Future Perspective, and Body Image. Three of the four QLQ-MY20 domains are multi-item scales: Disease Symptoms (includes bone aches or pain, back pain, hip pain, arm or shoulder pain, chest pain, and pain increasing with activity); Side Effects of Treatment (includes drowsiness, thirst, feeling ill, dry mouth, hair loss, upset by hair loss, tingling hands or feet, restlessness/agitation, acid indigestion/heartburn, and burning or sore eyes); and Future Perspective (includes worry about death and health in the future, and thinking about illness). The Body Image scale is a single-item scale that addresses physical attractiveness. As with the QLQ-C30, QLQ-MY20 domain scores are averaged and transformed linearly to a score ranging from 0–100. A high score for Disease Symptoms and Side Effects of Treatment represents a high level of symptomatology or problems, whereas a high score for Future Perspective and Body Image represents better outcomes [Proskorovsky, 2014].

Reason for change: Change in questionnaire from MDASI-MM to EORTC-QLQ-C30 and EORTC-QLQ-MY20.

69. Section 9.1.2. – Part 2: Expansion cohort

The primary goal of Part 2 is to characterize clinical activity of the combination and to detect if meaningful response rate (ORR) can be achieved. Based on historical information [Lokhorst, 2015] and clinical judgement, the null hypothesis has been defined as ORR ≤40%~~for the purpose of this study~~. The alternative hypothesis has been defined as ORR ≥60% based on clinically meaningful improvement of 20%. ~~A test will be performed using the stopping rules provided in Section 9.5.2. Descriptive statistics will be used to describe the observed ORRs in the expanded cohorts.~~

In Part 2, treatment-related Grade 4 or higher AEs will be continuously monitored starting from when 5 participants are dosed. Based on the 11% Grade 4 or higher AEs observed in the FTIH study (BMA117159), it is considered that the combination treatment has unacceptable toxicity if observed treatment-related Grade 4 or higher AEs is significantly higher than 12% at 1-sided alpha of 0.025.

Reason for change: Clarified that the increase of alternative hypothesis relates to clinical improvement and addition of FDA requested stopping criteria for Part 2.

70. Section 9.2. – Sample Size Considerations

Part 1: Dose-Escalation Phase

The total number of subjects to be enrolled into Part 1 will depend on the number of subjects needed to characterize individual dose cohorts. The sample size is not driven by statistical considerations. However, based on assumptions that 2~~3~~ different dose levels will be tested (up to 6 subjects per dose level) it is anticipated that up to 12~~18~~ evaluable subjects will be enrolled in Part 1.

Part 2: Expansion Cohort

Sample size for Part 2 is estimated based on hypothesis specified in Section 9.1.2 using the Predictive Probability design [Lee, 2008]. Details of sample size calculation are provided in Appendix 12. The optimal design has Nmax = 28, type I error rate of 0.10 and power of 80.6%. The expansion cohort may be stopped early for futility if the predicted probability of success is less than 1.5%. If the true ORR is 40%, the expected sample size is 20 and the probability of early termination is 86.1%; if the true ORR is 60%, the expected sample size is 28 and the probability of early termination is 15.6%.

~~Once the RP2 dose is established, at least 13 and up to 30 subjects in total will be enrolled into the Part 2 of the study. The enrollment may be stopped according to the decision rules defined in Table 12. The sample size and stopping rules are based on the methodology of Lee et al. [Lee, 2008]. The assumptions underlining the design are detailed below:~~
~~The null hypothesis is: H_0: ORR≤40%~~
~~The alternative hypothesis is: H_A: ORR≥60%~~
~~Overall response (ORR) will be defined as sCR+CR+VGPR+PR per standard evaluation criteria for definition of response assessments and criteria.~~

~~For expansion cohort, starting with 13 subjects and allowing for a maximum sample size of 30, this design will have a type I error rate α of 0.092 and 80.9% power when the true response rate is 60%. The trial is not designed to stop early for efficacy, but is designed to stop early for futility if the predictive probability of success is 3.0% or less. The type I error rate, power, and predictive probability of success to stop early for futility were derived from explicitly stating the minimum and maximum sample size, futility stopping rate and selection of the optimizing criterion as the maximization of the power under the alternative hypothesis. The Bayesian prior used in determining the design was Beta (0.04, 0.06), a distribution with a mean response rate of 40%. Under the null hypothesis, if the true response rate is 40%, the expected sample size of the design is 20 subjects and probability of early termination (PET) is 87.4%. Under the alternative hypothesis, if the true response rate is 60%, the expected sample size of the design is 29 subjects in the expansion cohort and PET is 15.7%.~~

Reason for change: Based on FDA comment, removed original starting dose; section revised due to sample size adjustment and corresponding calculations.

71. Section 9.4.1. – Analysis Populations

All Evaluable Subjects Population: This is the population used for decision-making at the futility analysis during part 2 (Expansion Cohort). This will be the population for Bayesian predictive adaptive design as defined in Section 9.5.2 and summaries of response if data warrant. <u>In general, subjects are evaluable if they have received at least 1 dose of treatment for both drugs and the time from the first dose to the time of data cut-off is more than 66 days, i.e., reached the time of three planned disease assessments. Details on deriving the evaluable population will be provided in the RAP.</u> ~~Subjects are considered evaluable if they are in the all treated population, have received at least 2 doses of treatment, and have had at least one disease assessment post 2nd dose. Subjects~~

~~are also considered evaluable if they are in the all treated population and have progressed or died or have permanently discontinued from the study treatment~~

Reason for change: Revised definition to allow flexibility based on possible delays with dosing based on FTIH experience.

72. Section 9.5 – Interim Analysis

Section 9.5.1. – Part 1: Dose Escalation

During dose escalation, no formal interim analysis will be performed. Data will be reviewed through data visualization tool to inform dose escalation decisions. The mTPI design will be utilized to guide dose escalation/de-escalation decisions. More details of the dose escalation procedure are described in Section 4.2.3.1.

After the last cohort of subjects in Part 1 complete the DLT observation period, a formal interim analysis will be performed to support the RP2D decision, except for scenarios where RP2D is clearly defined by the toxicity profile. Data considered to support RP2D decision will include but not limited to safety, available PK profile and observed signs of clinical activity. Details of the interim analysis will be provided in the RAP.

~~While no formal interim analysis is planned for Part 1, safety data will be examined on an ongoing basis to support dose escalation decisions. Prior to determining the GSK2857916 dose in combination with 200 mg pembrolizumab for the next cohort, analysis of safety data from previous dose cohort will be performed. The anlaysis will be performed after at least 3 evaluable subjects have been studied per dose level. To facilitate dose escalation/de-escalation decisions, a Bayesian logistic regression model (BLRM) may be utilized to predict the probability of DLT at the dose levels to be tested. Specifically, a BLRM for combination treatment will be fitted on the dose limiting toxicity data (i.e., absence or presence of DLT) accumulated throughout the dose escalation to model the dose-toxicity relationship of GSK2857916 in combination with pembrolizumab. The BLRM analysis will be performed to determine if a next dose level is expected to be safe and to support the dose escalation decision following the completion of each dose cohort. Further details regarding such analyses including prior specifications will be provided in the Reporting and Analysis Plan (RAP).~~

Section 9.5.2. – Part 2: Expansion

Continuous safety monitoring will be conducted for the expansion cohort starting from when 5 subjects are dosed. The observed number of treatment-related Grade 4 or higher AEs will be compared against the safety stopping rule in Table 12. Enrollment may stop if the safety stopping rule is met based on totality of safety data. For example, if there are 3 events out of 5 dosed subjects, enrollment may stop after review of all safety data, if there is 2 or fewer events out of 5 dosed subjects, enrollment will continue. Operating characteristics for the safety stopping rule are provided in Appendix 11.

Table 12 Safety Stopping Rules for the Expansion Cohort

Number of dosed subjects		Stop if treatment related Grade 4 or higher AEs larger or equal to this number
5		3
6-10		4
11-14		5
15-19		6
20-25		7
26-28		8

~~A Bayesian predictive adaptive design [Lee, 2008] as described in Section 9.2.2 that allows the trial to be monitored more frequently at multiple stages will be used.~~

~~For the expansion cohort, based on the size of expansion cohort and on anticipated enrollment pace, it is considered that a single futility analysis is practical and sufficient once approximately 15 subjects in Part 2 are evaluable for futility analysis. The number of best unconfirmed overall responses (PR+VGPR+CR+sCR) observed for the All Evaluable Subjects Population will be compared with the stopping rules provided in Table 13. Additional futility looks maybe performed, if necessary. These rules are intended as a guideline only. Actual decisions will depend on the totality of the data, in particular, the depth and duration of response will also be taken into account before declaring futility. Should the recommendation to stop for futility be disregarded in favor of a decision to continue the trial based on the totality of the data, the overall type I error rate of the expansion phase will be inflated. When the total sample size reaches 30 and 16 responders are observed, with the assumed beta prior distribution as described in Section 9.2.2., the posterior probability of ORR>40% is 92.9%.~~

Interim analyses for ORR will start when at least 10 subjects are evaluable as defined in Section 9.4.1. Subjects who initially received RP2D in Part 1 may also be included. The observed number of subjects with unconfirmed response of PR or better will be compared with the stopping boundary in Table 13. Enrolment may stop if the stopping rule is met. Final decision will be based on the totality of data. For example, if there are 2 unconfirmed responses out of 10 evaluable subjects, enrolment may stop after review of all available data; if there are 3 or more unconfirmed responses out of 10 evaluable subjects, enrolment will continue.

Table 12 updated to Table 13 due to inclusion of Table 12. Table 13 was updated with revised numbers for Decision Making Criteria for Futility Analysis based on the updated subject total.

Reason for change: Replaced BLRM with mTPI model for Dose Escalation part. Added safety monitoring criteria based on rate of Grade 4 treatment related AEs due to FDA request to add stopping criteria. Updated Part 2 Table 13 futility wording due to change in subject number.

73. Section 9.6 – Final Analysis

Final analysis of the data captured in Part 1 and Part 2 will be undertaken at the end of the study (Section 5.5.2). ~~after all subjects meet at least one of the following criteria: have received all prespecified treatment (32 cycles) or has progressed; or has died; or has been permanently withdrawn from the study.~~ Data from the two parts may be combined for some analyses at the end of the trial, as appropriate.

Reason for change: Revised criteria for end of study analysis.

74. Section 9.7.1. – Clinical Activity Analyses

The primary endpoint ORR and other applicable secondary endpoints (e.g., CBR, DoR, TTR, TTP, PFS) will be based on the responses assessed by the investigator.

At futility interim, the primary endpoint (ORR) will be analyzed based on the All Evaluable population. Otherwise, all efficacy endpoints will be analyzed based on the All Treated population unless otherwise specified.

The analytical methods planned for each endpoint are described in Table 14.

Table 14 Statistical Analysis Methods for Clinical Activity Endpoints (Part 2)

Endpoint	Statistical Analysis Methods
Primary	Overall Response Rate (ORR) is defined as the percentage of subjects with a confirmed PR or better (i.e. PR, VGPR, CR and sCR), according to the International Myeloma Working Group (IMWG) Response Criteria). The number and percentage of subjects in the following response categories will be presented: sCR, CR, VGPR, PR, overall response (sCR+CR+VGPR+PR), minimal response (MR), stable disease (SD), progressive disease (PD), and not evaluable (NE). The corresponding 95% CI for ORR will also be provided. Subjects with unknown or missing responses will be treated as non-responders, i.e., these subjects will be included in the denominator when calculating percentages of response.
Secondary	Secondary clinical activity endpoints of Part 2 of this study are CBR, DoR, TTR, PFS, TTP and MRD Negative Rate. **Clinical benefit rate (CBR),** defined as the percentage of participants with a confirmed minimal response (MR) or better per IMWG **Duration of response (DoR)** is defined as the time from first documented evidence of PR or better until disease progression (PD) per IMWG, or death due to PD among subjects who achieve an overall response (i.e. confirmed PR or VGPR or

	CR or sCR). Responders without disease progression will be censored at the censoring time point for TTP. **Time to response (TTR)** is defined as the time between the date of first dose and the first documented evidence of response (PR or better) for subjects who achieve an overall response (i.e. confirmed PR or VGPR or CR or sCR). **Time to best response,** defined as the time between the date of first dose and the first best documented response (PR or better) for subjects who achieve an overall response (i.e. confirmed PR or VGPR or CR or sCR). **Progression-free survival (PFS)** is defined as the time from first dose until the earliest date of disease progression (PD) per IMWG, or death due to any cause. Determination of dates of PFS event and dates for censoring will be described in the RAP. **Time to disease progression (TTP)** is defined as the time from first dose until the earliest date of PD per IMWG, or death due to PD. Determination of dates of TTP event and dates for censoring will be described in the RAP. For all the TTE endpoints described above, median TTE with 95% CI will be estimated employing the Kaplan-Meier method. A Kaplan-Meier survival curve will be generated. The number and percentage of subjects who had the event or were censored will also be reported. In addition, PFS rate with 95% CI at 6, 12 and 18 months will be estimated using Kaplan-Meier methods for the PFS endpoint. **OS** is defined as the time from first dose until death due to any cause. Subjects who withdraw consent from the study or are lost to follow-up will be censored at the time of withdrawal or lost to follow-up. Subjects who are still alive at the clinical cut-off date for the analysis will be censored at the last known alive date or last contact date. The last contact date will be determined by the maximum collection/assessment date from among selected data domains within the clinical database. Survival rate 12, 18 and 24 months will be reported from Kaplan-Meier analysis as data permits.

~~All subjects who have received study treatment will be evaluated for response according to their originally assigned cohort. The overall response rate (ORR) is defined as the percentage of subjects with confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR) at any time as per disease-specific criteria.~~

~~Subjects with unknown or missing response will be treated as non-responders, i.e. these subjects will be included in the denominator when calculating the percentage. The number and types of responses, as outlined in International Myeloma Working Group Uniform Response Criteria, will be listed and summarized separately, as appropriate.~~

~~The ORR will be reported at futility and at the time of final analyses. The estimates along with 95% exact confidence interval (CI) will be provided.~~

~~The clinical Benefit Rate (CBR) is defined as the percentage of subjects with confirmed sCR, CR, VGPR, PR and minimal response (MR) at any time as per disease specific~~

~~criteria. CBR will be reported at futility and at the time of final analyses. The estimates along with 95% exact confidence interval (CI) will be provided.~~

~~**Duration of response (DOR)** is defined as time from the first documented evidence of response until the first documented sign of disease progression or death for the subset of subjects who achieve a response (sCR, CR, VGPR, PR). Duration of response will be summarized descriptively, if data warrant, using Kaplan-Meier medians and quartiles. Details on rules for censoring will be provided in the RAP.~~

~~For the analysis of **Progression-free survival (PFS)**, PFS Duration is defined from start of the treatment to disease progression or death (due to any cause), whichever comes first. Further details on rules for censoring will be provided in the RAP. PFS will be summarized by dose using Kaplan-Meier quantile estimates along with 2-sided 95% CIs at the time of final analysis, if data warrant.~~

~~For the analysis of **overall survival (OS)**, the last date of known contact will be used for those subjects who have not died at the time of analysis; such subjects will be considered censored. Further details on rules for censoring will be provided in the RAP. OS will be summarized by dose using Kaplan-Meier quantile estimates along with 2-sided 95% CIs at the time of final analysis, if data warrant.~~

Reason for change: Revision of wording for clinical activity endpoints, clarification of ORR and clarification of included population.

75. Section 9.7.2.2. – Adverse Events

Adverse events (AEs) will be coded using the standard MedDRA and grouped by system organ class. Adverse events (AEs) will be graded by the investigator according to the National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), (version 4.03, [NCI, 2010]). <u>In addition, for GSK2857916 treatment related corneal events, the GSK grading scale for corneal events (Appendix 9) should be used.</u>

Characteristics (e.g. number of occurrences, action taken, grade, etc) of the following AEs of special interest will be summarized separately:

- <u>Corneal events</u>
- <u>Thrombocytopenia</u>
- <u>Infusion related reactions</u>

Reason for change: Addition of specific wording related to corneal events and inclusion of AEs which were unintentionally omitted in previous version.

76. Section 9.7.3. – Pharmacokinetic Analyses

9.7.3.1. – ~~Raw~~Concentrations~~ Time Data~~

Linear and semi-logarithmic individual concentration-time profiles and mean and median profiles (when applicable) by GSK2857916 dose will be plotted for GSK2857916 (ADC~~intact~~ and total mAb), cys-mcMMAF, and for pembrolizumab (if tested) in Part 1.

Concentrations of GSK2857916 (ADC~~intact~~ and total mAb), cys-mcMMAF, and pembrolizumab (if tested) will be listed for each subject and summarized (when appropriate) by planned time point and dose cohort in Part 1 and Part 2.

Derived Pharmacokinetic Parameters

Pharmacokinetic analysis will be the responsibility of the CPMS Department, QSci, GSK.

For Cycle 1,~~In Part 1 of the study,~~ GSK2857916 and pembrolizumab (if measured) concentration-time data will be analyzed by standard non-compartmental methods, if data permit~~using WinNonlin~~. Calculations will be based on the actual sampling times recorded during the study. From the concentration-time data, the following GSK2857916 (ADC~~intact~~ and total mAb), cys-mcMMAF, and pembrolizumab (if measured) PK parameters will be determined as data permit, for each dose of GSK2857916 or for pembrolizumab (if measured) and for each subject: ~~In part 1 cycle 1:~~ area under the concentration-time curve (AUC(0-t), AUC (0-tau) and/or AUC(0-∞)), maximum observed concentration (Cmax), time to Cmax (tmax), last time point where the concentration is above the limit of quantification (tlast), terminal phase elimination rate constant (λz) and terminal phase half-life (t½). In subsequent cycles (when measured): ~~as well as in part 2:~~ concentration at trough (Ctrough) and end of infusion concentration will be summarized.

Pharmacokinetic~~K~~ parameters will be listed and summarized descriptively (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, CV% and 95% confidence interval of log-transformed parameters) by dose cohort in Part 1 and Part 2.

GSK2857916 data from this study may be combined with data from other studies and analyzed using population pharmacokinetic methods. A nonlinear mixed effects model will be used to determine population pharmacokinetic parameters (clearances, CL and volumes of distribution, V) and identify important covariates (e.g., age, weight, or disease-related covariates). Summary exposure measures (e.g., Cmax, AUC) will also be computed. Results of this analysis may be provided in a separate report.

GSK2857916 pharmacokinetic results~~PK profile~~ will be assessed versus the expected profile based on previous~~the~~ data ~~from the FTIH study BMA117159~~ to evaluate the potential impact of pembrolizumab on GSK2857916 pharmacokinetics~~PK~~.

Reason for change: Clarification of analytes measured and addition of wording that multi-study analyses may occur.

77. Section 9.7.4.2. – Genetic Analyses

Cell surface BCMA and sBCMA pre dosing will be quantified as a potential predictive biomarker for clinical activity. Post dosing~~free surface BCMA and BCMA drug~~ sBCMA~~complex~~ will be quantified to assess dynamics during treatment~~proportion of target engagement~~.

~~Measurements of sBCMA will include separate assays for free sBCMA and sBCMA complexed with drug~~.

Reason for change: Update of wording based removal of separate assays.

78. Section 9.7.6. – Immunogenicity Assessment

For each subject, the results and titers of anti-GSK2857916 binding antibodies will be listed for each assessment time point with time-matched GSK2857916 plasma concentration. The frequency and percentage of subjects with positive and negative results will be summarized for each assessment time and overall for each subject by dose cohort. The detailed information will be included in the RAP.

Reason for change: Clarification of wording to clarify relationship of ADA and plamsa concentrations.

79. Section 10.9. – Review Committees

Section 10.9.1 – Internal Safety Review Committee

An Internal Safety Review Committee (iSRC) will be utilized in this study and comprise individuals who are not members of the clinical study team. The iSRC are positioned to offer an internal, independent review of safety data to protect the interests of subjects and ensure their safety. All efforts will be made to maintain the study integrity and validity of study data. The schedule of planned reviews of safety data and the analysis plan for iSRC review is described in the iSRC Charter, which is available upon request.

Reason for change: Inclusion of internal safety review committee as additional safety component.

80. Section 12.5. – Appendix 5: Liver chemistry stopping and monitoring criteria and required actions and follow up assessments

Section 12.5.1. – Liver Chemistry stopping criteria

Summary of changes include revision of liver chemistry criteria to specific GSK Phase I/II template information. Previously stopping criteria as specific to ALT-absolute of ALT ≥3xULN and specific SAE criteria. Revised stopping criteria include the following: ALT ≥5xULN, ALT increase of ALT ≥3xULN for ≥4 weeks, Bilirubin related to ALT with ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin), INR related to ALT with ALT ≥3xULN **and** INR >1.5, if INR measured, if ALT ≥3xULN and subject cannot be

monitored weekly for 4 weeks, and if ALT ≥3xULN is associated with symptoms believed to be related to liver injury or hypersensitivity. Guidance and instructions related to monitoring and follow-up have been updated.

Reason for change: Revision of section to include required Phase I/II wording per GSK template.

81. ~~Section 12.6. Appendix 6 P-gp Inhibitors~~

Removal of Appendix.

Reason for change: To ensure that the list of P-gp inhibitors is as current as possible without requiring a protocol amendment, the SRM is instead referenced in the protocol.

82. ~~Section 12.7. Appendix 7 International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma~~

Removal of Appendix.

Reason for change: To ensure that the updated criteria are being utilized as written, have referred to appropriate reference for 2016 IMWG criteria throughout the document.

83. Section 12.8.~~10~~ – Appendix 8~~10~~: Contraceptive Guidance and Collection of Pregnancy Information Definitions ~~Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information~~

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in

women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

a.	**CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
b.	**Highly Effective Methods[b] That Have Low User Dependency**
c.	Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
d.	Intrauterine device (IUD)
e.	Intrauterine hormone-releasing system (IUS)[c]
f.	Bilateral tubal occlusion
g.	Vasectomized partner
h.	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.
i.	**Highly Effective Methods[b] That Are User Dependent**
j.	Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
k.	oral
l.	intravaginal
m.	transdermal
n.	injectable
o.	Progestogen-only hormone contraception associated with inhibition of ovulation[c]
p.	oral
q.	injectable
r.	Sexual abstinence
s.	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 amenorrhoea 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)

Collection of Pregnancy Information

Male subjects 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 subjects 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 Subjects 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 resonas 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 subjects, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will discontinue study intervention.

~~12.10.1 Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)~~

~~The following is the all inclusive list of the highly effective methods for avoiding pregnancy that meets the definition specified in GSK SOP_54811 (i.e., have a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in~~

~~accordance with the product label). Therefore, this list is used to comply with GSK SOP_54811.~~

~~The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.~~

~~Contraceptive subdermal implant~~

~~Intrauterine device or intrauterine system~~

~~Combined estrogen and progestogen oral contraceptive [Hatcher, 2011])~~

~~Injectable progestogen [Hatcher, 2011]~~

~~Contraceptive vaginal ring [Hatcher, 2011]~~

~~Percutaneous contraceptive patches [Hatcher, 2011]~~

~~Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.~~

~~These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.~~

~~12.10.2 Contraceptive requirements for male subjects with female partners of reproductive potential (when applicable)~~

~~Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until [at least five half-lives of study medication OR for a cycle of spermatogenesis following five terminal half-lives] after the last dose of study medication.~~

~~Vasectomy with documentation of azoospermia. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview.~~

~~Male condom plus partner use of one of the contraceptive options below that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label:~~

~~Contraceptive subdermal implant~~

~~Intrauterine device or intrauterine system~~

~~Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]~~

~~Injectable progestogen [Hatcher, 2011]~~

~~Contraceptive vaginal ring [Hatcher, 2011]~~

~~Percutaneous contraceptive patches [Hatcher, 2011]~~

~~These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.~~

~~12.10.3 Collection of Pregnancy Information~~

~~Investigator will collect pregnancy information on any female subject, 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 subject's pregnancy.~~

~~Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on mother and infant, 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 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 treatment by the investigator, will be reported to GSK as described in Appendix 8. 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 subject who becomes pregnant while participating~~

~~will be withdrawn from the study~~

Reason for change: Revisions to the GSK standard language.

84. Section 12.9.~~11~~ – Appendix ~~9~~11: GSK2857916 associated Corneal Event Severity Grading and Mitigation Strategy ~~MITIGATION STRATEGIES FOR FOR CORNEAL TOXICITY~~

In order to minimize the corneal toxicity, subjects must receive steroid eye drops as prophylaxis (such as: prednisolone phosphate 1%, or dexamethasone 0.1%) 1 drop QID starting 1 day prior to each GSK2857916 infusion, and continuing for a total of consecutive 7 days. Other equivalent eye drops may be considered after confirming with GSK. Omission or discontinuation of prophylactic steroid eye drops may be allowed under certain circumstances (e.g., in the setting of intolerability, contraindication, or toxicity secondary to steroid eye drops) upon discussion with the Medical Monitor.

Prophylactic preservative-free artificial tears should be administered in each eye at least 4-8 times daily, beginning on Cycle 1 Day 1 until the End of Treatment (EOT). Allow at least 5-10 minutes between administration of artificial tears and steroid eye drops. 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.

While not yet clinically demonstrated, it is theoretically possible that the application of a cooling eye mask during GSK2857916 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 participant and the investigator, the following may be considered:

- Beginning with the start of each GSK2857916 infusion, subjects may apply cooling eye masks to their eyes for approximately 1 hour or as much as tolerated.
- Subjects 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.

Subjects must avoid the use of contact lenses during the study.

An ophthalmology (or optometrist, if an ophthalmologist is not available) consult is required for all subjects who develop signs or symptoms of corneal toxicity or require steroid eye drops for more than 7 days.

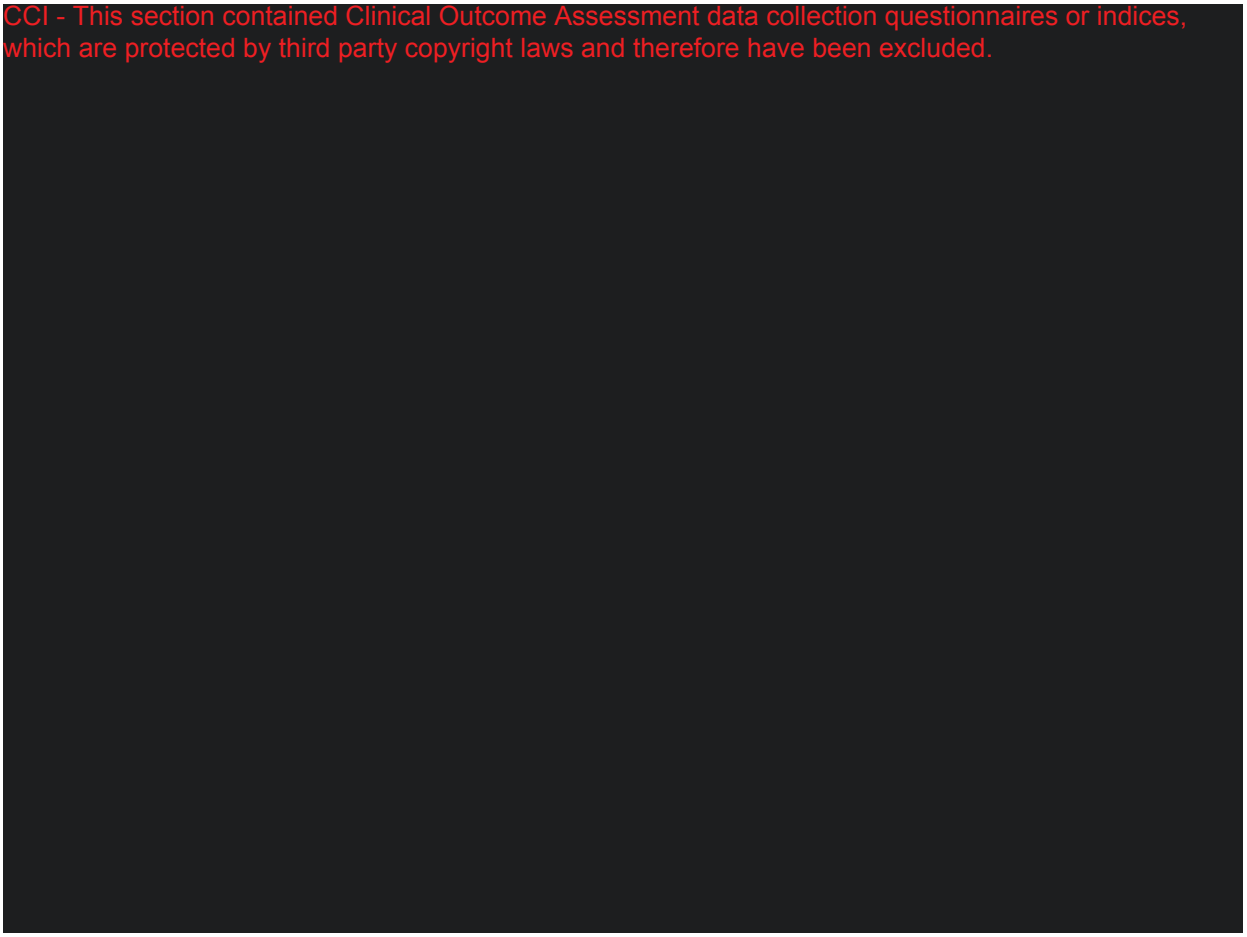
A summary of prophylactic interventions for corneal toxicity associated with GSK2857916 is provided in Table 15. Corneal toxicity must be graded according to the guidelines provided in Table 16. Additional guidance on grading visual acuity changes provided in Table 17.

Table 15 Prophylactic measures for corneal Events associated with GSK2857916

Prophylactic Measure[a]	Dose and Administration	Timing
Steroid eye drops[b]	Prednisolone phosphate 1%, or dexamethasone 0.1%, or equivalent, 1 drop QID	Begin 1 day prior to each dose of GSK2857916 infusion, and continuing for a total of consecutive 7 days
Preservative-free artificial tears	Administer in each eye at least 4-8 times daily	Administer daily beginning on Cycle 1 Day 1 until EOT. Allow 5-10 minutes between administration of artificial tears and steroid eye drops
Cooling eye mask	May apply cooling eye mask to both eyes for approximately 1 hour or as much as tolerated	During GSK2857916 infusion administration in the first hour for up to 4 hours, as tolerated

a. Dose modifications and treatment for ocular toxicities are discussed in Section 6.5.
b. Omission or discontinuation of prophylactic steroid eye drops may be allowed under certain circumstances (e.g., in the setting of intolerability, contraindication, or toxicity secondary to steroid eye drops) upon discussion with the Medical Monitor.

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

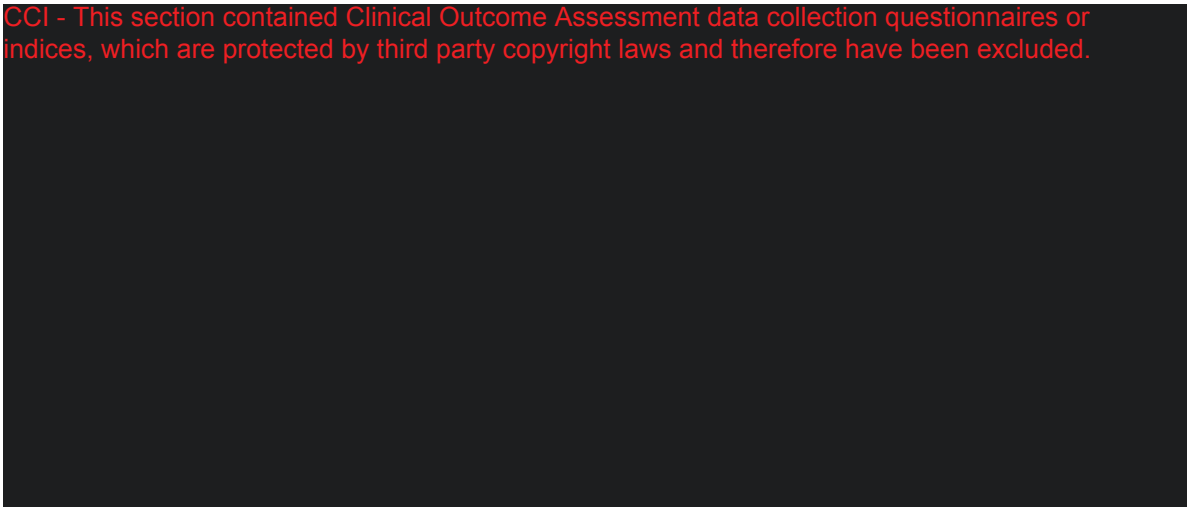
~~Corneal toxicity should be graded according to the guidelines provided in 10.~~
~~In order to minimize the corneal toxicity, subjects should receive steroid eye drops as prophylaxis (such as: prednisolone phosphate 1%, or dexamethasone 0.1%) 1 drop QID starting 1 day prior to each GSK2857916 infusion, and continuing for a total of consecutive 7 days. Other equivalent eye drops may be considered after confirming with GSK. Omission or discontinuation of prophylactic steroid eye drops may be allowed under certain circumstances (e.g., in the setting of intolerability, contraindication, or toxicity secondary to steroid eye drops) upon discussion with the medical monitor.~~
~~Prophylactic preservative-free artificial tears should be administered twice daily, at least one drop in each eye, beginning on Cycle 1 Day 1 until EOT. Allow at least 5-10 minutes between administration of artificial tears and steroid eye drops. In the event of ocular symptoms (i.e., dry eyes), the use of artificial tears may be increased up to every 2 hours as needed.~~
~~While not yet clinically demonstrated, it is theoretically possible that the application of a cooling eye mask during GSK2857916 administration, and in the first few hours after infusion may subsequently decrease ocular side effects. On the day of infusion, the following are recommended:~~
~~Beginning with the start of each GSK2857916 infusion, it is recommended that patients apply cooling eye masks to their eyes for approximately 1 hour or as much as tolerated by the patient. Patients are encouraged to 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.~~
~~Patients should avoid the use of contact lenses during the study.~~
~~An ophthalmology consult should be considered for all subjects who develop signs or symptoms of corneal toxicity. Treatment guidelines are provided in Section 6.5.1.~~
~~A summary of prophylactic interventions for corneal toxicity associated with GSK2857916 is provided in 9.~~

~~A grading scale is provided in 10 and an associated visual acuity scale is provided in 11.~~

~~Table 9 Prophylactic measures for corneal toxicity associated with GSK2857916[a]~~

~~Prophylactic Measure~~	~~Dose **and Administration**~~	~~Timing~~
~~Steroid eye drops[b]~~	~~Prednisolone phosphate 1%, or dexamethasone 0.1%, or equivalent, 1 drop QID~~	~~Begin 1 day prior to each dose of GSK2857916 infusion, and continuing for a total of consecutive 7 days~~
~~Preservative-free artificial tears~~	~~Administer twice daily, at least 1 drop in each eye.~~	~~Administer daily beginning on Cycle 1 Day 1 until EOT. Allow 5-10 minutes between administration of artificial tears and steroid eye drops.~~
~~Cooling eye mask~~	~~Apply cooling eye mask to both eyes for approximately 1 hour or as much as tolerated by the patient. The use beyond the first hour for up to 4 hours is encouraged.~~	~~During GSK2857916 infusion administration in the first hour for up to 4 hours, as tolerated.~~

~~Dose modifications and treatment for ocular toxicities are discussed in Section 6.5.1~~
~~Omission or discontinuation of prophylactic steroid eye drops may be allowed under certain circumstances (e.g., in the setting of intolerability, contraindication, or toxicity secondary to steroid eye drops) upon discussion with the medical monitor.~~



CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Reason for change: Revisions to the GSK standard language in management and grading of corneal events.

84. Section 12.11 – Appendix 11: Operating Characteristics of Safety Stopping Rule for Expansion Cohort

Figure added to provide visualization for stopping rule as defined in Section 9.5.2.

Reason for change: FDA requested stopping criteria be established for Part 2 subjects. Figure provides characteristics of stopping rules.

85. Section 12.12 – Appendix 12: Sample Size Calculation for the Expansion Cohort

Information and figure providing details for hypothesis of study as described in Section 9.2.2.

Reason for change: Additional detail for reviewers.

Amendment 02

Where the Amendment Applies

Protocol Amendment 02 applies to all sites and countries.

Amendment Changes with Rationale

The Amendment 01 dated 26 SEP 2018 is replaced by Amendment 02 dated 26 FEB 2020.

The following substantive protocol changes have been implemented based on review and comments from global agencies, inclusion of items noted in protocol clarification letters, revisions due to discrepancies, revision of study drug related language and other clarifications noted since Amendment #1. Revisions to the Table and Events Tables will be noted as summaries with changes to assessments and/or notes as summaries. Additionally, administrative corrections of minor typographical, and/or inconsistent language throughout the protocol were made as well as an update to the Reference section.

Original text is displayed as strikethrough indicates replaced or removed text. New text is displayed as underline. If applicable, revisions within the tables will be displayed as summarized text; revisions to figures will be summarized with text. Administrative changes will not be displayed in the summary of changes.

Summary of Changes

1. TITLE PAGE

Author (s): PPD

Reason for change: Change in author personnel.

2. SPONSOR SIGNATORY

~~Jessica Katz~~Katarina Luptakova, MD~~, PhD~~ Date

Project Physician Lead~~Director, Clinical Development~~

Reason for change: Change in personnel for sponsor signatory.

3. Medical Monitor/SAE Contact Information

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Site Address
Primary Medical Monitor	PPD PPD MD~~PhD~~	PPD	PPD	GlaxoSmithKline 1250 South Collegeville Road Mailstop UP4300 Collegeville, PA 19426, USA PPD
~~Secondary Medical Monitor~~	PPD PPD PPD ~~MDPhD~~	PPD	PPD	~~GlaxoSmithKline~~ ~~1250 South Collegeville Road~~ ~~Mailstop UP4300~~ ~~Collegeville, PA 19426, USA~~ ~~Email:~~
SAE Reporting		OAX37649@gsk.com		

Reason for change: Change in medical monitor.

4. Throughout the document:

Belantamab mafodotin~~GSK2857916~~

Reason for change: Addition and/or replacement of the compound number with the generic name.

5. Throughout the document:

~~Participant~~subjects

Reason for change: Document predominantly referred to subjects. Revised participants to subjects for continuity.

6. Objective(s)/Endpoint(s) Part 1 and Part 2 Synopsis and Section 3:

- ~~———~~Pharmacokinetic (PK) parameters following IV administration as data permit. ~~(e.g., area under the curve [AUCs], mean maximum concentration [Cmax], time of Cmax [tmax], terminal phase half-life [t½]) after the first dose; concentration at trough (Ctrough), and end of infusion concentration in subsequent cycles, when measured~~

Reason for change: Removal of examples as not required in Endpoint wording.

7. Section 1 and Section 5.1 – Key Inclusion Criteria

In adequate organ system function table, revision of footnote 1:

1. Without any Growth factor support (e.g.colony stimulating factors (including granulocyte colony stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GMCSF], recombinant erythropoietin) or any thrombopoietin receptor agonists) within 2 weeks before the first dose of study drug~~for the past 14 days, excluding erythropoietin~~.

Female and Male Inclusion Criteria:

- 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, as described in Appendix 8 during the intervention period and for 9 months ~~at least 120 days~~ 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. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

  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~~ of dosing on C1D1 and agree to use effective contraception during the study and for 9 months after the last dose of study medication.
- Male Subjects:
  - Male subjects are eligible to participate if they agree to the following from the time of first dose of study until 6 months after the last dose of study treatment to allow for clearance of any altered sperm ~~during the intervention period and for at least 140 days after the last dose of study intervention:~~
    - 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 as detailed below
      - Agree to use a male condom, even if they have undergone a successful vasectomy, and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Appendix 8 when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.
      - Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Reason for change: Revision of Inclusion Criteria due to clarification of allowed supportive therapy prior to first dose and update of contraception language.

8. Throughout the document: Female and Male contraception requirements:

Females:

.. ~~throughout the study period up to 120 days~~ during the study and for 9 months..

Males:

..~~140 days~~ 6 months

Reason for change: Update to the contraception timeframe based on emerging PK information and agency guidance.

9. Study Schema and Dose Escalation Schematic Figures in Synopsis and Section 4.2.1.:

Replaced GSK2857916 with belantamab mafodotin; as a result, replaced the figures.

Reason for change: Replaced compound number with generic in figures, not reflected in text.

10. Protocol Synopsis and Section 6.12.3. Corneal Supportive Care Guidelines:

Subjects will be assessed by ophthalmologists (or optometrist, if ophthalmologist is not available) at baseline, and then every three weeks~~-~~prior to each dose of belantamab mafodotin for the first 4 doses. After the 4th dose of belantamab mafodotin, i~~I~~f there are ~~is~~ no significant ocular symptoms or vision change s, the frequency~~in vision and no corneal signs consistent with toxicity at time of the cycle 4 exam, subjects may have their~~ of ophthalmologic exams may be decreased to once every ~~3~~6 months until end of study treatment. In case of persistent or newly developed ocular symptoms or vision changes, the ~~If a~~ subject ~~subsequently develops a change in visual acuity or other ocular symptoms, the subject should~~ will have further ophthalmologic exams, at least every 3 months until resolution (to Grade 1 or baseline) or more frequently as clinically indicated by the ~~be evaluated by an~~ eye care specialist~~professional~~. ~~Intraocular pressure must be monitored if steroid eye drops are used for more than 7 days.~~

Reason for change: Based on benefit/risk after review of data from the primary analyses of DREAMM-2 study it has been determined that participant symptoms should determine the need for ophthalmology exams, and dose modifications.

11. Protocol Synopsis Translational Research

BCMA expression in the plasma cells ~~of~~ from bone marrow aspirates will be evaluated at baseline, and at additional timepoints if available, by IHC. IHC markers may include but will not be limited to: BCMA, Blimp1, CD138, and CD38.

Soluble BCMA (sBCMA) concentrations in serum will be ~~followed~~ evaluated in all subjects.

Reason for change: Clarification of wording.

12. Section 2.2.2. Nonclinical Pharmacokinetics:

Removed the section wording and replaced with:

Detailed information is available in the Investigator's Brochure [GlaxoSmithKline Document Number 2013N175128_06].

Reason for change: Reduction of length of document by reference to updated Investigator Brochure document that contains the revised information.

13. Section 2.2.3. Toxicology

Removed/revised the section wording:

A range of nonclinical toxicology studies have been conducted to support the intravenous administration of belantamab mafodotin~~GSK2857916~~ to humans. Detailed information is available in the Investigator's Brochure [GlaxoSmithKline Document Number 2013N175128_06].

Reason for change: Reduction of length of document by reference to updated Investigator Brochure document that contains the revised information.

14. Section 2.2.5 Effects in Humans (belantamab mafodotin)

Data from two belantamab mafodotin single agent studies conducted in heavily pre-treated RRMM patients (Q3W schedule via IV administration) is summarized below.

In the FTIH study BMA117159/DREAMM 1 (NCT02064387), as of 28 August 2018 primary analysis data cut-off, a total of 73 subjects with RRMM received at least 1 dose of belantamab mafodotin frozen drug product ranging from 0.03 mg/kg to 4.6 mg/kg once every 3 weeks~~in BMA117159~~ [GSK2857916 IB]. Subjects were heavily pre-treated: 57% of subjects had 5 or more prior lines of therapy. Data from DREAMM 1 demonstrates a manageable safety profile with thrombocytopenia and corneal events being the most frequently reported AEs. All subjects in Part 2 (MM patient population) initiated belantamab mafodotin treatment at 3.4 mg/kg and experienced at least one AE. The most common events occurring in ≥30% of subjects were corneal events, thrombocytopenia (including the preferred term platelet count decreased), nausea, fatigue, anemia, and aspartate aminotransferase increased. In Part 2, Grade 3/4 AEs were reported in 29/35 subjects (83%) and SAEs were reported in 17/35 (49%) subjects. The most common SAEs were lung-associated infections, pneumonia, pyrexia, and IRR.

Corneal events are the most frequently reported adverse events associated with belantamab mafodotin in the clinic, which include keratopathy (microcyst-like superficial deposits in the corneal epithelium), blurred vision, dry eyes and photophobia. These findings are consistent with those previously reported with other antibody drug-conjugates utilizing monomethyl auristatin F in terms of manifestation and incidence of

events [Donaghy, 2016; Eaton, 2015]. In part 2 of DREAMM 1, corneal events were reported in 24/35 (69%) subjects, most commonly blurred vision (18/35; 51%), dry eye (13/35; 37%) and photophobia (10/35; 29%). Most subjects experienced Grade 1 or 2 corneal events (19/35; 54%); 5 (14%) subjects had Grade 3 events. The median duration of corneal events for subjects with a resolution date (n = 16) was 35 days (range 5–442). Corneal events led to dose reduction in 16 (46%) subjects, and dose interruptions or delays in 17 (49%) subjects [Trudel, 2019].

Thrombocytopenia/platelet count decreased was reported in a total of 40 subjects (55%) in the All Treated Population (N=73), and 22 subjects (63%) in Part 2 (N=35). Belantamab mafodotin may cause transient worsening of thrombocytopenia in some subjects, but in most cases these events are resolved during between-dosing intervals. In the Part 2 MM population, two serious bleeding events were reported: intracranial hemorrhage in a subject with a history of an intracranial bleeding in the setting of disease progression, and hematuria in a subject with a large bladder mass in the setting of progressive disease.

As of the efficacy cut-off date of 31 August 2018, a total of 35 subjects were treated at the 3.4 mg/kg dose in Part 2 of the ongoing DREAMM 1 study. The ORR was 60% (95% CI: 42.1, 76.1): comprised of PR, 6%; VGPR, 40%; CR, 9%; and stringent CR (sCR), 6%. The median duration of response (DoR) was 14.3 months (95% CI: 10.6, NR). The median PFS (mPFS) in this population was 12.0 months (95% CI: 3.1, NR). For subjects refractory to both IMiDs and PIs (n = 32/35), the confirmed ORR was 56% (95% CI: 37.7, 73.6) and mPFS was 7.9 months (95% CI: 2.3, Not Estimable [NE]) [Trudel, 2019].

A Bayesian logistic regression model (BLRM) was used to determine the dose-response relationship for both ORR and ≥Grade 2 corneal event rate (as determined by NCI-CTCAE Version 4.0) based on data from all 73 subjects with RRMM in DREAMM 1. The model showed that the posterior probability of observing an ORR ≥30% is 100% in the 3.4 mg/kg dose group and 83% in the 2.5 mg/kg dose group. Similarly, the posterior probability of observing ≥Grade 2 corneal event rate is also higher in the 3.4 mg/kg dose group. Based on this analysis, these two doses (2.5 and 3.4 mg/kg) were selected for further evaluation.

The ongoing Phase II study 205678/DREAMM 2 (NCT03525678) is evaluating these two IV single agent doses (2.5 and 3.4 mg/kg) administered Q3W until disease progression in subjects who have failed at least 3 prior lines of anti-myeloma therapy, including an anti-CD38 antibody, and who are refractory to an IMiD and a proteasome inhibitor. A total of 194 subjects received frozen drug product in the main cohort and 24 subjects received 3.4 mg/kg lyophilized drug product. Preliminary data from this study indicated no new safety signals, and the profile of adverse events was similar to the experience in the DREAMM 1 study for both arms. Both dose levels, 2.5 and 3.4 mg/kg, were shown to have a positive benefit/risk profile.

~~GlaxoSmithKline (GSK) initiated the clinical development of GSK2857916 in July 2014, with the FTIH study (BMA117159) in subjects with RRMM and other advanced hematologic malignancies expressing BCMA (ClinicalTrials.gov Identifier: NCT02064387). As of the data cut from 26 June 2017, a total of 73 subjects with~~

~~RRMM have been treated with at least one dose of GSK2857916. Thirty-eight subjects were treated in Part 1 (dose escalation): 0.03 mg/kg (n=1), 0.06 mg/kg (n=1), 0.12 mg/kg (n=4), 0.24 mg/kg (n=4), 0.48 mg/kg (n=4), 0.96 mg/kg (n=3), 1.92 mg/kg (n=4), 2.5 mg/kg (n=8), 3.4mg/kg (n=3), and 4.6mg/kg (n=6). Since the RP2D (3.4 mg/kg) selection (August 11, 2016), an additional 35 subjects have been enrolled into Part 2 (expansion cohort). Of these 35 subjects,40% had receive prior daratumumab. The ORR for this sub-population was 43% [Trudel, 2017].~~

~~The most frequently reported AEs (≥15.0%) in the All Treated Population included: vision blurred (37%), nausea (36%), fatigue (33%), anemia (29%), dry eye (29%), thrombocytopenia (26%), aspartate aminotransferase increased (25%), chills (23%), platelet count decreased (23%) pyrexia (22%), cough (18%), photophobia (16%), back pain (15%), headache (15%), and upper respiratory tract infection (15%).~~

~~In the Part 2 population, 59% (20/35) of subjects had 5 or more prior treatment lines. Among the subjects in Part 2 (N=35), the most frequently reported AEs (≥15.0%) included: vision blurred (46%), platelet count decreased (37%), dry eye (34%), anemia (29%), aspartate aminotransferase increased (29%), increased cough (26%), chills (23%), nausea (23%), photophobia (23%), pyrexia (23%), fatigue (20%), thrombocytopenia (20%), back pain (17%), and diarrhea (17%). As of 26 June 2017, a total of 14 (40%) patients in Part 2 had an SAE and there were no fatal SAEs. The related SAEs are described below.~~

- ~~**Infusion Related Reaction (IRR):** Two patients experienced serious, Grade 3 infusion-related reactions during the first infusion that were characterized by tachycardia, hypertension and pyrexia. These subjects subsequently received pre-medication and IRRs did not recur.~~
- ~~**Intracranial Hemorrhage:** A patient with a history of intracranial bleeding experienced a Grade 2 intracranial hemorrhage with concomitant Grade 4, thrombocytopenia. At the same time, the patient's disease was starting to progress; the patient was taken off study and salvage chemotherapy was started.~~
- ~~**Pericardial Effusion:** A Grade 4 pericardial effusion consistent with tamponade was found prior to Cycle 9 during a routine study echocardiogram in an asymptomatic patient who had a concurrent upper respiratory tract infection. The fluid was evacuated, and the effusion was resolving at the time of data cut-off. The patient received three more cycles of treatment after this event. This SAE is listed as "not resolved" at the time of data cut, however a subsequent echocardiogram has confirmed no evidence of a pericardial effusion.~~
- ~~**Lung Infection and Pyrexia:** A patient experienced a Grade 2 lung infection resulting in a dose delay. Approximately three months later, the patient developed a Grade 2 fever resulting in hospitalization. The fever resolved the same day; the patient was not neutropenic.~~

~~Overall, GSK2857916 has a manageable safety profile with thrombocytopenia / platelet count decreased and corneal events as the most commonly reported events, as described in the following subsections.~~

~~**2.2.5.1 Thrombocytopenia**~~

~~A total of 36 patients (49%) in the All treated population, and 20 patients (57%) in Part 2 have experienced thrombocytopenia/platelet count decreased. GSK2857916 may cause transient worsening of thrombocytopenia in some patients, but in most cases these events are resolved during between dosing intervals. In the Part 2 MM population, two serious bleeding events were reported: intracranial hemorrhage in a patient with a history of an intracranial bleeding and in the setting of disease progression, and hematuria in a patient with a large bladder mass in the setting of progressive disease.~~

~~**2.2.5.1 Corneal Events**~~

~~Corneal AEs have been observed with various ADC drugs and represent the most commonly reported types of AEs associated with GSK2857916. As there is no single term which appropriately captures these events, the term 'corneal events' includes reported preferred terms describing events associated with the corneal toxicity related to GSK2857916. The most commonly reported corneal events include vision blurred, dry eye, photophobia, and lacrimation increased. A total of 42 patients (58%) in the all treated population, and 22 patients (63%) in Part 2 have experienced corneal events which were predominantly low grade.~~

~~In Part 2, there were three patients with ≥ Grade 3 corneal events: one with Grade 3 keratitis resulting in a delay and a dose reduction, one with Grade 3 eye pain resulting in a delay; and one Grade 3 dry eye resulting in a dose delay. In Part 2, there were no serious corneal events and no patients permanently discontinued study treatment due to a corneal event.~~

~~In Part 1, there was one SAE of Grade 3 limbal stem cell deficiency (in a patient at the 1.92 mg/kg dose) that was characterized by blurred vision and dry eyes. The events resolved after treatment was discontinued, and the patient's vision returned to baseline. Another patient in Part 1 (4.6 mg/kg) discontinued treatment due to the feeling of a foreign object in the eye (Grade 2).~~

~~In addition to the AEs describing corneal events, 89% of patients 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 patients experiencing these clinical findings, but improved on average to near baseline in patients completing end of study treatment visits (n=13). Eleven of these 13 patients (84.6%) had corneal clinical signs at the end of study treatment visit, with most cases (9/11 or 81.8%) considered as having "mild" changes.~~

Reason for change: Updated language based on updated information from First Time in Human study.

15. Section 2.2.5.1. Pharmacokinetics

<u>The pharmacokinetics of belantamab mafodotin (antibody-drug conjugate, including the complex), total antibody (including the complex), and cys-mcMMAF were investigated</u>

in 70 subjects participants after IV administration at doses of 0.03 to 4.60 mg/kg in a preliminary analysis of BMA117159 (data as of 26 June 2017). Maximum concentrations of belantamab mafodotin and total antibody were observed at or shortly after the end of infusion (EOI), whereas maximum cys-mcMMAF concentrations peaked approximately 24 hours after dosing. There was limited accumulation of belantamab mafodotin or cys-mcMMAF during subsequent cycles. [GlaxoSmithKline Document Number 2013N175128_06].

The pharmacokinetics of belantamab mafodotin were linear over the range of doses tested, with exposure of all analytes increasing proportionately with increasing dose and were well-described in a preliminary population PK analysis using conventional allometry. On a molar basis, plasma concentrations of cys-mcMMAF were <1% of belantamab mafodotin. Total plasma clearance of belantamab mafodotin was 0.37 L/day, and the mean steady-state volume of distribution was 4.2L. The model-predicted terminal phase elimination half-life of belantamab mafodotin was 8.2 days (95% CI: 6.4 to 10.1), in keeping with the loglinear model estimate (8.7 days).

Reason for change: Updated language based on updated information from First Time in Human study.

16. Section 2.4 Assessment of Nonclinical Data for Belantamab Mafodotin when Co-Administered with Pembrolizumab

… In addition, the starting dose of belantamab mafodotin ~~GSK2857916~~ in this combination regimen has been selected to be 1 dose level below a dose that has been shown to be well tolerated during the belantamab mafodotin ~~GSK2857916~~ monotherapy dose escalation~~. The determination of the starting dose is based on an assumption that it is approximately 25% less than the declared safe dose of GSK2857916~~ and should provide a sufficient safety margin when pembrolizumab is added at 200 mg. In addition, close clinical monitoring will be implemented.

Reason for change: Updated language to simplify the dose reduction wording based on dose level.

17. Section 4.2.3.2 Completion of Dose Escalation and the Recommended Phase 2 Dose (RP2D)

The dose escalation will complete when RP2D is determined. A dose level at or below the pre-specified max dose of 3.4 mg/kg may be selected as RP2D in combination with the fixed dose of 200 mg pembrolizumab. All available data from Part 1 will be analyzed. The totality of the d~~D~~ata ~~considered for RP2D selection will~~ includinge, but not be limited to, safety, available PK profile, and observed signs of clinical activity will be considered for the RP2D selection of belantamab mafodotin to be admistered in combination with pembrolizumab. If necessary, alternative doses and schedules can be explored to determine additional clinically active regimens. …

Reason for change: Revision of language to allow flexibility and revision of subject numbers. Consolidation of language.

18. Section 4.6.1 Risk assessment

There is a risk of overlapping toxicities with the combitnation of belantamab mafodotin and pembrolizumab. Potential overlapping toxoicities and risk mitigation plans are provided in Table 2. The frequency and intensity of these assessments will allow Investigators and GSK to identify and to react to potential worsening of toxicities.

Table 2 Risk Assessment and Mitigation Strategy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential overlapping toxicities for ~~Investigational Product~~ (belantamab mafodotin in combination with pembrolizumab~~GSK2857916~~)		
Changes on Ocular ~~Corneal~~ examination ~~events~~ with belantamab mafodotin **Eye disorders associated with pembrolizumab**	**Belantamab mafodotin**: Changes in corneal epithelium on ocular examination have been frequently observed with belantamab mafodotin. This was most commonly associated with: blurred vision, dry eyes, photophobia, and changes in visual acuity. **Pembrolizumab**: Eye disorders including dry eye, uveitis, and rarely Vogt-Koyanagi-Harada syndrome have been reported with pembrolizumab. ~~Reversible corneal toxicity has been observed with various antibody drug conjugates (specific corneal changes with ADCs conjugated to MMAF).~~ ~~Corneal related AEs (blurred vision, dry / watery eyes, decreased visual acuity, photophobia) are among the most common AEs associated with GSK2857916 in the clinic. The majority of events have been non-serious and transient, some requiring dose delays and/or reductions. Time to recovery is variable and in some instances the resolution may take several weeks.~~	Active monitoring for corneal events according to Table 4. ~~Prophylactic use of steroid eye drops as outlined in Section 6.12.3 and Appendix 9.~~ Timely evaluation and management by an ophthalmologist (or an optometrist if an ophthalmologist is not available) ~~eye care professional~~ upon developing corneal related events (see Section 6.5.1 and Appendix 9). Recommendations for dose delays / reductions are provided in Section 6.5.1.
Infusion related reaction	**Belantamab mafodotin**: IRRs were reported in patients treated with belantamab mafodotin. Most IRRs observed to date were Grade 1 to 2 and manageable with medical treatment. **Pembrolizumab**: Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug	Subjects will be closely monitored for signs of IRR. Premedication prior to first infusion of belantamab mafodotin~~GSK2857916~~ is not mandatory but may be considered based on investigator judgement. If an IRR~~infusion related reaction~~ occurs during belantamab mafodotin administration~~, of GSK2857916 the~~ management may follow guidance in Table 4 or local standard of care.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	infusion and generally resolve completely within 24 hours of completion of infusion. ~~The majority of IRRs observed in the clinic without any premedication to date have been G1-2 and non-serious; however, there have also been serious IRRs. Overall, subjects who experienced an IRR during the initial infusion were pre-medicated prior to subsequent infusions and IRRs did not recur.~~	Management of pembrolizumab infusion reactions is provided in Table 6.
Thrombocytopenia	**Belantamab mafodotin**: Thrombocytopenic events of all grades (1-4) are among the most common AEs associated with belantamab mafodotin. **Pembrolizumab**: Thrombocytopenia has been reported with pembrolizumab therapy. ~~GSK2857916 in the clinic. The majority have been non-serious. There has been no clinically significant bleeding reported in association with the thrombocytopenic events.~~	Hematological panels are assessed frequently. Supportive therapy (including transfusions) is provided according to standard medical practice, and dose reductions or treatment discontinuations are outlined in Section 6.5.
Neutropenia	**Belantamab mafodotin**: Neutropenic events, including febrile neutropenia have been observed with treatment with belantamab mafodotin, In a study of belantamab mafodotin in combination with lenalidomide/ dexamethasone, two fatal cases of severe infections associated with neutropenia have been observed. **Pembrolizumab**: Neutropenia has been reported with pembrolizumab therapy. ~~Non-serious and serious neutropenia has been observed in the clinic with GSK2857916. There have been no events of febrile neutropenia reported to date.~~	Hematological panels are assessed frequently. Consider prophylactic antibiotics, per physician discreation and local institutional guidance, in subjects with Grade 3-4 neutropenia CCI [redacted] even if afebrile. Immediately hospitalize subjects with febrile neutropenia and initiation appropriate management, per local institutional guidance. Consider additional supportive treatment(s) per local practice (e.g., ~~therapy (~~growth factors).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		~~, antibiotics, and active treatment of infections) is provided according to standard medical practice, and d~~Dose reductions or treatment discontinuations are outlined in Section 6.5
Potential for cardiotoxicity related to an inflammatory response with belantamab mafodotin **Cardiac disorders associated with pembrolizumab**	**Belantamab mafodotin**: Nonclinical studies, predominantly in monkey, increased activation of macrophages was noted in a number of organs at ≥3 mg/kg/week, reflective of a systemic inflammatory response. Minimal inflammatory changes (inflammatory cell infiltrate and/or haemorrhage) were also noted in hearts (atrial epicardium, ventricle endocardium) of single monkeys, which were nonadverse and reversible. Incidence of cardiac events reported to date with belantamab mafodotin was relatively low and mostly grade 1-2. **Pembrolizumab**: Cardiac disorders including pericarditis, pericardial effusion, and myocarditis, have been reported with pembrolizumab therapy. ~~Preclinical inflammatory findings were seen in the rat mandibular and mesenteric lymph nodes, brachial/sciatic nerves, epididymides, lung, thymus, and atrial epicardium. In the monkey, microscopic effects in spleen and bone marrow at ≥3 mg/kg/week were reflective of a systemic inflammatory response. Electrocardiograms (ECG) were monitored in monkeys for up to 24 hours following repeat dosing and did not produce any evidence of test article induced electrocardiographic waveform abnormalities, arrhythmias or QTc changes. Serum cardiac troponin I was also measured in the rat and monkey 3-week studies and no treatment related effects were observed.~~	Subjects with significant cardiac risk factors will be excluded from study participoation. Close monitoring of vital signs and ECG, troponin, and ECHO will be performed. Treatment as medically indicated. Monitoring of other cardiac parameters as clinically indicated. Dose modifications for myocarditis with pembrolizumab are provided in Table 5.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	~~This potential risk was based on the described preclinical findings, however to date, there is no evidence of systemic inflammatory response or cardiotoxicity in the clinic~~	
~~**Laboratory abnormalities**~~	~~Reports of non-serious myalgia and asymptomatic elevations in LDH / CK levels have been observed in the clinic.~~	~~Monitoring of LDH, and CK will be performed.~~
Hepatotoxicity	**Belantamab mafodotin**: In nonclinical studies liver is a target organ for toxicity, with increased liver weights and/or raised hepatobiliary enzymes and transaminases observed I both rat and monkey. These changes in the liver were without clinical consequence in the shorter duration studies and in the rat 13-week study. In the monkey 13-week study, progression of liver toxicity to include minimal multifocal hepatocellular necrosis was observed at all doses administered (≥3 mg/kg/week). Mild elevations of liver enzymes have been reported in some patients treated with belantamab mafodotin. **Pembrolizumab**: Hepatitis has been reported with pembrolizumab treatment. ~~Non-clinical safety experiments demonstrated increased liver weight and elevated liver enzymes in rats. Elevations in liver enzymes and increased mitotic figures in Kupffer cells were observed in monkeys. All of these changes were dose dependent and reversible.~~ ~~Non serious elevations in ALT, AST have been observed in the clinic.~~	Only subjects with well-preserved liver function per the inclusion/exclusion criteria will be allowed on study. Subjects with Hepatitis B (HBV) and C will be excluded. ~~from the trial~~Liver function tests will be frequently monitored. ~~in all subjects on study and i~~In case of liver abnormalities, management will be implemented according to clinical practice. Subjects that meet liver stopping criteria (Section 5.4.1.1) will be withdrawn from the study.
Nephrotoxicity	**Belantamab mafodotin**: Non-clinical safety studies have demonstrated dose dependent and reversible primary glomerular injury and tubular degeneration (in rat and monkey), accompanied by large molecular proteinuria (albuminuria) and enzymuria. Single cell necrosis of the kidney and bladder urothelium was also noted in the 13-week monkey study. Severe tubular degeneration/regeneration and marked glomerulonephritis exacerbated by immune complex disease, likely	~~Only subjects with well-preserved kidney function will be allowed on study. During the study s~~Subjects will be monitored for kidney function by assessing creatinine, eGFR, electrolytes, and albumin/creatinine rations (spot urine). ~~protein excretion in 24 hr urine collection and albumin / creatinine ratios (spot urine).~~

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	associated with ADA, led to the early euthanasia of one monkey following 5 weekly doses of 10 mg/kg. No significant renal findings were reported from study BMA117159. **Pembrolizumab**: Renal disorders, including nephritis and acute kidney injury, have been reported with pembrolizumab treatment. ~~Non clinical safety experiments have demonstrated primary glomerular injury and tubular degeneration (in rat and monkey). The morphologic changes were accompanied by large molecular proteinuria (albuminuria). The renal changes were dose dependent and reversible. No kidney failure has been reported in the clinic to date~~.	Subjects will be educated about the need of maintaining adequate urinary output. Management will be implemented according to clinical practice. Dose reductions and treatment stopping criteria will be applied according to Section 6.5. Dose modifications for nephritis and renal dysfunction with pembrolizumab are provided in Table 5.
Pulmonary toxicity (pneumonitis)	**Belantamab mafodotin**: Nonclinical safety experiments have demonstrated the presence of progressive microscopic changes in the lungs (prominent alveolar macrophages associated with eosinophilic material; mixed perivascular/neutrophilic inflammation) in rats at all doses tested. To date no significant pulmonary toxicity has been reported in clinical trials. **Pembrolizumab**: Pneumonitis has been reported with pembrolizumab treatment. ~~Preliminary non clinical safety experiments have demonstrated the presence of microscopic changes in the lungs (prominent alveolar macrophages associated with flocculent eosinophilic material; mixed perivascular inflammation) in rats at all doses tested. As of to date no pulmonary toxicity / cases of pneumonitis have been observed in the clinic.~~	Monitoring for clinical signs and symptoms potentially related to pulmonary toxicity. Further diagnostic tests and management will be implemented immediately according to recommendations provided in Section 6.5.1. Dose modifications for pembrolizumab are provided in Table 5.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
~~**Immunosuppression**~~	~~In non-clinical studies GSK2857916 has been associated with decrease in immunoglobulins in monkeys. An increase in immunoglobulins was seen in rats (rats are not an antigen specific species for GSK2857916).~~	~~Immunoglobulin levels will be assessed throughout the study. Active monitoring for infections, especially opportunistic infections will be performed. Subjects will receive immediate treatment according to standard practice.~~
Potential for Other Laboratory abnormalities	**Belantamab mafodotin**: An increased magnitude of AST relative to ALT consistent with increased skeletal troponin I was observed in the single dose monkey study. Increased skeletal troponin I and/or creatine kinase and aldolase was observed in the rat 3-week study. Cases of elevated aspartate aminotransferase (AST), lactic dehydrogenase (LDH) and creatine kinase (CK) alone or concomitant with no clear clinical correlate have been observed in clinical studies. **Pembrolizumab**: AST and ALT increase have been reported with pembrolizumab treatment.	Laboratory parameters will be monitored as outlined in Section 7. Subjects with significant laboratory elevations (≥x3 ULN) should, where possible, have a sample sent to central testing of CK and LDH isoenzyme levels. Dose modifications for pembrolizumab ALT and AST elevations are provided in Table 5.
Embryo-Fetal Toxicity	**Belantamab mafodotin**: Nonclinical reproductive studies with belantamab mafodotin have not been conducted. Embryo-fetal toxicity is expected due to the cytotoxic component, cys-mcMMAF via nonspecific uptake and/or BCMA-mediated toxicity (due to reports of BCMA expression in human placental cells [Langat et al, 2008]). Use of belantamab mafodotin in pregnant women may cause fetal harm. **Pembrolizumab**: Animal reproduction studies have not been conducted with pembrolizumab; however, in murine models of pregnancy blockade of PD-L1 signaling has been shown to disrupt tolerance to the foetus and to result in an increased fetal loss. These results indicate a potential risk, based on its mechanism of action, that administration of pembrolizumab during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth.	See Contraception requirements in Section 6.11.1.
Risks Related to Belantamab mafodotin not listed under potential overlapping toxicities		

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Immunosuppression	In non-clinical studies belantamab mafodotin has been associated with decrease in immunoglobulins in monkeys at all doses. An increase in immunoglobulins was seen in rats (rats are not an antigen specific species for belantamab mafodotin). MM subjects frequently are immunodeficient due to the underlying condition. Assessment of changes in immunoglobulin levels is challenging in patients with MM.	Subjects who have active infection will be excluded. Subjects will be monitored for infections and those who develop infection will receive immediate treatment according to standard practice.
Impaired Male and Female Fertility	In animal studies, belantamab mafodotin treatment has resulted in testicular toxicity and adverse effects on spermatogenesis. Reversibility of testicular toxicity is unknown at this time. In addition, luteinized non-ovulatory follicles were observed in the ovaries of rats after 3 weekly doses. Ovarian toxicity not observed following 12 weeks off dose and only after weekly dosing.	Men who may wish to father children in the future will be advised to have sperm samples frozen and stored before treatment. Women of child bearing potential who may desire offspring in the future will be counselled about the option of having eggs frozen before treatment. See Contraception requirements in Section 6.11.1
Study Procedures		
Bone marrow aspiration/biopsy	Pain, infection, bleeding may occur after the procedure	Subjects will be treated according to institution's practice
Incidental findings during imaging data acquisition	During the acquisition of imaging data (e.g.., MRI, CT, PET, ECHO), non-MM disease or drug related clinical abnormalities could be found by the radiographer or echocardiographer performing the exams.	All imaging scans will be reported to the site by an appropriate imaging clinician (non-anonymized) for non- MM Disease or drug related clinical abnormalities.

Reason for change: Revisions to the GSK2857916 language based on updated available information, with additional changes based on agency feedback.

19. Section 4.6.3. Overall Benefit:Risk Conclusion

Although there is limited human experience with belantamab mafodotin~~GSK2857916~~, and no clinical experience with the combination of belantamab mafodotin~~GSK2857916~~ with pembrolizumab, given the currently available safety data and the low likelihood of drug-drug interactions between belantamab mafodotin~~GSK2857916~~ and pembrolizumab, combination therapy may have an acceptable safety profile. Additionally, the combination ~~, and~~ may provide anti-tumor effect in subjects with MM; but this is unknown.

Of note, excess deaths were noted with pembrolizumab in combination with lenalidomide and dexamethasone (Keynote-185) or in combination with pomalidomide and dexamethasone (Keynote-183) leading the FDA to suspend these phase 3 trials, in addition to other trials of anti-PD[L] therapies in combination with IMmiDs in myeloma or non- Hodgkin's lymphoma were suspended . Please refer to Section 2.3.3 for additional information. This statement does not apply to patients taking KEYTRUDA (pembrolizumab) for an approved indication. The safety and efficacy of using KEYTRUDA (pembrolizumab) for approved, on-label uses have been proven. (https://www.fda.gov/Drugs/DrugSafety/ucm574305.htm). Considering the measures taken and, described in Section 7, to minimize risk to subjects, the potential risks associated with belantamab mafodotin~~GSK2857916~~ in combination with pembrolizumab noted in Section 4.6.1 are justified by the anticipated benefits that may be afforded to subjects with MM.

Reason for change: Clarification of language.

20. Section 5.1 Inclusion Criteria

Note related to adequate organ function table:

NOTE: Laboratory results obtained during Screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the investigator may retest the subject and the subsequent within range screening result may be used to confirm eligibility. If laboratory results were obtained more than 72 hours before first dose, laboratory results must be redone within 72 hours prior to first dose to confirm eligibility.

Reason for change: Clarification of requirement of safety laboratory samples.

21. Section 5.4.1.6. Valvular Toxicity Stopping Criteria

- If repeat ECHO does not reveal valve recovery to baseline within 4 weeks, then the ~~participant~~ subject should permanently discontinue study treatment ~~GSK2857916 and GSK3174998~~. The valve should continue to be monitored via ECHO every 4 weeks for 16 weeks or until resolution.

Reason for change: Removal of incorrect combination.

22. Corneal Toxicity Stopping Criteria

…If subject is allowed to continue on study, the dose of belantamab mafodotin~~GSK2857916~~ will be reduced by 1 dose level.~~at least 25%.~~ ...

Reason for change: Revised language for simplification of belantamab mafodotin dose reduction wording.

23. Section 5.5.1. Subject completion

~~For Part 1: A subject is considered to have completed the study if the subject is treated through the DLT determinative period or has a DLT during the DLT determinative period, i.e., a completed subject is one who is evaluable for the determination of DLT rate.~~

For Part 1 and Part 2, a subject is considered to have completed the study if they received at least 1 cycle of combination study treatment, and:

- The subject is followed until death, or
- The subject is followed until the end of study

Reason for change: Clarification of completer status to ensure one definition of completer.

24. Section 6.1 Investigational Products

Product name:	**Belantamab Mafodotin~~GSK2857916~~**	**Pembrolizumab**
Route of Administration	Delivered as IV infusion over at least 30 minutes Infusions may be prolong in the event of an infusion reaction. If subjects experience clinically significant infusion reactions, the infusion rate may be slowed for all future administrations of study treatment(s) for each participant. Should a global change in infusion rate be required, it will be communicated to sites in writing. ~~Refer to SRM for details.~~	Delivered as 30 min IV infusion

Reason for change: Additions of administration language based on agency feedback.

25. Section 6.3.1.2. Pembrolizumab administration

… All subjects are required to remain under observation at the study site for at least three hours post-infusion of the last study drug administered for the first two study treatment dosing visits. At subsequent study treatment dosing visits, for subjects who experience infusion-related reactions, the post-infusion observation time should remain as at least three hours; for subjects who do not experience infusion reactions, these subjects should remain under observation for a time period not shorter than one hour ~~at least one hour~~ (or longer as per the judgement of the investigator or as per institutional guidelines.) …

Reason for change: Revision of observation timing language.

26. Section 6.5 Subject Specific Dose Adjustment Criteria

Subjects should have their dose (including the first dose and subsequent doses) delayed or reduced for toxicities according to the recommendations as listed in Table 4. Dose reductions are only allowed for belantamab mafodotin~~GSK2857916~~. ~~The rule of 25% or 50% dose reduction always refers to the original assigned dose.~~

Table 4 Dose Modification Guidelines for Belantamab Mafodotin~~GSK2857916~~ Related Adverse Events

Toxicity	Grade	Recommendations to belantamab mafodotin~~GSK2857916~~	Recommendations to pembrolizumab
Serum creatinine elevation or decrease in eGFR which cannot be explained by concomitant sepsis, TLS, other severe infection with fever or dehydration	If absolute serum creatinine increase from baseline of >0. 5 mg/dL	• Repeat serum creatinine within 48 hours • If confirmed: withhold therapy, institute treatment and monitoring as clinically indicated, and follow for resolution • Discuss any further dosing with Medical Monitor[a]	See Table 5 for guidance on pembrolizumab
Serum creatinine>Grade 3 (acute kidney injury)	~~>+4.0mg/dL Or >3.0x baseline or hospitalization indicated~~>3.0mg/dL from baseline Or 3.0-6.0xULN	• Provide appropriate medical treatment. • ~~Provide appropriate medical treatment.~~ • Permanently discontinue treatment with belantamab mafodotin ~~GSK2857916~~	Resume treatment with pembrolizumab only if treatment with belantamab mafodotin ~~GSK2857916~~ may be continued
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 ~~GSK2857916~~at current ~~100%~~ dose • If confirmed on re-test and no clear evidence of disease progression[c] ○ Interrupt treatment with belantamab mafodotin ~~GSK2857916~~ ○ Repeat testing within 4 weeks ○ If spot urine <2000 mg/g (224/mg/mmol) may restart belantamab mafodotin ~~GSK2857916~~with one ~~25%~~ dose level reduction ○ If spot urine remains >2000 mg/g (224/mg/mmol) after 4weeks; permanently discontinue belantamab mafodotin ~~GSK2857916~~and discontinue ~~withdraw subject from~~ study treatment; provide treatment as clinically indicated and follow for resolution	Resume treatment with pembrolizumab only if treatment with belantamab mafodotin ~~GSK2857916~~ may be continued

Toxicity	Grade	Recommendations to belantamab mafodotin~~GSK2857916~~	Recommendations to pembrolizumab
Thrombocytopenia (on days of dosing) ~~Thrombocytopenia~~ ~~(On days of dosing)~~	3-4	• Withhold treatment until thrombocytopenia recovered to Grade 2 or less (≤G2). • If Grade 3-4 thrombocytopenia is considered disease-related, treatment may be continued with dose reduction and more frequent hematology monitoring, until recovery to Grade 2 or less. • Implement supportive treatment (e.g. transfusion) as clinically indicated and per local practice.~~No bleeding: continue treatment with 25% dose reduction. Consider reversing to previous dose once thrombocytopenia recovered to G2, or less.~~	~~None~~Delay treatment until the next belantamab mafodotin dose
		• ~~With bleeding: withhold the dose, continue treatment after recovery with 25% dose reduction~~	~~Delay treatment until the next GSK2857916 dose~~
	4	• ~~Withhold the dose. Consider restarting with 25% dose reduction if recovered to ≤G3 only if there is no active bleeding at time of treatment re-start~~	~~Delay treatment until the next GSK2857916 dose~~
		• ~~If thrombocytopenia is considered disease related, is not accompanied by bleeding, and recovers with transfusion to >25 x109/L continuing treatment at 25-50% dose reduction may be considered after discussion with the GSK Medical Monitor~~	~~Delay treatment until the next GSK2857916 dose~~
Febrile neutropenia	~~3~~-4 CCI	• Withhold belantamab mafodotin ~~GSK2857916~~ and pembrolizumab and hospitalize ~~participant~~subject with appropriate management, per local institutional guidance • Consider additional supportive treatment per local guidance (e.g., ~~Implement treatment with antibiotics, antivirals and antifungals, as clinically indicated, consider~~ growth factors) • Upon recovery, consider a dose reduction of belantamab mafodotin, if neutropenia was drug related	• Delay treatment until the next belantamab mafodotin dose

Toxicity	Grade	Recommendations to belantamab mafodotin~~GSK2857916~~	Recommendations to pembrolizumab
Neutropenia	≥3 CCI [redacted]	• If noted on Day 1 of any cycle, withhold belantamab mafodotin. Repeat hematology (CBC) as clinically indicated until recovery to Grade 2 or less. • Resume belantamab mafodotin at pre-hold dose once neutropenia recovers to Grade ≤2 CCI [redacted] on Day 1 of the subsequent cycle. • Implement supportive care as clinically indicated per local practice	• Delay treatment until the next belantamab mafodotin dose
	In case of recurrence of frequent episodes of neutropenia <1.0 × 10^9 /L	• Consider dose reduction of belantamab mafodotin, if it was drug-related.	• Delay treatment until the next belantamab mafodotin dose
Belantamab mafodotin~~GSK2857916~~ Treatment Related Corneal events[b]	Corneal Management Care Regardless of Grade	~~**Steroid Eye Drops:**~~ ~~• If symptoms occur within the 7-day steroid eye drop prophylaxis window, increase the frequency to 1 drop every 2-4 hours (6-12 times daily) and continue until symptom resolution.~~ ~~• If symptoms occur after the 7-day prophylaxis window is complete, re-start ocular steroid drops at 4x daily until symptom resolution.~~ **Preservative-free artificial tears**: • Increase to 1 drop as frequently as every 2 hours, as needed	
	Grade 1 per GSK Scale	• Continue treatment with current ~~dose~~ treatment with ~~of~~ belantamab mafodotin ~~GSK2857916~~	• None
	Grade 2 per GSK Scale	• If Grade 2 finding (visual acuity and/or exam finding) and the participant is **asymptomatic,** continue dosing with belantamab mafodotin. • If Grade 2 finding (visual acuity and/or exam findings) and the patient is **symptomatic**. ○ **DOSE REDUCE** and continue treatment. ○ If already on 1.92 mg/kg, participant may continue at current dose.	• Hold/Delay treatment until the next belantamab mafodotin ~~GSK2857916~~ dose

Toxicity	Grade	Recommendations to belantamab mafodotin~~GSK2857916~~	Recommendations to pembrolizumab
		~~○~~ Upon improvement of either visual acuity or ophthalmic exam findings to ≤Grade 1 and improvement in symptoms, dose may be re-escalated to previous dose. ~~If **either** ophthalmic exam finding **or** visual acuity findings are **Grade 1,** continue dosing with GSK2857916 at current dose~~ ~~• If visual acuity **and** exam findings are **both** Grade 2, **HOLD** GSK2857916~~ • ~~Upon improvement of either visual acuity or ophthalmic exam findings to Grade 1 or baseline, resume with current dose~~	
	Grade 3 per GSK Scale	• If Grade 3 finding (exam finding) and the participant is **asymptomatic**: continue dosing with belantamab mafodotin. • If Grade 3 exam finding and the participant is **symptomatic or Grade 3 visual acuity**: ○ HOLD belantamab mafodotin . Upon improvement of either visual acuity or ophthalmic exam findings to ≤ Grade 2 and improvement in symptoms continue treatment with dose **REDUCTION**. ○ If already on 1.92 mg/kg participant may continue at current dose ~~○~~ If after event resolution eye symptoms are considered stable for at least 3 cycles consider re-escalation to previous dose.~~Hold GSK2857916~~ ~~• Upon improvement of either visual acuity or ophthalmic exam findings to Grade 1 or baseline, resume with 25% dose reduction (for subjects receive 1.92 mg/kg dose, continue at 1.92 mg/kg)~~ • ~~In case of recurring ≥Grade 3 events, consult GSK Medical Monitor~~	• Hold/Delay treatment until the next belantamab mafodotin ~~GSK2857916~~ dose

Toxicity	Grade	Recommendations to belantamab mafodotin~~GSK2857916~~	Recommendations to pembrolizumab
	Grade 4 per GSK Scale	• Hold treatment with belantamab mafodotin. • Treatment re-start may be possible after discussion and agreement between the treating ophthalmologist*, treating physician, the GSK Medical Monitor • *or optometrist, if an ophthalmologist is not available~~Stop treatment with GSK2857916~~ • ~~Additional topical treatment may be prescribed, as recommended by ophthalmologist~~ • ~~Treatment re-start may be possible after discussion and agreement between ophthalmologist (or optometrist if an ophthalmologist is not available), treating physician, GSK Medical Monitor and possibly a GSK ophthalmologist~~	• Stop treatment with pembrolizumab. • Further treatment only possible if belantamab mafodotin ~~GSK2857916~~is allowed to restart
Infusion Reaction[c]	2	Stop the infusion, provide medical treatment and continue at slower pace after resolution to Grade 0-1	See Table 6 for guidance on pembrolizumab
	3	Further treatment with belantamab mafodotin ~~GSK2857916~~needs to be discussed with Medical Monitor. Continuation only allowed after recovery to ≤Grade 1 and with pre-medication, and extension of infusion time to 2-4 hours. Any future infusion needs to be pre-medicated	
	4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Continue when toxicity resolves to Grade 0-1	See Table 5 for guidance on pembrolizumab
	Grade 3-4	Permanently discontinue	Permanently discontinue

a. Medical Monitor may consult GSK's nephrotoxicity panel about plans to continue therapy
b. Corneal toxicity should be graded according to GSK scale for belantamab mafodotin~~GSK2857916~~ treatment related Corneal Events (Appendix 9).
c. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose

AEs associated with pembrolizumab exposure may represent ~~an immunologic etiology. These~~ immune-related response. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. ~~Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.~~ Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 6.

Table 5 Dose Modification Guidelines for Pembrolizumab-Related Adverse Events

General instructions:

1. Severe and life-threatening irAEs, should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if AE does not resolve or the corticosteroid dose is ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the ~~initiated upon~~ irAE ~~improving to~~ is ≤Grade 1 and continue at least 4 weeks. ~~or less and continue to taper over at least 4 weeks.~~
4. If ~~For situations where~~ pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤Grade 1 after ~~can be resumed after AE has been reduced to Grade 1 or 0 and~~ corticosteroid ~~has been~~ taper. ~~Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.~~
5. ~~For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.~~

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.03)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • ~~Add prophylactic antibiotics for opportunistic infections~~
	Recurrent Grade 2, Grade 3 or 4~~, or recurrent grade 2~~	Permanently discontinue		
Diarrhea / colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST / ALT elevation or Increased Bilirubin	Grade 2[1]	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3[2] or 4[3]	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.03)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New~~ly~~ onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[4]	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[4]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue[1]		
Hypothyroidism	Grade 2, 3, 4	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis; grading according to increased creatinine or acute kidney injury ~~and renal dysfunction~~	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.03)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	~~Intolerable~~/ Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on ~~the type of~~ event[5]. ~~Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis~~		
	Recurrent Grade 4 or ~~recurrent~~ Grade 4	Permanently discontinue		

NOTES:

1. AST/ALT: >3.0 - 5.0 x ULN if baseline normal; >3.0 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal
2. AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal
3. AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal
4. The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ~~For~~ subjects with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2, pembrolizumab may be resumed. ~~and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM)~~.
5. Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

Table 6 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

~~NSAIDS~~

Reason for change: Revision of language and Tables based on update to guidelines for belantamab mafodotin and Merck standard language.

27. Section 6.7.2. Pembrolizumab

Administration

Pembrolizumab infusion solution should be intravenously administered over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes -5 min/+10 min).

Reason for change: Revision of language for consistency with other pembrolizumab wording in protocol.

28. Section 6.11.2 Subjects with Contact Lenses

Contact lenses are prohibited while on the study treatment (from first dosing to the end of study treatment). Contact lens use may be restarted after the ophthalmologist (or an optometrist if an ophthalmologist is not available) confirms there are no other contraindications.

Use of bandage contact lenses is permitted during study treatment as directed by the treating ophthalmologist (or optometrist if an ophthalmologist is not available).

Reason for change: Elaboration of the timing and type of contact lens use.

29. Section 6.12.3. Supportive Care Guidelines for Corneal Events

Subjects will be assessed by ophthalmologists (or optometrist, if an ophthalmologist is not available) at baseline, and then every three weeks prior to each dose of belantamab mafodotin for the first 4 doses. After the 4th dose of belantamab mafodotin, ~~I~~if there are ~~is~~ no significant ocular symptoms or vision changes ~~in vision and no corneal signs consistent with toxicity at time of the cycle 4 exam, subjects may have their~~ the frequency of ophthalmologic exams may be decreased to once every 6~~3~~ months until end of study treatment. In case of persistent or newly developed ocular symptoms or vision changes, the ~~If a participant~~ subject ~~subsequently develops a change in visual acuity or other ocular symptoms, the subject should be evaluated~~ will have further ophthalmologic

exams, at least every 3 months until resolution (to Grade 1 or baseline) or more frequently as clinical indicated by the~~an~~ eye care specialist~~professional. Intraocular pressure must be monitored if steroid eye drops are used more than 7 days.~~

Subjects who have signs or symptoms of corneal toxicity present at end of study will continue to be followed monthly for up to 12 months, or until deemed clinically stable by an ophthalmologist (or optometrist, if ophthalmologist is not available), whichever comes first. Clinically stable is defined as:

- Any GSK Grade 1 exam finding (CCI keratopathy) and a one-line change in vision when compared to baseline or,
- No exam findings, and a one-line change when compared to baseline or,
- Any GSK Grade 1 exam finding (CCI keratopathy) and no change in vision from baseline

Reason for change: Revision of language and provision of clinically stable language.

30. Section 6.12.5 Prohibited Medication(s)

… Elimination pathways for belantamab mafodotin and cys-mcMMAF have not been characterized in humans. However, cys-mcMMAF was shown to be a substrate of P-gp and OATP transporters, and to be a poor substrate of cytochrome P450 (CYP) enzymes in vitro. Caution should be exercised when combined with strong inhibitors of P-gp, and strong inhibitors of OATP should be avoided unless considered medically necessary. ~~Please refer to the SRM for further information~~

A list of Prohibited Concomitant Medications is provided in SRM, based on known interactions or characteristics of each component of the Study Treatment.

Reason for change: Update to GSK standard language.

31. Section 7. **STUDY ASSESSMENTS AND PROCEDURES**

Affected rows/items within tables are presented for changes in this section:

Table 7 Time and Events Table: Part 1 and Part 2 – Screening Assessments

Clinical chemistry ~~(with corrected calcium)~~

Footnotes:

4. Perform only in women of child-bearing potential. A serum pregnancy test must be performed at screening. If test is completed within 72 hours prior to the first dose, this assessment need not be repeated on C1D1. For questionable cases, follicle-stimulating hormone (FSH) and estradiol (as needed in women of non-childbearing potential only) should be performed at local lab.

12. In subjects with known or suspected extramedullary disease. May be performed up to 28 days prior to C1D1 as screening value. Needs to be performed by the same

method throughout the study as was done at baseline (i.e. if CT/PET scan was used as baseline, subject needs to be followed by CT/PET scans). Selected target lesion needs to be measured and followed over time. For sites in Germany, only MRI is allowed as imaging modality

14. FISH testing at least for: t(4;14), t(14;16), amp (1q), del(1p) and 17p13del. FISH results from samples taken within 60 days prior to first dose are acceptable.

15. Samples from within 28 days prior to first dose are acceptable. . A portion of the aspirate collected for disease assessment will be used for biomarker research (BM aspirate clot is preferred for BCMA analysis), for FISH testing, and MRD testing. MRD testing will be performed by a central lab.

16. Archival samples are acceptable; however, they should not replace fresh BM biopsies/aspirates …

Table 8 Time and Events Table: Part 1 and Part 2 – On Study Assessments Completed Independent of Dosing

Clinical chemistry ~~(with corrected calcium)~~

Urinalysis~~e Dipstick~~

BM aspirate for MRD testing ~~bone marrow aspirate~~

Footnotes:

1. All assessments will apply to Part 1 and 2 unless stated otherwise. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. Assessments for C1D8 can be performed up to +3 days of the scheduled date. All assessments from Cycle 2 can be performed +/-3 days ~~prior to the~~of the scheduled date unless otherwise specified.

3. AEs/SAEs will be collected ~~assessed~~ from first study dose up to 45 days post the last dose. All related SAEs are to be collected from consent through OS follow-up. AEs/SAEs will be followed until the event is resolved, stabilized, otherwise explained or subject is lost to follow up.

5. On-study ocular exams to be performed up to 5 days before scheduled study dose by an ophthalmologist (or an optometrist if an ophthalmologist is not available) every three weeks prior to each dose of belantamab mafodotin for the first 4 doses. See Section 7.3.5 for list of ophthalmic exam procedures. After the 4th dose of belantamab mafodotin, ~~If~~ there are~~is~~ no significant ocular symptoms or ~~change in~~ vision changes, the frequency of ~~and no corneal signs consistent with toxicity at time of the cycle 4 exam, subjects may have their~~ ophthalmologic exams may be decreased to once every 6~~3~~ months until end of study treatment. In case of persistent or newly developed ocular symptoms or vision changes, the ~~Additional exams may be performed by the eye care professional, as clinically indicated. If a subject subsequently develops a change in~~

~~visual acuity or other ocular symptoms, the~~ subject will have further ophthalmologic exams, at least every 3 months until resolution (to Grade 1 or baseline) or more frequently as clinically indicated by the eye care specialist~~should be evaluated by an ophthalmologist (or an optometrist, if an ophthalmologist is not available) and treated as clinically indicated. Intraocular pressure must be monitored if steroid eye drops are used more than 7 days.~~ –

7. For participants that develop Grade 3 or 4 thrombocytopenia and/or neutropenia, blood counts should be monitored more frequently until resolution to a ≤Grade 2. In addition, participants should be monitored for signs and symptoms of bleeding, infection and other associated events and evaluated promptly. Institute supportive care (e.g transfusion, growth factors) and other treatments as clinically indicated and in accordance with local institutional guidelines.

10. ECHOs to be done locally up to 7 days prior to scheduled visit. On treatment ECHOs will occur every 12 weeks from C1D1 first dose (e.g., Week 13, W25,W37, etc.) and will continue regardless of dose delays. All E~~H~~CHOs will be sent for central imaging storage.

13. Q12 weeks (±3 weeks) through 1 year and then as clinically indicated . To be performed by the same method throughout the study as was done at baseline (i.e. if CT/PET scan was used as baseline, subject needs to be followed by CT/PET scans). Selected target lesion needs to be measured and followed over time. For sites in Germany, only MRI is allowed as imaging modality. Imaging is from Cycle 1 Day 1.

15. Bone marrow aspirate sample to be collected at C3D1 (± 7 days). BM aspirate clot is preferred for BCMA analysis and immune cell characterization/profiling. ~~Optional Collection at time of Progressive Disease.~~

16. Optional a~~A~~dditional bone marrow aspirate samples may be collected at C1D8 or during any~~every~~ 3 week period, or at time of Progressive Disease for biomarker assessments.

17. MRD assessment to be performed by a central lab at the time of first achieving VGPR or CR., r~~R~~epeat MRD testing 6 and 12 months after achieving VGPR or CR (provided VGPR/CR is maintained). Additional samples to be collected for biomarker research are encouraged, as part of the same BM draw.

19. IHC only to confirm sCR at the time of confirmation of CR bone marrow biopsy~~x~~/aspirate is performed. IHC to confirm sCR on BM biopsy when CR is achieved. Absence of clonal cells in BM biopsy by IHC is required to determine sCR…..

Table 9 Time and Events Table: Part 1 and Part 2 – On Study Assessments with Dosing Days (Cycles)

Pregnancy Test	X[3]		X[3]
Soluble BCMA	X[10]	X[10]	X[10]

Serum cytokines/ chemokines[11]	X	X	X[11]
Plasma-cfDNA	X[12]		X[12]
Whole blood RNA	X[13]	X[13]	X[13]
Cryopreserved PBMCs	X[14]	X[14]	X[14]

Footnotes:

1. All assessments will apply to Part 1 and 2 unless stated otherwise. Assessments should be done prior to drug administration, unless otherwise specified. Assessments for C1D8 can be performed +3 days of the scheduled date. From Cycle 2, assessments can be performed +/-3 days of~~prior to~~ the scheduled date unless otherwise specified.

2. For the first infusion, Infusion vital signs must be assessed for each infusion (belantamab mafodotin~~GSK2857916~~ and pembrolizumab) at: pre-dose (within 30 min~~utes~~ prior to SOI); at the end of post each infusion (EOI) (+15 min); and 1 hr~~our~~ (±10 min) post EOI. For subsequent infusions, infusion vital signs must be assessed for each infusion (belantamab mafodotin and pembrolizumab) at pre-dose (within 30 min prior to SOI); at EOI (+15 min), and 30 min (±10 min) post EOI. **On dosing days with PK sampling time points, vital signs should be assessed prior to PK samples being drawn**. See Section 7.3.7.

7. Triplicate ECGs to be performed at pre-dose (within 30 minutes prior to SOI belantamab mafodotin~~GSK2857916~~) and at EOI (within 30 min after belantamab mafodotin~~GSK2857916~~ EOI) at each cycle. ECG recordings should be made after at least 10 min rest and collected no more than 2 min apart. On days with PK sampling time points, ECGs should be performed prior to PK samples being drawn.

8. PK samples to be obtained at as described in Section 7.4.1. The sBCMA samples must be taken at the same time of any belantamab mafodotin PK sample. ~~taken (in all subjects) for both belantamab mafodotinGSK2857916 and pembrolizumab measurements at: C1D1: pre-dose (within 30 min prior to SOI belantamab mafodotinGSK2857916), EOI belantamab mafodotinGSK2857916 (±5 min) , pre-dose pembrolizumab (within 10 min prior to SOI pembrolizumab), EOI pembrolizumab (±5 min), 4 h after belantamab mafodotinGSK2857916 SOI (±15 min), 9 h OR 24 h after belantamab mafodotinGSK2857916 SOI (±1 h) according to the subject's preference;~~
~~C1D4: one sample anytime;~~
~~C1D8 to C1D15: one sample anytime;~~
~~C2D1 and C5D1: pre-dose (within 30 min prior to SOI belantamab mafodotinGSK2857916, EOI belantamab mafodotinGSK2857916 (±5 min), pre-dose pembrolizumab (within 10 min prior to SOI pembrolizumab)), EOI pembrolizumab (±5 min);~~
~~C8D1 and C11D1: pre-dose (within 30 min prior to SOI belantamab mafodotin)GSK2857916; EOI belantamab mafodotinGSK2857916 (±5 min);~~
~~C14D1 and every 3 cycles thereafter (i.e., C17, 20, until EOT): pre-dose (within 30 min prior to SOI belantamab mafodotinGSK2857916). In Cycle 1, in the event the pembrolizumab infusion is delayed by at least 24 h, samples should also be taken prior to~~

~~SOI pembrolizumab dose, at EOI pembrolizumab, and at 2.5 h and 7 h post pembrolizumab SOI in addition to the time points listed above.~~

9. Pre-dose belantamab mafodotin (within 30 min prior to SOI) at ~~GSK2857916~~ C1 Day1 (week 1), C2, C5 and every 3 cycles thereafter (i.e., C8, C11,..) until EOT for both belantamab mafodotin and pembrolizumab ADA samples. If belantamab mafodotin is administered but pembrolizumab is planned to be held during any of the above Cycle timepoints, pre-dose pembrolizumab ADA should still be collected.

10. Serum sBCMA samples will be collected each cycle at pre-dose (within 30 minutes prior to SOI), ~~and at each PK timepoint in Cycle 1.~~ at every time a PK sample is collected, as indicated in Section 7.4.1., and at every MRD assessment timepoint.

11. Collect a cytokine/chemokine serum sample during~~at~~ C1D1 at pre-dose (within 30 minutes prior to SOI belantamab mafodotin), EOI of pembrolizumab (within 30 minutes after EOI~~±5 min~~) (even when infusion is interrupted or halted), 4 h after belantamab mafodotinGSK2857916 SOI, ~~9 h OR~~ 24 h after belantamab mafodotin~~GSK2857916~~ SOI (±1 h)~~, according to the subject's preference~~; ~~and~~ at C1D8 (+3 days, on same day as PK sample collection) and pre-dose belantamab mafodotin (within 30 min prior to SOI) at C2D1 and C5D1.

12. Collect pre-dose belantamab mafodotin (within 30 min prior to SOI) at C1D1, at every 12 weeks thereafter (pre-dose belantamab mafodotin), and at every MRD assessment timepoint.

13. Collect pre-dose belantamab mafodotin (within 30 min prior to SOI) at C1D1, C1D8 (+3 days, on same day as PK sample collection), and pre-dose belantamab mafodotin (within 30 min prior to SOI) at C2D1 and C5D1.

14. Collect during C1D1 at pre-dose (within 30 minutes prior to SOI belantamab mafodotin), EOI of pembrolizumab (within 30 minutes after EOI) (even when infusion is interrupted or halted), 4 h after belantamab mafodotin SOI, 24 h after belantamab mafodotin SOI (±1 h); at C1D8 (+3 days, on same day as PK sample collection), and one pre-dose belantamab mafodotin (within 30 min prior to SOI) at C2D1 and C5D1.

17. Corneal management information:
- ~~Prophylaxis with steroid eye drops (such as prednisolone phosphate 1% or dexamethasone 0.1%) 1 drop QID starting from 1 day prior to infusion and continuing for a total of 7 consecutive days. If dosing delayed for a non-corneal event, the prophylactic steroid drops can be stopped.~~
- Prophylactic preservative-free artificial tears must be administered in each eye at least 4-8 times daily beginning on Cycle 1 Day 1 until end of treatment.
- At the start of each infusion, subjects may apply cooling eye masks to their eyes for approximately 1 hour as long as tolerated.

Abbreviations:

PBMC = peripheral blood mononuclear cell

Table 10 Time and Events Table: Part 1 and Part 2 – End of Treatment and Follow-up Assessments

Clinical chemistry ~~(with corrected calcium)~~

Urinalysis ~~e Dipstick~~

BM aspirate for MRD testing ~~bone marrow aspirate~~

Footnotes:

5. AE/SAEs will be collected~~assessed~~ up to 45 days post the last dose. ~~SAEs will be assessed up to 90 days post last dose, or 45 days post last dose if the subject initiates a new anticancer therapy (whichever is shorter),~~ All related SAEs are to be collected from first dose through OS follow-up. AEs/SAEs will be followed until the event is resolved, stabilized, otherwise explained or subject is lost to follow up.

9. ~~Final pregnancy test (serum or urine) must be performed in women of childbearing potential 80 days (±7 days) after last study treatmen~~ Final pregnancy test (serum or urine) must be performed in women of childbearing potential at the EOT Visit. Follow up pregnancy assessment by telephone (for WOCBP only) should be performed 9 months after the last dose of belantamab mafodotin.

22. MRD assessment to be performed by a central lab at the time of first achieving VGPR or CR, repeat testing at 6 and 12 months after achieving VGPR or CR (provided VGPR/CR is maintained). Additional samples to be collected for biomarker research are encouraged, as part of the same BM draw. .MRD testing will be performed by a central lab.

24. Bone marrow aspirate sample to be collected at EOT. BM aspirate clot is preferred for BCMA analysis and immune cell characterization/profiling.

26. Exit Interview should ~~to~~ be performed within approximately 21 days of ~~last dose of study treatment~~ end of treatment visit.

Reason for change: Revision of assessments and/or footnotes for reasons which include revision, adding clarity, new assessments, and correction of errors in previous notes.

32. Section 7.1 Screening and Critical Baseline Assessments

- **…** Imaging studies CT, MRI or PET-CT (for subjects with extramedullary disease~~for MM~~)..

Reason for change: Clarify baseline imaging requirements.

33. Section 7.3.1.1. Time Period and Frequency of Detecting AEs and SAEs

… All SAEs will be collected from the time the first dose of study treatment is administered until ~~90 days following cessation of treatment, or~~ 45 days following cessation of study treatment ~~if the subject initiates new anticancer therapy, whichever is earlier~~. In addition, any SAE assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment or GSK concomitant medication must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 7.3.1.7~~7.3.1.6~~. …

Reason for change: Update of the GSK safety standard language.

34. Section 7.3.2 Pregnancy (similar changes also apply to Section 12.8. Appendix 8: Contraceptive Guidance and Collection of Pregnancy Information Definitions)

… Subjects with positive pregnancy test result must be excluded from the study. Subjects with negative pregnancy test result must agree to use an effective contraception method as described below during the study and for 9 months~~until 120 days~~ following the last dose of study treatment.

Details of all pregnancies in female participants will be collected after the start of study treatment and for 9 months following last dose of belantamab mafodotin.

Details of all pregnancies for female partners of male participants will be collected after the start of study treatment and 6 months following last dose of belantamab mafodotin.

~~Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of study treatment and until approximately 120 days.~~

If a pregnancy is reported, the investigator must inform GSK within 24 hours of learning of the pregnancy and must follow the procedures outlined in Appendix 8.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure ~~plus an additional 30 days~~ (9 months after the last dose of belantamab mafodotin) and correspond with the time frame for female subject contraception in Section 5.1. …

Reason for change: Update to the pregnancy language for belantamab mafodotin.

35. Section 7.3.5. Ocular Examinations and Procedures

Study sites must establish a close collaboration with an ophthalmologist (or an optometrist if an ophthalmologist is not available) who will be responsible for assessing subjects while they are on study and managing subjects who develop treatment-related changes in vision associated with belantamab mafodotin. Management of subjects with treatment-related changes in vision must be performed in close communication with the GSK Medical Monitor and the coordinating ophthalmologist (or an optometrist if an ophthalmologist is not available).

Subjects will be assessed by eye care specialist (ophthalmologist, or an optometrist if an ophthalmologist is not available) at screening/baseline.

A full screening/baseline ophthalmic examination for all subjects must include for both eyes (OU):
1. Best corrected visual acuity.
2. Documentation of manifest refraction and the method used to obtain best corrected visual acuity.
3. Current glasses prescription (if applicable).
4. Selected anterior segment (slit lamp) examination with focus on the cornea and lens, including fluorescein staining of the cornea
5. Intraocular pressure measurement.
6. Dilated funduscopic exam

The ***on treatment*** and ***follow-up*** ophthalmic exam should be performed for both eyes (OU) as described below and in the Time and Events Tables (Section 7):
1. Best corrected visual acuity.
2. Documentation of manifest refraction and the method used to obtain best corrected visual acuity.
3. Selected anterior segment (slit lamp) examination with focus on the cornea and lens, including fluorescein staining of the cornea and lens.
4. Intraocular pressure measurement (if clinically indicated)
5. Dilated funduscopic exam (if clinically indicated)

~~A full screening/baseline ophthalmic examination for all subjects must include for both eyes (OU):~~
~~1. Best corrected visual acuity~~
~~2. Documentation of manifest refraction used to obtain best corrected visual acuity~~
~~3. Current glasses prescription (if applicable)~~
~~4. Pupillary light reflex~~
~~Extraocular muscle movements (graded from one to four with (+) sign indicating over action, ( ) sign indicating under action and 0 representing normal movements~~
~~5. Intraocular pressure measurement & time checked~~
~~6. Full anterior segment (slit lamp) examination including fluorescein staining of the cornea. :~~
~~• Anterior segment exam (slit lamp) includes: orbit/lids/adnexa, conjunctiva, sclera, cornea, anterior chamber, iris, lens and anterior vitreous,~~
~~7. Anterior segment photography of a fluorescein stained cornea~~

~~8. Dilated funduscopic exam: fundus photography with interpretation~~
~~The on treatment and follow-up ophthalmic exam should be performed for both eyes (OU) must include everything except: dilated funduscopic/ fundus photography, anterior segment photography, and extraocular muscle movements (all of which must be performed as clinically indicated) and current glasses prescription (if applicable). The last follow-up visit should also include anterior segment photography of a fluorescein stained cornea. Representative images will be collected and stored centrally.~~

Reason for change: Upon review of 205678 (DREAMM 2) clinical trial ocular data, it was determined that ocular changes in patients treated with belantamab mafodotin are largely limited to the corneal epithelium and therefore data collection in clinical trial will be focused on corneal changes.

36. Section 7.3.7. Vital Signs

Removal of the following statement from both First and Subsequent Infusion:

~~Subjects may be discharged after the infusion has been completed if considered clinically stable and all other study procedures have been completed.~~

Reason for change: Statements contradicted another location which provided more detailed post infusion observation time frames.

37. Section 7.3.8. Electrocardiogram

… For triplicate ECGs, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. ~~The full set of triplicate ECGs should be completed in 4 minutes or less.~~

Reason for change: Removal of requirement to provide more flexibility in completion of triplicate ECGs.

38. Section 7.3.10. Clinical Safety Laboratory Assessments

… Asymptomatic elevations of lactate dehydrogenase (LDH) and creatine kinase (CK) and AST have been observed in study BMA117159. Subjects with significant elevations (≥x3 ULN) should, where possible, have a sample sent for central testing of CK and LDH isoenzyme levels…

Table 11 List of Clinical Laboratory Tests

… Corrected calcium with albumin …

…LDH and CK isoenzymes[4]… with footnote: Subjects with significant elevations (≥x3 ULN) and performed by central laboratory

… ~~Reticulocyte Count~~

Added peripheral blood mononuclear cell and whole blood RNA samples

Reason for change: One assessment deleted based on study team decision, and others added for additional efficacy and safety assessments.

39. Section 7.4.1. Blood Sample collection for Pharmacokinetics

Blood samples for pharmacokinetic (PK) analysis of belantamab mafodotin~~GSK2857916~~ (ADC and total monoclonal antibody [mAb]), cys-mcMMAF and corresponding blood samples for sBCMA as well as ~~and~~ pembrolizumab will be collected at the time points indicated in Table 12.~~Time and Events Table (Table 9 and Table 10). The actual date and time of each blood sample collection will be recorded.~~ The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring and need to be accompanied by a corresponding sBCMA sample. Note that sBCMA samples will also be collected independent from PK samples, as described in the Time and Events table. Samples for pembrolizumab will be collected and stored. Pembrolizumab PK samples will only be analysed if clinical observations warrant it (e.g. to rule out or confirm suspicion of DDI).

~~Blood samples for pharmacokinetic (PK) analysis of belantamab mafodotinGSK2857916 (ADC and total mAb), cys-mcMMAF, and for potential PK analysis for pembrolizumab will be collected at the time points indicated in the Time and Events Table (Table 9).~~ Each PK sample should be collected as close as possible to the planned time relative to the dose (i.e., time zero) administered to the subject on PK days. The actual date and time of each blood sample collection will be recorded.

Table 1219 Pharmacokinetic and sBCMA blood sampling times

Cycle Day	Sampling Times	Belantamab Mafodotin	sBCMA	Pembrolizumab	Sampling window
C1D1	**Pre-dose belantamab mafodotin**	X	X		Within 30 minutes prior to start of infusion
	EOI belantamab mafodotin	X	X		Within 30 min **after** EOI
	Pre-dose Pembrolizumab[1]			***P***	Within 30 minutes prior to start of infusion
	EOI Pembrolizumab[1]			***P***	Within 30 min **after** EOI
	2 hr SOI belantamab mafodotin	X	X		±15 min
	24 hr SOI belantamab mafodotin	X	X		±1 hr
C1D4	**Any time**	X	X		±1 day

C1D8	**Any time**	X	X		+3 days
C2D1 & C5D1	**Pre-dose belantamab mafodotin**	X	X		Within 30 minutes prior to start of infusion
	EOI belantamab mafodotin	X	X		Within 30 min **after** EOI
	Pre-dose Pembrolizumab[1]			P	Within 30 minutes prior to start of infusion
	EOI Pembrolizumab[1]			P	Within 30 min **after** EOI
C8D1 & C11D1	**Pre-dose belantamab mafodotin**	X	X	X	Within 30 minutes prior to start of infusion
	EOI belantamab mafodotin	X	X		Within 30 min **after** EOI
C14D1 and every 3 cycles thereafter (i.e., C17, 20, until EOT)	**Pre-dose belantamab mafodotin**	X	X	X	Within 30 minutes prior to start of infusion
End of Treatment		X	X	X	
EOI = end of the infusion; SOI = start of the infusion, EOT = end of treatment; X = time relative to belantamab mafodotin dose; P = time relative to pembrolizumab dose 1. To be obtained pre- and post- first dose of pembrolizumab irrespective of any dose delay					

Reason for change: Introduced a table for collection of PK and sBCMA samples based on feedback to provide clarity.

40. Section 7.5.1. sBCMA Analysis

To measure any changes in ~~the levels of~~ soluble BCMA (sBCMA) concentration during the study, serum will be collected ~~to measure concentrations of sBCMA~~ at the time points specified in the Time and Events Tables (refer to Table 9 and Table 10) and per PK Table 12.

Reason for change: Revised wording and linked sampling information to PK Table due to collection of sBCMA samples at all PK timepoints.

41. Section 7.5.3., Subject Stratification/Predictive Biomarkers

… Though the majority of MM subjects express BCMA, the intensity of expression varies. To evaluate whether BCMA expression has utility in patient stratification, BCMA protein expression will be measured by IHC in malignant plasma cells at baseline, and other timepoints if available, ~~will be measured for BCMA expression by IHC~~ and will be correlated with clinical outcomes and potentially other biomarker or disease assessments. Because BCMA can also be detected in circulation, the soluble form (sBCMA) has the potential to serve as a surrogate marker~~for~~ of BCMA at the cell surface.~~BCMA marker.~~ This study will correlate subjects sBCMA levels with BCMA cell surface expression and clinical response….

… The timing of the collections may be adjusted on the basis of emerging data from this study or other new information, in order to ensure optimal evaluation of the pharmacodynamic and/or biomarker endpoints. Novel or emerging candidate biomarkers associated ~~and subsequently discovered biomarkers of~~with the biological response associated ~~with~~to advanced multiple myeloma, hematological malignancies and/or medically related conditions, as well as the biological and clinical responses to belantamab mafodotinGSK2857916 in combination with pembrolizumab, may also be evaluated. These analyses may include but are not ~~be~~ limited to:

- Tumor/bone marrow BCMA receptor expression by IHC and/or by RNA analyses.
- Soluble factors, including circulating cfDNA, blood~~analysis~~ and derivatives including cytokine/chemokine analysis of serum
- Immune cell characterization and/or profiling of peripheral blood and/or bone marrow aspirate samples by protein and/or RNA analyses
- Additional soluble marker measurements ~~to~~that include serum levels of sBCMA
- RNA/DNA/gene and/or protein analysis of tumor tissue/bone marrow aspirates or samples in circulation

Reason for change: Revised based on additions and changes related to immune cell characterization/profiling plans.

42. Section 7.5.4., Tumor Biomarker Analysis

… BCMA expression in ~~the~~ plasma cells ~~of~~from bone marrow aspirates or trephines will be evaluated at baseline, and other timepoints if available, by IHC~~for tumor cell expression of BCMA~~. Analysis of the immune context (immune cell characterization) of the bone marrow aspirate samples may also be performed to analyse the tumor microenvironment….

Reason for change: Revisions based on update to biomarker sampling plan.

43. Section 7.7.3. Exit Interview

…. The Exit Interview should~~will~~ be scheduled to be completed within approximately 21 days of the ~~last dose of study treatment~~ end of treatment visit~~for all available subjects~~.

Reason for change: Provide flexibility.

44. Section 9.4.1. Analysis Populations

… DLT Evaluable Population: will consist of subjects fulfilling the 'All Treated' population criteria during part 1 (Dose Escalation) and are followed up for a 21-day period or withdrawn within 21 days due to an AE meeting the definition of a DLT as defined in Section 4.2.3.1. …

Reason for change: Addition of new population to be analyzed.

45. Section 10.6. Study and Site Closure

…~~GSK may also close study sites which fail to recruit subjects within a predefined timeframe, as defined within the SRM.~~

Reason for change: Alignment with updated GSK protocol template.

46. Appendix 9: Belantamab mafodotin associated Corneal Event Severity Grading and Mitigation Strategy

~~In order to minimize the corneal toxicity, subjects must receive steroid eye drops as prophylaxis (such as: prednisolone phosphate 1%, or dexamethasone 0.1%) 1 drop QID starting 1 day prior to each GSK2857916 infusion, and continuing for a total of consecutive 7 days. Other equivalent eye drops may be considered after confirming with GSK. Omission or discontinuation of prophylactic steroid eye drops may be allowed under certain circumstances (e.g., in the setting of intolerability, contraindication, or toxicity secondary to steroid eye drops) upon discussion with the Medical Monitor.~~ …

… An ophthalmology (or optometrist, if an ophthalmologist is not available) consult is required for all subjects who develop signs or symptoms of corneal toxicity.~~ or require steroid eye drops for more than 7 days.~~ …

Prophylactic Measure[a]	Dose and Administration	Timing
~~Steroid eye drops[b]~~	~~Prednisolone phosphate 1%, or dexamethasone 0.1%, or equivalent, 1 drop QID~~	~~Begin 1 day prior to each dose of belantamab mafodotinGSK2857916 infusion, and continuing for a total of consecutive 7 days~~
Preservative-free artificial tears	Administer in each eye at least 4-8 times daily	Administer daily beginning on Cycle 1 Day 1 until EOT. ~~Allow 5-10 minutes between administration of artificial tears and steroid eye drops~~

~~b. Omission or discontinuation of prophylactic steroid eye drops may be allowed under certain circumstances (e.g., in the setting of intolerability, contraindication, or toxicity secondary to steroid eye drops) upon discussion with the Medical Monitor~~

Reason for change: After review of data from the primary analyses in study 205678 (DREAMM 2), there is no evidence that steroid eye drops were beneficial in preventing or mitigating corneal events. As a result, corticosteroid eye drops are no longer required in belantamab mafodotin clinical trials but can be used if clinically indicated per discretion of an eye-care specialist.

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Reason for signing: Approved	Name: Timothy Crossman Role: Approver Date of signature: 21-Feb-2022 17:46:12 GMT+0000

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