NON-INTERVENTIONAL STUDY PROTOCOL

UNIQUE IDENTIFIER	218905 Amendment 1
TITLE	Real-World Use of Belantamab Mafodotin for Multiple Myeloma: A Retrospective Assessment of Safety and Effectiveness using the Flatiron Health Database
STUDY ACCOUNTABLE PERSON	PPD, MPH PPD GlaxoSmithKline (GSK) 1250 S Collegeville Road Collegeville, PA 19426 PPD
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ABBREVIATIONS

AE	Adverse event
AG	Analysis Group
AESI	Adverse event of special interest
ASCT	Autologous stem cell transplant
BCMA	B-cell maturation antigen
BCVA	Best Corrected Visual Acuity
BEaMM	BLENREP Effectiveness and Safety in Multiple Myeloma
BMI	Body mass index
CAR-T	Chimeric antigen receptor T-cell
CI	Confidence interval
CR	Complete response
Dex	Dexamethasone
DoR	Duration of response
DoT	Duration of treatment
ECOG	Eastern Cooperative Oncology Group
EDM	Enhanced Datamart
EHR	Electronic health record
FDA	Food and Drug Administration
GSK	GlaxoSmithKline
ICD	International classification of diseases
IHD	Individual Human Data
IMiD	Immunomodulatory imide drug
IRB	Institutional review board
ISS	International Staging System
KM	Kaplan-Meier
KVA	Keratopathy and Visual Acuity
LOT	Line of therapy
mAB	Monoclonal antibody
mg/kg	Milligram per kilogram
MM	Multiple myeloma
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PDC	Proportion of days covered
PI	Proteasome inhibitor
PFS	Progression-free survival
PR	Partial response
REMS	Risk evaluation and mitigation strategy
RRMM	Relapsed or refractory MM
rwPFS	Real-world progression-free survival

sCR	Stringent complete response
SD	Standard deviation
SSDI	Social Security Death Index
TTNT	Time to next treatment
US	United States
VEO	Value, Evidence and Outcomes
VGPR	Very good partial response

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1. BACKGROUND AND RATIONALE

Multiple myeloma (MM) is a rare and incurable hematological malignancy that typically affects adults 60 years of age and older. According to the latest Global Cancer Observatory (GLOBOCAN) statistics, there were an estimated 176,404 new cases of MM globally in 2020, accounting for 0.9% of all cancer diagnoses.[1] In the United States (US), MM accounts for almost 2% of cancer diagnoses and over 2% of cancer deaths (more than double the global proportion).[2] Incidence has risen by 126% globally and over 40% in the US since 1990; however, the 5-year survival in the US has more than doubled over the past decades with the introduction of new targeted therapies and transplant techniques.[2]

Current MM therapies include glucocorticoids (e.g., dexamethasone), chemotherapy, proteasome inhibitors (PIs, e.g., bortezomib), immunomodulatory agents (IMiD, e.g., thalidomide, lenalidomide, and pomalidomide), monoclonal antibodies (mAbs, e.g., daratumumab, isatuximab, and elotuzumab), the bispecific B cell maturation antigen (BCMA) antibody teclistamab and the histone deacetylase inhibitor panobinostat. However, some patients have relapsed or refractory MM (RRMM) and do not respond to these therapies[3]. There is a clear unmet need for these patients whose median overall survival (OS) is approximately 7 to 10 months.[4]

Belantamab mafodotin (BLENREP™) is a first in-class anti-BCMA therapy approved for use in the US by the FDA based on data from the pivotal Phase II DREAMM-2 study (Study 205678).[5,6] DREAMM-2 is a phase II, open label, randomized, two-arm study investigating the efficacy and safety of two doses of belantamab mafodotin (3.4 milligrams per kilogram [mg/kg] vs. 2.5 mg/kg) in participants with MM who had ≥3 prior lines of therapy (LOTs), were refractory to a PI and an immunomodulatory agent, and had failed an anti-CD38 mAb.[5,6] After a 13-month follow-up, DREAMM-2 results showed an overall response rate (ORR) of 32% (97.5% confidence interval [CI], 21.7-43.6%) for the 97 patients who received the registration dose (i.e., 2.5 mg/kg), with 58% of responders achieving a very good partial response (VGPR) or better, including 2 stringent complete responses (sCRs) and 5 complete responses (CRs).[6] Median estimated duration of response (DoR), OS, and progression-free survival (PFS) were 11.0 months (95% CI, 4.2 months to not reached), 13.7 months (95% CI, 9.9 months to not reached), and 2.8 months (95% CI, 1.6–3.6 months), respectively.[6] The most frequent adverse reactions (≥30%) reported from 95 patients in DREAMM-2 who received belantamab mafodotin 2.5 mg/kg were keratopathy (71%) and thrombocytopenia (38%). The most reported serious adverse reactions were pneumonia (7%), pyrexia (7%), and infusion-related reactions (3%). Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received belantamab mafodotin, with 3% related to ocular adverse reactions.[6] In addition, 54% of patients experienced a dosage interruption and 29% experienced a dose reduction due to an adverse reaction.

In the US, belantamab mafodotin obtained accelerated approval on August 5, 2020 for the treatment of adults with RRMM who have received at least four prior therapies, including a PI, an iIMiD, and an anti-CD38 mAb. In November 2022, GSK announced that the DREAMM-3 phase III open-label, randomised head-to-head superiority trial of belantamab mafodotin monotherapy versus pomalidomide in combination with low dose dexamethasone (PomDex) in patients with relapsed or refractory multiple myeloma (RRMM), did not meet its primary endpoint of progression-free survival (PFS). As a result, GSK voluntarily withdrew the US marketing authorization for belantamab mafodotin.

To better understand the real-world management of RRMM patients exposed to belantamab mafodotin and the occurrence of ocular toxicity in routine clinical practice, the current study builds upon the objectives of the European Union (EU) BLENREP Effectiveness and Safety in Multiple Myeloma (BEaMM) study (study number 217240, document number TMF-14038548) and adapts them to the Flatiron Health Database, accounting for differences between the prospective data collected for EU BEaMM and the structured and unstructured electronic health record (EHR) data provided by Flatiron Health. The Flatiron Health data will include data collected under the additional Spotlight project (e.g. chart abstraction of select data elements, including ophthalmic monitoring and ocular adverse events of special interest [AESIs]), which started under the EU BEaMM protocol for further investigation of the unstructured EHR data. Findings will provide important insights into the management of ocular toxicity in routine clinical practice as well as the benefits and risks of belantamab mafodotin in the real world.

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3. OBJECTIVES

The goal of this study is to characterize RRMM patients treated with belantamab mafodotin with respect to their demographics and clinical characteristics, treatment history, ocular adverse events (AEs), ophthalmic monitoring visits, and clinical treatment effectiveness. CCI [redacted]. If the sample size is sufficient, outcomes for patients on belantamab mafodotin plus other therapies will also be explored. Frequencies of belantamab mafodotin in combination with other therapies will be evaluated prior to evaluating the study objectives.

3.1. Primary Objective

1. To characterize RRMM patients treated with belantamab mafodotin CCI [redacted] therapy per routine clinical care in terms of demographics, disease status, clinical characteristics, and treatment history (overall and by LOT)

3.2. Secondary Objectives

1. To characterize patients with AESIs related to belantamab mafodotin treatment, overall and by subgroups (e.g., by belantamab mafodotin treatment dose and frequency, ophthalmic disease history, and ocular AESI type, duration, and severity [overall and by LOT])

2. To describe frequency and timing of ophthalmic monitoring visits relative to belantamab mafodotin administration (for each treatment cycle; overall and by LOT, occurrence of ocular AESIs, as well as treatment dose and frequency)

3. To assess ocular AESIs and their impact on treatment discontinuation, interruption/delay, and dose modification, overall and by subgroups (e.g., severity, grade, seriousness, action taken, duration, treatment dose and frequency, ophthalmic monitoring, as well as treatment impact)

4. To evaluate persistence and adherence of patients treated with belantamab mafodotin

5. To describe reasons for belantamab mafodotin treatment discontinuation

6. To describe reasons of belantamab mafodotin treatment interruptions/delays, or dose modifications

7. To evaluate effectiveness of belantamab mafodotin in terms of ORR, DoR, duration of treatment (DoT), time to next treatment (TTNT), real-world progression-free survival (rwPFS), and OS

3.3. Exploratory Objective

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4. RESEARCH METHODOLOGY

4.1. Data Source

The study objectives will be addressed using the Flatiron Health Database, a longitudinal and demographically diverse patient-level clinical database that provides rich real-world data on cancer patients from over 280 cancer clinics, primarily community-based oncology practices, visited by more than 2.4 million US cancer patients. The data, updated monthly, contains elements extracted from structured EHRs that are mapped to a common terminology and normalized across different source systems (i.e., normalized data) and unstructured information abstracted from physicians' notes and other unstructured documents, such as radiology, pathology, and biomarker reports, as well as patient discharge summaries (i.e., enhanced and derived data).

Flatiron's Enhanced Datamart (EDM) is a disease-specific (in this study, MM-specific) dataset reflecting cancer patients' journey from diagnosis to treatment, including real-world outcomes, and will be complemented by a Spotlight project, a customized project that includes data delivery tailored to answer a specific research question.

Flatiron EDM's normalized data elements include demographics, diagnoses, visits, labs and vitals, medication administration, medication orders, performance status, and insurance status. Enhanced data elements include core cancer registry data elements (e.g., date of initial diagnosis, cancer stage). Additionally, the Flatiron Health Database provides validated mortality data curated from both structured and unstructured EHR fields, as well as external sources such as the Social Security Death Index (SSDI), and a commercial death dataset that mines data from obituaries, funeral homes, and other sources to provide death data that is current within a week of the death.

Project-specific data elements, will be extracted from unstructured fields of patient charts via a Spotlight project and will include the following: Charlson comorbidity index-based comorbidities, derived response, refractory status, presence of extramedullary disease

at diagnosis, detailed dosing of belantamab mafodotin, ocular exam details, and real-world AEs occurring during patients' eligible belantamab mafodotin-containing LOTs.

4.2. Study Population

Patients with RRMM treated with belantamab mafodotin will be selected according to the following criteria to form the study population:

4.2.1. Inclusion Criteria

- Confirmed diagnosis of MM
- ≥1 record for belantamab mafodotin (first observed record defines the index date)
- ≥18 years at index date

4.2.2. Exclusion Criteria

- Participation in an interventional clinical trial during the baseline period or on the index date (i.e., time of the first belantamab mafodotin administration)
    - Identification of participation in an interventional clinical trial will be based on records for administration of clinical study drugs, contingent on data availability
    - If a patient participated in an interventional clinical trial after belantamab mafodotin administration, the date of the first record for participation in the interventional clinical trial would represent the end of the patient's study period

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4.3. Study Design

This study will use a retrospective, longitudinal, observational cohort design to address the proposed study objectives. The study design scheme is depicted in **Figure 1** below.

- The ***index date*** is defined as the date of the first observed administration of belantamab mafodotin.
- The ***baseline period*** is defined as the period from the first reported MM diagnosis to the index date (excluding the index date)

- The ***post-index period*** spans from the index date until the end of follow-up (defined as the start of participation in an interventional clinical trial, end of clinical activity, end of data availability, or death; whichever comes first).

    - Clinical activity will be defined from the date of the first recorded interaction to the date of the last recorded interaction, where a recorded interaction between the patient and a healthcare provider will include visits, use of therapies or lab tests, vital assessments, ECOG assessments, or comorbidity diagnoses.

- The ***post-index treatment period*** is defined as the duration of the belantamab mafodotin line of treatment. This spans from the index date until the permanent discontinuation of belantamab mafodotin treatment (as observed in the data [see description of **treatment discontinuation** below] or as recorded clinician decision), the confirmed date of a new line of treatment, or the end of follow-up; whichever comes first.

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- The ***study period*** spans from the first MM diagnosis observed in the data until the end of the follow-up.

- ***Line of treatment*** will be identified based on the Flatiron algorithm specific to MM and will include regimen name, line number, maintenance therapy designation, as well as start and end dates.

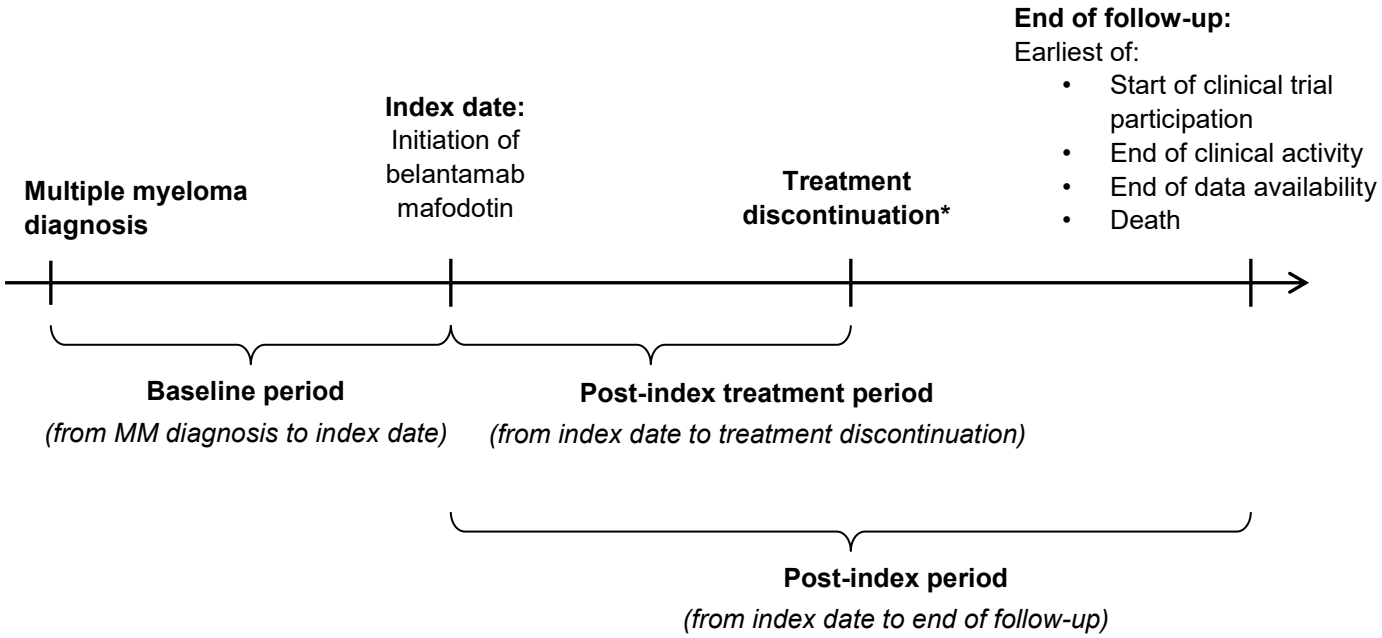
- A ***treatment cycle*** is defined as the belantamab mafodotin label-approved dosing interval, which is 21 days with a real-world scheduling grace period of +7 days (total of 28 days).

    - The treatment cycle length is currently based on the FDA-approved dosing interval but may be updated based on real-world data distributions observed in Flatiron Health

- ***Treatment discontinuation*** is defined as the earliest of the permanent discontinuation of belantamab mafodotin treatment (as observed in the data [e.g., minimum gap in days (e.g., 90 days) between last belantamab mafodotin administration and end of follow-up; gap length could be adjusted based on average length of treatment hold] or as recorded clinician decision), the confirmed date of a new line of treatment, or the date of the end of follow-up.

- ***Treatment interruption or delay*** is defined as a gap of at least 28 days and less than 90 days from the previous belantamab mafodotin administration.

Figure 1 Study Design Scheme



* Treatment discontinuation is defined as the earliest of the permanent discontinuation of belantamab mafodotin treatment (as observed in the data or as recorded clinician decision), the confirmed date of a new *line of treatment*, or the date of the end of follow-up.

4.4. Variables

The study variables include baseline characteristics, MM treatment patterns, ophthalmic monitoring, safety, and effectiveness.

4.4.1. Primary Endpoints

For the primary objective of characterizing RRMM patients treated with belantamab mafodotin per routine clinical care, data on demographics, disease and treatment history will be assessed on the index date or during the baseline period, as appropriate.

4.4.1.1. Demographics

Demographic characteristics will be assessed on the index date.

Variable	Definition	Timing
Age	Continuous variable (years)	Index date
Sex	Categorical variable: • Male • Female	Index date
Ethnicity/Race	Categorical variable • Asian • Black or African American • Hispanic or Latino • White • Other	Index date
Region	Categorical variable • Midwest • Northeast • West • South	Index date
Insurance type	Categorical variable • Commercial • Medicare • Medicaid	Index date
Practice type	Categorical variable • Community • Academic	Index date
Height	Continuous variable	Index date
Weight	Continuous variable	Index date
Body mass index (BMI)	Continuous variable	Index date
Smoking status	Categorical variable • Current smoker • Past smoker	

Variable	Definition	Timing
	• Never smoker • Unknown	

4.4.1.2. Disease and Treatment History

Disease history, treatment history, and other clinical variables will be assessed during the baseline period, unless otherwise specified, and conditional on availability in the Flatiron database or via the Spotlight project. Drug treatments for MM are listed in Appendix Table A1. MM treatments by category and class are described in Appendix Table A2.

Variable	Definition	Timing
ECOG Performance Status	Categorical variable: • 0 • 1 • 2 • 3 • 4	Index date
Year of MM diagnosis	Categorical variable: year at initial MM diagnosis (e.g., 2020, 2021)	Baseline period
Year of first observed belantamab mafodotin administration	Categorical variable: year at belantamab mafodotin administration • 2020 • 2021 • 2022	Index date
Extramedullary disease	Categorical variable (yes/no)	Baseline period
International Staging System (ISS) stage	Categorical variable: stage at initial MM diagnosis • I • II • III	Baseline period
MM subtype	Categorical variable: subtype at initial diagnosis • IgG • IgA • IgD • IgE • IgM • Biclonal (G,A) • Light chain MM • Other	Baseline period
Cytogenetic risk	Categorical variable:	Baseline period

Variable	Definition	Timing
	• High (i.e., del[17p], t[4;14], t[14;16], 1q21+ [gain or amplification]) • Standard	
Refractory status	Categorical variable, stratified by prior exposure to BMCA targeted therapy (e.g., chimeric antigen receptor T-cell [CAR-T] or bispecific antibodies): • Triple-class refractory • Quad-class refractory • Penta-class refractory	Index date

4.4.1.3. MM treatment history stratified by LOTs

These variables will be assessed for all prior LOTs as well as, specifically, for the latest medication used prior to initiation of belantamab mafodotin.

Variable	Definition	Timing
Number of previous LOTs	Categorical variable • 1 • 2 • 3 • 4 • 5+	Baseline period
Duration of previous LOT	Continuous variable (days)	Baseline period
Progression status on last LOT	Categorical variable (yes/no)	Baseline period
Description of each prior MM therapies[10,11]	Categorical variable • Regimen combination, based on all drugs in a regimen (e.g., PI + immunomodulatory drug [IMiD] + dexamethasone [Dex], IMiD + Dex, PI + Dex) • Drugs and drug classes (i.e., bendamustine/chemotherapy, bortezomib/PI, daratumumab/mAB, dexamethasone/corticosteroid)	Baseline period
Other therapies	Categorical variable (yes/no) • Autologous stem cell transplant (ASCT) • CAR-T • CCI [redacted]	Baseline period
Number of agents in the regimen	Categorical variable • Monotherapy	Baseline period

Variable	Definition	Timing
	• Doublet • Triplet • Quad • Other	

4.4.1.4. Other Clinical Characteristics

Variable	Definition	Timing
Pre-existing comorbidities	Categorical variable (yes/no): • Bone disease • Renal diseases, including diabetes • Pulmonary diseases • Cardiac diseases • Eye diseases, including history of dry eye, eye injuries affecting the best corrected visual acuity (BCVA) • Peripheral neuropathy • Cardiovascular disease • Cardiovascular toxicity	Baseline period
Ophthalmic health - BCVA	Continuous variable	Baseline period, and at the index date (separately)
Ophthalmic health - Corneal diagnoses	Categorical variable (yes/no): • Keratopathy • Microcyst-like epithelial changes • Other corneal findings/ conditions	Baseline period, and at the index date (separately)
Laboratory measurements	Continuous variables • Lactate dehydrogenase • Serum creatinine • Creatinine clearance using the Cockcroft-Gault formula	Baseline period
Frailty score	Categorical variable (conditional on availability) • 0 • 1 • ≥2	Baseline period

4.4.2. Secondary Endpoints

4.4.2.1. Belantamab Mafodotin Treatment Patterns

In addition to the primary endpoints, belantamab mafodotin treatment patterns will be assessed during the post-index treatment period, unless otherwise specified.

Variable	**Definition**	**Timing**
Average length of post-index period	Continuous variable, days	Post-index period
Average length of post-index treatment period	Continuous variable, days	Post-index treatment period
Average administered dose	Continuous variable, mg Average administered dose will also be reported among patients with 1, 2, 3, 4+ doses separately	Post-index treatment period
Average cycle length	Continuous variable, days	Post-index treatment period
Dose modification	Categorical variable (yes/no) Continuous variable Among patients with at least 2 doses: Proportion of patients who had: • increased dose • reduced dose Continuous variable Among patients with increased or reduced dose: • Average dose in mg prior to dose modification • Average dose in mg after dose modification • Mean change pre-post dose modification	Post-index treatment period
Time from index date to dose modification	Continuous variable, days	Post-index treatment period
Number of belantamab mafodotin administrations prior to first dose modification	Continuous variable	Post-index treatment period
Number of belantamab mafodotin administrations prior to subsequent dose modification(s)	Continuous variable	Post-index treatment period

Variable	**Definition**	**Timing**
Treatment interruption/delay	Categorical variable (yes/no) Continuous variable: Among patients with a treatment interruption/delay: Proportion of patients with dose modification Continuous variable Among patients with treatment interruption/delay and dose modification: • Average dose in mg prior to treatment interruption/delay • Average dose in mg after treatment interruption/delay • Mean change pre-post dose treatment interruption/delay	Post-index treatment period
Time from index date to treatment interruption/delay	Continuous variable, days	Post-index treatment period
Treatment discontinuation	Categorical variable (yes/no)	Post-index treatment period
Time from index date to treatment discontinuation	Continuous variable, days	Post-index treatment period
Number of belantamab mafodotin administrations prior to treatment discontinuation	Continuous variable	Post-index treatment period
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Concomitant medications,	Type of medication	Index date and post-index treatment

Variable	Definition	Timing
including ocular treatments if available	• MM medications (e.g., pomalidomide, dexamethasone) • Bone disease medications (e.g., bisphosphonates, cholecalciferol) • Diabetes and renal disease medications (e.g., insulin, angiotensin-converting enzyme inhibitors) • Pulmonary disease medications (e.g., bronchodilators, inhaled steroids) • Cardiovascular medications (e.g., anticoagulants, antiplatelets) • Eye disease medications (e.g., immunomodulators, prostaglandin analogs) Dose of most important concomitant medications will also be reported (assessed at index date only; based on data availability)	period, during belantamab mafodotin treatment cycles only (not including treatment interruptions/delays)

4.4.2.2. Ophthalmic Monitoring

Conditional on availability in the Flatiron EHR data and the Spotlight project, the following variables related to ophthalmic monitoring will be reported for each treatment cycle.

Variable	Definition	Timing
Time from belantamab mafodotin administration to ophthalmic examination	Continuous variable (days)	Index date and post-index treatment period
Time from ophthalmic examination to subsequent belantamab mafodotin administration	Continuous variable (days)	Baseline, index date and post-index treatment period
Type(s) of ophthalmic examination(s)	Categorical variable: • BCVA score (Snellen test or equivalent test) • Slit lamp examination • Other	Index date and post-index treatment period

Variable	**Definition**	**Timing**
Number of ophthalmic examinations	Continuous variable	Index date and post-index treatment period
Ratio of number of ophthalmic visits to belantamab mafodotin administrations	Continuous variable	Index date and post-index treatment period
Result of examination	Categorical variable, result for each eye: • BCVA score (continuous variable) • Corneal examination findings (categorical variable) – No change – Mild superficial keratopathy – Moderate superficial keratopathy – Severe superficial keratopathy – Corneal epithelial defect /ulcer • KVA scale grade for worst eye – Normal – Grade 1 – Grade 2 – Grade 3 – Grade 4	Index date and post-index treatment period
Use of contact lenses while on treatment	Categorical variable (yes/no)	Index date and post-index treatment period
Use of preservative-free lubricant eye drops while on treatment	Categorical variable (yes/no)	Index date and post-index treatment period
Use of bandage contact lenses while on treatment	Categorical variable (yes/no)	Index date and post-index treatment period
Use of cooling eye masks while on treatment	Categorical variable (yes/no)	Index date and post-index treatment period

4.4.2.3. Ocular AESIs

All ocular AESIs will be assessed (regardless of a causal relationship to belantamab mafodotin) on the index date and during the post-index period, separately.

Variable	Definition	Timing
Ocular AESI type	Categorical variable • Keratopathy • Blurred vision • Dry eye • Keratitis (ulcerative, infective, not specified)	Index date and post-index period
Ocular AESI severity at onset (based on data availability in physician notes)	KVA scale grade for worst eye • Normal • Grade 1 • Grade 2 • Grade 3 • Grade 4	Index date and post-index period, at AESI onset
Ocular AESI severity increase after onset	Increase in KVA grade for worst eye • Yes - specify highest grade • No	Post-index period
Ocular AESI seriousness at onset (based on data availability in physician notes)	Categorical variable • Fatal • Life-threatening • Persistent or significant disability/incapacity • Inpatient (or prolongation of existing) hospitalization • Medically important event • None of the above	Index date and post-index period
Ocular AESI seriousness increase after onset	Categorical variable Increase in seriousness (e.g., from medically important to inpatient or from life-threatening to fatal) • Yes – specify most serious event • No	Post-index period
Action taken within 70 days[1]	Categorical variables (yes/no) • Concomitant medication and other mitigation strategies (i.e., bandage contact lenses; based on data availability)	Index date and post-index period

Variable	Definition	Timing
	• Belantamab mafodotin treatment change and sequence of treatment changes – Dose decrease – Treatment interruption/delay – Treatment discontinuation • Change in ophthalmic monitoring (whether there was a greater number of ophthalmic monitoring visits in the 90 days following the AESI compared to the 90 days prior to the AESI) • No action taken	

[1] The 60-day time window may be modified based on clinical input.

4.4.2.4. Persistence and Adherence

Persistence and adherence to belantamab mafodotin will be assessed during the post-index treatment period.

Variable	Definition	Timing
Belantamab mafodotin persistence rate	Belantamab mafodotin non-persistence will be defined as treatment discontinuation or interruption (see Section 4.3 for complete definitions) Persistence to belantamab mafodotin will be defined as the proportion of patients still on treatment up to the end of follow-up (assessed using KM analysis) and KM rates at 3, 6, 9, and 12 months after the index date will also be reported	Index date and post-index period
Proportion of days covered (PDC)	PDC will be calculated for each patient as the total number of days with belantamab mafodotin during the time interval of interest divided by the duration of the interval of interest (i.e., 3, 6, 9, and 12 months), among the subset of patients with a minimum follow-up	Index date and post-index period

Variable	Definition	Timing
	period corresponding to the time interval of interest	

4.4.2.5. Reasons for Treatment Discontinuation

Reasons for treatment discontinuation will be assessed during the post-index treatment period.

Variable	Definition	Timing
Reasons for treatment discontinuation	Categorical variable • Ophthalmic AESIs • Other AEs • Patient decision unrelated to AEs (based on data availability) • Disease progression • End of treatment (based on data availability) • Death • Other reasons (Other reasons will be qualitatively analyzed and classified into categories)	Index date and post-index period

4.4.2.6. Reasons for Treatment Interruptions/Delays, or Dose Modifications

Reasons for treatment interruptions/delays, or dose modifications will be assessed during the post-index treatment period.

Variable	Definition	Timing
Reasons for treatment interruption/delays or dose modifications	Categorical variable • Ophthalmic AESIs • Other AEs • Other reasons (Other reasons will be qualitatively analyzed and classified into categories)	Index date and post-index period

4.4.2.7. Effectiveness of Belantamab Mafodotin

Effectiveness of belantamab mafodotin will be assessed during the post-index period.

Variable	Definition	Timing
Treatment response (i.e., overall response)	Categorical variable • Stringent complete response (sCR) • Complete response (CR) • Very good partial response (VGPR) • Partial response (PR) • No change/stable disease • Progressive disease (PD)	Post-index period
Duration of response (DoR)	Continuous variable calculated as the time from date of first response following the index date to the date of the first documented disease progression or death, whichever occurs first	Post-index period
Duration of treatment (DoT)	Continuous variable calculated as the time from the start of belantamab mafodotin treatment to the date of treatment discontinuation or death, whichever occurs first	Post-index period
Time to next treatment (TTNT)	Continuous variable calculated as the time from the end of the last administration of belantamab mafodotin treatment to the start of a new LOT	Post-index period
Real-world progression free survival (rwPFS)	Continuous variable calculated as the time from the start of belantamab mafodotin treatment to the date of the first documented disease progression or death, whichever occurs first	Post-index period
Overall survival (OS)	Continuous variable calculated as the time from the start of belantamab mafodotin treatment to the date of death due to any cause	Post-index period

4.5. Sample Size

The intent of this descriptive study is to obtain estimates of various patient characteristics. However, the final sample size will impact the precision of all estimates (i.e., 95% CIs around a proportion or a mean).

The expected number of unique patients with at least one prescription of belantamab mafodotin in the Flatiron Health Database is reported below (**Table 1**). The sample size of patients using belantamab mafodotin is around 300 patients (with the updated data cut which ranges up to December 31, 2022), CCI [redacted]

At a sample size of 250 patients, the 95% CI for a proportion of 50% (chosen because CIs are at their widest around 50%) would range from 43.6% to 56.4% (width 12.7%). See

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[redacted]

Notes:

1. Precision calculations based on these values were performed using the software PASS 2023, version 23.0.1.
2. Reference: Fleiss, J. L., Levin, B., Paik, M.C. 2003. Statistical Methods for Rates and Proportions. Third Edition. John Wiley & Sons. New York.
3. Reference: Newcombe, R. G. 1998. 'Two-Sided Confidence Intervals for the Single Proportion: Comparison of Seven Methods.' Statistics in Medicine, 17, pp. 857-872.

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Notes:

1. Precision calculations based on these values were performed using the software PASS 2023, version 23.0.1
2. Reference: Hahn, G. J. and Meeker, W.Q. 1991. Statistical Intervals. John Wiley & Sons. New York.

4.6. Data Analysis Considerations

This section summarizes the descriptive analytical approaches that will be implemented to address the study objectives outlined in **Section 3** CCI [redacted] All analyses will be conducted using SAS Enterprise Guide, Version 7.15 or its latest version (SAS Institute, Cary, NC).

4.6.1. Primary Objective: Characterization of RRMM Patients Treated with Belantamab Mafodotin per Routine Clinical Care

Demographics, clinical characteristics (including disease history), and treatment history will be assessed during the baseline period. Specifically, characteristics will include demographics evaluated on the index date, as well as clinical characteristics and treatment history assessed during the baseline period (see **Section 4.4.1** for a complete list of characteristics).

Descriptive statistics will include mean, SD, and median, Q1 and Q3 values for continuous variables, and relative frequencies and proportions for categorical variables.

4.6.2. Secondary Objective 1: Characterization of Patients with Ocular AESIs Related to Belantamab Mafodotin Treatment, Overall and by Subgroups

Patients with ocular AESIs will be identified using the International Classification of Diseases (ICD) diagnosis codes and via the Spotlight project. Demographics, clinical characteristics, and treatment history as described in **Section 4.4.1** will be assessed in patients with AESIs, overall and by subgroups (i.e., stratified by treatment dose, ophthalmic disease history, ocular AESI type, AESI duration, and/or AESI severity). Belantamab mafodotin treatment patterns as described in **Section 4.4.2.1** will be assessed in the overall population of patients with AESIs. Average cycle dose will be calculated as the sum of all doses divided by the total number of administrations per patient in a given cycle.

Descriptive statistics will include mean, SD, and median values for continuous variables, and relative frequencies and proportions for categorical variables.

4.6.3. Secondary Objective 2: Description of Ophthalmic Monitoring Relative to Belantamab Mafodotin Administration for Each Treatment Cycle

Endpoints related to ophthalmic monitoring (see **Section 4.4.2.2** for a complete list of endpoints) relative to belantamab mafodotin administration will be summarized for each treatment cycle, overall and stratified by monitoring before/after ocular AESIs, as well as by treatment administration.

Descriptive statistics will include mean, SD, and median values for continuous variables, and relative frequencies and proportions for categorical variables.

4.6.4. Secondary Objective 3: Assessment of Ocular AESIs and Impact on Treatment Discontinuation, Interruption/Delay, and Dose Modification

4.6.4.1. Ocular AESIs

This assessment will include descriptive analyses and the calculation of exposure-adjusted incidence rates and event rates for AESIs. The first analysis will report the number and proportion of patients as well as time to (specific) ocular AESIs, overall and stratified by subgroups of interest (e.g., severity, grade, seriousness, action taken, duration, as well as treatment dose and frequency). The second analysis will report the number and proportion of patients, severity, grade, seriousness, and duration of ocular AESIs by ophthalmic monitoring frequency, types, and timing relative to belantamab mafodotin administration. The third analysis will report the severity, grade, seriousness, and duration of ocular AESIs by treatment impact (i.e., dose modifications, duration of interruptions/delays, discontinuation). Descriptive statistics will include mean, SD, and

median values for continuous variables, and relative frequencies and proportions for categorical variables.

Exposure-adjusted incidence rates and event rates along with corresponding 95% CIs will be reported in the overall study population. The exposure-adjusted incidence rate is defined as the number of patients with at least one (specific) AESI during follow-up divided by the sum of person-months at risk in the study, where person-months at risk is defined as the sum of duration of follow-up among patients without AESIs and duration of follow-up until the date of the first (specific) AESI among patients with an AESI. The exposure-adjusted event rate is defined as the number of (specific) AESIs during follow-up divided by the sum of person-months at risk in the study (i.e., duration of duration of follow-up.

4.6.4.2. Dose Modifications, Treatment Interruptions/Delays, or Treatment Discontinuations Related to an Ocular AESI

This assessment will include descriptive statistics and time-to-event analyses. Descriptive statistics will summarize the number and proportion of patients with dose modifications, treatment interruptions/delays, or treatment discontinuations, as well as belantamab mafodotin treatment patterns after occurrence of an ocular AESI (i.e., order of treatment changes and timing) and the duration of dose modifications, treatment interruptions/delays, or discontinuations among patients with dose modification, treatment interruptions/delays, or discontinuations due to an ocular AESI. Descriptive statistics will include mean, SD, and median values for continuous variables, and relative frequencies and proportions for categorical variables.

Time to first dose modification, interruption/delay, or discontinuation will be assessed using Kaplan-Meier (KM) analysis. The median time to event (i.e., time point when 50% of patients had the event, if reached) will also be reported. The index date will be the date of initiation of belantamab mafodotin (as defined in **Section 4.3**). The event date will be the date of the first dose modification, interruption/delay, or discontinuation. Patients who do not experience the event will be censored at the end of follow-up.

4.6.5. Secondary Objective 4: Evaluation of Persistence and Adherence with Belantamab Mafodotin

Persistence to belantamab mafodotin (defined as patients still on treatment up to the end of follow-up) will be assessed using KM analyses. KM rates at 3, 6, 9, and 12 months after the index date as well as up to the end of the follow-up will be reported. Of note, patients not experiencing the event (i.e., treatment discontinuation) will be censored at the end of follow-up (see **Section 4.3** for complete definitions).

Adherence to belantamab mafodotin will be defined as the PDC over 3, 6, 9, and 12 months of follow-up and calculated as the total duration of treatment in days over 3, 6, 9, and 12 months divided by the total number of days in the corresponding period among

the subset of patients with a minimum follow-up period corresponding to the time interval of interest.

4.6.6. Secondary Objective 5: Description of Reasons for Treatment Discontinuation

Reasons for treatment discontinuation will be qualitatively analyzed and classified into main categories (i.e., ophthalmic AESIs, other AEs, and other reasons). Other reasons will be qualitatively analyzed and classified into broad subcategories. The relative frequency and proportion of reasons for discontinuations will be reported among patients with discontinuations.

4.6.7. Secondary Objective 6: Description of Reasons for Treatment Interruptions/Delays, or Dose Modifications

Reasons for treatment interruptions/delays, or dose modifications will be qualitatively analyzed and classified into main categories (i.e., ophthalmic AESIs, other AEs, and other reasons). Other reasons will be qualitatively analyzed and classified into broad subcategories. The frequency and proportion of reasons for treatment interruptions/delays, or dose modifications will be reported among patients with treatment interruptions/delays, or dose modifications.

4.6.8. Secondary Objective 7: Evaluation of Effectiveness

ORR will be reported using frequencies and proportions. Time to event outcomes (DoR, DoT, TTNT, rwPFS, and OS) will be analyzed using KM analysis and median with corresponding 95% CIs will also be reported.

4.6.8.1. Overall Response Rate

ORR will be defined as the proportion of patients with clinician-assessed response of any duration for each treatment response. ORR will be reported using frequencies and proportions, overall and by response type (i.e., sCR, CR, VGPR, and PR).

4.6.8.2. Duration of Response

The event date will be the earliest date of either disease progression or death. Patients still responding to treatment at the end of follow-up will be censored.

4.6.8.3. Duration of Treatment

The event date will be the earliest date of discontinuation or death. Patients still receiving treatment at the end of follow-up will be censored.

4.6.8.4. Time to Next Treatment

The event date will be the start of a new LOT that does not include belantamab mafodotin treatment. Patients who did not start a new LOT at the end of follow-up will be censored.

4.6.8.5. Real-World Progression-Free Survival

The event date will be the earliest date of the first documented disease progression or death. Patients who do not experience progression or death at the end of follow-up will be censored.

4.6.8.6. Overall Survival

The event date will be the date of death due to any cause. Patients still alive at the end of follow-up will be censored.

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[redacted]

4.7. Quality Control and Quality Assurance

AG maintains a policy to conduct standard internal audit of all literature review, market research, data collection, analytical modeling, and written materials. An internal audit consists of a review of all final work product materials and the underlying analysis and supporting source documentation by a team member or another AG conflict-clear employee who was not involved in the creation of the original work product. We will document and retain a quality review of all final deliverables, completed by a qualified individual independent of the writing team which incorporates the following steps:

1. Confirm that the source of the data and/or results has been documented and that results and data have been verified against the source

2. Check the internal consistency of any data presented in the document

3. Confirm that the conclusions are accurate, objective, balanced, and consistent with other published released results

4. Confirm that the format and content of the document are aligned with applicable external requirements

This study will be conducted according to GSK SOP52213 (Conducting Quality Control Review of Study Results generated using Existing Data in VEO and USVEO). This procedure requires documented evidence that the study protocol has been correctly interpreted and executed.

5. LIMITATIONS

Several limitations should be considered when interpreting results that are generated from this retrospective analysis. Unlike clinical trial settings, which describe specific definitions of study outcomes and scheduled assessments in the protocol, the assessment of outcomes in real-world clinical practice settings may not be consistent across subjects and across physicians. Specifically, in real-world observational studies, particularly those performed retrospectively, it is not possible to implement consistent monitoring and application of homogenous evaluation criteria that are inherent to clinical trial design. Therefore, outcomes may be subject to surveillance bias, which occurs when the outcome is more likely to be captured among patients who are followed more closely. For example, patients may be assessed less frequently in the real world compared to clinical trial settings, which could result in underestimating ocular toxicity or overestimating PFS (e.g., lack of regular assessments may result in delayed or even non-identification of toxicity or progression). Moreover, patients may seek care at different practices or hospitals, which may not always be captured in the EHR that feeds into the Flatiron Health Database. The real-world outcomes assessed in the present study will be defined as accurately as possible based on available data and the rigorous procedures in place at Flatiron Health.

Limitations may also arise from the complexities of extracting clinically relevant data using current EHR standards that have largely been designed for oncologists treating patients, tracking billing, and managing clinical care, although strict quality assurance procedures will serve to maximize the data integrity. Previously described quality control practices (see Section 4.7) that will be implemented from both the data preparation and data analysis aspects will further minimize any errors.

Additionally, the treatment patterns observed in this study are largely from the community setting, which may differ from treatment patterns observed elsewhere, such as academic medical centers. As such, the generalizability of the study results may be limited. Compliance related to oral therapies is also assumed. Given the observational nature of the study, causal relationships cannot be stated without additional evidence and methods. Information on concomitant medications received may be underreported since data captured in the Flatiron Health Database are from oncology-related visits only.

Baseline comorbidities of patients from the study sample will be identified by diagnosis codes in the EHR or presence of laboratory results as applicable, which may be incomplete, particularly if a patient was diagnosed in a non-Flatiron medical center. Therefore, identification of comorbidities may be underestimated and misclassification due to miscoding of these conditions or absence of the laboratory results may occur.

Finally, missing data from the EDM or the Spotlight project will be reported. Some data elements, such as information on reasons for treatment discontinuation, may only be available for a subset of patients.

6. STUDY CONDUCT, MANAGEMENT & ETHICS

This study will comply with all applicable laws regarding subject privacy. No direct subject contact or primary collection of individual human subject data will occur. Study results will be in tabular form and aggregate analyses that omits subject identification, therefore informed consent, ethics committee or institutional review board (IRB) approval are not required. Any publications and reports will not include subject identifiers.

6.1. Legal Basis for Processing Individual Human Data

The authors confirm that study data is Individual Human Data (IHD) not owned by GSK, but that the proposed use of the IHD aligns with the 'purpose of use' outlined in the source contract and/or the terms and conditions of use of the data source and will it comply with any specified prohibitions of use.

6.2. Adverse Event, Pregnancy Exposure, and Incident Reporting

This is a non-interventional database study based on secondary use of data collected for other purposes. No reporting of individual adverse events to regulatory agencies is planned for this database study because the Sponsor has no access to individual patient/subject records and it is not possible to link (i.e., identify a potential causal association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual adverse event reports. Where safety relevant results are considered, reporting will be provided at the aggregate level only. Pre-specified health outcomes of interest, including any that qualify as adverse events, will be summarized (e.g., the overall association between exposure and outcome) as part of any interim analysis and in the final study report as required.

7. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final study report will be prepared describing methods, results, and interpretation of results upon completion of the study. In addition, the results are intended to be presented at appropriate scientific meeting(s) and published in a peer-reviewed journal.

8. REFERENCES

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9. APPENDICES

9.1. Table A1. Drug treatments for multiple myeloma

Category[1]	Generic name[1]	Brand name[1]	Approval year for myeloma unless indicated otherwise[2]
Chemotherapy	Bendamustine	Bendeka, Treanda	2008, CLL, B-cell NHL
Proteasome inhibitor (PI)	Bortezomib	Velcade	2003
Proteasome inhibitor (PI)	Carfilzomib	Kyprolis	2012
Chemotherapy	Cisplatin	Platinol	1978, bladder, ovarian, testicular cancer
Chemotherapy	Cyclophosphamide	Cytoxan	1959, various
Monoclonal antibody	Daratumumab	Darzalex	2015
Corticosteroid	Dexamethasone	Decadron	1958, various
Chemotherapy	Doxorubicin	Doxil	2007
Monoclonal antibody	Elotuzumab	Empliciti	2015
Chemotherapy	Etoposide	Etopophos	1983, testicular cancer, SCLC
Proteasome inhibitor (PI)	Ixazomib	Ninlaro	2015
Immunomodulatory imide drug (IMiD)	Lenalidomide	Revlimid	2005
Histone deacetylase (HDAC) inhibitor	Panobinostat	Farydak	2015
Immunomodulatory imide drug (IMiD)	Pomalidomide	Pomalyst	2013
Targeted inhibitor	Selinexor	Xpovio	2019
Immunomodulatory imide drug (IMiD)	Thalidomide	Thalomid	2006
Targeted inhibitor	Venetoclax	Venclexta	2016, CLL, SLL

Source: Megan Braunlin, Rajesh Belani, Jacqueline Buchanan, Travis Wheeling & Christopher Kim (2021) Trends in the multiple myeloma treatment landscape and survival: a U.S. analysis using 2011–2019 oncology clinic electronic health record data, Leukemia & Lymphoma, 62:2, 377-386, DOI: 10.1080/10428194.2020.1827253

Abbreviations: CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma; SCLC, small cell lung cancer; SLL, small lymphocytic lymphoma.

Notes:

1. List primarily derived from 2020 National Comprehensive Cancer Network guidelines.
2. i.e., the medication is used off-label for multiple myeloma.

9.2. Table A2. Multiple myeloma treatment description by category

Combination	Class groups	Description
Monotherapy	Monoclonal antibody	Any of the following: daratumumab OR elotuzumab
	Proteasome inhibitor (PI)	Carfilzomib OR bortezomib OR ixazomib. If regimen includes other PIs assign category based on hierarchical priority: carfilzomib > bortezomib > ixazomib
	Immunomodulatory imide drug (IMiD)	Thalidomide OR lenalidomide OR pomalidomide
	Steroid monotherapy	Dex OR prednisone monotherapy only
	Targeted inhibitor	Selinexor OR venetoclax
	Other	Any other monotherapy not listed above including any clinical trial drugs
Doublet	Monoclonal antibodies + dex	Daratumumab OR elotuzumab AND dex
	PI + dex	Carfilzomib OR bortezomib OR ixazomib AND dex
	IMiD + dex	Thalidomide OR lenalidomide OR pomalidomide AND dex
	Other	Any other doublet not listed above including any doublet with a clinical trial drug
Triplet	Monoclonal antibodies + PI + IMiD	Daratumumab OR elotuzumab AND carfilzomib OR bortezomib OR ixazomib AND thalidomide OR lenalidomide OR pomalidomide
	PI + IMiD + chemotherapy	Carfilzomib OR bortezomib OR ixazomib AND thalidomide OR lenalidomide OR pomalidomide AND bendamustine OR bendamustine HCl OR cisplatin OR cyclophosphamide OR etoposide OR melphalan OR panobinostat OR vincristine OR vincristine sulfate OR vorinostat OR doxorubicin pegylated liposomal
	Monoclonal antibodies + PI + dex	Daratumumab OR elotuzumab AND carfilzomib OR bortezomib OR ixazomib AND dex
	Monoclonal antibodies + IMiD + dex	Daratumumab OR elotuzumab AND thalidomide OR lenalidomide OR pomalidomide AND dex
	PI + IMiD + dex	Carfilzomib OR bortezomib OR ixazomib AND thalidomide OR lenalidomide OR pomalidomide AND dex
	PI + chemotherapy + dex	Carfilzomib OR bortezomib OR ixazomib AND bendamustine OR bendamustine HCl OR cisplatin OR cyclophosphamide OR etoposide OR melphalan OR panobinostat OR vincristine OR vincristine sulfate OR

Combination	Class groups	Description
		vorinostat OR doxorubicin pegylated liposomal AND dex
	IMiD + chemotherapy + dex	Thalidomide OR lenalidomide OR pomalidomide AND bendamustine OR bendamustine HCl OR cisplatin OR cyclophosphamide OR etoposide OR melphalan OR panobinostat OR vincristine OR vincristine sulfate OR vorinostat OR doxorubicin pegylated liposomal AND dex
	Other	Any other triplet not listed above including any triplet with a clinical trial drug
Quad	Monoclonal antibodies + PI + IMiD + dex	Daratumumab OR elotuzumab AND carfilzomib OR bortezomib OR ixazomib AND thalidomide OR lenalidomide OR pomalidomide AND dex
	Other	Any other quad not listed above including any quad with a clinical trial drug

Source: Megan Braunlin, Rajesh Belani, Jacqueline Buchanan, Travis Wheeling & Christopher Kim (2021) Trends in the multiple myeloma treatment landscape and survival: a U.S. analysis using 2011–2019 oncology clinic electronic health record data, Leukemia & Lymphoma, 62:2, 377-386, DOI: 10.1080/10428194.2020.1827253

Abbreviations: Dex, dexamethasone; IMiD, immunomodulatory imide drug; HCl, hydrochloride; PI, proteasome inhibitor.

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