1. ABSTRACT

- **Title**

A retrospective study to identify cohorts of relapsed and/or refractory multiple myeloma (R/R MM) patients treated with carfilzomib by baseline characteristics and levels of risk of select cardiovascular adverse events (CV AEs).

- **Keywords**

Multiple myeloma, Carfilzomib, risk factors, cardiovascular adverse events

Rationale and Background

Multiple myeloma, a plasma cell neoplasm, is the second most common hematologic malignancy and responsible for approximately 80,000 annual deaths worldwide (1% of all cancer deaths). Carfilzomib has been shown to improve outcomes including overall survival in multiple myeloma when used in combination with dexamethasone (Kd) as in the ENDEAVOR trial and when used in combination with Lenalidomide (KRd) as in the ASPIRE trial. Multiple myeloma is a disease of older adults: median age at diagnosis of 69 years, a predominantly elderly patient population, with a high prevalence of pre-existing cardiovascular disease and a high frequency of CV AEs Higher rates of cardiovascular adverse events have were observed for carfilzomib treated subjects in key pivotal trials, typically dyspnea, hypertension and cardiac failure. However, attempts to define which pre-existing conditions are clinical predictive factors for cardiovascular events have been unsuccessful. The goal of this study is to explore if there are baseline characteristics common to those patients who went on to experience a serious CVAE during the study so that high or non-high- risk subjects can be characterized before those events occurred. This study focused on clinically relevant CV AE, which included grade 3 and above per (CTCAE v4.03, 2009 and v5.0,2017).

In the ASPIRE study, the rate of grade ≥ 3 cardiac failure, hypertension, dyspnea and ischaemic heart disease in the carfilzomib arm versus the control arm were (grouped term) 3.8% v 1.8%; 4.3% v 1.8%; 2.8 % v 1.8 % and 3.3% v 2.1% respectively (Stewart 2015). In the ENDEAVOR study, the same figures were (using MedDRA grouped term cardiac failure and preferred term for hypertension, dyspnea and ischemic heart disease) 6.0% v 2.0%; 15.0% v 3.06%; 6.0% v 2.0%; and 1.7% v 1.5% respectively Dimopoulos 2017). Across both studies between 40% and 50% of subjects had prior hypertension, 1% to 4% had a history of cardiac failure and 5% to 11% had arrhythmias at study entry (Chari 2018). Deaths from cardiac failure and ischemic heart disease events in ASPIRE and ENDEAVOR were rare at

≤ 1% and <1% respectively. No deaths occurred from hypertension or dyspnea adverse events (Chari 2018),

Concerns about adverse cardiovascular outcomes may limit use of carfilzomib and lead to suboptimal dosing or scheduling despite the favorable benefit risk ratio demonstrated in phase 3 clinical trials. Healthcare providers are uncertain how to identify which patients harbor a high risk of a CV adverse event and which patients are unlikely to encounter such an event The question of how to detect high risk patients and how to identify in advance those that do go on to have a CV AE from the majority who do not develop a serious CVAE has been attempted in the past but without success. There have also been attempts to identify what monitoring methods might allow earlier detection of evolving complications before they arise, also without success. In the ENDEAVOR cardiac sub-study no benefit was found from increased frequency of echocardiogram testing during carfilzomib treatment to try to detect abnormalities of cardiac function. This sub-study also showed that the anytime occurrences of a reduction in left-ventricular ejection fraction (LVEF) were the same whether treated with carfilzomib or not and such reductions were largely reversible.

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor (PI) that binds selectively and irreversibly to the 20S proteasome, the proteolytic core particle within the 26S proteasome. Consequently, proteasome function after therapy can only be regained by de novo proteasome synthesis. Specifically, carfilzomib inhibits the chymotrypsin-like catalytic activity of the β5 subunit over the caspase-like catalytic activity of the β1 subunit or the trypsin-like catalytic activity of the β2 subunit, resulting in the accumulation of proteasome substrates and ultimately growth arrest and apoptosis (Hoy 2016). Carfilzomib extensively penetrates all tissues, except the brain. An intact ubiquitin proteasome system (UPS) is critical if constantly active cardiac myocytes are to manufacture new proteins and degrade damaged or misfolded proteins. UPS dysfunction is found in human heart failure as evidenced by histopathologic findings of ubiquinated proteins, soluble protein aggregates and autophagic cell death in end-stage failing human hearts is highly suggestive that UPS dysfunction may be responsible. It has therefore been thought that carfilzomib's effective inhibition of UPS is the likely mechanism behind carfilzomib induced cardiac failure although some investigators have published an alternative hypothesis based on rodent data involving the autophagy pathway, inactivation of AMPKa and upregulation of PP2A phosphatase activity (Efentakis 2019).

- **Research Question and Objectives**

This study will undertake an analysis of pooled data from A.R.R.O.W , ASPIRE, ENDEAVOR and FOCUS, all phase 3 trials of carfilzomib with the objective of partitioning the carfilzomib-treated population into cohorts defined by baseline attributes (demographics, vital signs, cardiac assessments, results of bedside clinical and laboratory testing and medical comorbidities) and presenting high, medium or low levels of risks of select, clinically relevant high grade cardiovascular adverse events.

Objectives	Endpoints
Primary	
• Identify cohorts of carfilzomib-treated R/R MM patients defined by baseline characteristics that confer different levels of risks for high grade selected CV AEs	• Rate of ≥3 CVAEs in cohorts of patients identified as having high, intermediate, or low risks for the select CVAEs
Secondary	
None	
Exploratory	
• Explore the impact on cohort definition and AE rates of patient medical history records vs. measured baseline characteristics (demographics, vital signs, cardiac signs, and labs)	• Assessment of whether patient medical history records improve the quality of patient classification

- Hypothesis(es)/Estimation
  This is a descriptive study to cluster R/R Multiple Myeloma population treated with Kyprolis into groups with varying risk of developing a clinically relevant cardiovascular adverse event.

- **Study Design**

Retrospective cohort study

- **Subjects and Study Size, Including Dropouts**

The study population consists of subjects with relapsed and/or refractory Multiple Myeloma enrolled in one of four phase 3 clinical trials. All studies where global and recruited at multiple sites across several continents.

FOCUS (20130396), *A Randomized, Open-label, Phase 3 Study of Carfilzomib vs Best Supportive Care in Subjects with Relapsed and Refractory Multiple Myeloma*, was a multi-center study, with 81 sites screening subjects for participation; 77 sites enrolled at least 1 subject from countries in Eastern and Western Europe, Israel, Australia, New Zealand, and South Korea enrolling 315 subjects between 06 September 2010 (first subject enrolled date) and 10 Jul 2014 (data cut-off date). Subjects had had 1 to 5 prior regimens and were refractory to the most recent therapy.
In the ASPIRE study (20130395), *A Randomized, Multi-center, Phase 3 Study Comparing Carfilzomib, Lenalidomide, and Dexamethasone (CRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects With Relapsed Multiple Myeloma,* recruited 792 subjects at 155 centers in 20 countries in Eastern and Western Europe, North America, and Israel between 14 July 2010 (first subject enrolled) to 28 April 2017 (data cut-off date).

In ENDEAVOR (20130398) a study of Carfilzomib and dexamethasone was compared to bortezomib and dexamethasone for patients with relapsed and/or refractory multiple myeloma in a multicentre study of 929 subjects enrolled between 20 June 2012 (first subject enrolled date) and 30 June 2014 (data cut-off date) across 198 sites across Western and Eastern Europe, South America and Australia.

In ARROW, a study of once weekly versus twice weekly carfilzomib dosing in patients with relapsed and/or refractory multiple myeloma, recruited 578 patients from 118 sites in North America, Europe and Asia between September 2015, and August 2016 (data cut-off date, June 2017). All subjects were patients (aged 18 years and older) refractory to most recent therapy (including bortezomib or ixazomib).

- Summary of Subject Eligibility Criteria

R/R MM patients that were enrolled in four Amgen clinical trials and received treatment with carfilzomib in these trials were included. Eligibility in all four trials required subjects to be > 18 years of age with relapsed and/or refractory multiple myeloma, measurable disease, Eastern Cooperative Oncology Group performance status of not more than 2 (0- 1 in A.R.R.O.W), at least one previous treatment, and at least a partial response to at least one previous treatment. In both FOCUS and A.R.R.O.W, subjects had to be refractory to the most recent line of therapy. Studies differed in the number of prior lines of therapy permitted and the interval between the most recent proteasome inhibitor treatment and study enrollment.

Table 6-1. Company-sponsored Studies and Ono-sponsored Clinical Program

Study Number	Subject Population	Design	Objectives	Drug Combination/Carfilzomib Dose Schedule[1]	No. of Subjects[2]	Study Status[3]
Phase 3						
PX-171-009 (ASPIRE)	Relapsed MM; 1 to 3 prior tx	Randomized, active-control	Efficacy; safety	Carfilzomib + lenalidomide + dexamethasone vs lenalidomide + dexamethasone CFZ 20/27 mg/m² (10 min) up to 18 cycles	792	Completed
2011-003 (ENDEAVOR)	Relapsed MM; 1 to 3 prior tx	Randomized, active-control	Efficacy	Carfilzomib + dexamethasone vs bortezomib + dexamethasone CFZ 20/56 mg/m² (30 min) DEX 20 mg; BTZ 1.3 mg/m²	929	Completed
PX-171-011 (FOCUS)	Relapsed and refractory MM; 3 prior tx	Randomized, active-control	Efficacy; safety	Carfilzomib vs best supportive care CFZ 20/27 mg/m² (10 min) Corticosteroid (prednisolone 30 mg or DEX 6 mg every other day) Optional CYC 50 mg OD	315	Completed
2012-005 (CLARION)	Transplant-ineligible, newly diagnosed MM	Randomized active-control	Efficacy	Carfilzomib + melphalan + prednisone vs bortezomib + melphalan + prednisone CFZ 20/36 mg/m2 (30 min); 42-day cycles; BTZ 1.3 mg/m²; MEL 9 mg/m2; PRED 60 mg/m²; up to 9 cycles	955	Completed
20140242 (CFZ005)	Relapsed and refractory MM	Single group	Efficacy	Carfilzomib + dexamethasone CFZ 20/27 mg/m² (30 min)	120 planned; 126 enrolled	Ongoing

- Follow-up

For this study, patients will be censored at the end of their respective trial end dates, all qualifying patients who do not have a record of CV event within the observation window will be treated equivalently in the analysis.

Data cut-off for these trials were FOCUS (10 July 2014), ASPIRE (28 April 2017), ENDEAVOR (10 November 2014), and ARROW (4 March 2014) respectively.

- Study Sample Size

  This analysis will be of Carfilzomib-treated subjects enrolled in the following four trials, all of which are closed and have reported their findings.

  - ARROW: 235 and 238 subjects in the two (Carfilzomib) arms
  - ASPIRE: 392 subjects in the Carfilzomib arm
  - ENDEAVOR: 463 subjects in the Carfilzomib arm
  - FOCUS: 157 subjects in the Carfilzomib arm

- **Variables and Data Sources**
  - Outcome Variable(s) ≥ Grade 3 cardiovascular adverse events:
    - Cardiac Failure
    - Hypertension
    - Ischemic Heart Disease

- Cardiac Arrhythmias
- Pulmonary Hypertension
- Exposure Variable(s)
  NA
- Other Covariate(s)
- Demographics
- Sex
- Race
- Age
- Vital signs
- Weight
- Height
- Body Surface Area
- Systolic Blood Pressure
- Diastolic Blood Pressure
- Respiratory Rate
- Cardiac signs
- Summary Mean Ventricular Rate
- Summary Mean PR Duration
- Summary Mean QRS Duration
- QTcF Fridericia's Correction Formula
- ECG Interpretation
- Left Ventricular Ejection Fraction
- Labs
- Hemoglobin
- Glucose
- Activated Partial Thromboplastin Time
- Bilirubin
- Cockcroft-Gault Calculated Creatinine Clearance
- Uric Acid
- Basophils
- Presence of comorbidity conditions
- Myocardial infarction
- Congestive heart failure
- Peripheral vascular disease
- Cerebrovascular accident or transient ischemic attack

  - Diabetes mellitus
  - Moderate to severe chronic kidney disease
  - Kyprolis regimen
- Data analysis:
  - The analysis uses three techniques in sequence:
    - Topological data analysis to produce network representations of data.
    - Network clustering known as cold-spot detection to identify coherent sets of non-AE subjects; and
    - Multi-class single-decision-tree learning to discover groups of subjects and conditions on variables that explain them.
    - The sequence may be repeated more than once. A more detailed description of the analysis is in Section 9.

- **Marketing Authorization Holder(s)**

  Amgen Inc
- **Names and Affiliations of Principal Investigators**

  See links to clinical trials

2. LIST OF ABBREVIATIONS

AE Adverse Event

CV Cardiovascular

MM Multiple Myeloma

R/R Relapsed and/or Refractory

TDA Topological Data Analysis