Observational Study Protocol

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REAL-WORLD ANALYSIS OF BELANTAMAB MAFODOTIN - BLMF CARE PATTERNS IN PATIENTS WITH RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA

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ABBREVIATIONS

ADC	antibody–drug conjugate
AE	adverse events
BCMA	B-cell maturation antigen
BLENREP	Belantamab mafodotin - blmf
CI	confidence interval
DCI	Duke Cancer Institute
EMR	electronic medical record
HCRU	Healthcare resource utilization
ICD	International Classification of Diseases
IHD	Individual Human Data
IMiD	immunomodulatory drugs
IQR	interquartile range
IRB	Institutional review board
NCCN DT	National Comprehensive Cancer Network Distress Thermometer
NLP	natural language processing
PI	proteasome inhibitors
REDCap	Research Electronic Data Capture
RRMM	refractory multiple myeloma
SAP	statistical analysis plan
SAS	Statistical Analytical Software
SD	standard deviation
SME	subject matter expert

1. BACKGROUND AND RATIONALE

Belantamab mafodotin - blmf (BLENREP) is a first-in-class anti-B-cell maturation antigen (BCMA) antibody–drug conjugate (ADC) that recently gained regulatory approval for the treatment of relapsed and/or refractory multiple myeloma (RRMM). As the first BCMA-targeted therapy to receive approval for multiple myeloma with an "off-the-shelf" outpatient administration, BLENREP addresses a significant unmet need in RRMM that is refractory to immunomodulatory drugs (IMiD), proteasome inhibitors (PI), and anti-CD38 mAb therapy, otherwise known as triple-class refractory myeloma. However, BLENREP is associated with frequent corneal ocular adverse events, which represents a unique toxicity in multiple myeloma therapeutics. Due to the potential of ocular adverse events, the administration of BLENREP requires a multidisciplinary approach with oncologists and eye care specialists to safely and effectively manage patients on the therapy.

2. OBJECTIVES

This study aims to describe the real-world use of BLENREP and associated patterns of care, including dosing and dose modification, and eye care specialist visits, and associated healthcare utilization and clinical outcomes in patients with relapsed and/or refractory multiple myeloma (RRMM) seen in the Duke Cancer Institute (DCI) clinics.

2.1. Primary Objectives

- Describe the demographic and clinical characteristics of RRMM patients who receive BLENREP treatment at the DCI clinics.
- Describe the treatment characteristics of BLENREP therapy (e.g. dose, length of treatment, delays and dose reductions, reasons for discontinuation) in these patients.
- Describe the clinical outcomes of RRMM patients who receive BLENREP treatment at the DCI clinics, as available.

2.2. Secondary Objectives

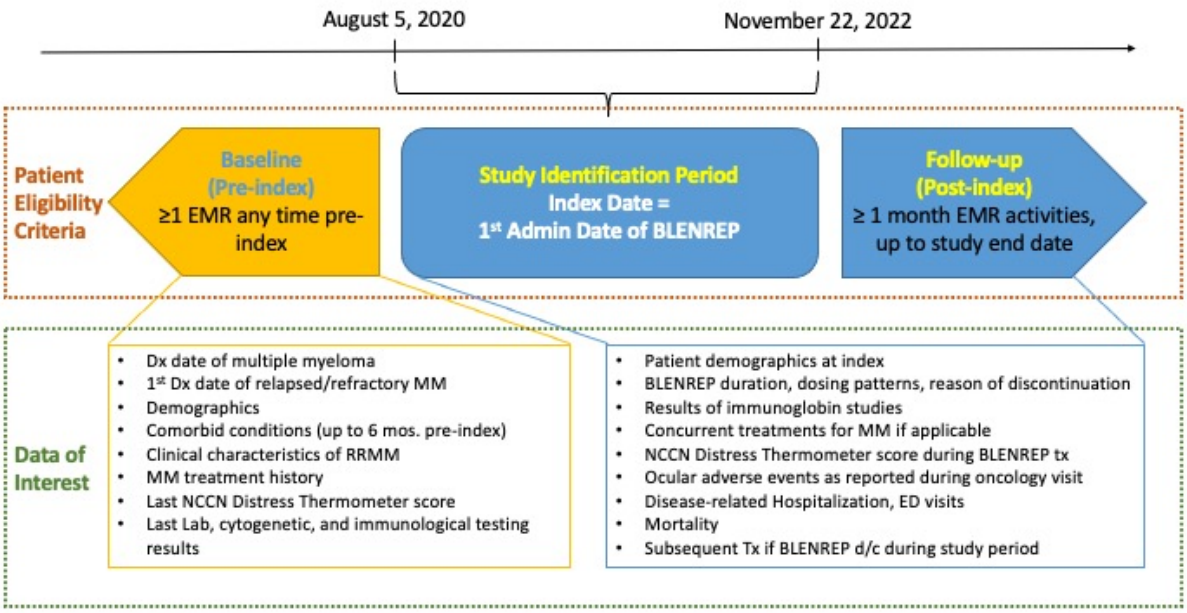
- Describe Ophthalmology visit patterns before and during treatment, investigating the specific adverse event of interest (keratopathy) as available.
- Explore the magnitude and sources of distress for these patients via the National Comprehensive Cancer Network Distress Thermometer (NCCN DT) instrument, as already collected in the DCI clinics per routine care.
- Describe the health care resource utilization (HCRU) at Duke Health for patients receiving BLENREP.

3. RESEARCH METHODOLOGY

3.1. Study Design

This is a single center retrospective observational study using electronic health record (EHR) data from routine cancer care practices at the DCI clinics. The study incorporates both cross-sectional and longitudinal components to yield novel insights regarding real-world use of BLENREP to treat RRMM and to describe the patient experience thereof. The study will analyze clinical data from adult patients with RRMM who were seen in the DCI outpatient oncology clinics on or after August 5, 2020. Demographic data, disease and treatment characteristics, data on comorbid conditions, and NCCN Distress Thermometer results will be manually abstracted from the medical record for each eligible patient using a standardized research electronic data capture (REDCap) case report form, to ensure data quality. Study feasibility was assessed in November 2021 via a preliminary medical record search. This search identified approximately 6000 patients with a corresponding ICD-9 or ICD-10 diagnosis code consistent with multiple myeloma who were seen in some capacity at Duke since January 2014. Approximately 30 of those patients also had a record of treatment with BLENREP between August 5, 2020, and Nov. 11, 2021. Note that BLENREP / Belantamab mafodotin – blmf received accelerated approval on August 5, 2020, by the Food and Drug Administration (FDA) for RRMM, and GSK (Glaxo SmithKline) requested withdrawal from the market on November 22, 2022.

Figure 1. Study Design Schema



3.2. Data Source / Data Collection

DCI's clinical EHR system will be used as the data source for chart abstractions into the REDCap case report forms.

3.2.1. DCI's EHR

The DCI EHR system, called Maestro Care, utilizes Epic (i.e., Epic Systems Corporation) healthcare software. Epic is a proprietary clinical database containing EHR data including medical diagnosis and procedures, prescriptions, laboratory results, provider notes, and practice-management data with longitudinal electronic patient data.

A particularly unique aspect of the data available within DCI standard care records is the inclusion of patient-reported outcomes (PRO) data. All patients seen in DCI clinics are asked to complete the NCCN Distress Thermometer instrument. This validated tool describes patients' experiences of illness, and contributors to their overall wellbeing (or lack thereof)[1]. The NCCN DT also collects information regarding patients' physical symptoms, emotional or social difficulties, functional issues, and spiritual well-being. Our team has successfully used these data in other studies[2,3,4], which have yielded unexpected and important findings about the relationship between patient-reported distress and clinical outcomes.

3.2.2. Sources of Data

Maestro Care captures a comprehensive collection of clinical and operational information that providers reference at the time of an encounter. This includes all details of a patient's office visit, including but not limited to laboratory results, procedures, and diagnoses, as well as provider, pathology, radiology notes, detailed records of all biologics administrations and the results from the NCCN Distress Thermometer. Data pertaining to prescription medications includes Generic Product Identifier, generic and brand names, date of prescription start, strength, administration instructions, and reasons for discontinuation. Maestro Care also contains data pertaining to patient demographics (e.g., age, gender, ethnicity, insurance type and state).

3.2.3. Data Collection (Structured and Unstructured Data)

The study will utilize carefully developed methods to input manually abstracted chart data into explicitly structured data elements within a set of standardized case report forms that we design for each unique research project. The structured data elements are then actively managed within the REDCap data environment, ensuring data provenance, security, and completeness.

Maestro Care leverages structured data as well as extensive unstructured data to diagnose and develop patient care plans. The structured data, such as those described in section 3.2.2 are combined with unstructured data that are included in clinicians' notes and clinical reports. These notes may provide additional details relevant to the patient profile and symptoms that may lead to treatment differences and patterns. The notes can be used to provide pre-categorized information that may be codified into structured variables (such as severity of disease and rationale behind treatment changes, etc.). Text fields often include valuable information, regarding signs and symptoms, family history, disease-severity scores, medication changes, and physician rationale behind prescribing decision. Abstracted physicians' notes are key to identify patients in the RRMM cohort as well as their disease burden.

3.3. Study Population

3.3.1. Inclusion Criteria

To be included in the final study sample, patients must meet the following inclusion criteria provided below:

- Age ≥ 18 years of age as of start of treatment with Belantamab mafodotin - blmf
- Patients with a corresponding ICD-9 or ICD-10 diagnosis code consistent with multiple myeloma seen at Duke.
- Patients with a record of starting treatment with Belantamab mafodotin - blmf for RRMM between August 5, 2020 and November 22, 2022.
- Patients having healthcare encounters at DCI ≥ 1-month post index

3.3.2. Exclusion Criteria

- Patients who were included in any clinical trial for BLENREP including expanded access clinical trials
- Age > 89 years of age as of start of index therapy

3.4. Variables

General descriptions of the study variables are provided below. Additional operational details will be included in the statistical analysis plan (SAP).

3.4.1. Patient Characteristics

The following patient characteristics will be measured as listed in the table below. Demographics will be summarized for the most recent measures on or prior to the index date, and all the other characteristics (i.e., clinical characteristics) will be abstracted at each clinic visit thereafter, until the end of follow-up. The end of follow-up will be defined as the date of the last clinical encounter available in the database prior to the IRB cut-off date.

Category	Variable	At Baseline	At Subsequent Clinical Encounters
Demographics	**Age:** Defined as of the index year.	**x**	
	Age groups: Patients will be assigned to one of the following age groups: 18-34, 35-44, 45-54, 55-64, 65-74, 75+.	**x**	
	Sex: Male, Female, Unknown	**x**	
	Weight	**x**	
	Height	**x**	
	Body mass index	**x**	

	Current Payer type: Whether the patient is covered by commercial, Medicaid, Medicare, self-insured, or was missing insurance payer type.	**x**	
	Race	**x**	
	RRMM diagnosed by DCI (yes/no)	**x**	
Comorbid Conditions	**NCI Comorbidity Index**	**x**	
Clinical Characteristics of RRMM	• Subtype (e.g., IgA, IgG, light chain only, etc.) • Cytogenetics • Immunologic Studies • Molecular testing results	**x**	
Administered systemic treatments for MM prior to index	• Medication Name • Start/end dates of treatment • Reason for discontinuation or change of treatment • Line of therapy • Prior HCST	**x**	**x**
Treatment with BLENREP	• Start/Re-start and end dates of treatment (as applicable) • Dosing • Line of therapy • Reasons for discontinuation or delays of therapy	**x**	**x**
NCCN Distress Thermometer	• DT Score • Problem List items	x	x
Clinical Outcomes assessments	• Myeloma markers (differs per patient and MM subtype; includes M-spike, UPEP, serum free light chains, etc.) • Physician Reported Notes • Disease response if available (using IMWG response criteria) • Lab tests/assessments • Death, if documented		x
Ophthalmologic Status	• Date of eye exam and results, as available. • Documentation of ocular-toxicity		x
HCRU	• Disease-related hospitalizations • Disease-related ED visits • Disease-related outpatient visits		x

3.5. Feasibility Counts/Sample Size/Power Calculation

In order to determine the feasibility of conducting the study, a query of structured EMR data was conducted in November 2021. Since January 2014, approximately 6000 patients with a corresponding ICD-9 or ICD-10 diagnosis code consistent with multiple myeloma were seen in some capacity at Duke. Approximately 30 of those patients also had a record of treatment with Belantamab mafodotin - blmf for RRMM between August 5, 2020 and Nov. 11, 2021. For this study, we would exclude patients who were included in any clinical trial, including expanded access clinical trials (approximately 2 patients). Thus, our cohort would include up to approximately 30 patients (accounting for additional patients starting on BLENREP between the proposal date and the final IRB approval date).

As the intention of this study is to be descriptive in nature to provide insight into patient characteristics, treatment patterns, and dosing, no formal hypothesis/power calculations/sample size estimates are required.

3.6. Data Analysis Considerations

Analyses will be undertaken by Duke University statisticians with expertise in patient-centered outcomes research. Details of the analyses will be furthered described in the statistical analysis plan (SAP) to be created at a later date.

Primary Objectives: Describe patient characteristics and treatment patterns for patients treated with BLENREP

Patient demographics and clinical characteristics (including diagnosis, laboratory measurements, general symptoms, and other comorbidities) will be summarized using descriptive statistics, consisting of the mean (± standard deviation [SD]) and median (with interquartile range [IQR]) values for continuous variables and frequency distributions and proportions for categorical variables.

Demographics will be described for the most recent measures on or prior to the index date. Clinical outcomes will be described until the end of follow-up. The end of follow-up will be defined as the date of the last clinical encounter available in the database prior to the IRB cut-off date. Summary statistics such as mean (± SD) and median (with IQR) values for continuous variables and frequency distributions and proportions for categorical variables will be calculated.

Time to clinical outcomes (i.e., time to response, duration of response, OS) will be analyzed using Kaplan-Meier analysis and median times to event will be reported (if the medians are achieved). 95% CIs will be reported in addition to the medians.

Treatment use and treatment patterns will be summarized using proportions (i.e., proportion of patients with select treatment for the control of symptoms). Sequences of treatment will also be described.

Secondary Objective: Describe Ophthalmology visit patterns and events

To the extent that they are available, events related to Ophthalmology outcomes (i.e., eye exams, outpatient visits, treatments for ocular toxicity, and other related HCRU events) will be summarized by the mean (± SD) and median (with IQR) number of events per patient per year and by the proportion and frequency distribution of patients with any occurrence of the respective

outcome. Treatment use and treatment patterns associated with ocular toxicity will be summarized using proportions (i.e., proportion of patients with select treatment for the control of symptoms).

Secondary Objective: Explore magnitude and sources of distress for these patients

The main outcome variable is the occurrence of actionable distress, defined as a NCCN DT score of 4 or higher. This outcome is clinically relevant because it is aligned with the medical practice guidelines for management of distress in cancer patients. The analysis will describe the proportion of clinic visits where actionable distress is reported during treatment with BLENREP, and the frequency of actionable distress over time.

Sources of distress will be assessed using the NCCN DT Problem List by examining the proportion of visits where types of problems are reported (e.g., physical or emotional problems). The frequency of individual types of problems, and the most commonly-reported problems will be examined descriptively.

Secondary Objective: Describe healthcare resource utilization (HCRU)

To the extent that they are available, HCRU (i.e., inpatient admissions, treatment-related outpatient visits, and emergency department visits) will be summarized by the mean (± SD) and median (with IQR) number of events per patient per year and by the proportion and frequency distribution of patients with any occurrence of the respective outcome. Likewise, mean (± SD) and median (with IQR) length of stay per year will be summarized for inpatient visits.

3.7. Quality Control and Quality Assurance

Duke ensures quality control of the data collection and analysis in several ways. First, the case report form is developed in a rigorous, iterative approach, and reviewed for clear and accurate data abstraction. The case report form (CRF) is then piloted with a few patients in an iterative trial and error approach, to ensure it functions as intended, and is able to capture even unanticipated scenarios, thus facilitating high-quality data abstraction. In addition, the study relies on initial cohort selection based upon data from the Duke Enterprise Data Unified Content Explorer (DEDUCE), a query platform for Duke's enterprise data warehouse, which ensures high-quality data cohorts based upon disease and treatment characteristics. Furthermore, our data abstraction tool, REDCap, is designed with data checks throughout to eliminate implausible entries (i.e. date ranges, branching logic, integers vs. decimals, etc.). REDCap also features access control logs, which ensure audit trails exist, tracking who and what was entered or changed in the participant records, and is thus superior to spreadsheets and other such databases. Finally, data analyses are reviewed by the team to ensure meaningful reports without unexplained anomalies potentially created by erroneous data.

4. LIMITATIONS

The limitations of the study are primarily a function of the descriptive nature of the study objective; thus, lacking a control group by which to put the study results in context. However, given the nature of disease and treatments under consideration, the study may provide key insights into RRMM and belamaf use from a real-world, clinical practice setting.

The retrospective nature of this study also calls for caution in the interpretation of the study findings:

- This study may be affected by potential biases including reporting bias, selection bias, measurement error, and non-random missing data.

- Data are from locations/facilities within the DCI network only, so resources used outside of the network may be underestimated.

- Assessment of symptoms and treatment characteristics in real-world settings may be based on heterogeneous criteria and frequency, and the level of recording may vary across healthcare sites and providers.

- Comorbidities may be underestimated as they will be captured using ICD 9/10 diagnosis codes and diagnoses recorded in oncology clinical practices. Physicians may not include comorbidities that do not require active interventions or workups, and diagnoses made in primary care settings may not necessarily be captured.

- The study population includes RRMM patients which is heterogeneous in terms of disease severity, symptoms and treatments.

- Assessment of lab and clinical measures will be based on patients with data on the relevant tests or records. The results may not be representative of the full RRMM study population.

- The study population identified through this data set may not be generalizable to other populations in the US.

- The analyses are exploratory and descriptive in nature; no formal hypothesis-testing will be performed.

5. STUDY CONDUCT, MANAGEMENT, AND 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 omit subject identification. Institutional Review Board (IRB) approval will be obtained prior to any data collection. Any publications and reports will not include subject identifiers.

5.1. 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 comply with any specified prohibitions of use.

6. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

All abstracts, posters or manuscripts for publication must be submitted to GSK for review and approval 30 days in advance.

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 meetings and published in a peer-reviewed journal.

7. REFERENCES

1. Baken DM, Woolley C. Validation of the Distress Thermometer, Impact Thermometer and combinations of these in screening for distress. *Psycho-oncology.* Jun 2011;20(6):609-614.

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