Summary Table of Study Protocol

Title	A retrospective analysis of pre-existing and acquired major adverse cardiovascular events (MACE) in a real world cohort of multiple myeloma (MM) patients treated with proteasome inhibitors
Protocol version identifier	20160154
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EU Post Authorisation Study (PAS) Register No	NA
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Product Reference	NA
Procedure Number	NA
Marketing Authorisation Holder(s)	NA
Joint PASS	No
Research Question and Objectives	1. Estimate the incidence of MACE and extended MACE in bortezomib- and carfilzomib- treated patients with MM 2. Compare pre-treatment cardiovascular risk profile and overall comorbidities in bortezomib- and carfilzomib-treated patients with MM 3. To identify risk factors for MACE and extended MACE in MM patients: overall, bortezomib-treated, and carfilzomib- treated
Country(-ies) of Study	USA
Author	John Groarke, Anju Nohria

Marketing Authorisation Holder

Marketing authorisation holder(s)	
MAH Contact	

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Investigator's Agreement

I have read the attached protocol entitled **A RETROSPECTIVE ANALYSIS OF PRE-EXISTING AND ACQUIRED CARDIOVASCULAR DISEASE IN A REAL WORLD COHORT OF PATIENTS TREATED WITH PROTEASOME INHIBITORS,** dated 26 August 2016, and agree to abide by all provisions set forth therein.

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<<I agree to ensure that Financial Disclosure Statements will be completed by:

- *me (including, if applicable, my spouse [or legal partner] and dependent children)*
- *my Subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)*

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.>>

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature	01 August 2016
John David Groarke	
Name of Investigator	Date (DD Month YYYY)

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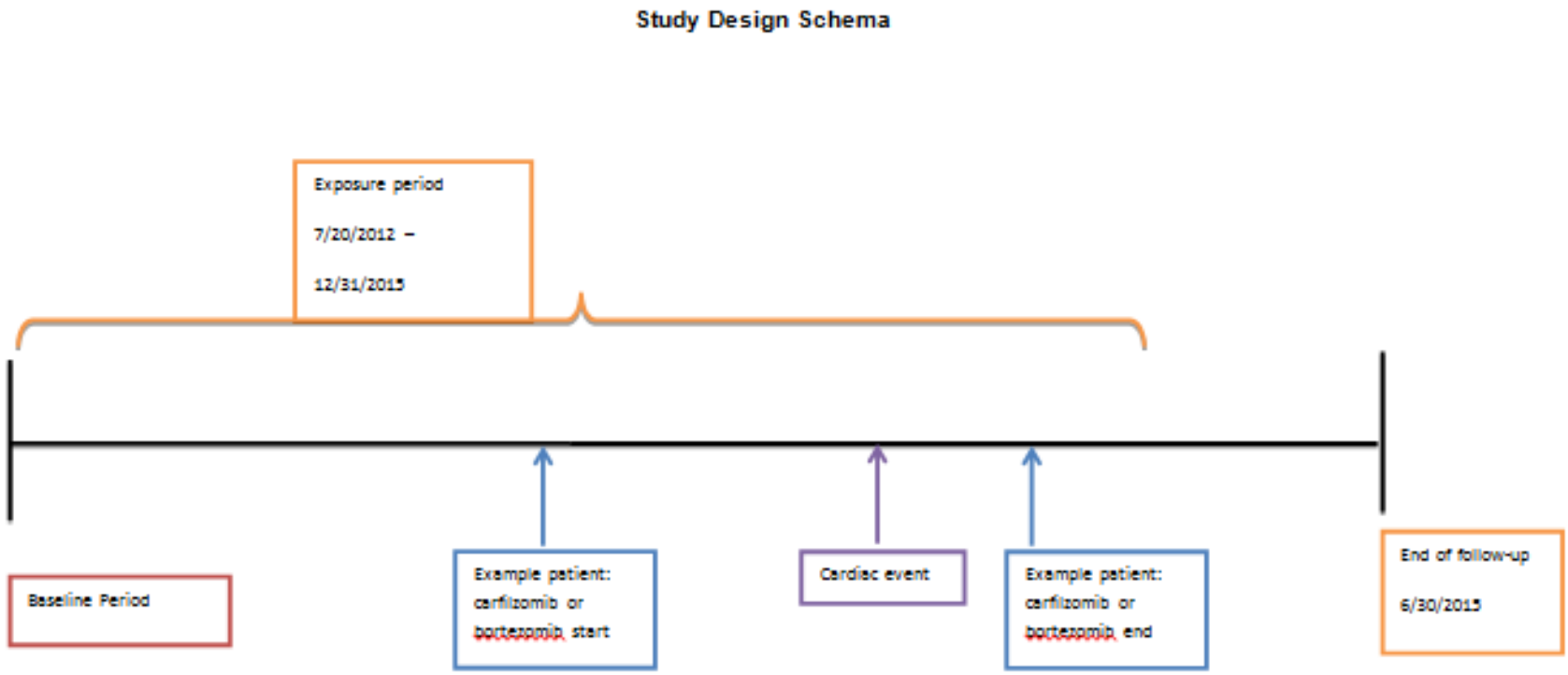
Study Design Schema



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1. Table of Contents

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List of Appendices

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2. List of Abbreviations

CRd- carfilzomib, lenalidomide, and dexamethasone
CTCAE- Common Terminology Criteria for Adverse Events
CV – cardiovascular
CVD – cerebrovascular disease
ECOG- Eastern Cooperative Oncology Group
EMR- electronic medical record
FDA- Food and Drug Administration
HF- heart failure
ICJME- International Committee of Medical Journal Editors
LVEF - left ventricular ejection fraction
IRB/IEC- institutional review board / independent ethics committee
MACE- major adverse cardiovascular events
MM- multiple myeloma
PVD- peripheral vascular disease
Rd- lenalidomide and dexamethasone
RPDR- Research Patient Data Registry
RRMM- relapsed and/or refractory MM
VTE - venous thromboembolic event

3. Responsible Parties

Key Sponsor Contacts:
Winifred Werther, PhD
Wwerther@amgen.com
Phone: (650) 244-3710

Primary Investigators:
John D Groarke MBBCh MSc MPH
Instructor of Medicine, Harvard Medical School,
Cardio-Oncology Program, Brigham and Women's Hospital/Dana Farber Cancer Institute,
Boston, MA 02115.
Email: jgroarke@partners.org

Anju Nohria MD MS,
Assistant Professor of Medicine, Harvard Medical School,
Cardio-Oncology Program, Brigham and Women's Hospital/Dana Farber Cancer Institute,
Boston, MA 02115.
Email: anohria@partners.org

4. Abstract

- Study Title

  A retrospective analysis of pre-existing and acquired major adverse cardiovascular events (MACE) in a real world cohort of multiple myeloma (MM) patients treated with proteasome inhibitors

- Study Background and Rationale

  Carfilzomib, a potent second-generation irreversible proteasome inhibitor, is being incorporated earlier and at higher doses in the treatment of MM. Cardiovascular (CV)

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toxicities have emerged as a potential complication of carfilzomib during clinical trials involving patients with both newly diagnosed and advanced multiple myeloma, and are reported to exceed CV toxicities associated with bortezomib. Given documented improvements in patient survival with the advent of novel therapies for multiple myeloma, there is a growing need to distinguish between pre-existing CV risk and treatment-specific risk. Furthermore, there is a need to define mechanisms underlying carfilzomib-associated CV toxicity, such that optimal preventive and early treatment strategies can be identified

- Research Question and Objective(s)
  - Primary objective:
    Estimate the incidence of MACE and extended MACE in bortezomib- and carfilzomib-treated patients with MM
  - Secondary objective:
    Compare pre-treatment cardiovascular risk profile and overall comorbidities in bortezomib- and carfilzomib-treated patients with MM
  - Exploratory objective:
    To identify risk factors for MACE and extended MACE in MM patients: overall, bortezomib-treated, and carfilzomib- treated
- Study Design/Type

  Retrospective analysis of cardiovascular outcomes of patients with MM treated with proteasome inhibitors.
- Study Population or Data Resource

  Patients eligible for this study will have received treatment for MM at one of the following institutions: Brigham & Women's Hospital, Dana Farber Cancer Institute, or Massachusetts General Hospital, Boston.

  Patient cohorts will include:
  a) 400 consecutive patients treated with bortezomib with MM who have received ≥ 1prior treatments, and
  a) 250 consecutive patients with relapsed and/or refractory MM treated with carfilzomib, who have received ≥ 1prior treatments prior to initiating carfilzomib.
- Summary of Patient Eligibility Criteria

  Inclusion Criteria:
  - Patients with a diagnosis of MM who have received ≥ 1prior treatments prior to treatment with carfilzomib or bortezomib
  - Treatment for at least 1 cycle with bortezomib (21 day cycle) or carfilzomib (28 day cycle)
  - Age ≥ 18 years

  Exclusion Criteria:
  - Use of bortezomib or carfilzomib as first line treatment for MM (i.e. no prior treatment).

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- Follow-up

  Follow up data on primary and secondary end points will be collected for all patients from time of exposure to bortezomib or carfilzomib through date of censoring, as defined by date of death or date of last known status.

  For patients in the bortezomib arm who subsequently transition to carfilzomib, follow-up will be censored at the time of carfilzomib initiation. Time from initiating bortezomib/carfilzomib to event will be sought for all end points. Length of follow-up will be recorded for each patient and will be defined as the period from initiation of proteasome inhibitor to date of death or date of last known follow-up/censoring.

- Variables

  Exposure Assessment
  Dose and frequency of proteasome inhibitor use will be recorded for each patient. Details of previous MM treatment regimens will be recorded for all patients. Data pertaining to duration of medication usage will be collected as comprehensively as is possible with retrospective data collection.

  Outcome Assessment
  Primary end point for this study is a composite of MACE defined as:
  death due to cardiovascular cause,
  surgical or percutaneous coronary revascularization,
  hospital admission for arterial thrombosis or heart failure (HF). Arterial thrombosis is defined as cardiovascular thrombosis in the form of non-fatal myocardial infarction, non-hemorrhagic stroke and peripheral arterial disease.

  Secondary end point is extended MACE defined as MACE plus:
  all-cause death,
  venous thromboembolic event (VTE) hospitalization,
  addition of antihypertensive or diuretic medications.

  Definitions of MACE and extended MACE events will be in keeping with published literature (Appendix A).

  Covariate Assessment
  Pre-treatment CV risk factors will be determined, and Charlson comorbidity score (Charlson et al. 1987) will be calculated for all patients. Eastern Cooperative Oncology Group (ECOG) performance status score will be recorded when available in the patient record. Hypertension, hyperlipidemia, diabetes mellitus, ischemic heart disease, cerebrovascular disease (CVD), peripheral vascular disease (PVD), congestive heart failure, arrhythmias, smoking history, obstructive sleep apnea, and obesity (body mass index > 30 kg/m2) will all be considered as CV risk factors. The electronic medical record (EMR) will be reviewed to determine pre-treatment status of these CV risk factors and of conditions included in Charlson comorbidity score (Appendix B). Pre-treatment use of cardiovascular medications (ANY antiplatelet agents, anticoagulants, beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, or antiarrhythmic agents) will also be sought. Data pertaining to duration of CV risk factors and duration of medication usage will be collected as comprehensively as is possible with retrospective data collection.

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The following laboratory values from within 1 week of initiating treatment with bortezomib/carfilzomib will also be recorded: hematocrit, platelets, creatinine, estimated glomerular filtration rate, albumin, sodium, and liver function tests.

- Study Sample Size

  Assuming an incidence of all-grade cardiotoxicity of 22.1% in the carfilzomib cohort(Siegel et al. 2013) and of 3.8% in the bortezomib arm(Xiao et al. 2014), we anticipate approximately 85 events with 250 patients in the carfilzomib cohort and 400 patients in the bortezomib cohort.

- Data Analysis

Primary objective

The incidence of MACE and extended MACE will be calculated separately for bortezomib- and carfilzomib- treated patients. Incidence of MACE and extended MACE will be calculated by counting incident events in the carfilzomib-treated cohort or bortezomib-treated cohort (numerator) and counting total person-years of eligible event time in the carfilzomib-treated cohort or bortezomib-treated cohort (denominator).

Secondary objective

Pre-treatment cardiovascular risk profile and overall comorbidities in bortezomib- and carfilzomib-treated patients will be compared. Categorical data will be presented as percentages and group comparisons made using Fisher exact test. Continuous data that are normally distributed will be presented as means +/- standard deviation and compared using Student t-test. Continuous data that are not normally distributed will be presented as medians with interquartile ranges and compared using Wilcoxon rank sum test.

Exploratory objective

Risk factors for MACE and extended MACE in MM patients will be analyzed overall and for bortezomib-treated and carfilzomib- treated cohorts, separately. A generalized logistic regression model will be used to identify predictors of MACE and extended MACE by a stepwise selection algorithm using each cohort separately and also both cohorts combined. Candidate variables will include pre-treatment CV risk factors, CV medications, ECOG score, and Charlson comorbidity score. Log rank test and Kaplan Meier curves will be used to compare time to event of MACE and extended MACE between bortezomib and carfilzomib cohorts, and hazard ratios for end points associated with bortezomib and carfilzomib will be calculated using Cox proportional hazards regression models; multivariate models will be used to adjust for differences identified between groups in univariate analyses. Given that propensity scores are a good alternative to matching to control for imbalances when there are seven or fewer events per confounder, additional analyses using propensity score matching are also proposed.

5. Amendments and Updates

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Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
Update	24 Oct 2016	Section 6 Milestones	The dates for the study timeline have been updated	In order to meet PASS regulations changes to the study contract have been made and are reflected in the timeline

6. Milestones

Protocol finalization	September 2016
IRB approval	September 2016
Start of data collection	November 2016
End of data collection	May 2017
Data Analyses	June/ July 2017
Report preparation	August 2017
Final report of study results	September2017
Manuscript preparation	October/ November 2017

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7. Rationale and Background

7.1 Diseases and Therapeutic Area

Treatment options for MM have significantly improved over the last decade with the advent of immunomodulatory agents (thalidomide, lenalidomide and pomalidomide) and proteasome inhibitors (e.g. bortezomib, carfilzomib), which have each impacted favorably on overall survival in this otherwise incurable hematologic malignancy (Laubach et al. 2009; Lonial et al. 2011; Pulte et al. 2014; Richardson et al. 2007). Carfilzomib is a second-generation irreversible proteasome inhibitor that received accelerated approval by the US Food and Drug Administration (FDA) in July 2012 for the treatment of patients with MM who have received at least two prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression during or within 60 days of completing treatment (Herndon et al. 2013). In 2015, carfilzomib was approved in combination with lenalidomide and dexamethasone for relapsed MM based on the results of a randomized trial of the carfilzomib combination regimen versus lenalidomide and dexamethasone alone. This phase 3 clinical trial comparing carfilzomib, lenalidomide, and dexamethasone (CRd) versus lenalidomide and dexamethasone (Rd) in patients with relapsed MM (ASPIRE trial) who received 1-3 prior regimens confirmed improved progression-free survival in CRd-treated patients (hazard ratio for progression or death= 0.69, 95% confidence interval: 0.57-0.83)(Stewart et al. 2015). In 2016, carfilzomib was approved in combination with dexamethesasone at a dose of 56mg/m2. Results from the ENDEAVOR trial indicated that progression free survival was greater among those who received carfilzomib/dexamethasone compared to bortezomib/dexamethasone (18.7 months vs. 9.4 months; P<0.0001).(Dimopoulos et al. 2016)

7.2 Rationale

Uncertainties surround the CV safety data available for carfilzomib. Cardiac safety data for single-agent carfilzomib is available for 526 patients with relapsed and/or refractory MM (RRMM) who took part in one of 4 phase II studies. These data indicate that any cardiac adverse event occurred in 22.1% of patients, hypertension in 14.3%, cardiac arrhythmia in 13.3%, and ischemic heart disease in 3.4% (Siegel et al. 2013). Aggregated cardiac failure events including congestive heart failure, pulmonary edema and decreased left ventricular ejection fraction (LVEF) were reported in 7.2% of patients; with the majority of events classified as grade 3 (severe) or 4 (life threatening) in severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (Siegel et al. 2013). Additionally, several deaths due to cardiac events reportedly occurred within hours or a few days of carfilzomib administration (Herndon et al. 2013). Overall, cardiac adverse events appear to have contributed to death in 8 of these 526 (1.5%) patients (Siegel et al. 2013). The nature of this acute and fatal cardiotoxicity is unclear. Cardiac adverse events of any type occur after just one dose of carfilzomib in 11.8% of patients and ultimately lead to drug discontinuation in 4.4% (Siegel et al. 2013). Although not exclusively cardiac in etiology, it is important to note that dyspnea is a common adverse effect of carfilzomib, reported in 19-42% of patients (Papadopoulos et al. 2013; Siegel et al. 2013; Stewart et al. 2015), which may have resolved without any change in carfilzomib therapy in 61% of patients (Siegel et al. 2013).

The frequencies of cardiac adverse events in patients treated with the CRd regimen, or in patients with newly diagnosed MM, are less well described and perhaps are not as common. Significant edema and dyspnea were reported in 47% and 15%, respectively, in 53 patients with newly diagnosed MM treated with this regimen, and interestingly patients with dyspnea responded promptly to diuretics (Jakubowiak et al. 2012). In another study of 84 patients with RRMM treated with CRd, cardiac adverse events of any grade and ≥

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grade 3 occurred in 19% and 7%, respectively; grade 3/4 cardiac adverse events included myocardial infarction, bradycardia, tachycardia, sick sinus syndrome, and coronary artery disease, but not all events were considered related to carfilzomib, reflecting the complexity of such patients in the advanced disease setting (Wang et al. 2013). All-grade hypertension, cardiac failure and ischemic heart disease were observed in 14.3%, 6.4%, and 5.9%, respectively of CRd-treated patients (n= 392), exceeding corresponding rates of 6.9%, 4.1%, and 4.6% among Rd only-treated patients (n= 389) of the ASPIRE trial (Stewart et al. 2015). In addition, the venous thromboembolic rate was 13% in the CRd-arm and 6% in the Rd-arm despite protocol-mandated use of thromboprophylaxis (FDA 2015). The propensity for hypertension with carfilzomib exposure appears consistent across trials (Siegel et al. 2013; Stewart et al. 2015).

Early indications suggest that there may be a dose response relationship governing carfilzomib-induced adverse CV events. In a recent trial where higher dose (56 mg/m^2) carfilzomib was utilized in a cohort of 44 RRMM patients, who were heavily pre-treated, the prevalence of carfilzomib-related grade 3/4 hypertension and heart failure (defined as LV systolic dysfunction, pulmonary edema, and/or other criteria) increased to 25% and 11% respectively (Lendvai et al. 2014). Hypertension necessitated carfilzomib dose reductions in 11% of this patient cohort. Although heart failure appears more prevalent during early treatment with carfilzomib, later presentations were observed after 12 and 14 cycles of treatment. Adverse cardiac events were again observed with higher frequency during the first 18 cycles of carfilzomib than in later cycles in the ASPIRE trial (Stewart et al. 2015).

It is important to note that not all cardiotoxicities are a direct consequence of carfilzomib treatment. Patients who have been heavily pre-treated with previous chemotherapies may be predisposed to future CV events during subsequent carfilzomib treatment. MM can also have direct effects on the CV system that are unrelated to treatment. For example, heart failure may be due to cardiac amyloidoisis, hyperviscosity syndrome, or high-output failure (Allegra et al. 2010). Coronary microvascular dysfunction, even in the absence of epicardial coronary disease, is highly prevalent in patients with light chain cardiac amyloidosis and can complicate MM or predispose patients to further cardiotoxicity (Dorbala et al. 2014). Finally, MM is most frequently diagnosed in the older population, with nearly half of patients over 70 years of age at the time of diagnosis (Pulte et al. 2014), an age group that has a high prevalence of CV risk factors and/or pre-existing CV disease. Importantly, CV risk factors likely predispose to carfilzomib-related cardiotoxicity. For example, a pre-treatment history of hypertension increases the likelihood of developing carfilzomib-related hypertension (Lendvai et al. 2014). Similarly, pre-treatment history of anthracycline exposure, hypertension, hyperlipidemia, and smoking history are prevalent among patients who develop carfilzomib-related heart failure (Lendvai et al. 2014). Thus, the relative contribution of MM, prior treatments, underlying CV disease and/or risk factors, or any combination of these factors, to the overall incidence of cardiac adverse events among patients receiving treatment for MM is uncertain.

Expanding indications for carfilzomib will undoubtedly increase the population at risk for drug-specific adverse events. This emphasizes the need to accurately quantify the incidence of CV adverse events and to better understand the mechanism of cardiotoxicity, such that optimal preventive and early treatment strategies can be identified to facilitate continued safe use of this effective therapy. Identification of patient factors that predispose to carfilzomib CV toxicity should help risk stratify patients embarking on carfilzomib treatment. Pre-treatment optimization of CV status, such as controlling hypertension, may reduce subsequent cardiotoxicity but there is a need for data to support such strategies. In conclusion, carfilzomib is an increasingly prescribed and highly effective second-generation irreversible proteasome inhibitor with promising clinical activity and otherwise favorable tolerability. However, it appears carfilzomib can be associated with significant

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CV toxicity. The true incidence and mechanisms underlying carfilzomib-associated CV toxicity remain uncertain and warrant further study, especially as in a minority of patients, this can be manifest as fulminant congestive heart failure and/or sudden death. Importantly, this cardiotoxicity signal was identified in previously treated patients and in a population of MM patients with advanced disease where the CV risk profile is not entirely known. Recognizing that carfilzomib provides meaningful clinical benefit to patients with MM, close collaboration is needed between hematologists and cardiologists to better identify patients at risk for CV events in order to develop mitigation strategies and/or optimize management. This is of particular importance as carfilzomib is incorporated earlier into treatment and tested at higher doses, as well as used in combination as part of rational multi-agent regimens with known synergy that continue to further improve patient outcome.

7.3 Statistical Inference (Estimation or Hypothesis[es])

The primary objectives are observational and descriptive. The purpose of the study is to estimate the incidence of CV outcomes for bortezomib- and carfilzomib- treated patients. For the exploratory objective, Kaplan Meier curves will compare time to CV event rate between the two groups- bortezomib- and carfilzomib- treated patients.

8. Research Question and Objectives

8.1 Primary

Estimate the incidence of MACE and extended MACE in bortezomib- and carfilzomib-treated patients with MM

8.2 Secondary

Compare pre-treatment cardiovascular risk profile and overall comorbidities in bortezomib- and carfilzomib-treated patients with MM

8.3 Exploratory

To identify risk factors for MACE and extended MACE in MM patients: overall, bortezomib-treated, and carfilzomib- treated

9. Research Methods

9.1 Study Design

Retrospective analysis of cardiovascular outcomes of patients with MM treated with proteasome inhibitors.

9.2 Setting and Study Population

Patients eligible for this study will have received treatment for MM at one of the following institutions: Brigham & Women's Hospital, Dana Farber Cancer Institute, or Massachusetts General Hospital, Boston. Patient cohorts will include:
a) 400 consecutive patients treated with bortezomib with MM who have received ≥ 1prior treatments, and
a) 250 consecutive patients with relapsed and/or refractory MM treated with carfilzomib, who have received ≥ 1prior treatments prior to initiating carfilzomib.

9.2.1 Study Period

All patients will have received treatment at one of the above mentioned institutions between 20 July 2012 and 31 December 2015.

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9.2.2 Selection and Number of Sites

The study will be conducted at Brigham & Women's Hospital. The investigator will have access to patient data at the following institutions: Brigham & Women's Hospital, Dana Farber Cancer Institute, and Massachusetts General Hospital, Boston

9.2.3 Subject/Patient/Healthcare Professional Eligibility

9.2.3.1 Inclusion Criteria

- Patients with a diagnosis of MM who have received ≥ 1prior treatments prior to treatment with carfilzomib or bortezomib
- Treatment for at least 1 cycle with bortezomib (21 day cycle) or carfilzomib (28 day cycle)
- Age ≥ 18 years

9.2.3.2 Exclusion Criteria

- Use of bortezomib or carfilzomib as first line treatment for MM (i.e. no prior treatment).

9.2.4 Matching

Matching will not occur during patient selection. Patients who meet inclusion criteria will be selected consecutively. For exploratory analysis of risk factors, candidate variables for propensity score matching will include pre-treatment CV risk factors, CV medications, ECOG score, and Charlson comorbidity score.

9.2.5 Baseline Period

The baseline period during which relevant baseline covariates will be assessed includes assessments carried out within 4 weeks prior to initiation of treatment with bortezomib or carfilzomib.

9.2.6 Study Follow-up

Follow up data on primary and secondary end points will be collected for all patients from time of exposure to bortezomib or carfilzomib through date of censoring, as defined by date of death or date of last known status.
For patients in the bortezomib arm who subsequently transition to carfilzomib, follow-up will be censored at the time of carfilzomib initiation. Time from initiating bortezomib/carfilzomib to event will be sought for all end points. Length of follow-up will be recorded for each patient and will be defined as the period from initiation of proteasome inhibitor to date of death or date of last known follow-up/censoring.

9.3 Variables

9.3.1 Exposure Assessment

Dose and frequency of proteasome inhibitor use will be recorded for each patient. Details of previous MM treatment regimens will be recorded for all patients. Data pertaining to duration of medication usage will be collected as comprehensively as is possible with retrospective data collection

9.3.2 Outcome Assessment

- **Primary end point** for this study is a composite of MACE defined as:
  - death due to cardiovascular cause,
  - surgical or percutaneous coronary revascularization,

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  - hospital admission for arterial thrombosis or heart failure (HF). Arterial thrombosis is defined as cardiovascular thrombosis in the form of non-fatal myocardial infarction, non-hemorrhagic stroke and peripheral arterial disease.

- **Secondary end point** is extended MACE defined as MACE plus:
  - all-cause death,
  - venous thromboembolic event (VTE) hospitalization,
  - addition of antihypertensive or diuretic medications.

- Definitions of MACE and extended MACE events will be in keeping with published literature (Appendix A).

9.3.3 Covariate Assessment

Pre-treatment CV risk factors will be determined, and Charlson comorbidity score (Charlson et al. 1987) will be calculated for all patients. Eastern Cooperative Oncology Group (ECOG) performance status score will be recorded when available in the patient record. Hypertension, hyperlipidemia, diabetes mellitus, ischemic heart disease, cerebrovascular disease (CVD), peripheral vascular disease (PVD), congestive heart failure, arrhythmias, smoking history, obstructive sleep apnea, and obesity (body mass index > 30 kg/m2) will all be considered as CV risk factors. The electronic medical record (EMR) will be reviewed to determine pre-treatment status of these CV risk factors and of conditions included in Charlson comorbidity score (Appendix B). Pre-treatment use of cardiovascular medications (ANY antiplatelet agents, anticoagulants, beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, or antiarrhythmic agents) will also be sought. Data pertaining to duration of CV risk factors and duration of medication usage will be collected as comprehensively as is possible with retrospective data collection.
The following laboratory values from within 1 week of initiating treatment with bortezomib/carfilzomib will also be recorded: hematocrit, platelets, creatinine, estimated glomerular filtration rate, albumin, sodium, and liver function tests.

9.3.4 Validity and Reliability

Primary and secondary end points will be determined for all patients using a combination of EMR review, Partners Healthcare Research Patient Data Registry (RPDR), and National Death Index. All CV events will be adjudicated by two cardiologists who will be blinded to type of proteasome inhibitor. The cause of death will be considered of CV origin if the primary cause is defined as: cardiac, vascular, non-hemorrhagic stroke, other and unknown as outlined in Appendix A.

9.4 Data Sources

Data sources for determining exposures, outcomes and all other variables relevant to the study objectives will be sought for all patients by review of EMR, Partners Healthcare RPDR, and National Death Index.

9.5 Study Size

Assuming an incidence of all-grade cardiotoxicity of 22.1% in the carfilzomib cohort (Siegel et al. 2013) and of 3.8% in the bortezomib arm (Xiao et al. 2014), we anticipate approximately 55 events among the 250 patients in the carfilzomib cohort and approximately 20 events among the 400 patients in the bortezomib cohort.

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Assuming 250 patients will be treated with carfilzomib in this time span, the estimated confidence interval of the event proportion in this population will be as follows (Wald statistic):

Estimated Events	Estimate	Lower, Upper 95%
25	10%	6.3%-14%
50	20%	15%-25%
75	30%	24%-36%

EpiTools: http://epitools.ausvet.com.au/content.php?page=home

9.6 Data Management

9.6.1 Obtaining Data Files

Data will be sought for all patients by review of EMR, patient questionnaires, Partners Healthcare RPDR, and National Death Index.

9.6.2 Linking Data Files

Not applicable to this study.

9.6.3 Review and Verification of Data Quality

Partners RPDR data have been used extensively by the investigators and the quality of the data is high with a very low frequency of patients with missing values or with values out of range for core clinical and demographic variables. Edit, range, and logic checks will nonetheless be performed on each variable of interest by the study programmer to ensure quality and completeness.

9.7 Data Analysis

9.7.1 Planned Analyses

9.7.1.1 Primary Analysis

Primary objective
The incidence of MACE and extended MACE will be calculated separately for bortezomib- and carfilzomib- treated patients. Incidence of MACE and extended MACE will be calculated by counting incident events in the carfilzomib-treated cohort or bortezomib-treated cohort (numerator) and counting total person-years of eligible event time in the carfilzomib-treated cohort or bortezomib-treated cohort (denominator).

Secondary objective
Pre-treatment cardiovascular risk profile and overall comorbidities in bortezomib- and carfilzomib-treated patients will be compared. Categorical data will be presented as percentages and group comparisons made using Fisher exact test. Continuous data that are normally distributed will be presented as means +/- standard deviation and compared using Student t-test. Continuous data that are not normally distributed will be presented as medians with interquartile ranges and compared using Wilcoxon rank sum test.

Exploratory objective
Risk factors for MACE and extended MACE in MM patients will be analyzed overall and for bortezomib-treated and carfilzomib- treated cohorts, separately. A generalized logistic regression model will be used to identify predictors of MACE and extended MACE by a stepwise selection algorithm using each cohort separately and also both cohorts combined. Candidate variables will include pre-treatment CV risk factors, CV medications, ECOG score, and Charlson comorbidity score. Event rates will be compared between the carfilzomib and the bortezomib cohorts.

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Assuming time to event data are available for a sufficient number of events, log rank test and Kaplan Meier curves will be used to compare time to event of MACE and extended MACE between bortezomib and carfilzomib cohorts. Hazard ratios for end points associated with bortezomib and carfilzomib treated cohorts will be calculated using Cox proportional hazards regression models; multivariate models will be used to adjust for differences identified between groups in univariate analyses. Given that propensity scores are a good alternative to matching to control for imbalances when there are seven or fewer events per confounder, additional analyses using propensity score matching are also proposed.

All analyses will be performed using SAS, version 9.3 (SAS Institute).

9.7.1.2 Final Analysis

All analyses will be performed when data collection complete. Data will be analyzed at this single time point only for this study.

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Given the retrospective nature of this study, it is anticipated that there will be missing data and incomplete follow up data. However, the data sought for all patients is standard and should be available for the majority of patients. Patients will be omitted from the study if key variables are missing despite all reasonable efforts to obtain these data. Key variables include confirmed exposure to carfilzomib or bortezomib and confirmed cardiac event. A consort diagram will be presented with the final results to highlight how many subjects were omitted from the study due to missing data. All patients will be censored at time of death or time of last confirmed status update.

9.7.2.3 Descriptive Analysis

9.7.2.3.1 Description of Study Enrollment

Patients will be enrolled consecutively during a specified time period when carfilzomib was available for treatment in the participating institutions.

9.7.2.3.2 Description of Subject/Patient Characteristics

Patients treated for MM at the participating institutions will be enrolled.

9.7.2.4 Analysis of the Primary, Secondary and Exploratory Endpoint(s)

The primary endpoint is the incidence of MACE and the secondary endpoint is extended MACE. Incidence rates for each type of cardiac event will be estimated using traditional methods (eliminating those with prevalent cardiac events at treatment start date from the numerator and denominator; prevalent cardiac conditions is defined by occurrence of a MACE prior to bortezomib or carfilzomib exposure). A patient will be counted in the numerator of the incidence rate at the time of the first diagnosis of the primary or secondary endpoint. Patient follow up begins at treatment index and continues until first occurrence of the outcome for those experiencing an event of interest. For event-free patients, follow-up begins at treatment index and ends 30 days after the end of active bortezomib- or carfilzomib-treatment.

An exploratory analysis of the primary and secondary endpoints will include logistic regression and time to event modeling to identify risk factors for MACE and extended MACE. The models will be checked to ensure they meet all model assumptions. Multivariate logistic regression will use stepwise methods for selecting covariates. Stepwise criteria will be $p<0.1$ for inclusion and $p<0.05$ to stay in the model. The initial

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model will be run with the exhaustive covariate list which will include all demographic characteristics and comorbidities (Charlson comorbidity score; yes/no of all comorbidities). Event rates will be compared between the carfilzomib and the bortezomib cohorts. Assuming time to event data are available for a sufficient number of events, hazard ratios for end points associated with exposure to bortezomib and carfilzomib will be calculated using Cox proportional hazards regression models; multivariate models will be used to adjust for differences identified between groups in univariate analyses. Propensity score matching will also be employed. A p value of < 0.05 will be considered statistically significant.

9.7.2.5 Sensitivity Analysis

Not applicable to this study.

9.7.2.5.1 Subgroup Analysis

Subgroup analyses of primary and secondary end points will be carried out based on dose of proteasome inhibitor, duration of treatment with proteasome inhibitor, and pre-treatment categorical CV risk.

9.7.2.5.2 Stratified Analysis

Not applicable to this study.

9.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

Not applicable to this study.

9.7.2.5.4 Other Sensitivity Analysis

Not applicable to this study.

9.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

Primary and secondary endpoints are safety endpoints. See section 9.7.2.4 for the description of the analysis.

9.8 Quality Control

A SAS programmer from BWH will write and execute the analytics. An additional programmer will be assigned to QC and verify the results from the analysis.

9.9 Limitations of the Research Methods

9.9.1 Internal Validity of Study Design

9.9.1.1 Measurement Error(s)/Misclassification(s)

Our use of routine data is advantageous since the study itself does not affect the diagnostic process or treatment choices and thus does not introduce bias due to surveillance in follow-up studies. The vast majority of the data coming from this study are part of the routine medical practice at the participating institutions. Misclassification of endpoints or exposure may occur in EMR, however, it is unlikely to be differential in nature and will likely only bias any analyses towards the null.

9.9.1.2 Information Bias

Data from the EMR and other health information sources used in this study are not expected to be missing data points in an informative way or rather the missing data is expected to be random and nondifferential.

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9.9.1.3 Selection Bias

This is a multi-site rather than single-site study to improve generalizability of study findings. Furthermore, the patients that will be included in this study will be subject to minimal exclusion criteria and represent a 'real world' cohort of patients receiving treatment with proteasome inhibitors, thereby maximizing generalizability.
To characterize the generalizability, cohorts from major clinical trials of carfilzomib and bortezomib in patients with MM will be reviewed to understand the patient characteristics of previously exposed patients. We anticipate to highlight differences between 'real world' patient cohorts treated with these agents and patients enrolled in clinical trials. Similarly, the prevalence of pre-existing and post-exposure CV disease observed in the carfilzomib and bortezomib cohorts included in this registry of patients will be compared to published studies.

9.9.1.4 Confounding

Comprehensive data will be collected on potential confounders (e.g. include pre-treatment CV risk factors, CV medications, ECOG score, Charlson comorbidity score, dose of proteasome inhibitor and duration of exposure) to facilitate for adjusted analyses.

9.9.2 External Validity of Study Design

Patients that will be included in this study will be subject to minimal exclusion criteria and represent a 'real world' cohort of patients receiving treatment with proteasome inhibitors, thereby maximizing generalizability. Furthermore, there are no restrictions to patient selection based on certain healthcare plans, gender or age groups (other than inclusion criterion of age > 18 years).

9.9.3 Analysis Limitations

Ability to comprehensively control for all potential confounders may be limited if the number of adverse CV events observed over follow-up is low. Given that propensity scores are a good alternative to matching to control for imbalances when there are seven or fewer events per confounder, additional analyses using propensity score matching are also proposed.

9.9.4 Limitations Due to Missing Data and/or Incomplete Data

This study design is limited by its retrospective nature. Complete data may not be available for all patients due to this retrospective design, but data will be sought from multiple sources (described above) to minimize missing data.

9.10 Other Aspects

Not applicable.

10. Protection of Human Subjects

10.1 Informed Consent

Patient consent will not be required for retrospective data collection. However, we will seek patient consent to agree to collection of follow-up data using questionnaires and contact with additional healthcare providers.

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10.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The study will be submitted to the Partners Institutional Review Board at Dana Farber Cancer Institute for approval.

10.3 Subject Confidentiality

Access to research data will be limited to study staff only. Data will be stored on a password protected computer with active anti-virus software in a locked office at Brigham & Women's Hospital. If data will be transmitted outside the Partners firewall, data will be encrypted during transit with the use of SSL/https.

11. Collection of Safety Information and Product Complaints

This study is a combined data collection study. Safety information and product complaints identified during the data collection through the patient follow-up questionnaire will be collected for all patients and reported to FDA per standard practice; in addition for carfilzomib, safety information and product complaints will be reported to Amgen for carfilzomib treated patients.

11.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a subject/patient administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.
An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an adverse event includes:

- Worsening of a pre-existing condition or underlying disease
- Events associated with the discontinuation of the use of a product(s), (e.g., appearance of new symptoms)

It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen.

11.1.2 Serious Adverse Events

A serious adverse event is any adverse event as defined above that meets at least one of the following serious criteria:

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an "other significant medical hazard" that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.
"Other significant medical hazards" refer to important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

11.1.3 Other Safety Findings

Other Safety Findings (regardless of association with an adverse) include:

- Medication errors, overdose, whether accidental or intentional, misuse, or abuse, , involving an Amgen product,
- Pregnancy and lactation exposure,
- Transmission of infectious agents,

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- Reports of uses outside the terms for authorized use of the product including off-label use,
- Occupational exposure,
- Any lack or loss of intended effect of the product(s).

11.1.4 Product Complaints

Product Complaints include any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product or device after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s) or device(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.

11.2 Safety Reporting Requirements

The investigator is responsible for ensuring that safety events (adverse events, product complaints and other safety findings) observed by the investigator or reported by the subject that occur after signing of the informed consent form through the final study contact are recorded in the subjects appropriate study documentation. Safety events must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of investigator awareness.

Individual Case Safety reports are to be reported to Amgen using Safety Report Forms (see Appendix C) and for Additional Safety Reporting Information regarding the adverse event grading scale used in this study (see Appendix D)

The Investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record.

11.2.1 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required to regulatory authorities, Investigators/institutions, institutional review board and independent ethics committee (IRBs/IECs) or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The Investigator is to notify the appropriate IRB/IEC or other relevant ethical review board of Serious Adverse Events in accordance with local procedures and statutes.

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12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The Partners IRB at Dana Farber Cancer Institute must be informed of all amendments and give approval. The Investigator **must** send a copy of the approval letter from this IRB to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the contractual agreement. The Investigator is to notify the Partners IRB at Dana Farber Cancer Institute in writing of the study's completion or early termination and send a copy of the notification to Amgen.

13. Plans for Disseminating and Communicating Study Results

13.1 Publication Policy

Results of the study will be submitted for publication. Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

14. Compensation

Not applicable to this study.

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15. References

Allegra A, et al. (2010) Cardiac involvement in patients with hematologic malignancies. Journal of investigative medicine : the official publication of the American Federation for Clinical Research 58(7):859-74 doi:10.231/JIM.0b013e3181efbc4e

Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases 40(5):373-83

Dimopoulos MA, et al. (2016) Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. The Lancet Oncology 17(1):27-38 doi:10.1016/s1470-2045(15)00464-7

Dorbala S, et al. (2014) Coronary microvascular dysfunction is related to abnormalities in myocardial structure and function in cardiac amyloidosis. JACC Heart failure 2(4):358-67 doi:10.1016/j.jchf.2014.03.009

Carfilzomib/Kyprolis (2015) http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm455873.htm. Accessed August 18 2015

Herndon TM, et al. (2013) U.s. Food and Drug Administration approval: carfilzomib for the treatment of multiple myeloma. Clinical cancer research : an official journal of the American Association for Cancer Research 19(17):4559-63 doi:10.1158/1078-0432.CCR-13-0755

Jakubowiak AJ, et al. (2012) A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. Blood 120(9):1801-9 doi:10.1182/blood-2012-04-422683

Laubach JP, et al. (2009) The use of novel agents in the treatment of relapsed and refractory multiple myeloma. Leukemia 23(12):2222-32 doi:10.1038/leu.2009.179

Lendvai N, et al. (2014) A phase 2 single-center study of carfilzomib 56 mg/m2 with or without low-dose dexamethasone in relapsed multiple myeloma. Blood 124(6):899-906 doi:10.1182/blood-2014-02-556308

Lonial S, Mitsiades CS, Richardson PG (2011) Treatment options for relapsed and refractory multiple myeloma. Clinical cancer research : an official journal of the American Association for Cancer Research 17(6):1264-77 doi:10.1158/1078-0432.CCR-10-1805

Papadopoulos KP, et al. (2013) A phase I/II study of carfilzomib 2-10-min infusion in patients with advanced solid tumors. Cancer chemotherapy and pharmacology 72(4):861-8 doi:10.1007/s00280-013-2267-x

Pulte D, Redaniel MT, Brenner H, Jansen L, Jeffreys M (2014) Recent improvement in survival of patients with multiple myeloma: variation by ethnicity. Leukemia & lymphoma 55(5):1083-9 doi:10.3109/10428194.2013.827188

Richardson PG, Hideshima T, Mitsiades C, Anderson KC (2007) The emerging role of novel therapies for the treatment of relapsed myeloma. Journal of the National Comprehensive Cancer Network : JNCCN 5(2):149-62

Siegel D, et al. (2013) Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase II clinical studies. Haematologica 98(11):1753-61 doi:10.3324/haematol.2013.089334

Stewart AK, et al. (2015) Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. The New England journal of medicine 372(2):142-52 doi:10.1056/NEJMoa1411321

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Wang M, et al. (2013) Phase 2 dose-expansion study (PX-171-006) of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed or progressive multiple myeloma. Blood 122(18):3122-8 doi:10.1182/blood-2013-07-511170

Xiao Y, Yin J, Wei J, Shang Z (2014) Incidence and risk of cardiotoxicity associated with bortezomib in the treatment of cancer: a systematic review and meta-analysis. PLoS One 9(1):e87671 doi:10.1371/journal.pone.0087671

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16. Appendices

Appendix A: Endpoint definitions and adjudication

A Clinical End Points Committee (CEC) of two cardiologists (Drs. Nohria and Dr. Groarke) will adjudicate all end points in a consistent and unbiased manner. The CEC will be blinded to type of proteasome inhibitor used in patients.

A research assistant will be responsible for compiling and sending end point packages for review by the CEC being careful to remove any reference to type of proteasome inhibitor. The CEC will expect to receive only clean data. The CEC may seek additional information from the research assistant as needed. The physician reviewers will independently review the cases assigned to them, document and provide supporting information for each event's adjudication directly in the endpoint package. A copy of all signed adjudication forms will be filed in each respective CEC folder. It is the policy of the CEC that all adjudications are properly documented as to how a patient did/did not meet criteria for a particular event, or, for death cases, why a death was classified in the final adjudication.

Death will be classified in five categories, Cardiac, Vascular, Non---hemorrhagic Stroke, or Other or as Unknown if no data are available.

<u>Death Classification:</u>

Death will be classified in the following categories:

1. Cardiac

Cardiac deaths include the following causes of death:

a) Acute Myocardial Infarction

i) Death occurring after a documented myocardial infarction in which there is not conclusive evidence of another cause of death. Patients who are being treated for myocardial infarction and who have a sudden death, as the terminal event related to the MI will be classified as having a myocardial infarction related death.

ii) Autopsy evidence of a recent infarct, including cases of stent thrombosis, with no other conclusive evidence of another cause of death.

iii) A Fatal Myocardial Infarction may be adjudicated for an abrupt death that has suggestive criteria for an infarct but does not meet the strict definition of a myocardial infarction. The suggestive criteria are as follows:

Presentation of symptoms suggestive of myocardial ischemia AND one of the following: (1) ECG changes indicative of a myocardial injury or new LBBB

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(2) Abnormal markers without evolutional changes (i.e. patient died before a subsequent draw) or

(3) Other evidence of new wall motion abnormality

b) Sudden Death

Defined as death that occurred suddenly and unexpectedly in which the time of death is known.

c) Non---Sudden Death

This category refers to a patient who had had symptoms of a cardiovascular nature and has had gradual deterioration prior to death. For example, a patient admitted with worsened heart failure that despite therapy gradually deteriorates and ultimately dies. This would imply a deterioration in a patient who may have started off at New York Class I or II but deteriorated over time. It could also apply to a class III or IV patient who also deteriorates with time.

d) Unwitnessed Death (not seen > 24 hrs.)

Death that occurred unexpectedly and had no known other major causes of death.

e) Procedural

Related to any of the usual coronary artery procedures such as surgery, PTCA, or angiography. This applies to any or all complications occurring during the same hospitalization, or within seven days of the event.

f) Other Cardiovascular Disease (Non-Atherosclerotic)

This includes, but is not limited to cardiac (other than coronary) and vascular (other than cerebrovascular) causes of death such as pulmonary embolism, endocarditis, valvular heart disease.

2. Vascular

a) Atherosclerotic Vascular Disease (Excluding Coronary and Cerebrovascular Disease)

This includes deaths related to atherosclerotic aortic, mesenteric, renal vascular or peripheral vascular disease and procedural deaths occurring during a hospitalization for or after a vascular procedure (e.g., AAA repair), when the circumstances surrounding the death can be linked to a vascular procedure.

b) Other Vascular Disease (Excluding Coronary and Cerebrovascular Disease)

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This includes deaths related to aortic, mesenteric, renal vascular or peripheral vascular disease which are not related to underlying atherosclerosis. Causes may include vasculitis, connective tissue diseases or congenital anomalies.

3. Non---Hemorrhagic Stroke

A non---hemorrhagic stroke is defined as an abrupt onset, over minutes to hours, of a focal neurological deficit that is generally in the distribution of a single brain artery (including the retinal artery) and that is not due to an identifiable non---vascular cause (i.e., brain tumor or trauma), and is not due primarily to an intracranial hemorrhage. The deficit must satisfy at least one of the following criteria:

a) Is associated with neurologic symptoms lasting more than 24 hours

b) Is associated with a new or presumably new defect on brain imaging that corresponds to the neurologic deficit. In this case, the symptoms may last less than 24 hours.

c) Result in death within 24 hours of symptom onset.

Since strokes may have variable clinical presentations (e.g., a large stroke presenting with sudden syncope, embolic stroke with multiple deficits in >1 vascular territory), the use of supplementary information such as brain imaging, may be used by the CEC to determine if a stroke has occurred. Ischemic/embolic strokes with microhemorrhages and ischemic/embolic strokes with hemorrhagic conversion will be classified as non---hemorrhagic strokes. Strokes that are primarily hemorrhagic in nature (intracerebral, intraventricular, subarachnoid hemorrhages) without an underlying primary ischemic/embolic stroke, will not be classified as non---hemorrhagic strokes.

4. Other

All other known causes of death not described above, such as death due to bleeding, hemorrhagic stroke, infection, malignancy, pulmonary disease, gastrointestinal disease, accidents, diabetes, and renal disease.

5. Unknown

There is no information available to allow classification of the cause of death.

<u>Non-Fatal End Point Classifications</u>

The following non---fatal endpoints will be reviewed by the CEC:

1. Non---Fatal Myocardial Infarction

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revised to incorporate Third Universal Definition per ESC/ACCF/AHA/WHF (Thygesen et al., JACC 2012; 60:1581---98)

Non---Fatal MI is defined as evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia, using the following criteria:

a) Detection of a rise and/or fall of cardiac biomarkers [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

i) symptoms of ischemia

ii) new or presumed new significant ST---segment---T wave (ST---T) changes or new left bundle branch block (LBBB)

iii) development of pathological Q waves in the ECG

iv) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
v) identification of an intracoronary thrombus by angiography or autopsy

b) Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99thpercentile URL) in patients with normal baseline values (≤ 99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, at least one of the following is required:

i) symptoms suggestive of myocardial ischemia

ii) new ischemic ECG changes

iii) angiographic findings consistent with a procedural complication

iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality

c) Stent thrombosis associated with MI must be detected by coronary angiography in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.

d) Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤ 99th percentile URL). In addition, at least one of the following is required:

i) new pathological Q waves or new LBBB

ii) angiographic documented new graft or new native coronary artery occlusion

iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

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2. Coronary Revascularization

Coronary revascularization is an invasive procedure which usually follows coronary angiography, wherein either Percutaneous Coronary Intervention (PCI) with balloon angioplasty with or without stent placement, or CABG is performed to relieve obstructed coronary arteries.

3. Non---Fatal, Non---Hemorrhagic Stroke

Stroke is defined as the rapid onset of a new persistent neurological deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent nonvascular cause. Non---hemorrhagic (ischemic) stroke is defined as a stroke caused by an arterial occlusion due to either a thrombotic (atherosclerotic or lacunar) or embolic etiology, and fulfilling the following criteria:

a) Rapid onset of a focal/global neurological deficit with duration ≥24 hours (unless treated with thrombolysis or intracranial angioplasty)

b) Available brain imaging clearly documents a new, primarily ischemic, infarct

4. Heart Failure Requiring Hospitalization

Heart failure requiring hospitalization is defined as an event that meets the following criteria:

a) An admission to an inpatient unit or a visit to an emergency department that results in at least a 12---hour stay (or a date change if the time of admission/discharge is not available). In general, the primary discharge diagnosis should be consistent with heart failure.

AND

b) Clinical manifestation of heart failure including at least one of the following (new or worsening):

Dyspnea, or orthopnea, or PND

Edema

Pulmonary basilar crackles

Radiological evidence of worsening heart failure

AND

c) Additional/increased therapy

Initiation of IV loop diuretic, inotrope or vasodilator therapy

Uptitration of IV therapy, if already on therapy

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iii) Initiation of mechanical or surgical intervention, or use of ultra---filtration, hemofiltration or dialysis that is specifically directed at the treatment of heart failure.

Biomarker results (e.g. brain natriuretic peptide) consistent with congestive heart failure will be supportive of this diagnosis.

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Charlson Comorbidity Index

Table 3. Weighted index of comorbidity

Assigned weights for diseases	Conditions
1	Myocardial infarct
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end organ damage
	Any tumor
	Leukemia
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS

Assigned weights for each condition that a patient has. The total equals the score. Example: chronic pulmonary (1) and lymphoma (2) = total score (3).

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Appendix B. Sample Safety Reporting Form(s)

All studies that report safety data are required to include a sample version of the Form(s) intended to capture all events that must be reported directly to Amgen Safety. This allows sites to familiarize themselves with the form reporting requirements.]

Project ID: 20160154	**A**	**Safety Reporting Form** **Primary Data Collection**	**Date of Report:**
	Fax reports to: Amgen Local Office	*<<populate LAO fax here or delete language>>*	

1. Indicate event type: ☐ **AE/Other safety finding** ☐ **AE/Other safety finding with Product Complaint** ☐ **Product Complaint only**

2. Vendor Contact Details			**3. Reporter ID**		
name	*phone*	*fax*	*Name or ID*	*phone*	*fax*
address			*address*		
city	*state/province*		*city*	*state/province*	
postal code	*country*		*postal code*	*country*	

4. HCP Contact Details (if other than reporter)			**5. Patient**			
name			*Initials (optional)*	*Sex* ☐ F ☐ M	*Age (at time of event)*	*Was consent obtained to follow-up with HCP?* ☐ Yes ☐ No
country						
address						
city	*state/province*	*postal code*	*Weight* ☐ lbs ☐ kg	*Height* ☐ in ☐ cm	*Race*	*Is patient also reporter?* ☐ Yes ☐ No
phone	*fax*					

6. Medical History (include primary diagnosis)	**7. Suspect Product Information (include dosing details)**				
	Product:				
	Indication:				
	Start Date day month year	Stop Date day month year	Dose	Route	Freq
Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No Allergy:	Prefilled Syringe? ☐ Yes ☐ No Other Device	Lot # ☐ Unknown Serial # ☐ Unavailable / Unknown	Vial size		

8. AE, other safety finding, or product complaint information **HCP ONLY**

Finding (List main event first; one event per line)	**Onset Date**	**Resolved Date** *(If patient died, list date of death)* ***Cause of Death:*** *(provide autopsy report)*	**Hospitalization** Hospitalized? ☐ Yes ☐ No Hospitalization Prolonged? ☐ Yes ☐ No **Admitting dx** (provide discharge	**Serious Criteria** **01** Fatal **02** Immediately life-threatening **03** Required hospitalization **04** Prolonged hospitalization **05** Persistent or significant disability /incapacity	**Action Taken** 1=none 2=dose reduced 3=dose increased 4=drug withdrawn 5=Drug	**Outcome** 1=resolved 2=resolved w/ sequelae 3=resolving	**Severity** 1=mild 2=moderate 3=severe	**Relationship to Product/ Device** Is there a reasonable possibility that this event may have been caused by the Product / Device?

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			summary) **Date Admitted** **Date Discharged**		**06** Congenital anomaly / birth defect **07** Other significant medical hazard	rechallenge (state outcome)				
	day month year	day month year	day month year	day month year					Product	Device
									Y N	Y N
									Y N	Y N
									Y N	Y N

9. Description: chronological summary of symptoms or product complaint from above (signs, diagnosis, treatment, concomitant medications including those used to treat event.)

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Appendix C. Additional Safety Reporting Information

Adverse Event Severity Scoring System

For oncology studies, the CTCAE is to be used. The Common Terminology Criteria for Adverse Events (CTCAE) is available at the following location:

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

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