



pan-Canadian Oncology Drug Review Final Clinical Guidance Report

Carfilzomib (Kyprolis) for Multiple Myeloma

March 30, 2017

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

TABLE OF CONTENTS

DISCLAIMER	ii
FUNDING	ii
INQUIRIES	iii
TABLE OF CONTENTS	iv
1 GUIDANCE IN BRIEF	1
1.1 Introduction	1
1.2 Key Results and Interpretation	1
1.2.1 Systematic Review Evidence	1
1.2.2 Additional Evidence	3
1.2.3 Factors Related to Generalizability of the Evidence	6
1.2.4 Interpretation	8
1.3 Conclusions	10
2 BACKGROUND CLINICAL INFORMATION	11
2.1 Description of the Condition	11
2.2 Accepted Clinical Practice	11
2.3 Evidence-Based Considerations for a Funding Population	13
2.4 Other Patient Populations in Whom the Drug May Be Used	13
3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT	14
3.1 Condition and Current Therapy Information	15
3.1.1 Experiences Patients have with Multiple Myeloma	15
3.1.2 Patients’ Experiences with Current Therapy for Multiple Myeloma	16
3.1.3 Impact of Multiple Myeloma and Current Therapy on Caregivers	18
3.2 Information about the Drug Being Reviewed	19
3.2.1 Patient Expectations for and Experiences To Date with Carfilzomib	19
3.3 Additional Information	24
4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT	25
4.1 Factors Related to Comparators	25
4.2 Factors Related to Patient Population	25
4.3 Factors Related to Dosing	26
4.4 Factors Related to Implementation Costs	26
4.5 Factors Related to Health System	26
4.6 Factors Related to Manufacturer	20
5 SUMMARY OF REGISTERED CLINICIAN INPUT	28
5.1 Current Treatment(s) for this Type of Cancer	28
5.2 Eligible Patient Population	28
5.3 Identify Key Benefits and Harms with Carfilzomib	29
5.4 Advantages of Carfilzomib Over Current Treatments	29
5.5 Sequencing and Priority of Treatments with Carfilzomib	29
5.6 Companion Diagnostic Testing	30
5.7 Additional Information	30
6 SYSTEMATIC REVIEW	31
6.1 Objectives	31
6.2 Methods	31
6.2.1 Review Protocol and Study Selection Criteria	31
6.2.2 Literature Search Methods	32

6.2.3	Study Selection	32
6.2.4	Quality Assessment	32
6.2.5	Data Analysis	32
6.2.6	Writing of the Review Report	32
6.3	Results	34
6.3.1	Literature Search Results	34
6.3.2	Summary of Included Studies	35
6.4	Ongoing Trials	58
7	SUPPLEMENTAL QUESTIONS	60
8	COMPARISON WITH OTHER LITERATURE	61
9	ABOUT THIS DOCUMENT	64
	APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY	65
	REFERENCES	69

1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding carfilzomib (Kyprolis) plus dexamethasone for multiple myeloma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding carfilzomib (Kyprolis) plus dexamethasone for multiple myeloma conducted by the Lymphoma/Myeloma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; supplemental issue; and comparison with other literature relevant to the implementation of a funding decision.

The systematic review, supplemental issues and comparison with literature are fully reported in Sections 6, 7 and 8. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on carfilzomib (Kyprolis) plus dexamethasone for multiple myeloma, a summary of submitted Provincial Advisory Group Input on carfilzomib (Kyprolis) plus dexamethasone for multiple myeloma, and a summary of submitted Registered Clinician Input on carfilzomib (Kyprolis) plus dexamethasone for multiple myeloma, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the safety and efficacy of carfilzomib (Kyprolis) plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three prior therapies.

The appropriate comparators for carfilzomib plus dexamethasone in this setting include other proteasome inhibitors (e.g. bortezomib) and/or an immunomodulatory agent (e.g. lenalidomide) and/or chemotherapy (e.g. cyclophosphamide) and/or dexamethasone. The patient population under review is similar to the population for whom Health Canada market authorization has been granted.

The recommended dose for carfilzomib includes a starting dose of 20 mg/m² on days 1 and 2 of cycle 1. If tolerated, the dose is increased to 56 mg/m² thereafter as 30 min intravenous infusion on days 1, 2, 8, 9, 15, and 16. Dexamethasone is administered as 20 mg PO or IV on Days 1, 2, 8, 9, 15, 16, 22, and 23 of the 28 day cycles. Dexamethasone should be administered 30 minutes to 4 hours before carfilzomib.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one trial, ENDEAVOR, an open label randomized controlled trial that randomized 929 patients with relapsed or refractory multiple myeloma to receive carfilzomib plus dexamethasone (n=464) or bortezomib plus dexamethasone (n=465). Treatments were given until disease progression, withdrawal of consent, or occurrence of unacceptable toxic effects. The median duration of treatment was 39.9 weeks in the carfilzomib group and 26.8 weeks in the bortezomib group.¹ The median relative dose intensity was 93% in the carfilzomib group and 86% in the bortezomib group.¹

Baseline patient characteristics are listed in Table 9 below and were generally well balanced across groups.

The median age of patients in the ENDEAVOR study was 65.0 years and 15% of patients were over the age of 75. The majority of patients in the study had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 (49.0%) or 1 (44.5%) while 30 (6.5%) of patients had an ECOG PS of 2. Patients had received a median of 2 previous therapies and 266 patients (57.3%) in carfilzomib group and 272 (58.5%) in bortezomib had prior transplant.^{1,2} Prior therapy included carfilzomib (<1% in both groups), bortezomib (54% in both groups), and lenalidomide (38% in both groups) and thalidomide (45% and 53% in the carfilzomib and bortezomib groups, respectively).¹ Patients previously treated with carfilzomib or bortezomib were permitted entry into the trial provided they achieved at least a partial response before relapse or progression, were not discontinued due to toxic effects, and had at least a six-month proteasome inhibitor treatment-free interval before enrolment.¹

Efficacy

The primary outcome in the ENDEAVOR study was progression free survival (PFS). The study met its primary endpoint with a statistically significant longer PFS in favour of the carfilzomib group with a 47% reduction in the risk of progression or death during the study period. Median PFS was 18.7 versus 9.4 months in the carfilzomib and bortezomib groups respectively (HR=0.53; 95%CI: 0.44-0.65, $p<0.0001$). As a secondary outcome, overall survival data were immature at the interim analysis^{1,3} and did not cross the pre-specified monitoring boundary (two-sided significance level of 0.0002). In an updated overall survival analysis (2016),⁴ the 3-year survival rate was 58.6% (95%CI, 52.0% to 64.6%) for patients in the carfilzomib group and 51.1% (95 CI: 43.9% to 57.9%) for patients in the bortezomib group. The hazard ratio estimate for OS (Cd versus Bd) was 0.805 (95%CI: 0.646 to 1.003) with a 1-sided log-rank test p-value of 0.0263 (Not statistically significant). While the interim OS analysis did not demonstrate a statistically significant difference between treatment groups, it was noted that the OS data are still not yet mature, therefore no definitive conclusions on OS can be drawn at this time.

Global health status / Quality of life (GHS/QoL) were assessed with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core Module (QLQ-C30), Multiple Myeloma Module (QLQ-MY20) and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity (subscale questionnaire) (FACT/GOG/Ntx). Patients treated with Carfilzomib (Cd) had on average better global health status/QoL compared with patients with bortezomib (Bd) (between group difference [Cd - Bd]: 3.51; 95% CI, 1.97 to 5.06) and was statistically significant; however, the minimal important difference (MID, 5 point) was not met. Following the receipt of feedback from the manufacturer on patient reported outcomes (PRO's) measured in the ENDEAVOR trial, the methods team noted the following. The manufacturer reported that MID's were met at weeks 60 and 72 and approached the MID at weeks 36 and 48 for between group differences. The methods team noted that although PRO's were an exploratory outcome in the ENDEAVOR trial, only limited data were available for assessment. Based on the evidence available publically and within the submission materials during the pCODR review, the Methods team was unable to verify that the MID's were met or approaching the MID at any time point. It is also important to assess results along with statistical analysis, which were not provided along with the feedback, at different time periods to support the feedback suggesting that meaningful differences may exist. Overall, the Methods team was unable to provide a fulsome

appraisal of the data referenced by the manufacturer in the feedback document and caution should be used in interpreting the results.

Harms

In a post-hoc analysis among patients ≥ 75 years, all grades cardiac failure occurred in four times as many patients in the carfilzomib compared to the bortezomib groups.⁴ Therefore the risk of cardiac failure is increased in elderly patients (≥ 75 years).

All grades SAEs: All grades serious adverse events (SAEs) occurred in 48% and 36% of patients in the carfilzomib and bortezomib groups respectively (See Table 18 below). The most common grade 3 or higher SAEs in the carfilzomib group were pneumonia (Cd versus Bd: 5.8% versus 6.8%). The most common all grades SAEs in the carfilzomib group were pneumonia (Cd versus Bd: 6.0% versus 8.6%), pyrexia (Cd versus Bd: 3.2% versus 0.7%), dyspnea (Cd versus Bd: 3.0% versus 0.2%) and cardiac failure (Cd versus Bd: 1.7% versus 0.7%).^{1,4}

Grade 3 or higher AEs: Grade 3 or higher AEs were reported in 339 (73%) and 305 (67%) patients in carfilzomib and bortezomib groups, respectively (see Table 19) The most common grade 3 or higher adverse events of interest (see Table 19 below) included anemia (Cd versus Bd: 14.5% versus 9.9%), thrombocytopenia (8.4% versus 9.4%), hypertension (8.9% versus 2.6%), peripheral neuropathy (2.2% versus 8.1%), pneumonia (6.9% versus 7.9%), acute renal failure (Cd versus Bd: 4.1% versus 2.6%), cardiac failure (4.8% versus 1.8%) (see Table 19).

Table 1: Highlights of Key Outcomes

	ENDEAVOR	
	Cd (N= 464)	Bd (N=465)
PFS, median ¹	18.7 (95% CI: 15.6-NE)	9.4 (95% CI: 8.4-10.4)
HR (95%CI)	HR 0.53 (0.44-0.65)	
p-value	p<0.0001	
OS, (3 year survival) ⁴	58.6%	51.1%
HR (95%CI)	0.805 (0.646, 1.003)	
p-value (one side)	0.0263 (NSS)	
ORR, % (95%CI)	77 (73, 81)	63 (58, 67)
ORR, Odds ratio (95% CI)	2.03 (1.52-2.72); p<0.0001	
CR or better	58 (13)	29 (6)
	P = 0.001	
Very good PR or better	252 (54)	133 (29)
	P < 0.0001	
	Cd =(N=463)	Bd (N=456)
HrQoL ^{4,5}		
Between Group Difference (95%CI)	3.51 (1.97, 5.06)	
Harms Outcome, n (%)		
Any grade SAEs	223 (48.2)	162 (35.5)
Grade ≥ 3 AEs ($\geq 2\%$ in any arm) ^{1,4}	339 (73.2)	305 (66.9)
WDAE ¹	65 (14)	73 (15.7)
AE = adverse event, Bd = Carfilzomib plus dexamethasone; Cd = Bortezomib plus dexamethasone CI = confidence interval, HR = hazard ratio, HRQoL = health-related quality of life, NR = not reported, NSS = not statistically significant, ORR = overall response rate, CR = complete response, PR = partial response, SD = standard deviation, WDAE = withdrawal due to adverse event.		

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient's perspective, the most important aspect of myeloma to control was infections, followed by kidney problems, pain, mobility, neuropathy, fatigue, shortness of breath, mood/emotional issues, and stomach issues including diarrhea, nausea, gastrointestinal. Respondents indicated that symptoms associated with myeloma affected their ability to work the most, followed by ability to exercise, travel, volunteer, conduct household chores, fulfill family obligations, and spend time with family. Respondents identified the following current treatments that they have used: dexamethasone, bortezomib, lenalidomide, autologous stem cell transplant, melphalan, cyclophosphamide, pomalidomide, thalidomide, VAD and allogenic stem cell transplant. Respondents reported that the side effects experienced with these treatments included: fatigue, neuropathy, insomnia, stomach issues, nausea, shortness of breath, pain and confusion. The respondents stated that it was very important to them to have access to effective treatments. Respondents who have not had experience with carfilzomib indicated that they expect the new treatment bring improvement in their physical condition, and that the expected benefit of the treatment would be lack of disease progression. For respondents who have experience with carfilzomib, when asked in an open-ended question about how carfilzomib changed or is expected to change long-term health and well-being, some respondents indicated that it was discontinued or stopped working; while some reported that it achieved disease control and others indicated that it was too early to tell. Respondents reported that side effects were generally tolerable compared to other treatments taken for myeloma, and that the least tolerable side effects with carfilzomib were: shortness of breath, diarrhea, fatigue, nausea, pneumonia, anemia, fever, thrombocytopenia and neutropenia. When respondents were asked on a scale of 1 to 5 to rate their quality of life while taking carfilzomib, where 1 was "*poor quality of life*" and 5 "*excellent quality of life*"; the majority of respondents rated this as a "3" and "4".

Please see Section 3 for more details

Provincial Advisory Group (PAG) Input

Clinical factors:

- Clarity on patient groups eligible for treatment

Economic factors:

- Drug wastage
- Intense dosing schedule for intravenous infusion and the intense hydration protocol with intravenous fluids required impact health care resources
- Duration of treatment unknown as treatment is until progression
- Dosing at 56mg/m²

Please see Section 4 for more details

Registered Clinician Input

The oncologists from Myeloma Canada Research Network (MCRN) identified that multiple myeloma patients require sequential lines of therapy to control their disease and extend survival, and carfilzomib-based regimens offer another line of effective therapy, particularly for patients who are refractory, intolerant or have contraindications to bortezomib. The key benefits of carfilzomib identified are the prolonged progression free

survival, improvement in disease control, durable response and minimal peripheral neuropathy adverse event. The harms identified are the cardiotoxicities and cytopenias. The oncologists from MCRN noted that patients with cardiac disease should not be treated with carfilzomib and patients with significant marrow burden would require greater oversight and frequent dose adjustments. Overall, the oncologists from MCRN felt that carfilzomib has a good response rate with deep and durable response and manageable toxicities.

Please see Section 5 for more details

Summary of Supplemental Questions

No supplemental question was identified during development of the review.

Comparison with Other Literature

Given the issuance of a final pERC recommendation on the results of the ASPIRE trial,⁶ conducted in patients with relapsed or refractory multiple myeloma who received 1 - 3 prior lines of therapies, the pCODR review team considered whether there were important similarities or differences in the patient population included in the ASPIRE versus ENDEAVOR trials. Both the ENDEAVOR study and the ASPIRE study were conducted in relapsed or refractory patients multiple myeloma who received 1 - 3 prior lines of therapies. The ASPIRE study was reviewed by pCODR in June 2016.⁶ When comparing the findings from ENDEAVOR with that in ASPIRE in terms of the PFS, it is found that the PFS observed in ENDEAVOR was much shorter than that in ASPIRE study (Intervention versus comparator: 18.7 months versus 9.4 months in ENDEAVOR and 26.3 months versus 17.6 months in ASPIRE respectively), although the HRs in the two studies were similar (Table 21). It is found that the main baseline differences of demographic and patients characteristics between study ENDEAVOR and ASPIRE were as follow (see Table 21 and Table 22:): nearly 20% patients in ENDEAVOR had CrCL < 50 ml/min; numerically, more patients in ENDEAVOR had ISS stage II-III, high cytogenetics risk, history of peripheral neuropathy, received prior immunomodulatory agent treatment than that in ASPIRE; numerically more female and Asian patients included in ENDEAVOR than that in ASPIRE study. However, more patients in ENDEAVOR were in ECOG 0 than that in ASPIRE; few patients received 3 prior lines of treatments including bortezomib in ENDEAVOR than that in ASPIRE (Table 21 and Table 22:). It is unknown whether the observed differences of PFS between the two studies were caused or related to the differences of the baseline characteristics of patients included in the two studies mentioned above (See section 8). Further to the confounding due to the observed differences in baseline characteristics, there could also be bias due to differences in unknown confounding variables.

Please see Section 8 for more details

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for Carfilzomib in relapsed/refractory MM

Domain	Factor	Evidence - ENDEAVOR Trial	Generalizability Question	CGP Assessment of Generalizability
Population	ECOG status	ECOG status: 0: 49%; 1: 44.5% 2: 6.5%	Are the overall findings from the ENDEAVOR trial generalizable to patients with ECOG status ≥ 2 ?	While data on the efficacy and safety of using carfilzomib in patients with an ECOG PS of >2 was very limited, the CGP agreed that use of carfilzomib in this population may be appropriate. The CGP noted that the indication for treatment is often symptoms related to the disease. If that symptoms is a fracture, or symptomatic anemia, then ECOG can drop to 3 very easily. Myeloma often responds to therapy, and as hemoglobin can rise, or pain settle from fracture, patients PS can likewise improve with treatment. Given the data available and the manageable toxicity profile of carfilzomib and dexamethasone, patients should not be excluded from this regimen based on performance status alone. Based on clinical opinion, using this regimen in patients with disease-related ECOG performance status of 2 or greater may be appropriate, and this would be consistent with standard practice with other myeloma therapies.
	Age:	Age of patients: <65 years: 46.5% 65 - 74 yrs:38% ≥ 75 years: 15.5%	Are the overall findings from the ENDEAVOR trial generalizable to patients who are aged ≥ 75 years old?	Fifteen percent of patients were over 75 years old in the ENDEAVOR trial. This age group is represented quite well. As a result, the results are generalizable to patients over the age of 70. The CGP acknowledged some concern that there may be an increased risk of heart failure in older subjects, but further study is necessary to clarify this risk.
Comparator	The pCODR Provincial Advisory group (PAG) noted that the common comparator used in the Canadian setting is cyclophosphamide, bortezomib and	The comparator arm used in the ENDEAVOR trial used bortezomib plus dexamethasone.	Are the overall findings from the ENDEAVOR trial generalizable to patients in the Canadian setting who would receive cyclophosphamide, bortezomib and dexamethasone	There is no direct comparison of carfilzomib and dexamethasone with cyclophosphamide, bortezomib and dexamethasone. Consequently, comparing these regimens is not possible without a randomised controlled trial.

Domain	Factor	Evidence - ENDEAVOR Trial	Generalizability Question	CGP Assessment of Generalizability
	dexamethasone. Bortezomib plus dexamethasone was noted to be uncommonly used in Canada.		and not bortezomib plus dexamethasone (as in the ENDEAVOR trial)	
Setting	Regions from which patients were enrolled	65% patients were from Europe, 20 % from Asia-pacific and 8.5% from North America	Are the overall findings from the ENDEAVOR trial generalizable to North American/Canadian patients?	The Standard of care in Europe—65% of the trial population—is similar to Canada and the CGP would not expect that any differences in the continuum of care between the Canadian setting and the European setting would lead to differences in outcomes. The results of the Endeavor study are generalizable to the Canadian populations.

1.2.4 Interpretation

Burden of Illness and Need:

In 2016, 2700 patients will be diagnosed with myeloma, and 1450 patients will die of the disease.⁷ Despite significant advancement in the treatment and life expectancy of patients with myeloma, it still remains an incurable disease. After frontline therapy, all patients will eventually relapse. Second line therapy using either a bortezomib or lenalidomide based therapy has been standard of care. Superiority of one regimen over the other is unknown, and regardless of therapy used, life expectancy is limited. Patients will eventually become resistant to both bortezomib and lenalidomide. Finding novel therapies that can improve progression free survival and ideally overall survival is a continued need. Novel treatment options, such as carfilzomib lead to improvement in outcomes, as demonstrated in this review.¹

Effectiveness:

Progression-free Survival (PFS)—Primary Outcome:

At a pre-specified checkpoint, the median progression free survival favored carfilzomib and dexamethasone compared to bortezomib and dexamethasone. (18.7 vs. 9.4 months, respectively). This benefit was seen across almost all subgroups, including those with high risk cytogenetics. Patients refractory to bortezomib and lenalidomide had a trend toward benefit, but did not reach statistical significance. Sample size was small in these subgroups and further follow-up may be necessary to clarify the magnitude of benefit in patients refractory to these treatments. Given the magnitude of benefit seen in the primary endpoint for all patients, and the trend toward improvement in patients refractory to lenalidomide and bortezomib, this patient subgroup would still be candidates for carfilzomib and dexamethasone.

The absolute magnitude of benefit in PFS was 9.3 months. This would be considered a clinically significant improvement based on the HR of 0.53 (CI: 0.44-0.65, $p < 0.0001$). Interestingly, this is a comparable absolute magnitude of benefit seen in the ASPIRE trial comparing carfilzomib, lenalidomide and dexamethasone (CLd) compared to lenalidomide and dexamethasone (Ld).⁸ In this study, PFS was 26.3 months in the CLd arm, and 17.6 months yielding an absolute benefit of 8.7 months (HR 0.69; 0.57-0.83, $p = 0.0001$). There are significant differences in patient populations in the two studies that can explain the greater PFS in the ASPIRE trial. In particular, the ENDEAVOR study had more patients previously treated with lenalidomide, and had a more liberal inclusion criteria for patients refractory to bortezomib and lenalidomide.

The inclusion criteria for participation in this study also permitted patients previously treated with carfilzomib. However, only 1% of patients enrolled in the trial had previously been treated with this drug. Consequently, there are insufficient data to be able to draw conclusions on the magnitude of benefit with retreatment. However, based on the experience with bortezomib, it is the opinion of the CGP that it would be reasonable to consider retreatment with carfilzomib after a period of remission in patients previously treated for a fixed duration with this drug provided there was no prior evidence of resistance to carfilzomib.

Overall Survival (OS):

Although the study reports an overall survival benefit, the median OS had not been reached in either arm. In an updated overall survival analysis, the 3 year survival rate demonstrated a trend favoring carfilzomib and dexamethasone (HR 0.805; 95% CI: 0.646-1.003, 1-sided p -value 0.0263) as it did not cross the pre-specified boundary for statistical

significance. However, the data needs time to further mature to draw conclusions regarding survival benefit.

Quality of Life (QOL) analysis:

Health related quality of life data suggested no impairment in QOL in the carfilzomib and dexamethasone arm, compared to bortezomib and dexamethasone. Whether the carfilzomib arm is associated with an improvement in QOL is uncertain. Several scales to measure quality of life and symptom scales were used, including QLQ-C30, QLQ-MY20, and FACT/GOG/NTx. Although the trend is for improvement favoring the carfilzomib arm, the minimal important difference was not met in any of these scales.

Safety:

Toxicity:

Serious Adverse Events (SAE), grade 3 or higher, were greater in the carfilzomib and dexamethasone arm compared to bortezomib and dexamethasone (73.2% versus 66.9%, respectively). Acute renal failure was more common in the carfilzomib arm (4.1% versus 2.6%). Rates of anemia were also higher (14.5% versus 9.9%) in the carfilzomib arm. Overall, these, and other adverse events using carfilzomib are considered predictable and manageable.

Grade 3 or higher peripheral neuropathy was 8.3% in the bortezomib arm compared to 2.2 % in patients treated with carfilzomib and dexamethasone. This higher rate of peripheral neuropathy with bortezomib may be related to the dosing regimen of this drug. Peripheral neuropathy is less when bortezomib is given subcutaneously (bortezomib was given subcutaneously in 79% of patients in the bortezomib plus Dex arm of the ENDEAVOR trial), and/or once a week instead of twice a week as was given in the ENDEAVOR trial [4,5]. These alternate dosing strategies have a comparable efficacy with less toxicity. Extrapolating these dosing strategies to this trial would theoretically lessen the rates of peripheral neuropathy in the control arm of this study.

Of particular interest is the rate of heart failure. The carfilzomib arm had a heart failure rate of 4.8 % for grade 3 or greater events, compared to 1.8% in the bortezomib group. This rate of heart failure in patient treated with Carfilzomib is similar to results of the ASPIRE trial comparing, carfilzomib, lenalidomide and dexamethasone, and lenalidomide and dexamethasone.⁸ In a subgroup analysis of patients over the age of 70 in the ASPIRE trial, the rate of heart failure was 8.7% in the carfilzomib, lenalidomide, dexamethasone group, compared to 1.8% in the control group.⁹ In a cardiac substudy for the ENDEAVOR trial, there was a similar incidence of heart failure reported as an SAE (10.8% versus 4.1% in the carfilzomib and dexamethasone group compared to the bortezomib and dexamethasone group). Serial monitoring with echocardiogram did not seem to reliably distinguish this patient group, and was not a reliable test to mitigate the risk of heart failure.¹⁰ Caution is advised for the use of carfilzomib in patients with a prior history of heart failure.

Death:

Deaths due to adverse events were 5.0 % in the carfilzomib arm, and 3.4% in the bortezomib arm during the treatment or within 30 days of the last dose in the carfilzomib and bortezomib arms, respectively. Deaths due to adverse events after 30 days of the last dose were 1.5% in the carfilzomib arm and 0.9% in the bortezomib arms.

1.3 Conclusions

The Clinical Guidance Panel concluded that there *is* a net overall clinical benefit to carfilzomib and dexamethasone compared to bortezomib and dexamethasone in relapsed myeloma. The CGP based its conclusion on one high-quality randomized controlled trial that demonstrated a clinically and statistically significant benefit in progression-free survival (PFS) for the carfilzomib arm of the study, compared to the bortezomib arm. The adverse event profiles were similar between the two groups. The current data also demonstrates a trend toward improvement in overall survival, but the data needs time to mature to clarify if there is, in fact, a benefit. This conclusion on net clinical benefit is acknowledging that PFS is considered a reasonable surrogate endpoint for overall survival amongst clinicians that treat myeloma, and it is also consistent with other pCODR reviews in myeloma accepting this endpoint as clinically relevant.

In making this conclusion, the Clinical Guidance Panel also considered that:

- The patient population included in this study were predominantly younger patients (median age 65 yrs. old). Although the number of patients over the age of 70 included in this trial is small, the magnitude of benefit would likely be similar in the elderly. There is some concern that there may be an increased risk of heart failure in older subjects, but further study is necessary to clarify this risk.
- The use of carfilzomib and dexamethasone may be appropriate in patients with progression while on lenalidomide therapy, or maintenance lenalidomide, and therefore not considered candidates for triplet therapy with carfilzomib, lenalidomide and dexamethasone.
- Carfilzomib and dexamethasone may be appropriate for patients who are in second relapse following bortezomib-based first-line therapy of fixed duration and after second line therapy with lenalidomide and dexamethasone.
- There is no efficacy or safety data for using this regimen for patients with ECOG performance status of greater than 2. Caution is advised in this patient cohort, and further data are required. However, based on the data available and the manageable toxicity profile of this regimen, patients should not be excluded from this regimen based on performance status alone. Using it in patients with disease-related ECOG performance status of 3 or greater may be appropriate, and this would be consistent with standard practice with other myeloma therapies.
- The CGP recommends dosing carfilzomib and dexamethasone as per the ENDEAVOR trial. Lower doses used in the ASPIRE trial were used in conjunction with lenalidomide. Therefore efficacy using this lower dose in conjunction with dexamethasone alone may be suboptimal.
- Patients with pre-existing cardiomyopathy or history of congestive heart failure may be at risk for cardiac complications. Caution is advised using carfilzomib in this patient population.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Lymphoma/Myeloma Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Multiple myeloma is an incurable plasma cell neoplasm that makes up 1.3% of all new cancers in Canada.⁷ In 2016, it is estimated that 2700 Canadians will be diagnosed with myeloma, and 1450 patients will die of this disease.⁷ The median age at presentation is 70 years old with a slightly higher incidence in males. Although there is significant heterogeneity within myeloma, the five-year survival for all patients is 48.5%.¹

The diagnosis of myeloma is made based on excess clonal plasma cells in the bone marrow. Patients are further classified as having asymptomatic or symptomatic disease based on organ dysfunction caused by the excess plasma cells in the bone marrow or by the monoclonal proteins they produce. The hallmark features of symptomatic disease include hypercalcemia, renal insufficiency, anemia, and lytic bone disease. In the absence of symptoms, observation is appropriate and no therapy is required.⁸

2.2 Accepted Clinical Practice

Treatment of myeloma is reserved for patients with symptomatic disease. Chemotherapy is the primary modality of treatment, and radiation therapy is only used to help with symptom control due to painful bone involvement or a symptomatic plasmacytoma that cannot be controlled with chemotherapy alone. The three main classes of chemotherapy used to treat myeloma are alkylators (melphalan or cyclophosphamide), proteasome inhibitors (bortezomib or carfilzomib), and immunomodulatory drugs (thalidomide or lenalidomide). Various combinations of these drugs in combination with steroids (prednisone or dexamethasone) have proven to be highly effective therapy for myeloma, and the utilization of these drugs have improved survival of myeloma patients.¹¹ There is no consensus with respect to the optimal sequencing or combination of drugs that should be used.

For patients under the age of 70, an autologous stem cell transplant (ASCT) can be considered in the initial therapy of myeloma. However, the toxicity of this treatment may preclude its use in some patients, and furthermore, combination chemotherapy may be equally effective with less toxicity particularly in patients over the age of 65.⁸ Choosing the appropriate patients for ASCT is at the discretion of the treating physician. Although overall survival is the same if transplantation is performed at relapse or at time of diagnosis, early transplantation has a longer progression free survival, and less treatment related toxicity. For this reason, ASCT is not routinely used in the relapsed setting. Prior to receiving high dose melphalan chemotherapy conditioning for the transplant, three or four cycles of induction chemotherapy with a regimen containing Bortezomib, Lenalidomide or Thalidomide is used to control the disease, improve the health of the patient, and clear the bone marrow to allow for easier stem cell collection.

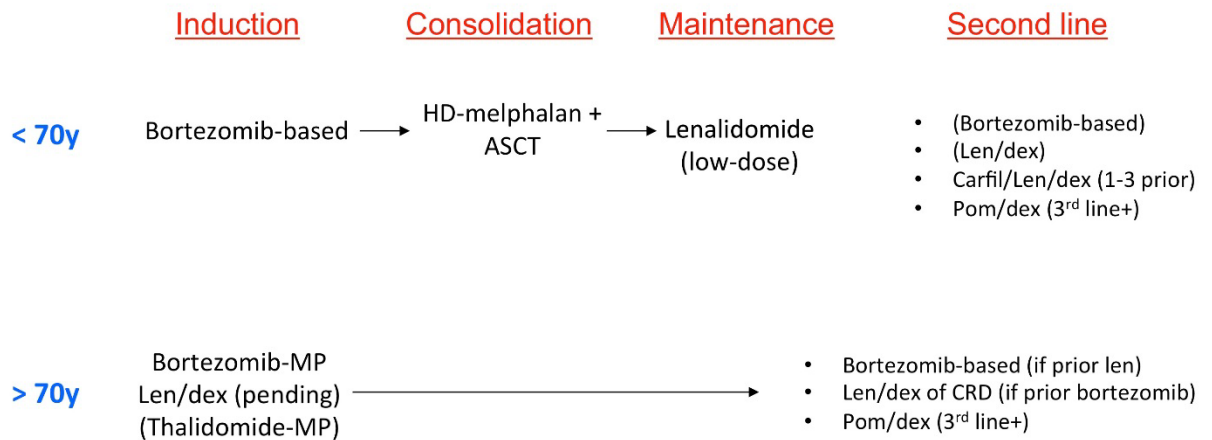
There is considerable debate surrounding the role of maintenance therapy in myeloma post-ASCT. Recent studies using newer agents such as Thalidomide, Lenalidomide, and Bortezomib have demonstrated improvement in progression free survival but there are conflicting studies with respect to a benefit in overall survival.¹² There are also concerns of tolerability of treatment, and long-term side effects of the maintenance therapy. For these reasons, use of maintenance therapy has not been uniformly accepted across

Canada. Further research is necessary to clarify questions with respect to appropriate patient selection, drug of choice, and safety.

Historically, melphalan and prednisone (MP) was the standard treatment for patients that were transplant ineligible or had relapsed disease post-ASCT. The introduction of newer agents using triplet therapy by adding bortezomib or thalidomide to MP demonstrated a significant survival advantage compared to MP alone for newly diagnosed transplant ineligible patients.⁹ More recently, Lenalidomide and dexamethasone continuous therapy proved to be a better tolerated regimen with an improved overall survival compared to melphalan, prednisone and thalidomide.¹³ This adds another option to potential first line therapies for newly diagnosed myeloma patients, not eligible for transplant. There is no clinical trial evidence to clarify whether using a bortezomib-based regimen or a lenalidomide-based regimen is superior in the first line setting. The choice of regimen is based on patient-specific factors determined by the treating physician.

Regardless of the initial therapy, myeloma will relapse and further therapy will be required. Combination therapy with dexamethasone and either bortezomib or lenalidomide is the treatment of choice at the time of relapsed disease.⁸ Both of these regimens are associated with an improvement in overall survival compared to dexamethasone alone and the superiority of one regimen over the other is not known. Consequently, the choice of agents used in second line may depend on the regimen previously used in first line therapy.

Figure 1. Sample treatment algorithm for patients with multiple myeloma based on age



Carfilzomib is a second generation proteasome inhibitor. Compared to bortezomib, it is more selective, and binds irreversibly to proteasomes leading to improved efficacy in the clinical setting.⁷ This was confirmed in a phase III clinical trial, where carfilzomib and dexamethasone had an improved progression free survival (PFS) compared to bortezomib and dexamethasone in patients with relapsed or refractory disease (18.7 months versus 9.4 months; HR 0.53, p<0.0001).¹⁴ These benefits included patients previously treated with bortezomib. Further follow-up is necessary to determine if this translates to an overall survival advantage. The ASPIRE study in the relapsed setting compared carfilzomib in combination with lenalidomide and dexamethasone, versus lenalidomide and dexamethasone.¹⁵ This triplet therapy was associated with an improvement in progression free survival and a trend towards improvement in overall survival. The efficacy and safety of the carfilzomib plus dexamethasone regimen will be the focus of this review. It is

notable that treatment protocols in multiple myeloma are moving towards triplet therapy and therefore it is anticipated that available triplet therapies will be the preferred option. Oral therapies are also preferable in this patient population. Additionally, the treatment landscape for multiple is rapidly evolving. Other therapies currently available through compassionate access (i.e., ixazomib and Daratumumab) are likely to change the treatment landscape if and when they become more widely available.

2.3 Evidence-Based Considerations for a Funding Population

The population under consideration here includes patients with relapsed multiple myeloma, who have previously failed at least one line of therapy that included bortezomib or lenalidomide. All patients with progressive myeloma could be potential candidates for this therapy, assuming they are able to tolerate the potential toxicities of treatment.

2.4 Other Patient Populations in Whom the Drug May Be Used

Carfilzomib and dexamethasone may be a treatment option in patients who have exhausted other options and have resistance to bortezomib, lenalidomide or both.¹⁶ Using triplet therapy for this resistant patient population using Carfilzomib, lenalidomide and dexamethasone requires further research to determine efficacy. For patients progressing on maintenance therapy with lenalidomide or bortezomib, they may be candidates for this doublet therapy if chemotherapy-sensitive disease is demonstrated on the most recent line of therapy.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group provided input on carfilzomib in combination with dexamethasone alone in the treatment of patients with relapsed multiple myeloma who have received 1 to 3 prior lines of therapy.

Myeloma Canada conducted two online surveys between August 15, 2016 and August 31, 2016. One survey was directed to myeloma patients and the second survey was directed to caregivers to help understand the impact of myeloma on their lives and the effect of treatments from the perspective of the patient and the caregiver. The surveys included specific questions directed to patients and caregivers of patients who have used carfilzomib to treat their myeloma.

A total of 344 responded to the patient survey. Among these respondents, 238 respondents were from Canada (representing each province except New Brunswick, and none were from the territories), 104 respondents were from the US and two were from Israel. Among the patient respondents, 41 respondents are using or have used carfilzomib and 10 respondents who have used it in combination with dexamethasone were doing so following one or more prior treatments.

A total of 123 responded to the caregiver survey. Among these respondents, 82 respondents were from Canada (representing each province except New Brunswick, Prince Edward Island, and none were from the territories), 40 respondents were from the US and one respondent was from Australia. Among the caregiver respondents, 19 respondents are providing care for patients who have used carfilzomib and seven respondents who have used it in combination with dexamethasone only following one or more prior treatments.

Myeloma Canada also conducted interviews with two patients who had used carfilzomib in combination with other therapies, one with prednisone and the other in combination with several other therapies.

From a patient's perspective, the most important aspect of myeloma to control was infections, followed by kidney problems, pain, mobility, neuropathy, fatigue, shortness of breath, mood/emotional issues, and stomach issues including diarrhea, nausea, gastrointestinal. Respondents indicated that symptoms associated with myeloma affected their ability to work the most, followed by ability to exercise, travel, volunteer, conduct household chores, fulfill family obligations, and spend time with family. Respondents identified the following current treatments that they have used: dexamethasone, bortezomib, lenalidomide, autologous stem cell transplant, melphalan, cyclophosphamide, pomalidomide, thalidomide, VAD and allogenic stem cell transplant. Respondents reported that the side effects experienced with these treatments included: fatigue, neuropathy, insomnia, stomach issues, nausea, shortness of breath, pain and confusion. The respondents stated that it was very important to them to have access to effective treatments. Respondents who have not had experience with carfilzomib indicated that they expect the new treatment bring improvement in their physical condition, and that the expected benefit of the treatment would be lack of disease progression. For respondents who have experience with carfilzomib, when asked in an open-ended question about how carfilzomib changed or is expected to change long-term health and well-being, some respondents indicated that it was discontinued or stopped working; while some reported that it achieved disease control and others indicated that it was too early to tell. Respondents reported that side effects were generally tolerable compared to other treatments taken for myeloma, and that the least tolerable side effects with carfilzomib were: shortness of breath, diarrhea, fatigue, nausea, pneumonia, anemia, fever, thrombocytopenia and neutropenia. When respondents were asked on a scale of 1 to 5 to rate their quality of life while taking carfilzomib, where 1 was "poor quality of life" and 5 "excellent quality of life"; the majority of respondents rated this as a "3" and "4".

Please see below for a summary of specific input received from the patient advocacy group. Quotes are reproduced as they appeared in the survey and interviews, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Multiple Myeloma

Myeloma Canada asked respondents to rate on a scale of 1-5 (where 1=not important and 5=very important), how important it is to control various aspects of myeloma. According to Myeloma Canada, infections were the most important aspect of myeloma to control, followed by kidney problems, pain, mobility, neuropathy, fatigue and shortness of breath. The results collected from the respondents are reproduced in the Table 3 below.

Table 3 Patient reported AEs reported by Myeloma Canada

	1 - Not important	2	3	4	5 - Very important	N/A	Total
Infections	0.34% 1	1.34% 4	4.36% 13	10.40% 31	83.22% 248	0.34% 1	298
Kidney problems	2.01% 6	1.34% 4	3.68% 11	9.36% 28	80.60% 241	3.01% 9	299
Mobility	0.34% 1	1.01% 3	4.70% 14	21.14% 63	70.81% 211	2.01% 6	298
Pain	0.67% 2	1.67% 5	9.03% 27	20.07% 60	66.56% 199	2.01% 6	299
Fatigue	0.00% 0	1.71% 5	10.92% 32	20.48% 60	65.87% 193	1.02% 3	293
Neuropathy	0.33% 1	2.34% 7	9.70% 29	21.07% 63	64.55% 193	2.01% 6	299
Shortness of breath	1.01% 3	2.03% 6	13.85% 41	18.92% 56	62.16% 184	2.03% 6	296

Myeloma Canada also asked respondents to rate on a scale of 1-5 (where 1=not at all and 5=significant impact), how much symptoms associated with myeloma impact or limit day-to-day activity and quality of life. Myeloma Canada submitted that patients indicated their ability to work was most affected, followed by ability to exercise, travel, volunteer, conduct household chores, fulfill family obligations, and spend time with family. The results collected from the respondents are reproduced in the table 2 below.

Table 2

Ability to	1 - Not at all	2	3	4	5 - Significant impact	N/A	Total
Work	10.23% 31	14.19% 43	16.83% 51	14.19% 43	29.70% 90	14.85% 45	303

Exercise	8.61% 26	19.21% 58	24.17% 73	24.83% 75	21.85% 66	1.32% 4	302
Travel	13.25% 40	16.23% 49	27.15% 82	17.88% 54	24.17% 73	1.32% 4	302
Volunteer	16.33% 49	18.00% 54	23.33% 70	18.33% 55	19.00% 57	5.00% 15	300
Concentrate	12.67% 38	24.33% 73	23.00% 69	21.00% 63	17.33% 52	1.67% 5	300
Conduct household chores	14.62% 44	22.26% 67	29.24% 88	20.60% 62	12.62% 38	0.66% 2	301
Fulfill family obligations	18.94% 57	25.58% 77	27.91% 84	13.62% 41	11.96% 36	1.99% 6	301
Spend time with family and friends	22.85% 69	25.17% 76	24.83% 75	14.57% 44	11.92% 36	0.66% 2	302

Myeloma Canada has excerpted some of the key responses to help illustrate the effects and impact on patients with myeloma:

- *extra care when going out into the public to minimize the potential exposure to disease and germs - easier to get sick, takes longer to get better*
- *My emotional well being is significantly impacted due to treatment which includes steroids.*
- *The impact is cyclical depending on where I am in my disease control, sometimes all of these things (the list above) see(m) very difficult and sometimes not as much.*
- *Diarrhea limits my day plan - have to plan around it all the time*
- *Ability to work n/a as Retired, but often unable to do what I used to enjoy e.g. Woodworking, "outside chores". Certainly could not have done my job - renovations, building etc.*

3.1.2 Patients' Experiences with Current Therapy for Multiple Myeloma

Myeloma Canada reported that 261 respondents indicated the following when asked "*what is important to you when it comes to treating your myeloma*":

- Maintain Quality of Life or normal life: 36%
- Manage/minimize side effects: 20%,
- Control the disease: 19%
- Access to effective treatments: 15%
- Control symptoms: 13%,
- Achieve or maintain remission: 7%
- Prolong survival: 7%

- Access to a skilled medical team: 6%
- To be cured: 5%
- Affordable treatments: 3%
- Disease status: 2%
- Maintain physical fitness: 1%
- Minimal use of drugs: 0.5%
- To feel hopeful: 0.5%.

Other than carfilzomib, respondents (n=295) were asked to identify treatment(s) used to treat their myeloma. It is important to note that some respondents selected more than one answer. These treatments included:

- dexamethasone (Decadron®): 84%
- bortezomib (Velcade®): 77%
- lenalidomide (Revlimid®): 71%
- autologous stem cell transplant: 60%
- melphalan (Alkeran®): 57%
- cyclophosphamide (Cytosan®): 44%
- pomalidomide (Pomalyst®): 17%
- thalidomide (Thalidomid®): 16%
- vincristine, doxorubicin, dexamethasone (VAD): 9%
- allogeneic stem cell transplant: 9%

Respondents reported that the side effects experienced with these treatments included: fatigue (88%), neuropathy (62%), insomnia (57%), stomach issues (48%), nausea (46%), shortness of breath (43%), pain (38%), confusion (30%), does not apply to me as I have yet to be treated (2%), I don't know or can't remember (0.3%). Under "other" an additional 7% cited stomach related issues (diarrhea, constipation) as a side effect, 3% cited skin rash, 2% cramps, and 2% emotional issues.

According to Myeloma Canada, when respondents were asked to rate the importance of access to effective treatments for myeloma on a scale of 1-5, (with 1 = *not important* and 5 = *very important*), 97% (n=294) of respondents selected "5", as being very important.

Myeloma Canada also asked respondents to rate on a scale of 1-5 (where 1=*not important* and 5=*very important*), how important it is for them and their physician to have choice based on each drug's known side effects. Most respondents (86%, n=294) rated this as "5 - *very important*." Most respondents (89%, n=294) reported that improvement of quality of life was a "*very important*" consideration with any treatment for myeloma.

Myeloma Canada reported that 202 respondents responded to the question about the financial implications of their treatment for myeloma. It is important to note that some respondents selected more than one answer. The following were key challenges that respondents found:

- drug costs and parking costs: 51%
- travel costs: 33%
- lost income due to work absence: 32%
- drug administration fees: 17%
- medical supply costs: 16%
- accommodations costs: 15%

25% of respondents reported that they had no financial implications related to treatment for myeloma.

When respondents were asked in an open-ended question about hardships accessing treatment for myeloma, 155 Canadian respondents reported that:

- “No, not that I’m aware of, not so far and not yet”: 74%,
- “yes”: 23%,
- “too soon to tell”: 1%
- “N/A”: 2%.

The yes responses included:

- denied treatment: 6%
- drug not covered: 5%
- limited to covered treatments: 3%
- travel to treatment: 2%
- cost of drugs: 2%
- access to physician, access to available bed, treatment not available, or waited for treatment approval: 1%

3.1.3 Impact of Multiple Myeloma and Current Therapy on Caregivers

To help illustrate the caregiver perspectives, Myeloma Canada conducted a survey that was focused on caregivers. Group A includes caregiver respondents who care for someone who has used carfilzomib (n=19). Group B includes only the caregiver respondents who care for someone who has used carfilzomib in combination with dexamethasone only following one or more prior treatments (n=7).

Group A. Caregivers were asked in an open-ended question what challenges they encountered while helping to manage treatment side effects for the person they are caring for. Caregiver respondents (n=17) reported the following: Patient had side effects (29%), Patient had severe side effects (26%), Emotional issues (12%). Caregiver respondents also stated: Reduced quality of life, Patient was end stage quit treatment, Little support for side effects, Minimal side effects, Nothing major, Caregiver had to provide support with chores, Trying to live a normal life (6%).

In particular respondents stated the following:

- *It made him feel yucky, tired, teeth hurt and were sensitive, achy.*
- *Severe rage and personality shift on Dex, more severe fatigue and shortness of breath on Kyprolis*
- *Emotional distress Difficult to watch someone you love suffer daily*

Group A. Caregivers were asked if there was anything else about carfilzomib they would like us to know and include. Caregiver respondents (n=13) reported the following: Best treatment, Effective treatment, Patient responded well to the treatment, There were side effects (15%). Respondents also noted the following: Care should focus on the whole patient, not just the cancer, Grateful for the treatment, Treatment improved life (8%). 15% of respondents had nothing more to add, and another 15% of respondents provided responses that were not relevant.

Some key responses to help illustrate the above included:

- *Was the best treatment - had two years off treatment after using carfilzomib.*
- *Serious respiratory side effects Very successful in reducing counts*
- *It seems to have worked well. We are grateful to have it available.*

Group B. Caregivers were asked in an open-ended question what challenges they encountered while helping to manage treatment side effects for the person they are caring for. Caregiver respondents (n=5) reported the following: Patient had side effects (43%). Respondents also noted

the following: Reduced QOL, Patient was end stage quit treatment, Little support to manage side effects, Patient had severe side effects, Try to live a normal life (14%).

Group B. Caregivers were asked if there was anything else about carfilzomib they would like us to know and include. Caregiver respondents reported the following: Best treatment, Patient care should focus on the whole patient, not just the cancer, Patient responded well to the treatment, There were side effects (20%).

When caregiver respondents were asked to rate on a scale of 1-5, with 1 = "not at all" and 5 = "significant impact", how much caring for someone with myeloma limits their day-to-day activity and quality of life, respondents indicated that their ability to travel was most affected, followed by ability to volunteer, spend time with family and friends, to concentrate, fulfill family obligations, to work, exercise, and to conduct household chores. The total respondents for this question ranged between 115- 120.

To help illustrate how much a caregiver's life can be affected along with the patient, the following quotes have been excerpted:

- *My concentration is great because I keep a notebook on all my husbands visits to the oncologist, which was 3 hr trip one way, and we sometimes went 2-3 xs/week. My mind was very sharp when it came to his MM cancer details. Just sometimes I'd forget to put on deodorant!!!*
- *It depends, varying according to involvement in treatment or not.*
- *Multiple Myeloma attacks the entire family structure at its very core. Prayer & a good support system, along with a better class of medications, help. There is a need for more advocacy for what the caregiver does!*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Carfilzomib

Patients' Expectation with Carfilzomib

Among the patients who have no experience with carfilzomib, most respondents (82%; n= 251) indicated that it was "*extremely important*" that the treatment bring improvement in their physical condition. The majority of these respondents (93%; n=250) indicated that the expected benefit (i.e., lack of disease progression) of the treatment was "*extremely important.*" Myeloma Canada reported that 91% of respondents (n=251) specified that it was very important to them to choose which drug would be best suited for them.

Myeloma Canada stated that patients are willing to tolerate some side effects. A total of 8% of respondents indicated that they were willing to tolerate significant side effects, while 7% of respondents indicated that they were not willing to tolerate side effects (N=253).

Patients' Experience with Carfilzomib

Myeloma Canada provided the following summary analysis.

- Group 1 (n=39) includes all respondents who indicated that they have used carfilzomib in combinations with more than dexamethasone following one or more courses of therapy.
- Group 2 (n=10) includes only the respondents who have used carfilzomib in combination with dexamethasone only following one or more prior treatments.

No statistical analysis was performed to compare these two groups because of the low number of patients in each of them.

Group 1 (n=39) respondents reported the following:

When asked about the length of time patients have been on carfilzomib, the 39 respondents reported that it ranged from 1-6 months to 3-4 years. The breakdown were as follows:

- 1 - 6 months: 58%
- 7 -12 months: 18%
- 1 -2 years: 18%
- 3 - 4 years: 5%

Respondents reported that based on their personal experience, carfilzomib was very effective in controlling their myeloma. On a scale of 1 - 5, with 1 being *“not effective”* and 5 being *“extremely effective”*; 41% of respondents rated it is a “5” and 10% of respondents rated it as a “1”.

When asked to rate its effectiveness compared to other therapies to treat their myeloma on a scale of 1 - 5, with 1 being *“not as effective”* and 5 being *“far more effective”*; 25% of respondents rated carfilzomib a “5” and 10% of respondents rated it as a “1”.

The same respondents were asked to rate the tolerability of the side effects of carfilzomib on a scale of 1 - 5, with 1 being *“completely intolerable”* and 5 *“very tolerable”*. 31% of respondents rated it as a “5”, 26% of respondents rated it as a “4” and 5% of respondents rated it as a “1”.

The common side effects with carfilzomib for these respondents are listed in the table below with the most tolerable to the least tolerable side effects. The least tolerable side effects were: fatigue, shortness of breath, diarrhea, anemia, neutropenia, nausea, fever, thrombocytopenia and pneumonia.

Table 4: AEs reported by patient group

	1 - Completely intolerable	2	3	4	5 - Very tolerable	N/A	Total
Pneumonia	2.86% 1	5.71% 2	8.57% 3	11.43% 4	25.71% 9	45.71% 16	35
Thrombocytopenia (low platelet count)	0.00% 0	10.53% 4	18.42% 7	28.95% 11	28.95% 11	13.16% 5	38
Fever	2.78% 1	8.33% 3	8.33% 3	11.11% 4	25.00% 9	44.44% 16	36
Nausea	0.00% 0	17.65% 6	8.82% 3	17.65% 6	26.47% 9	29.41% 10	34
Neutropenia (low white blood cell count)	0.00% 0	5.71% 2	34.29% 12	31.43% 11	14.29% 5	14.29% 5	35
Anemia (low red blood cell count)	2.63% 1	10.53% 4	28.95% 11	21.05% 8	23.68% 9	13.16% 5	38
Diarrhea	0.00% 0	19.44% 7	30.56% 11	11.11% 4	22.22% 8	16.67% 6	36

	1 - Completely intolerable	2	3	4	5 - Very tolerable	N/A	Total
Shortness of breath	5.26% 2	15.79% 6	21.05% 8	26.32% 10	15.79% 6	15.79% 6	38
Fatigue	2.63% 1	28.95% 11	31.58% 12	13.16% 5	18.42% 7	5.26% 2	38

In addition to the above, there were additional comments under “other” from 3 respondents who did not experience side effects and “PN = severe (feet)”. Other responses reported “*short term memory loss*”, “*I did have pneumonia several years ago - in hospital for 8 days*”; “*developed “hot” spot in shoulder that need Rad Therapy even though my numbers were good*”; “*sinus infection is bad*”, “*created a lung problem from which I had to suspend treatment after 7 cycles; Frankly, continuing would have me killed me. My lungs were filling with fluid*”, and “*high blood pressure*”.

The respondents were asked to rate on a scale of 1 - 5 how the side effects of carfilzomib compared to other treatments taken for myeloma. 1 was “*many more side effects*” and 5 was “*far fewer side effects*”; 23% of respondents rated it as a “5” and 74% of respondents rated it as a “3” or higher; 3% of respondents rated it is a “1”.

When asked to rate the convenience for taking this drug on a scale of 1 - 5 in terms of day-to-day activities and immediate or intolerable side effects, the majority rated it as convenient. 1 was “*not at all convenient*” and 5 was “*extremely convenient*”; 62% of respondents rated it as a “3” or higher, and 13% of respondents rated it as a “1”.

On a scale of 1 - 5, respondents were asked to rate their quality of life while taking carfilzomib. 1 was “*poor quality of life*” and 5 “*excellent quality of life*”; 80% of respondents rated this as a “3” or higher, 44% of respondents rated it as a “4” or higher.

Myeloma Canada reported that 67% of respondents (n=36) indicated that carfilzomib met their expectations. When asked in an open-ended question about their expectations, the responses were as follows: Disease control (39%), Remission (28%), Little or no side effects (19%), No expectations (17%), Extend life (6%). Other expectations included: High expectations, Lots of side effects, Symptom control, Unsure, Work better than other treatments (3%).

When asked in an open-ended question about how carfilzomib changed or is expected to change long-term health and well-being, respondents (n=36) reported the following: Achieved disease control (19%), Discontinued/stopped working (19%), too early (14%), Achieved remission (11%), Worked well (11%), Prolong life (3%), Improved QOL (3%). Some respondents reported that: Decreased QOL (6%), Significant side-effects (6%), Remission not achieved (6%). The remainder of respondents reported: No change (3%) and Unsure (3%).

Myeloma Canada has excerpted key responses to highlight the above points:

- *It is battling the cancer well and my M spike continues to go down along with the free light chain numbers*
- *it didn't work for my strain of myeloma*
- *I am in remission before the end of my treatments - this is working!!!*
- *FATIGUED takes away from working. And volunteering more.*
- *Carfilzomib is why I am healthy today.*
- *Side effects have been brutal but my counts have never been so low*

- *I think it is important to have an echogram and EKG before starting treatment and to monitor the heart shortly after starting treatment and often during treatment. If you are short of breath, see a cardiologist immediately!*

In an open-ended question, respondents were asked why access to carfilzomib and future therapies are important to them. Respondents (n=35) indicated the following: Prolong life (40%), Improve QOL (29%), Future options for treatment (26%), Disease control (11%), Achieve remission (9%), Find a cure (9%), Little/no side effects (9%), Effective treatments (6%), To help others (6%), and Reduce symptoms (3%). Some respondents (6%) indicated that it was not relevant.

Below are key responses reported by the respondents:

- *Keep my MM in check prolonging my life and helping the quality of my life*
- *Every new treatment extends my life.*
- *If it can prolong my life and provide minimum side effects I consider it a successful treatment*
- *To extend and maintain quality of life.*
- *I like as many options as possible especially when trying to avoid side effects.*
- *Carfilzomib and other therapies are important to slow progression of the disease and reduce bone pain and fractures*
- *always looking for a cure or long remission time*

When this same patient group was asked in an open-ended question if there was anything else about carfilzomib that they wanted us to know and include, the respondents (n=23) indicated the following: Treatment was effective (17%), Treatment effective but significant side effects (13%), Commented on side effects (9%), Need for tests with the treatment (9%). Some respondents (4%) provided the following: Access can be complicated, Dosage should be adjusted, Inconvenient, Not effective, Side effects are more about other treatment, and Tolerable. Some respondents (22%) indicated that they had nothing more to add, and 4% of respondents provided answers that were not relevant.

Group 2 (n=10) respondents reported the following:

When asked about the length of time patients have been on carfilzomib, the 10 respondents reported that it ranged from 1-6 months to 1-2 years. The breakdown were as follows:

- 1 - 6 months: 80%
- 7 -12 months: 10%
- 1 -2 years: 10%

Respondents reported that based on their personal experience, carfilzomib was very effective in controlling their myeloma. On a scale of 1 - 5, with 1 being "*not effective*" and 5 being "*extremely effective*". It was reported that 30% of respondents rated it is a "5" and 20% of respondents rated it as a "1".

When asked to rate its effectiveness compared to other therapies to treat their myeloma on a scale of 1 - 5, with 1 being "*not as effective*" and 5 being "*far more effective*". It was reported that 10% of respondents rated carfilzomib a "5" and 20% of respondents rated it as a "1".

The same respondents were asked to rate the tolerability of the side effects of carfilzomib on a scale of 1 - 5, with 1 being "*completely intolerable*" and 5 "*very tolerable*". It was reported that 20% of respondents rated it as a "5", 20% of respondents rated it as a "4" and 10% of respondents rated it as a "1".

The common side effects with carfilzomib for these respondents are listed in the table below with the most tolerable to the least tolerable side effects. The least tolerable side effects were: shortness of breath, diarrhea, fatigue, nausea, pneumonia, anemia, fever, thrombocytopenia and neutropenia.

Table 5: AEs reported by patient group

	1 - Completely intolerable	2	3	4	5 - Very tolerable	N/A	Total
Neutropenia (low white blood cell count)	0.00% 0	11.11% 1	22.22% 2	55.56% 5	0.00% 0	11.11% 1	9
Thrombocytopenia (low platelet count)	0.00% 0	20.00% 2	30.00% 3	30.00% 3	10.00% 1	10.00% 1	10
Fever	0.00% 0	22.22% 2	22.22% 2	22.22% 2	11.11% 1	22.22% 2	9
Anemia (low red blood cell count)	0.00% 0	20.00% 2	30.00% 3	20.00% 2	10.00% 1	20.00% 2	10
Pneumonia	12.50% 1	12.50% 1	12.50% 1	25.00% 2	12.50% 1	25.00% 2	8
Nausea	0.00% 0	37.50% 3	0.00% 0	37.50% 3	0.00% 0	25.00% 2	8
Fatigue	0.00% 0	40.00% 4	30.00% 3	10.00% 1	10.00% 1	10.00% 1	10
Diarrhea	0.00% 0	30.00% 3	40.00% 4	20.00% 2	0.00% 0	10.00% 1	10
Shortness of breath	11.11% 1	33.33% 3	11.11% 1	33.33% 3	0.00% 0	11.11% 1	9

In addition to the above, there were additional comments under "other", which included: "*had no side effects*", and "*sinus infection is bad*", and "*I did have pneumonia several years ago - in hospital for 8 days.*"

Respondents were asked to rate on a scale of 1 - 5 how the side effects of carfilzomib compared to other treatments taken for myeloma, where 1 was "*many more side effects*" and 5 was "*far fewer side effects*". No respondents rated it as a "1" or "5", and 70% of respondents rated it as a "3" or higher.

Respondents were also asked to rate the convenience for taking this drug on a scale of 1 - 5 in terms of day-to-day activities and immediate or intolerable side effects, where 1 was "*not at all convenient*" and 5 was "*extremely convenient*". It was reported that 50% of respondents rated it as a "3" or higher, and 10% of respondents rated it as a "1".

On a scale of 1 - 5, respondents were asked to rate their quality of life while taking carfilzomib, where 1 was "*poor quality of life*" and 5 "*excellent quality of life*". It was reported that 90% of respondents rated this as a "3" or higher, and 20% of respondents rated it as a "4" or higher.

Of the eight respondents who answered this question, Myeloma Canada found that 50% of respondents reported that carfilzomib met their expectations. When asked in an open-ended question about their expectations, the respondents indicated the following: Disease control (50%), Remission (38%). Respondents also stated: High expectations, Little or no side effects, No expectations (13%).

When asked in an open-ended question about how carfilzomib changed or is expected to change long-term health and well-being, respondents (n=7) indicated the following: Discontinued/stopped working (43%), Achieved disease control (14%), Decreased QOL (14%), Too early (14%), Unsure (14%).

In an open-ended question, respondents were asked why access to carfilzomib and future therapies are so important to them. Respondents (n=9) reported the following: Disease control, Little/no side effects, Prolong life (22%), Achieve remission, Future options for treatment, Improve QOL, Reduce symptoms (11%). Some respondents (22%) noted that it was not relevant. When respondents (n=6) were asked in an open-ended question if there was anything else about carfilzomib that they wanted us to know and include, they responded as follows: 50% responded "No", 17% noted that it was "Effective but significant side effects", 17% commented on "side effects", and 17% stated "Need for tests with the treatment".

Myeloma Canada also conducted interviews with two patients who had used carfilzomib in combination with other therapies, one with prednisone and the other in combination with several other therapies.

Patient 1 - Diagnosed in 1998, has been on many different treatments since that time. The respondent was on carfilzomib for a year. It worked at first and then it stopped working. The respondent found it hard to go to hospital for treatments. It took time to recover. The respondent reported that they were grateful to have different treatment options, and specifically stated: "*I wouldn't still be here if there weren't all these choices (of treatment)*".

Patient 2 - Diagnosed in 2013, has been on several different treatments since that time. The respondent has been on carfilzomib for 4 months. The respondent has achieved remission and is now on maintenance therapy. The respondent expected to achieve remission and therefore treatment met expectations. The respondent found that "*It is a very powerful medication with minimal side effects.*"

3.3 Additional Information

N/A

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact implementation of carfilzomib for previously treated multiple myeloma:

Clinical factors:

- Clarity on patient groups eligible for treatment

Economic factors:

- Drug wastage
- Intense dosing schedule for intravenous infusion and the intense hydration protocol with intravenous fluids required impact health care resources
- Duration of treatment unknown as treatment is until progression
- Dosing at 56mg/m²

Please see below for more details.

4.1 Factors Related to Comparators

PAG noted that cyclophosphamide, bortezomib and dexamethasone would be the more appropriate comparator for this group of patients. The bortezomib plus dexamethasone as prescribed in the ENDEAVOR trial is not commonly used in Canada.

PAG noted that pomalidomide plus dexamethasone is used in the third-line setting after failure with lenalidomide and with bortezomib. PAG noted that patients who were refractory to lenalidomide in the ENDEAVOR trial did not perform as well with carfilzomib plus dexamethasone.

In addition, PAG noted that the ENDEAVOR trial enrolled patients who have had one, two or three prior therapies and that 54% of these patients had prior bortezomib therapy, which may skew outcomes in favour of carfilzomib.

4.2 Factors Related to Patient Population

Carfilzomib provides another treatment option for patients who cannot receive bortezomib and has lower risk for peripheral neuropathy compared to that drug. This is an enabler to implementation.

If ASPIRE regimen were to be funded, the ENDEAVOR trial regimen allows patients who had previous carfilzomib combination therapy and had a response to carfilzomib and progressed after 6 months, to be rechallenged with carfilzomib and dexamethasone.

PAG noted that lenalidomide plus dexamethasone in first-line treatment for patients ineligible for stem cell transplant is under provincial consideration for funding. Carfilzomib

with lenalidomide/dexamethasone for second-line is currently under negotiations with the manufacturer.

PAG is interested to understand how current treatment algorithms and eligibility criteria of other therapies for multiple myeloma may need to be re-evaluated with the addition of carfilzomib.

4.3 Factors Related to Dosing

The intense dosing schedule of two consecutive days every week for three weeks out of a four-week cycle is challenging for scheduling chemotherapy chair time and for patients to travel to receive therapy. In addition, for the ENDEAVOR regimen, the dose of carfilzomib is higher, at 56mg/m², than the ASPIRE regimen. PAG has concerns that there is the potential for dosing errors.

Also, the multiple changes in dosing (e.g. dose escalation after cycle 1, decrease frequency of doses after cycle 12 (which does not apply to the dosing schedule of ENDEAVOR), and different dose adjustment for weight changes) may be a challenge for implementation.

4.4 Factors Related to Implementation Costs

Carfilzomib will increase drug preparation and administration times. Additional resources are also required to monitor for multiple severe adverse effects including infusion reactions, renal function, and cardiac complications. PAG noted that toxicities on recent clinical experience have been significant.

Although the infusion time for carfilzomib is fairly short, additional chemotherapy chair time and nursing resources are required for the intense hydration protocol with intravenous fluids, pre and post each carfilzomib infusion in the first cycle and in subsequent cycles as needed, especially in patients at high risk of tumor lysis syndrome or renal toxicity. PAG noted that hydration requirements add a minimum additional two hours (one hour pre and one hour post carfilzomib) to chemotherapy chair time and impacts human resource time. Pre-medication with dexamethasone is also required in the first cycle and with each cycle of dose escalation.

PAG noted that there may be a large prevalent population who would be eligible for treatment with carfilzomib. As carfilzomib is an additional line of treatment, there could be a significant impact on human resources and budget.

PAG has concerns for incremental costs due to drug wastage, specifically in centers where vial sharing would be difficult. Dose is based on weight and there is only one vial size available. Any unused portion would be discarded as the stability of reconstituted drug is 24 hours refrigerated and 4 hours at room temperature. PAG noted that at the 56mg/m² dosing, the drug wastage is more significant with the currently available single vial size.

4.5 Factors Related to Health System

The dosing schedule of two consecutive days every week for 3 weeks of a 4-week cycle is challenging for scheduling of chemotherapy chair time and preparation time.

4.6 Factors Related to Manufacturer

The cost of carfilzomib will be a barrier to implementation.

PAG noted that the anticipated vials sizes of 10mg and 30mg (to be made available in February 2017) will minimize drug wastage.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One clinician input was provided on carfilzomib for multiple myeloma. The input was provided as a joint submission from four oncologists who are members of Myeloma Canada Research Network (MRCN). Their input is summarized below.

The oncologists from MCRN identified that multiple myeloma patients require sequential lines of therapy to control their disease and extend survival, and carfilzomib-based regimens offer another line of effective therapy, particularly for patients who are refractory, intolerant or have contraindications to bortezomib. The key benefits of carfilzomib identified are the prolonged progression free survival, improvement in disease control, durable response and minimal peripheral neuropathy adverse event. The harms identified are the cardiotoxicities and cytopenias. The oncologists from MCRN noted that patients with cardiac disease should not be treated with carfilzomib and patients with significant marrow burden would require greater oversight and frequent dose adjustments. Overall, the oncologists from MCRN felt that carfilzomib has a good response rate with deep and durable response and manageable toxicities.

Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for this Type of Cancer

The oncologists providing input identified that the current treatments for relapsed/refractory multiple myeloma include lenalidomide, bortezomib, cyclophosphamide, melphalan, pomalidomide. A repeat stem cell transplant could be considered for eligible patients.

5.2 Eligible Patient Population

The oncologists providing input are from four different provinces (Ontario, New Brunswick, Quebec and Alberta) and estimated that a range of 10% to 75% of patients would be eligible to receive treatment with carfilzomib as per the funding request.

- The use of carfilzomib and dexamethasone is an attractive option in patients who relapse after stem cell transplant followed by lenalidomide maintenance. It is superior to bortezomib and dexamethasone in the phase 3 trial, which included patients relapsing after lenalidomide. It may also be useful in elderly patients not refractory to bortezomib who relapse after a period of remission, or who are in a second relapse following bortezomib-based first-line therapy of fixed duration and then second-line therapy with lenalidomide and dexamethasone.
- If the progression-free survival of transplant-eligible patients is around 3 years depending if they receive maintenance or not, and the progression-free survival of non-transplant-eligible patients is around 2-3 years, an estimated 30% of patients per year will reach the second-line treatment. As an estimation, around 10% more patients will reach third line of treatment or above.
- Using our local myeloma program database, about 55% of patients being followed are alive and are in second line therapy or beyond. Around 10% are outside the third line window leaving between 40-45% meeting the approved criteria.
- Most patients will benefit from this but the field is moving fast and so the treatment algorithm will change over time. Some will be treated in clinical trials.

5.3 Identify Key Benefits and Harms with Carfilzomib

Benefits identified by the oncologists providing input:

- Good response rate and progression free survival with minimal risk of peripheral neuropathy
- Improves disease control and well tolerated
- It doubles the progression-free survival compared to bortezomib, both in combination with dexamethasone
- Very deep and durable responses are achievable even in pre-treated patients.
- Manageable side effect profile

Harms identified by the oncologists providing input:

- Inconvenient administration schedule for patients with limited mobility; need to watch blood pressure.
- Modest increase in toxicity rates
- A low incidence of cardiac toxicity
- Inconvenient for patients given the twice weekly dosing of an intravenous drug for a prolonged period of time. In a small subset of patients there are cardiovascular complications. The restriction that it cannot be used alone (despite phase III data) and that it MUST be used with lenalidomide is too restrictive and ignores evolving data.

Oncologists providing input identified patients for whom carfilzomib should not be used:

- Those with uncompensated cardiac disease should not receive due to a small, poorly understood risk of worsening. Whether this is due of intravenous fluids administration or the drug is unclear.
- Patients with an active cardiac problem or with cardiac insufficiency. One of the oncologists feels that carfilzomib could be used in patients refractory to bortezomib but noted this is controversial and these patients were not included in ENDEAVOR trial.

While not an absolute contraindication, patients with significant marrow burden may have challenges with cytopenias that require greater oversight and dose adjustments. This adds to the workload in caring for these patients

5.4 Advantages of Carfilzomib Over Current Treatments

The oncologists providing input identified that an effective proteasome inhibitor for relapsed myeloma is needed to use in patients in whom an immunomodulatory derivative is no longer effective or is contraindicated. The phase 3 head-to-head study with bortezomib indicates that carfilzomib exerts a more potent anti-myeloma effect, with acceptable toxicity. It was noted that carfilzomib has a more durable and deep responses in patients with relapsed disease and carfilzomib is better than bortezomib, at least in terms of progression-free survival improvements and probably in terms of overall survival (not yet shown in clinical trial). Disease control in excess of two years is unprecedented in this population.

5.5 Sequencing and Priority of Treatments with Carfilzomib

For transplant-eligible patients, induction therapy currently includes CyBorD (cyclophosphamide + bortezomib + dex) followed by high-dose melphalan/autologous stem cell transplant and lenalidomide maintenance; those patients then relapsing on lenalidomide maintenance would be good candidates for carfilzomib at first or second relapse; patients with high-risk cytogenetics would be particularly high priority to receive a proteasome inhibitor such as carfilzomib for

relapse. Elderly patients currently receive VMP (bortezomib + melphalan + prednisone) or as a variation CyBORd for nine cycles. Second line therapy usually consists of lenalidomide + dexamethasone. In this population, most would likely be offered carfilzomib and dexamethasone as third-line therapy, although those with high-risk cytogenetics would preferentially be treated with carfilzomib.

It is important to note in Ontario that even high-risk myeloma patients do not have access to any proteasome inhibitor therapy for relapse, which has been a painful situation for both patients and physicians, as this has become the standard of care elsewhere in Canada, the US and Europe.

Currently bortezomib-based therapy is a standard treatment in first-line treatment, both for transplant-eligible and non-transplant eligible patients. For those not refractory to bortezomib, this would be second line for patients not previously treated with carfilzomib and for those who are not refractory to lenalidomide.

In transplant-eligible patients, it could be used in second or third line treatment depending if lenalidomide maintenance was used, in patients are not refractory to Bortezomib. In non-transplant eligible patients it could be used in second or third line treatment.

It would likely become the standard second line option for anyone currently eligible for lenalidomide beyond frontline therapy. For those beyond second line use it will also become the treatment of choice assuming the patient is fit enough to tolerate the combination

5.6 Companion Diagnostic Testing

None

5.7 Additional Information

The oncologists providing input noted that there are several expensive new drugs that can be added to lenalidomide/dexamethasone to improve outcome and that there is no way to tell which is the best. The clinician input indicated that patients are not likely to receive more than one lenalidomide/dexamethasone based triplet therapy but believes that making them all available might help drive down cost through market forces.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of carfilzomib plus dexamethasone (Cd) compared with bortezomib plus dexamethasone (Bd) for the treatment of patients with relapsed/refractory multiple myeloma following 1-3 prior therapies.

Note: Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were not identified while developing the review protocol.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the Table 6. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 6. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Randomized controlled trials	Patients with relapsed or refractory MM who have received 1-3 prior lines of therapy Subgroups: Prior therapies Relapsed disease Prior transplant Cytogenetics	Carfilzomib in combination with dexamethasone	Regimens including the following drugs: Proteasome Inhibitors (e.g. bortezomib) <i>AND/OR</i> Immunomodulatory Drugs (e.g. lenalidomide, thalidomide, pomalidomide) <i>AND/OR</i> Chemotherapy (e.g. cyclophosphamide) <i>AND/OR</i> Dexamethasone	OS PFS HrQoL TTP DOR ORR SAE AE WDAE Death AEs of Interest: Cardiac disorders (e.g. Cardiac failure) Hematological toxicity Neuropathy Infections Hepatic toxicity Renal toxicity Pulmonary disorders SPM
AE = adverse event; DOR = duration of response; HrQoL = health-related quality of life; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SAE = serious adverse event; SPM = secondary primary malignancies; TTP = time to progression; WDAE = withdrawal due to adverse event.				

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (November 2015) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Kyprolis/carfilzomib and multiple myeloma.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year. The search is considered up to date as of January 6, 2017.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health - clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

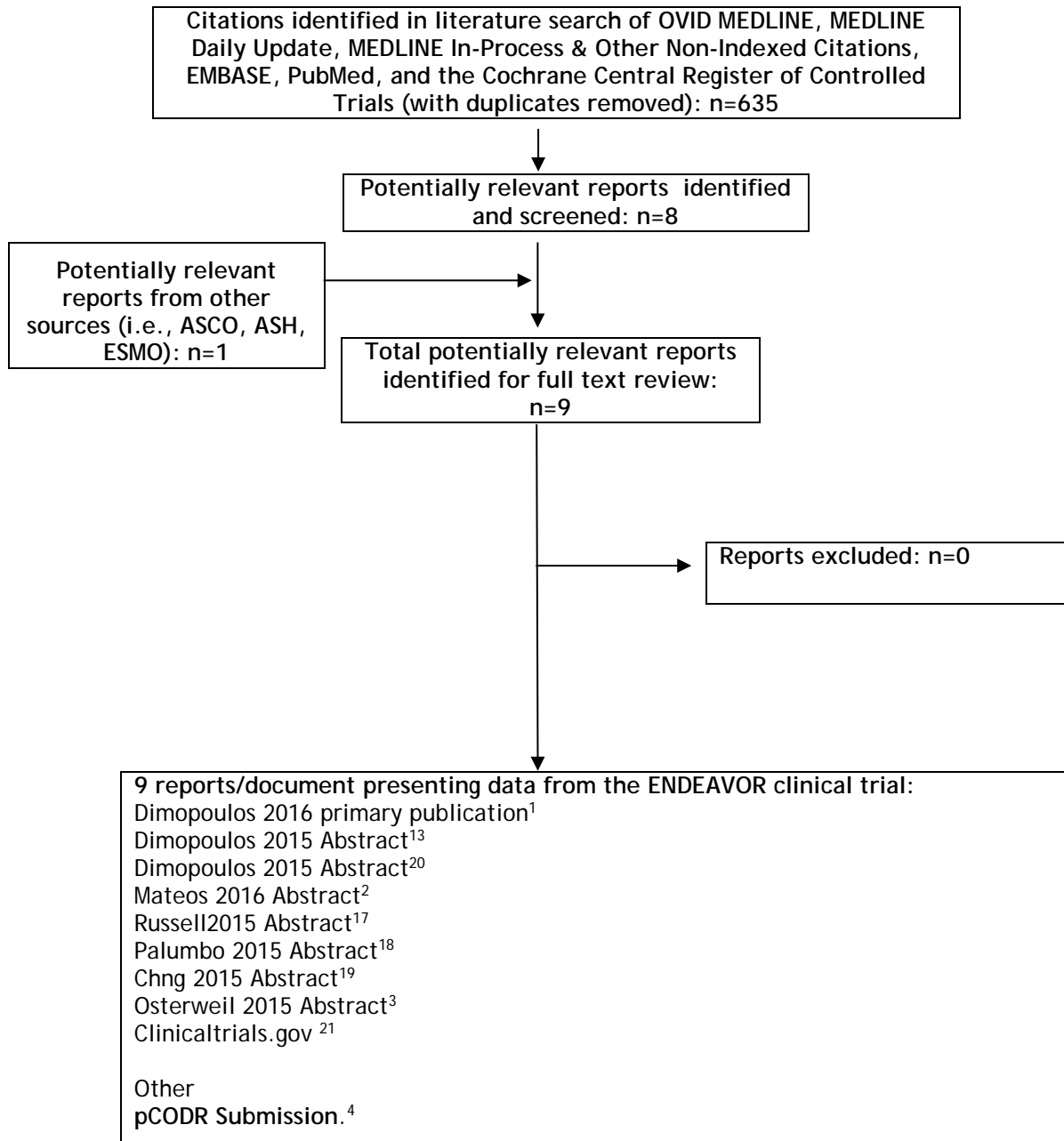
This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental issues.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information, the interpretation of the systematic review and wrote guidance and conclusions for the report.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 9 potentially relevant reports identified for full text review, all (one full text article,¹ seven conference abstracts,^{1-3,13,17-20} and clinical trial registry²¹ based on one RCT (ENDEAVOR) were included in the pCODR systematic review.



6.3.2 Summary of Included Studies

One clinical trial, the ENDEAVOR trial, met the inclusion criteria for this systematic review. The ENDEAVOR study is an ongoing RCT and expected to be completed in 2018. The data reported in the review was based on a pre-specified interim analysis (November 2014) except the overall survival data was based on an updated analysis in 2016. The key characteristics of this trial are summarized in Table 7 specific features of trial quality are summarized in Table 8 below.

a) *Trials*

The ENDEAVOR study was a phase III trial which randomized patients with relapsed or refractory multiple myeloma to carfilzomib plus dexamethasone or bortezomib plus dexamethasone. This trial was conducted in 198 sites in 27 countries located in North America (including Canada), Europe, South America, and the Asia-Pacific regions. ENDEAVOR is an ongoing study.²¹

Key eligibility criteria for screened patients are listed in Table 7. Briefly, patients with multiple myeloma were required to be relapsed or refractory on one to three prior treatments.¹ Other inclusion criteria included performance status (ECOG PS 0-2), and adequate hepatic, hematologic, and renal function. Patients previously treated with carfilzomib or bortezomib were permitted entry into the trial if patients achieved at least a partial response before relapse or progression, were not discontinued due to toxic effects, and had at least a 6-month proteasome inhibitor treatment-free interval before enrolment.¹

The ENDEAVOR trial randomized patients in a 1:1 ratio between two treatment groups with an interactive voice and web response system. Central stratified randomization procedures were used, randomization was stratified by previous proteasome inhibitor therapy, previous lines of treatment, International Staging System stage, and planned route of bortezomib administration (intravenous vs subcutaneous) if randomly assigned to the bortezomib group. Within each stratum, patients were randomly assigned using a block randomisation scheme (block size of four). Due to the different dosing schedules of the treatment regimens, the study was open label, and therefore the allocated treatment was not masked from study investigators or patients. Potential bias in the assessment of the primary endpoint was mitigated by using an independent review committee (IRC), masked to treatment allocation, for the determination of disease status. Furthermore, the funder remained masked to per-group treatment results during the study. The success of masking was not assessed. Baseline patient characteristics are listed in Table 9 below.

The primary outcome was progression-free survival (PFS) defined as the time from randomization (using International Myeloma Working Group [IMWG] Uniform Response Criteria) until disease progression or death due to any cause. The survival curves and median PFS are derived by unstratified Kaplan-Meier method. Other statistics reported in the figure are derived from Cox proportional hazards model stratified by randomization stratification factors.

Secondary outcomes included overall survival (OS), overall response rate (ORR), duration of response (DoR), and safety. The exploratory outcome included health-related quality of life (HrQoL). Treatment response and disease progression were evaluated by IRC that was blinded and did not have knowledge of the randomization assignments. HrQoL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Module (QLQ-C30) questionnaire and the EORTC QLQ-MY20 and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity (subscale questionnaire) (FACT/GOG/Ntx).⁴ The EORTC QLQ-C30 is comprised of five functional scales (physical, role, emotional, social and cognitive), three symptom scales

(fatigue, nausea & vomiting and pain) and a global health status/QOL scale and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties).²² The EORTC QLQ-MY20 is a disease-specific module for Multiple Myeloma. Adverse events were collected until 30 days after administration of the last treatment dose and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Efficacy analyses were based on intention-to-treat population and the safety analysis included all patients who received at least one dose of study treatment. The trial was sponsored by Onyx Pharmaceuticals. Data collection and analysis was performed by the sponsor.

Table 8 Selected quality features of the included ENDEAVOR trial comparing carfilzomib with dexamethasone versus bortezomib with dexamethasone in patients with relapsed or refractory multiple myeloma

Trial	Treatment vs. Comparator	Primary Outcome	Required Sample Size ²³	Sample Size	Randomization Method ²⁴	Allocation Concealment	Blinding	ITT analysis	Final Analysis	Early Termination	Ethics Approval
ENDEAVOR	Cd vs. Bd	PFS	888a patients required for 526 progression events to provide 90% power to detect a 25% reduction in the risk of disease progression or death (Cd versus Bd: HR=0.75 , median PFS of 13.3 versus 10.0 months) at a two-sided overall significance level of 0.05. ¹	464 vs. 465	Central IVWRS, stratified, using blocked schemeb	No	Open-label study Response and disease progression determined by IRC (blinded)	Yesc	No	Yesd	Yes

^a Original planned sample size was 888 patients to achieve the required PFS events within 22 months of study initiation. ¹ An O'Brien-Fleming stopping boundary for efficacy was calculated with the use of a Lan-DeMets alpha-spending function so that the overall type I error was less than or equal to 0.05 (two-sided). The stopping boundary was to be based on the actual number of events (disease progression or death) recorded up to the data cutoff date. An independent data and safety monitoring committee which monitored overall study conduct and assessed safety and efficacy data, reviewed the study data; unmasking of the study occurred at the interim analysis.

^b Stratified by previous proteasome inhibitor therapy, previous lines of treatment, International Staging System stage (I vs II-III), and planned route of bortezomib administration (intravenous vs subcutaneous) if randomly assigned to the bortezomib group. (clinical summary ⁴)

^c Two analyses of progression-free survival were planned: the interim analyses and the final analysis. An interim analysis was scheduled after about 395 events had occurred (75% of the required total). The interim analysis cut-off date was 10 November 2014 to monitor differences between treatment groups for evidence of substantial benefit of Cd versus Bd. ^{1,21}

^d At the planned interim analysis for PFS, the observed p value was less than the stopping boundary for efficacy, therefore the study is considered to have met its primary endpoint. The study is however still ongoing as secondary endpoints (overall survival, overall response, and the incidence of grade 2 or higher neuropathy events) are to be tested based on adjustment for multiplicity.

Abbreviations: Bd = Bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; HR = hazard ratio; IRC = Independent Review Committee; IVWRS = Interactive Voice and Web Response System; PFS = progression free survival.

If the data monitoring committee determined that the observed p value at the interim analysis of progression free survival was less than or equal to the stopping boundary (nominal significance level), then the study was to be regarded as having met its primary endpoint. An O'Brien-Fleming

stopping boundary for efficacy was calculated with the use of a Lan-DeMets alpha-spending function so that the overall type I error was less than or equal to 0.05 (two-sided). If the primary endpoint showed a significant difference between treatment groups at the interim analysis, then the secondary endpoints of overall survival, overall response, and the incidence of grade 2 or higher neuropathy events were to be tested. The multiplicity in the secondary endpoint testing was adjusted by the group sequential Holm procedure to ensure a strong control of the overall study wise type 1 error at 0.05. For the interim overall survival analysis, a two-sided significance level of 0.0002 was used for the pre-specified monitoring boundary for efficacy.¹

6.3.2.1 Detailed Trial Characteristics

Table 7: Summary of trial characteristics of the included study (ENDEAVOR)

Trial Design	Key Inclusion Criteria	Intervention and Comparator ¹	Outcomes ^{1,21}
<p>NCT01568866</p> <p>ENDEAVOR (Ongoing study, estimated complete date: Dec. 2018)</p> <p>Open label phase 3 RCT</p> <p>Patient Enrollment (study start date): June 20, 2012 to June 30, 2014.^{1,21}</p> <p>Data cut-off date: 10 November 2014⁴</p> <p>Randomized: n = 929 Treated: n = 919¹</p> <p>Funded by: Onyx Pharmaceuticals</p>	<p>Key Inclusion Criteria:^{1,21} Adults with relapsed or refractory multiple myeloma and measurable disease who had received one to three prior treatments (including carfilzomib or bortezomib).</p> <p>ECOG PS 0-2</p> <p>At least a partial response to at least one previous treatment</p> <p>≥ 6-month proteasome inhibitor treatment-free interval before enrolment</p> <p>Adequate hepatic, hematologic, and renal function (CrCl: ≥ 15 mL/min) at screening</p> <p>Key Exclusion Criteria:^{1,21} Significant neuropathy (Grade 2 with pain, grade 3 to 4 peripheral neuropathy within 14 days before randomisation, Myocardial infarction within 4-month before randomisation, or New York Heart Association class III or IV heart failure.</p>	<p>Intervention: Carfilzomib + dexamethasone (Cd)</p> <p>The Carfilzomib group <u>Carfilzomib</u> The carfilzomib group received carfilzomib (20 mg/m² on days 1 and 2 of cycle 1; 56 mg/m² given thereafter; 30 min intravenous infusion) on days 1, 2, 8, 9, 15, and 16.</p> <p><u>Dexamethasone</u> (20 mg oral or intravenous infusion) on days 1, 2, 8, 9, 15, 16, 22, and 23 of a 28-day cycle.</p> <p>Comparator: Bortezomib + dexamethasone (Bd)</p> <p>Bortezomib group <u>Bortezomib</u> The bortezomib group received bortezomib (1-3 mg/m²; 3-5s intravenous bolus or subcutaneous injection) on days 1, 4, 8, and 11,</p> <p><u>Dexamethasone</u> (20 mg oral or intravenous infusion) on days 1, 2, 4, 5, 8, 9, 11, and 12 of a 21-day cycle.</p>	<p>Primary: PFS</p> <p>Secondary: OS, ORR, DoR, Safety</p> <p>Exploratory:⁴ HrQoL</p>
<p>Abbreviations: CrCl = creatinine clearance; DoR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; HrQoL = health-related quality of life; ORR = overall response rate; OS = overall survival; PFS = progression free survival; RCT = randomized controlled trial;</p>			

b) *Trials*

The ENDEAVOR study was a phase III trial which randomized patients with relapsed or refractory multiple myeloma to carfilzomib plus dexamethasone or bortezomib plus dexamethasone. This trial was conducted in 198 sites in 27 countries located in North America (including Canada), Europe, South America, and the Asia-Pacific regions. ENDEAVOR is an ongoing study.²¹

Key eligibility criteria for screened patients are listed in Table 7. Briefly, patients with multiple myeloma were required to be relapsed or refractory on one to three prior treatments.¹ Other inclusion criteria included performance status (ECOG PS 0-2), and adequate hepatic, hematologic, and renal function. Patients previously treated with carfilzomib or bortezomib were permitted entry into the trial if patients achieved at least a partial response before relapse or progression, were not discontinued due to toxic effects, and had at least a 6-month proteasome inhibitor treatment-free interval before enrolment.¹

The ENDEAVOR trial randomized patients in a 1:1 ratio between two treatment groups with an interactive voice and web response system. Central stratified randomization procedures were used, randomization was stratified by previous proteasome inhibitor therapy, previous lines of treatment, International Staging System stage, and planned route of bortezomib administration (intravenous vs subcutaneous) if randomly assigned to the bortezomib group. Within each stratum, patients were randomly assigned using a block randomisation scheme (block size of four). Due to the different dosing schedules of the treatment regimens, the study was open label, and therefore the allocated treatment was not masked from study investigators or patients. Potential bias in the assessment of the primary endpoint was mitigated by using an independent review committee (IRC), masked to treatment allocation, for the determination of disease status. Furthermore, the funder remained masked to per-group treatment results during the study. The success of masking was not assessed. Baseline patient characteristics are listed in Table 9 below.

The primary outcome was progression-free survival (PFS) defined as the time from randomization (using International Myeloma Working Group [IMWG] Uniform Response Criteria) until disease progression or death due to any cause. The survival curves and median PFS are derived by unstratified Kaplan-Meier method. Other statistics reported in the figure are derived from Cox proportional hazards model stratified by randomization stratification factors.

Secondary outcomes included overall survival (OS), overall response rate (ORR), duration of response (DoR), and safety. The exploratory outcome included health-related quality of life (HrQoL). Treatment response and disease progression were evaluated by IRC that was blinded and did not have knowledge of the randomization assignments. HrQoL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Module (QLQ-C30) questionnaire and the EORTC QLQ-MY20 and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity (subscale questionnaire) (FACT/GOG/Ntx).⁴ The EORTC QLQ-C30 is comprised of five functional scales (physical, role, emotional, social and cognitive), three symptom scales (fatigue, nausea & vomiting and pain) and a global health status/QoL scale and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties).²² The EORTC QLQ-MY20 is a disease-specific module for Multiple Myeloma. Adverse events were collected until 30 days after administration of the last treatment dose and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Efficacy analyses were based on intention-to-treat population and the safety analysis included all patients who received at least one dose of study treatment. The trial was

sponsored by Onyx Pharmaceuticals. Data collection and analysis was performed by the sponsor.

Table 8 Selected quality features of the included ENDEAVOR trial comparing carfilzomib with dexamethasone versus bortezomib with dexamethasone in patients with relapsed or refractory multiple myeloma

Trial	Treatment vs. Comparator	Primary Outcome	Required Sample Size ²³	Sample Size	Randomization Method ²⁴	Allocation Concealment	Blinding	ITT analysis	Final Analysis	Early Termination	Ethics Approval
ENDEAVOR	Cd vs. Bd	PFS	888 ^a patients required for 526 progression events to provide 90% power to detect a 25% reduction in the risk of disease progression or death (Cd versus Bd: HR=0.75 , median PFS of 13.3 versus 10.0 months) at a two-sided overall significance level of 0.05. ¹	464 vs. 465	Central IVWRS, stratified, using blocked scheme ^b	No	Open-label study Response and disease progression determined by IRC (blinded)	Yes ^c	No	Yes ^d	Yes

^a Original planned sample size was 888 patients to achieve the required PFS events within 22 months of study initiation. ¹ An O'Brien-Fleming stopping boundary for efficacy was calculated with the use of a Lan-DeMets alpha-spending function so that the overall type I error was less than or equal to 0.05 (two-sided). The stopping boundary was to be based on the actual number of events (disease progression or death) recorded up to the data cutoff date. An independent data and safety monitoring committee which monitored overall study conduct and assessed safety and efficacy data, reviewed the study data; unmasking of the study occurred at the interim analysis.

^b Stratified by previous proteasome inhibitor therapy, previous lines of treatment, International Staging System stage (I vs II-III), and planned route of bortezomib administration (intravenous vs subcutaneous) if randomly assigned to the bortezomib group. (clinical summary ⁴)

^c Two analyses of progression-free survival were planned: the interim analyses and the final analysis. An interim analysis was scheduled after about 395 events had occurred (75% of the required total). The interim analysis cut-off date was 10 November 2014 to monitor differences between treatment groups for evidence of substantial benefit of Cd versus Bd. ^{1,21}

^d At the planned interim analysis for PFS, the observed p value was less than the stopping boundary for efficacy, therefore the study is considered to have met its primary endpoint. The study is however still ongoing as secondary endpoints (overall survival, overall response, and the incidence of grade 2 or higher neuropathy events) are to be tested based on adjustment for multiplicity.

Abbreviations: Bd = Bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; HR = hazard ratio; IRC = Independent Review Committee; IVWRS = Interactive Voice and Web Response System; PFS = progression free survival.

If the data monitoring committee determined that the observed p value at the interim analysis of progression free survival was less than or equal to the stopping boundary (nominal significance level), then the study was to be regarded as having met its primary endpoint. An O'Brien-Fleming stopping boundary for efficacy was calculated with the use of a Lan-DeMets alpha-spending function so that the overall type I error was less than or equal to 0.05 (two-sided). If the primary endpoint showed a significant difference between treatment groups at the interim analysis, then the secondary endpoints of overall survival, overall response, and the incidence of grade 2 or higher neuropathy events were to be tested. The multiplicity in the secondary endpoint testing was adjusted by the group sequential Holm procedure to ensure a strong control of the overall study wise type 1 error at 0.05. For the interim overall survival analysis, a two-sided significance level of 0.0002 was used for the pre-specified monitoring boundary for efficacy.¹

c) Populations

A total of 929 patients were randomized in the ENDEAVOR trial. Baseline characteristics were generally balanced between the two groups, including age, gender, ECOG PS, high risk genetic mutations and baseline ISS stage III disease. Geographic region included Europe (Cd versus Bd: 62% versus 68%), North America (8% versus 11%), Asian -pacific (22% versus 24%) and South America (2% versus 3%). The median age of patients in the ENDEAVOR study was 65.0 years (range: 30 to 89) and 93% to 94% of patients had an ECOG PS of 0 or 1. The median time since diagnosis was 3.7 years in the ENDEAVOR trial.⁴ Patients received a median of two previous regimens. Two hundred and sixty six patients (57.3%) in carfilzomib group and 272 (58.5%) in bortezomib had prior transplant.^{1,2} Prior therapy included carfilzomib (<1%), bortezomib (54%), and lenalidomide (38%) and thalidomide (45% to 53%).¹ Baseline characteristics including a breakdown of prior therapies are summarized in Table 9.

Table 9 Baseline Patient Characteristics of all randomized patients in the ENDEAVOR trial

	Cd (n=464)	Bd (n=465)
Age (years)		
Median (range)	65 (35-89)	65 (30-88)
<65	223 (48)	210 (45)
65-74	164 (35)	189 (41)
≥75	77 (17)	66 (14)
Sex		
Male	240 (52)	229 (49)
Female	224 (48)	236 (51)
ECOG performance status		
0	221 (48)	232 (50)
1	211 (45)	203 (44)
2	32 (7)	30 (6)
ISS stage		
I	205 (44)	204 (44)
II-III	259 (56)	261 (56)
Cytogenetics		
High risk	97 (21)	113 (24)
Standard risk	284 (61)	291 (63)
Unknown	55 (12)	30 (6)
Missing	28 (6)	31 (7)
Race		
White	348 (75)	353 (76)
Black	8 (2)	9 (2)
Asian	58 (13)	57 (12)
Not reported	50 (11)	45 (10)
Multiple	0	1 (<1)
Geographical region		
Europe	317 (68)	290 (62)
North America	35 (8)	49 (11)
South America	10 (2)	15 (3)
Asia-Pacific	102 (22)	111 (24)
Creatinine clearance (mL/min)		
Mean (SD)	76.7 (31.8)	75.1 (32.4)
<30	28 (6)	28 (6)
30 to <50	57 (12)	71 (15)
50 to <80	186 (40)	177 (38)

	Cd (n=464)	Bd (n=465)
≥80	193 (42)	189 (41)
Serum β2 microglobulin (mg/L)		
Mean (SD)	4.6 (3.0)	4.8 (3.9)
<3·5	220 (47)	216 (46)
≥3·5	244 (53)	249 (54)
Previous regimens		
Median (IQR)	2 (1-2)	2 (1-2)
One	232 (50)	232 (50)
Two	157 (34)	145 (31)
Three	75 (16)	87 (19)
History of peripheral neuropathy		
No	249 (54)	221 (48)
Yes	215 (46)	244 (52)
Ongoing peripheral neuropathy at screening		
Grade 1	133 (29)	159 (34)
Grade 2	10 (2)	10 (2)
Previous proteasome inhibitor treatment†		
Carfilzomib	2 (<1)	1 (<1)
Bortezomib	250 (54)	252 (54)
None	212 (46)	212 (46)
Previous immunomodulatory agent treatment		
Lenalidomide	177 (38)	177 (38)
Thalidomide	211 (45)	247 (53)

Bd = Bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; ECOG=Eastern Cooperative Oncology Group; ISS=International Staging System.

Note: data presented as n(%), unless specified otherwise.

Source: Dimopoulos 2016.¹

d) Interventions

Of the 929 patients in the ENDEAVOR trial, the patients in carfilzomib group received carfilzomib (20 mg/m² on days 1 and 2 of cycle 1; 56 mg/m² given thereafter; 30 min intravenous infusion [IV]) on days 1, 2, 8, 9, 15, and 16 and dexamethasone (20 mg oral or IV) on days 1, 2, 8, 9, 15, 16, 22, and 23 of a 28-day cycle. Based on what is reported in the main publication for the ENDEAVOR trial, the stepped-up dosing rationale for using these higher doses (20/56 mg/m²) rather than the lower dose used in prior studies (20/27 mg/m² in the ASPIRE trial) was based on preliminary efficacy results from the phase 1b/2 study PX-171-007²⁵ and PX-171-003-A1.²⁶ In study PX-171-007,²⁵ the cohort of patients with relapsed or refractory multiple myeloma or both receiving 56 mg/m² of carfilzomib had a higher proportion of responders than those patients in a similar population from PX-171-003-A1,²⁶ the pivotal phase 2 study of single-agent carfilzomib (27 mg/m²), but with a qualitatively comparable safety profile.^{1,4} In the bortezomib group, 360 (79%) patients received subcutaneous (S.C) bortezomib throughout study treatment; all others received IV bortezomib at some point during treatment. The patients in the bortezomib group received bortezomib (1.3 mg/m²; 3-5 s IV bolus or SC injection) on days 1, 4, 8, and 11, and dexamethasone (20 mg oral or IV infusion) on days 1, 2, 4, 5, 8, 9, 11, and 12 of a 21-day cycle. Treatment cycles were repeated until disease progression, withdrawal of consent, or unacceptable toxic effects. Dose reductions were permitted to manage adverse events. All patients received proton pump inhibitor and antiviral therapies.¹

The median treatment durations were 39.9 weeks (median of 10 cycles) and 26.8 weeks (median of 8 cycles) in carfilzomib arm and bortezomib arm respectively (Table 10).^{1,4,13} The cycle length for the 2 treatment arms was different, with a 4-week cycle in the carfilzomib arm and a 3-week

cycle in the bortezomib arm. The majority of patients (346 [75.9%]) in the bortezomib arm received bortezomib SC as the sole route of administration, 90 (19.7%) patients received bortezomib IV exclusively, and the remaining 20 (4.4%) patients received both IV and SC bortezomib.^{4,13}

Table 10: Duration of Exposure to Study drugs

	ENDEAVOR	
	Cd (N = 463)	Bd (N = 456)
# of weeks exposure		
Mean (SD)	39.8 (22.8)	30.0 (19.3)
Median (Range)	39.9 (1 - 108)	26.8 (1 - 106)
# of cycles of treatment ^a - n (%)		
Mean (SD)	10.0 (5.6)	9.3 (5.7)
Median (Range)	10.0 (1 - 26)	8.0 (1 - 35)
# of Patients on treatment in each cycle ^a - n (%)		
Cycle 6	358 (77.3)	321 (70.4)
Cycle 12	169 (36.5)	141 (30.9)
Cycle 18	49 (10.6)	44 (9.6)
Cycle 24	7 (1.5)	7 (1.5)
Cycle 30	0	2 (0.4)
Cumulative carfilzomib dose (mg)		
Mean (SD)	5406 (3418)	-
Median (Range)	5141(52 - 18564)	-
Relative dose intensity of carfilzomib ^b (%)		
Mean (SD)	89 (13)	-
Median (Range)	93 (30 - 105)	-

Bd = bortezomib plus dexamethasone; Cd = carfilzomib plus dexamethasone; SD = standard deviation;

^a Regimen Cd has a 28-day cycle, whereas regimen Bd has a 21-day cycle.

^b Relative Dose Intensity (%) = actual dose intensity/planned dose intensity × 100, where actual (planned) dose intensity is the actual (planned)

Source: ⁴ ¹³

e) Patient Disposition

One patient in the carfilzomib group and nine patients in the bortezomib group did not receive the study drug. As of the data cut-off date, 201 (43%) and 114 (23%) patients in the carfilzomib and bortezomib groups, respectively were continuing treatment.¹ A total of 22 (2.3%) patients had died at the time of the data cut-off. ¹ Discontinuation rates were 56.7% and 75.5% in the carfilzomib and bortezomib groups, respectively, with disease progression being the most common reason for discontinuation in both treatment groups. As seen in Table 11, the overall and per category number of patients discontinuing treatment were relatively similar between arms; although discontinuations were numerically lower in patients who received carfilzomib compared to those who received bortezomib with the exception of non-compliance and death. In addition, it was observed that the patients discontinuation rate due to patients consent or investigators decision were higher in bortezomib group than the carfilzomib group. No exact reasons were provided by manufacturer for above numerical imbalance.²⁷

Table 11 Patient Disposition (ENDEAVOR)

	Cd (N=464)	Bd (N=465)
	N (%)	
Screened	1096	
Randomized	464(100)	465 (100)
Received treatment	463 (99.8)	456 (98.1)
Efficacy (ITT) analysis	464(100)	465 (100)

	Cd (N=464)	Bd (N=465)
Safety analysis	463 (99.8)	456 (98.1)
Discontinued treatment	263 (56.8)	351 (75.5)
<ul style="list-style-type: none"> • Disease progression • AEs • Patient request • Investigator's decision • Withdrew consent^{a 1} • Death¹ • Non-compliance • Lost to follow-up 	117 (25.3) 65 (14.0) 40 (8.6) 18 (3.9) 6 (1.3) 13 (2.8) 4 (0.9) 0	168 (36.8) 73 (16.0) 45 (9.9) 35 (7.7) 19 (4.2) 9 (2.0) 1 (0.2) 1 (0.2)

Bd = bortezomib + dexamethasone; Cd= carfilzomib + dexamethasone; ITT = intention to treat

^aManufacturer provided further information showed that discontinuation rates due to withdrew consent in Bd group was higher than Cd group (6.5% vs.1.5%).²⁷

Source: Dimopoulos, ¹ HC Module 2.7.4 p.26, ⁴ manufacturer additional data.²⁷

f) *Limitations/Sources of Bias*

- The trial was open label and therefore investigators and patients were not blinded to treatment assignment. Therefore, the trial is at high-risk for a number of different biases that can affect the internal validity (e.g., patient selection for eligibility, performance bias due to knowledge of assigned treatment).
- In addition, in open-label trials, the assessment of subjective measures, such as HrQoL (also an exploratory endpoint), and the reporting of adverse events are likely to be biased. Although survival (in this ongoing study with immature results for OS) a hard endpoint and less prone to bias, other more subjective outcomes like disease progression may be biased by an unblinded investigator. However, a central independent review of the primary outcome and tumour response was performed which would increase the objectivity and thus the potential for bias in this outcomes would decrease. In addition, the sponsor remained blinded to per-arm treatment results during the study. No analysis comparing treatment arms was performed by the sponsor prior to the planned interim analysis.
- Pre-specified subgroups analyses were reported in the trial, however subgroups lacked power to detect a difference. Hence the interpretation of results for subgroup analyses is difficult due to the lack of statistical power. Furthermore, statistically significant differences should be interpreted with caution due to the small number of patients in the subgroups.
- High proportions patients withdraw due to patients request or investigator's decision. No further detail were given upon CADTH request.
- The study protocol was amended during the study as planned. The impact of these amendments on results is unknown. However, the Methods Team and Clinical Guidance Panel were of the opinion that these amendments that occurred at the midpoint of the trial (e.g., including changes in imaging practice) would have a minimal impact on results.) none of the changes were deviations from the guidance received during the health authority discussions.
- The sponsor Onyx Pharmaceuticals funded the trial and were involved in all aspects of conducting the trial including design of the study, data collection, performing data analysis, and interpreting results. The extent to which the use of independent investigators and data analysts may have influenced the results and reporting of the trials is unknown.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Key outcomes except overall survival reported at the interim analysis are shown Table 12. The overall survival data analysed in an updated analysis in 2016 (Table 12).

Table 12: Key efficacy and harms outcomes

Analysis date	Study arms	OS, median (months)	PFS, median (months) (95% CI)	ORR (%)	HrQoL ^{4,5} Change from baseline Mean (SD)
Interim analysis (November, 2014) OS was analysed in 2016 ⁴	Cd n=464	NE	18.7 (15.6-NE)	77 (73 - 81)	-7.3 (23.8)
	Bd n=465	NE	9.4 (8.4-10.4)	63 (58 to 67)	-12.5(23.1)
	Cd versus Bd	HR=0.805 (95%CI: 0.646-1.003) p=0.0263 (1-sided) ⁴ * Prespecified stopping boundary of p = 0.05 was not crossed, therefore not significant ^{1,4}	HR 0.53 (0.44-0.65); p<0.0001 ¹	OR= 2.03; 95% CI 1.52 - 2.72; p < 0.0001	EORTC QLQ-C30C overall difference (Cd - Bd) at cut-off: ⁴ 3.51 (95% CI: 1.97, 5.06; p < 0.0001) EORTC QLQ-C30C MCID (5 points) was not met.
Harms Outcomes, n (%)					
		Cd (n=463)		Bd (n=456)	
Death ⁴		153 (33.0)		169 (36.3)	
SAEs (all grades) ¹		224(48.2)		162 (35.5)	
≥Grade 3 AEs n (%) ^{1,4}					
Overall ≥ Grade 3 AE's		339 (73.2)		305 (66.9)	
Peripheral neuropathy ^a		10 (2.2)		37 (8.1)	
Acute renal failure ^b		19(4.1)		12 (2.6)	
Cardiac failure ^c		22 (4.8)		8 (1.8)	
Pneumonia		32 (6.9)		36 (7.9)	
Ischemic heart disease ^d		8 (1.7)		7 (1.5)	
Pulmonary embolism		8 (1.7)		4 (0.9)	
Pulmonary hypertension ^e		3 (0.6)		1 (0.2)	
Anaemia		67 (14.5)		45 (9.9)	
Thrombocytopenia		39 (8.4)		43 (9.4)	
Neutropenia		10 (2.2)		10 (2.2)	
Alanine aminotransferase increased		5 (1.1)		2 (0.4)	
WDAEs¹		65 (14.0)		73 (16.0)	
<p>AE = adverse events; Bd = bortezomib + dexamethasone; Cd= carfilzomib + dexamethasone ; CI = confidence interval; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HR = hazard ratio; HrQoL = health-related quality of life; MCID = minimal clinically important difference; NE= not estimable; NR = Not reported; OR = odds ratio; ORR = overall response rate; OS = overall survival; PFS = progression free survival; SAE = serious adverse event; WDAE = withdrawal due to adverse event</p> <p>¹HR/OR <1 favours carfilzomib</p> <p>⁴Minimal clinically important difference was ≥5 points for EORTC QLQ-C30 between-group differences</p>					

^a Peripheral neuropathy including peripheral neuropathy, peripheral sensory neuropathy, neuralgia, decreased vibratory sense, polyneuropathy, sensory loss, amyotrophy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, sensory disturbance, and toxic neuropathy.

^b Acute renal failure including acute renal failure, renal failure, renal impairment, acute prerenal failure, anuria, oliguria, and prerenal failure.

^c Cardiac failure including cardiac failure, ejection fraction decreased, pulmonary oedema, acute cardiac failure, congestive cardiac failure, acute pulmonary oedema, acute left ventricular failure, chronic cardiac failure, cardiopulmonary failure, hepatojugular reflex, right ventricular failure, and left ventricular failure.

^d: Ischaemic heart disease including angina pectoris, acute coronary syndrome, myocardial infarction, increased troponin T, coronary artery disease, increased troponin I, acute myocardial infarction, myocardial ischemia, and cardiomyopathy stress.

^e Pulmonary hypertension including pulmonary hypertension, right ventricular failure, and pulmonary arterial hypertension.¹

Source: Dimopoulos, ^{1,13} Osterweil, ³ Chng, ¹⁹ and mfr. additional data⁵

a) *Efficacy Outcomes*

In the ENDEAVOR study, the median duration of treatment was 39.9 weeks in the carfilzomib group and 26.8 weeks in the bortezomib group respectively.¹ Median follow-up for progression-free survival was 11.9 months in the carfilzomib group and 11.1 months in the bortezomib group.¹

Progression-free Survival

Progression-free survival (PFS) was defined as the duration from the date of randomization to the date of confirmed progressive disease or death due to any cause. This was determined by IRC using the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma. As of the November 2014 data cut-off, 414 PFS events had occurred (Cd versus Bd: 171 versus 243). The median PFS was 18.7 months compared to 9.4 months in the carfilzomib and bortezomib groups, respectively (HR = 0.53 [95% CI 0.44 - 0.65]; p<0.0001. see **Error! Reference source not found.**)^{1,3,20} In pre-planned exploratory subgroup analyses, the effect of carfilzomib on progression-free survival in patients with or without previous bortezomib treatment and in other pre-specified subgroups of interest was similar to that in the overall population.^{1-3,17-19}

Because of the small number of patients with previous carfilzomib exposure in this study, the effect of carfilzomib plus dexamethasone on progression-free survival in patients with or without previous carfilzomib exposure was not analysed. A statistically significant improvement in favor of carfilzomib was observed in patient subgroups such as cytogenetic risk at study entry, previous treatment with bortezomib, previous treatment with immunomodulatory drugs, prior transplant, and previous lines of treatments. However, no statistically significant improvement in carfilzomib compared with bortezomib were observed in those patients who were refractory to prior bortezomib or lenalidomide. (Table 13)

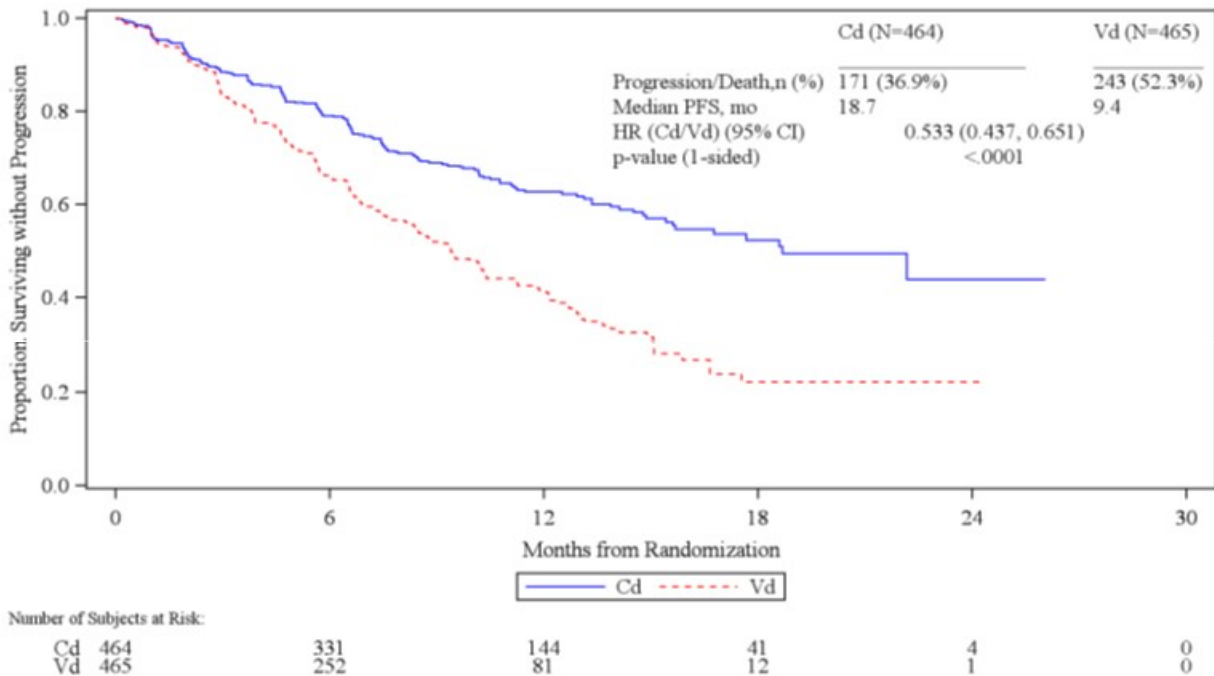


Figure 1: Study ENDEAVOR: Kaplan-Meier Curve of Progression-Free Survival

Source: Figure 14.2.1.2 in 2011-003 CSR⁵. Cd = carfilzomib plus dexamethasone; CI = confidence interval; CSR = Clinical Study Report; HR = hazard ratio; mo = months; PFS = progression-free survival; Vd = bortezomib (Velcade) plus dexamethasone. Note: The survival curves and median PFS are derived by unstratified Kaplan-Meier method. Other statistics reported in the figure are derived from Cox proportional hazards model stratified by randomization stratification factors.

Table 13 Subgroup data for PFS

Subgroup	Cd		Bd		Cd vs. Bd PFS HR (95%CI)
	n	Median PFS (months)	n	Median PFS (months)	
Prior Transplant for MM ²					
Yes	266	NE	272	10.2 (8.5 -12.2)	0.61 (0.47, 0.79)
No	198	17.7 (14.1 to NE)	193	8.5 (6.6 -10.2)	0.43 (0.32, 0.59)
Risk cytogenetics ¹⁹					
Standard-risk cytogenetics	284	NE	291	10.2 (9.3-12.2)	0.44 (0.33, 0.58)
High-risk cytogenetics	97	8.8 (6.9-11.3)	113	6.0 (4.9-8.1)	0.65 (0.45, 0.92)
# of previous therapies					
1	231	22.2[17.66, NE]	229	10.3[8.75, 12.93]	0.45 (0.33, 0.61)
2 to 3	233	14.5[10.76, NE]	236	8.4[6.55, 10.16]	0.60 (0.47, 0.78)
Received prior bortezomib					
Yes	250	NR	252	NR	0.56 (0.44, 0.73)
No	214	NR	213	NR	0.48 (0.36, 0.66)
Received prior immunomodulatory drug					
Yes	325	NR	348	NR	0.60 (0.48, 0.75)
No	139	NR	117	NR	0.38 (0.25, 0.58)

Subgroup	Cd		Bd		Cd vs. Bd
	n	Median PFS (months)	n	Median PFS (months)	PFS HR (95%CI)
Refractory to prior bortezomib					
Yes	15	NR	19	NR	0.37 (0.13, 1.08)
No	449	NR	446	NR	0.54 (0.44, 0.66)
Refractory to prior lenalidomide					
Yes	113	NR	122	NR	0.80 (0.57, 1.11)
No	351	NR	343	NR	0.44 (0.34, 0.56)
Refractory to bortezomib and immunomodulatory drug					
Yes	158	NR	167	NR	0.64 (0.47, 0.86)
No	306	NR	298	NR	0.47 (0.36, 0.61)

Bd = bortezomib + dexamethasone; Cd= carfilzomib + dexamethasone; HR = hazard ratio; MM= multiple myeloma; NE = not estimable; NR = not reported, PFS = progression free survival.

Source: Dimopoulos 2016,¹ osterweil,³ Chng,¹⁹ Mateos,² Manufacturer additional data ²⁷

Time to Progression

At the November 2014 data cutoff, the rate of disease progression was 32.3% in the carfilzomib plus dexamethasone arm (Dex, Cd) and 49% in the bortezomib plus dexamethasone arm (Dex, Bd). The median time to progression was longer in the carfilzomib plus Dex arm (22.2 months [95% CI: 17.7, NE]) than in the bortezomib plus Dex arm (10.1 months [95% CI: 8.8, 11.7]). The median follow-up for disease progression was 11.3 months (95% CI: 11.1, 12.1) in the carfilzomib plus Dex arm (Cd) and 11.0 months (95% CI: 9.5, 11.3) in the bortezomib plus Dex arm (Bd).⁵

Overall Survival

Overall survival (OS) was defined as the duration from the date of randomization to the date of death due to any cause.⁴ An ad hoc analysis of the OS that included 322 events was conducted in 2016.⁴ Median follow-up time for patients in carfilzomib group was 27.3 months and 26.2 months for patients in bortezomib group. A total of 153 (33.0%) patients in the carfilzomib and 169 (36.3%) in the bortezomib group had died.⁴ The 3-year survival rate was 58.6% (95%CI, 52.0% to 64.6%) for patients in carfilzomib and 51.1% (95% CI: 43.9% to 57.9%) for patients in bortezomib respectively. Based on an updated 3 year OS analysis, the hazard ratio estimate (Cd versus Bd, i.e., Cd versus Bd) was 0.805 (95%CI: 0.646 to 1.003) with a 1-sided p-value of 0.0263, which did not cross the pre-specified boundary for statistical significance. The results demonstrate a positive benefit-risk profile of carfilzomib, and superior treatment effect of Carfilzomib over bortezomib. However, it was indicated that the overall survival data were not yet mature.⁴ Post hoc subgroup analysis showed that the overall survival is in favor of the carfilzomib group compared with bortezomib in patients who had not received prior transplant for multiple myeloma or treatment with a proteasome inhibitor (Table 14).²⁷

A sensitivity analysis assuming patients died immediately after their consent withdrawal or loss to follow-up date yielded an OS hazard ratio (Cd vs Bd) of 0.660 [95% CI (0.499, 0.871)] with median OS not estimable (NE) [95% CI (NE, NE)] for Cd and 22.5 months [95% CI (19.8, NE)] for Bd. The sensitivity analysis results suggested the imbalance in censoring for OS for reasons “other than alive” yielded favorable efficacy estimates (HR, 95%CI, median OS etc.) for the Bd arm. Therefore, if the imbalance in “other than alive” censoring remains in future OS analyses, it is expected that Bd versus Cd OS efficacy estimates will be conservative.²⁷

Next interim data is expected to be available in January 2017 and final OS analysis in 2018 but as the analyses is event driven, the actual timeline may change.

Table 14 Subgroup data for OS and ORR

	Cd		Bd		Cd vs. Bd
Overall survival					
Subgroup	n	Median (months)	n	Median (months)	OS HR (95%CI)
Prior Transplant for MM ²⁷					
Yes	266	NE	272	NE	0.92(0.687, 1.233)
No	198	NE	193	31.8(25.92, NE)	0.68(0.486, 0.942)
# of previous therapies					
1	231	NE	229	NE	0.82(0.577, 1.156)
2 to 3	233	33.2 (30.16, NE)	236	30.2 (23.49, NE)	0.80(0.602, 1.059)
Received prior proteasome inhibitor					
Yes	258	NE	259	31.6 (28.19, NE)	0.90(0.683, 1.195)
No	206	NE	206	NE	0.69(0.482, 0.978)
Overall response rate					
Subgroup	n	Median (months)	n	Median (months)	ORR OR (95%CI)
Prior Transplant for MM ²⁷					
Yes	266	73.3(67.6, 78.5)	272	66.9(61.0, 72.5)	1.358 (0.937, 1.968)
No	198	81.8(75.7, 86.9)	193	56.5(49.2, 63.6)	3.468 (2.190, 5.492)
# of previous therapies					
1	231	81.4(75.8, 86.2)	229	65.1(58.5, 71.2)	2.347 (1.529, 3.603)
2 to 3	233	72.5(66.3, 78.2)	236	60.2(53.6, 66.5)	1.748 (1.186, 2.577)

Bd = bortezomib + dexamethasone; Cd= carfilzomib + dexamethasone; HR = hazard ratio; MM= multiple myeloma; NE = not estimable; OR = odds ratio; ORR = overall response rate
 Source: Manufacturer additional data.²⁷

Response

Overall response rate (ORR) was defined as the proportion of patients who achieved a best response of stringent complete response, complete response, very good partial response or partial response according to IMWG-URC.¹ The proportion of patients achieving an objective overall response was 77% (95% CI, 73% to 81%) in the carfilzomib group compared with 63% (95%CI, 58% to 67%) in the bortezomib group (odds ratio [OR] 2.03 [95% CI, 1.52 to 2.72]; p<0.0001, Table 15).^{1,13,20} Post hoc subgroup analysis showed that the overall response rate were statistically significant higher in carfilzomib than in bortezomib among patient who received two to three lines prior treatments and patients without prior transplant for multiple myeloma. (see Table 14).

Table 15 Treatment responses

	Cd (n=464)	Bd (n=465)
	N (%)	
Overall response rate, % (95%CI)	77 (73, 81)	63 (58, 67)
Overall response rate, Odds ratio (95% CI)	2.03 (1.52-2.72); p<0.0001	
Complete response or better	58 (13)	29 (6)
	P = 0.001	
Stringent complete response	8 (2)	9 (2)
Complete response	50 (11)	20 (4)
Very good partial response or better	252 (54)	133 (29)
	P < 0.0001	
Very good partial response	194 (42)	104 (22)
Partial response	104 (22)	157 (34)
Minimal response	24 (5)	53 (11)
Stable disease	40 (9)	53 (11)
Progressive disease	25 (5)	31 (7)
Time to response (months), median (IQR)	1.1 (1.0-2.0)	1.1 (1.0-1.9)
Duration of Response (month) median (95%CI)	21.3 (21.3 to NE)	10.4 (9.3 to 13.8)

Bd = bortezomib + dexamethasone; Cd= carfilzomib + dexamethasone; IQR = interquartile range
Note: International Myeloma Working Group uniform response criteria ¹

Complete Response: Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow (confirmation with repeat bone marrow biopsy not needed);

Stringent Complete Response: Complete response plus normal free light chain ratio and absence of clonal cells in bone marrow (confirmation with repeat bone marrow biopsy not needed) by immunohistochemistry or immunofluorescence;

Overall response: defined as partial response or better. **Duration of response:** defined as the time from first evidence of a partial response or better to confirmation of disease progression or death from any cause, incidence of grade 2 or higher peripheral neuropathy events, and adverse event. **Stringent complete response:** defined by a negative immunofixation test for myeloma protein in urine and the disappearance of any soft-tissue plasmacytomas, with less than 5% of plasma cells in bone marrow, a normal serum free light chain ratio, and an absence of clonal cells in the bone marrow;

Very Good Partial Response: Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100 mg per 24 h;

Partial Response: ≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h. If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required;

Stable Disease: Not meeting criteria for complete response, very good partial response, partial response, or progressive disease.

Source: Dimopoulos 2016,^{1,13}

Duration of Response

Duration of response (DoR) was defined as the duration in months from the start of response to documented progressive disease or death due to any cause, whichever was earlier.⁴ (p. 30) DoR was calculated for patients achieving a partial response or better. The median DoR was 21.3 (95%CI, 21.3 to NE) and 10.4 (9.3 to 13.8) months in the carfilzomib and bortezomib groups, respectively.^{1,3,13}

Health-related Quality of Life

Health-related quality of life (HrQoL) was a pre-specified exploratory secondary endpoint and assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Module QLQ-C30), Quality of Life Questionnaire for multiple myeloma (QLQ-MY20), and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity (subscale questionnaire) (FACT/GOG/Ntx).⁴ Questionnaire completion rates were calculated for expected subjects (expected subjects included randomized subjects who were still alive and had not discontinued study treatment at that visit). The percentage of expected patients completing QLQ C30 assessments was high (73.1 to 93.9% with 66.7% at End of Treatment). Using a restricted maximum likelihood-based mixed model for repeated measures (MMRM) analysis on the QLQ-C30 under the assumption of missing at random (MAR), at cut-off date, it was reported that patients treated with carfilzomib (Cd) had on average better global health status (GHS)/QoL compared with patients with bortezomib (Bd) (between group difference [Cd - Bd]: 3.51; 95% CI, 1.97 to 5.06); however, the minimal important difference (MID, 5 point) was not met.¹ The restricted maximum likelihood method is a form of maximum likelihood estimation which does not base estimates on a maximum likelihood fit of all the information, but instead uses a likelihood function calculated from a transformed set of data, so that nuisance parameters have no effect. It is used as a method for fitting linear mixed models, which can produce unbiased estimates of variance and covariance parameters.²⁸ The treatment difference was also observed on the QLQ-C30 Fatigue, Pain, and QLQ-MY20 Side Effects of Treatment subscales, with lower scores in the

carfilzomib group, indicating lower levels of these symptoms (fatigue, pain, and side effects) compared with that in the bortezomib group. However, the MID was not reached. No treatment difference was observed between carfilzomib and bortezomib for the subscales of nausea/vomiting, Physical Functioning, Role Functioning and Disease Symptoms. Patients treated with Cd had, on average, better FACT/GOG-NTx scores, with an estimated overall treatment difference between carfilzomib and bortezomib groups (Cd - Bd) of 0.84. The MID for the FACT/GOG-NTx score has yet to be determined but is estimated to be between 3.3 and 4.4 points.^{4,29} The GHS/QOL change from baseline in each treatment group was reported in Table 16.

Two sensitivity analyses showed similar results. The first sensitivity analysis based on a pattern mixture model using an ancillary variable to account for dropout group showed a consistent between group treatment difference (Cd - Bd: 2.59 [95% CI, 1.05 to 4.12], $p = 0.0009$);⁴ and the second sensitivity analysis excluding data collected after the first time when more than 60% of randomized patients dropped out showed similar results (Cd - Bd: 3.29 [95% CI: 1.69, 4.89], $p < 0.0001$).⁴ No treatment group differences were observed between Cd and Bd on the pre-specified subscales of the Physical Functioning, Role Functioning, or Nausea/Vomiting or QLQ-MY20 Disease Symptom scale using a restricted maximum likelihood-based MMRM analysis.

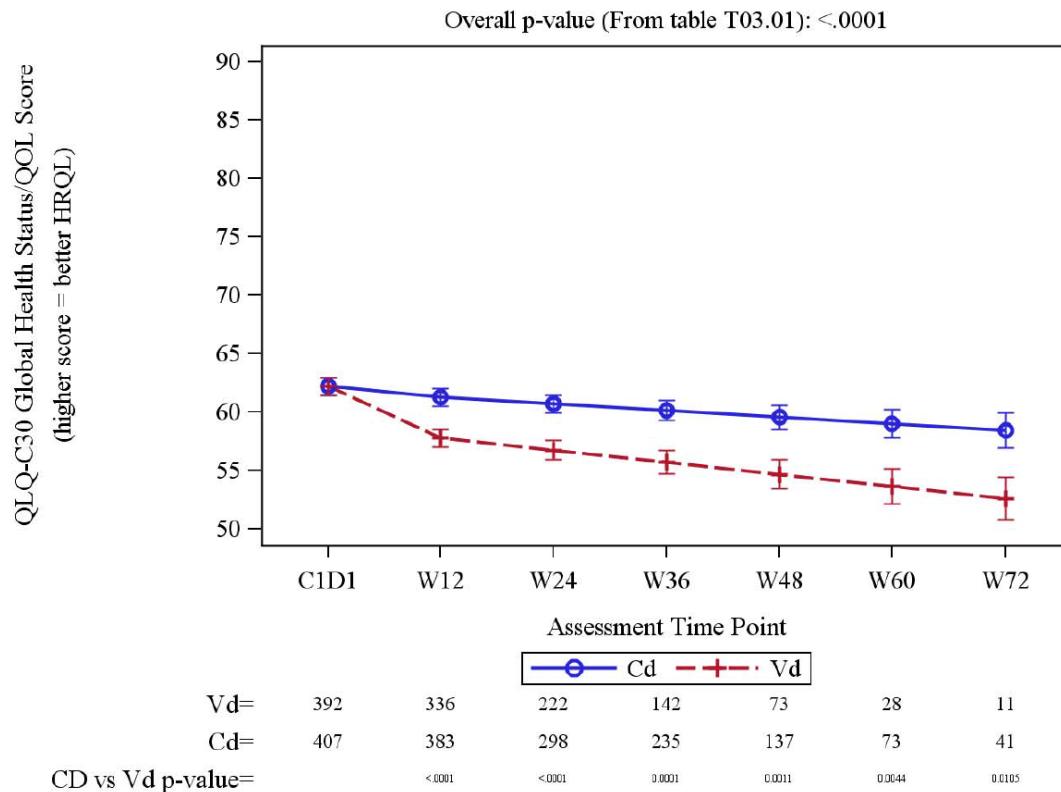


Figure 2: QLQ-30 Least Squares Mean Difference with Treatment-by-Time Interaction (Population: Intent-To-Treat)

C1D1 = Cycle 1 Day 1; Cd = carfilzomib plus dexamethasone; HRQL= health-related quality of life; MMRM = mixed model for repeated measures; PRO = Patient-Reported Outcomes; QOL = Quality of Life; Vd = bortezomib (Velcade) plus dexamethasone (or Bd); W = week. Note: Cycle p-values are 2-sided p-values from MMRM model with treatment-by-time interaction. Source: HC Module 2.7.3.⁵

Table 16: Quality of Life Score

	Cd (n=464)	Bd (n=465)
Baseline (C1D1)		
n ^a (%)	407/464 (87.7)	392/465 (84.3)
QLQ-C30 GHS/QoL Mean (SD)	61.5 (21.3)	63.7 (21.7)
EOT		
n ^a	176/264 (66.7)	240/360 (66.7)
QLQ-C30 GHS/QoL	NR	NR
Change from baseline at EOT		
QLQ-C30 GHS/QoL Mean (SD)	-7.3 (23.8)	-12.5(23.1)

Bd = bortezomib + dexamethasone; Cd= carfilzomib + dexamethasone; C1D1 = Cycle 1 Day 1; EOT= end of treatment; GHS = global health status; NR = not reported; QoL = quality of life; SD= standard deviation; ^aProportion of patients with QLQ-C30 Questionnaire Completed Out of the Number of Expected patients. Source: manufacturer additional data.⁵

b) Harms Outcomes

Harms outcomes are summarized in Table 18 and Table 19 below. All patients who received at least one dose of study treatment were included in analyses of safety, 463 patients were in the carfilzomib group and 456 in the bortezomib group respectively.

Deaths

Based on an ad hoc updated analysis in 2016⁴ and additional data provided by the manufacturer to pCODR (post-checkpoint meeting),³⁰ a total of 153 (33.0%) patients in the carfilzomib and 171 (36.8%) in the bortezomib group died. The hazard ratio (Cd versus Bd) was 0.805 (95%CI: 0.646 to 1.003) with a 1-sided log-rank test p-value of 0.0263 (Error! Reference source not found.). One patient in bortezomib group who died was not dosed.

Death during treatment or within 30 days of receiving the last dose of study treatment were reported in 6.0% and 4.5% of patients in the carfilzomib and bortezomib group, respectively.²⁷ The reasons for the death were adverse events (Cd versus Bd: 5.0% vs 3.4% respectively); disease progression (0.9% vs. 0.6%); and unknown (Cd versus Bd: 0.2% versus 0.2%).

Death due to adverse event over 30 days after the date of last dose of study treatment was reported in 26.9% and 32.0% of patients in the carfilzomib and bortezomib group, respectively.²⁷ The reasons for the death were adverse events (Cd versus Bd: 1.5% vs 0.9% respectively); disease progression (Cd versus Bd: 19.2% versus 20.4%); other (Cd versus Bd: 2.8% versus 6.5%), unknown (Cd versus Bd: 3.4% versus 4.3% respectively).³⁰

Serious Adverse Events (all grades SAE)

Overall, all grades serious adverse event (SAE) occurred in 224 (48%) and 162 (36%) patients in the carfilzomib and bortezomib groups, respectively (see Table 18).¹ The most common SAEs in the carfilzomib group were pneumonia (Cd versus Bd: 6.0% versus 8.6%), pyrexia (Cd versus Bd: 3.2% versus 0.7%), dyspnea (Cd versus Bd: 3.0% versus 0.2%) and cardiac failure (Cd versus Bd: 1.7% versus 0.7%), (Table 18).^{1,4}

Adverse Events of Interest(≥grade 3 AEs)

The grade 3 or higher AEs were presented in Table 19. Overall, 73% and 67% patients reported grades 3 or higher adverse events in grouped (or broader, term included (Cd vs Bd) were:

peripheral neuropathy (2.2% versus 8.1%), acute renal failure (4.1% vs 2.6%), cardiac failure (4.8% vs 1.8%). These are described further below, see Table 19.^{1,4}

Cardiac failure

Overall, a broader term (or grouped term - defined in Table 10) cardiac failure (\geq grade 3) including cardiac failure, ejection fraction decreased, pulmonary edema, acute cardiac failure, congestive cardiac failure, acute pulmonary edema, acute left ventricular failure, chronic cardiac failure, cardiopulmonary failure, hepatojugular reflex, right ventricular failure, and left ventricular failure occurred in 22 (4.8%) and 8 (1.8%) in carfilzomib and bortezomib respectively.^{1,3,4}

Ischaemic heart disease

Ischaemic heart disease (in broader or grouped term) occurred in 12(2.6%) and 9(2.0%) patients in the carfilzomib and bortezomib groups, respectively.^{1,4} The broader term ischaemic heart disease included angina pectoris, acute coronary syndrome, myocardial infarction, increased troponin T, coronary artery disease, increased troponin I, acute myocardial infarction, myocardial ischemia, and cardiomyopathy stress.¹

Hematological toxicity

There was an increase in the frequency of \geq 3 grade anemia in the carfilzomib compared to the bortezomib group. The frequency of \geq 3 grade neutropenia and thrombocytopenia for the carfilzomib compared to bortezomib was similar (see Table 19).^{4 1}

Neuropathy

Peripheral neuropathy (in broader or grouped term) included peripheral neuropathy, peripheral sensory neuropathy, neuralgia, decreased vibratory sense, polyneuropathy, sensory loss, amyotrophy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, sensory disturbance, and toxic neuropathy. Peripheral neuropathy was the most common adverse event to result in treatment discontinuation in either treatment group.⁴ peripheral neuropathy AEs (\geq 3 grade) were reported at a lower patient incidence of 2.2% in the carfilzomib group compared with 8.1% in the bortezomib group. Less than 1% of peripheral neuropathy AEs was reported as SAEs in either group. The rate of discontinuation due to a peripheral neuropathy AEs was 0.2% and 7.5% in the carfilzomib group and bortezomib group respectively. No death caused by peripheral neuropathy AEs.

Infections

Infections and infestations (in system organ class, SOC): The incidence of \geq Grade 3 events (SOC) was higher in the carfilzomib group (Cd versus Bd: 24.4% vs.19.1%). Serious AEs within the infections and infestations were also higher in the carfilzomib group (21.8% versus 16.7%). Eight patients (1.7%) in the carfilzomib group and 6 (1.3%) in the bortezomib group discontinued the treatment due to an AE within the infections and infestations. Fatal infections and infestations AEs occurred in 1.3% and 1.8% of patients in the carfilzomib and bortezomib group respectively.⁴

Hepatic toxicity

Hepatic toxicity includes patients with ALT \geq 10 x ULN and (ALT or AST \geq 3 x ULN) and (total bilirubin \geq 2 x ULN).⁴ The incidence of hepatobiliary disorders including hepatic failure, fibrosis and cirrhosis and other liver damage related conditions was reported in 25 (5.4%) and 16 (3.5%) patients in the carfilzomib and bortezomib groups, respectively.⁴ Two patients with hepatic failure and one with hepatotoxicity were reported in bortezomib group; one in carfilzomib.^{1,4}

Renal toxicity

Acute renal failure(in broader or grouped term) included acute renal failure, renal failure, renal impairment, acute prerenal failure, anuria, oliguria, and prerenal failure.¹ Grade 3 or higher

acute renal failure was reported in 19 (4.1%) and 12 (2.6%) in the carfilzomib and in the bortezomib group respectively.¹

Pulmonary disorders

Respiratory, thoracic and mediastinal disorders (SOC): The grade 3 or higher pulmonary AEs were 50 (10.8%) in the carfilzomib group compared to 28 (6.1%) bortezomib group.⁴ Pulmonary hypertension (In broader term) including pulmonary hypertension, right ventricular failure, and pulmonary arterial hypertension was reported in 6 (1.3%) and 1 (0.2%) in carfilzomib and bortezomib groups, respectively.¹

Second Primary Malignancy

Two patients in bortezomib group reported the second primary malignancy (SPM, 1 subject pleuric mesothelioma and 1 subject lung cancer), which caused the death.⁴ The overall rate of SPM was not reported.

Cardiac Sub-Study:

The cardiopulmonary substudy was conducted to explore the impact of carfilzomib on echocardiographic parameters and their correlation with cardiac events. A total of 151 patients (75 patients in the carfilzomib plus dexamethasone and 76 patients in the bortezomib plus dexamethasone groups) were enrolled. Median age of patients was 66 years, with 35.8% being 65-74 years and 17.9% over 75 years old. Baseline echocardiogram parameters (Left Ventricular Ejection Fraction (LVEF), Fractional Area Change, Tricuspid Annular Plane Systolic Excursion, Tissue Doppler Imaging, and Pulmonary Artery Systolic Pressure) were generally balanced between treatment groups. The mean baseline LVEF was 63.1% and 64.3% in the carfilzomib plus dexamethasone and bortezomib plus dexamethasone groups, respectively.^{6,17}

Cardiac arrhythmias were reported in three patients in each arm. There was a higher incidence of cardiac failure (in all grades, 10.8% and 4.1% in the carfilzomib plus dexamethasone and bortezomib plus dexamethasone groups, respectively), which was consistent with the overall safety population in the ENDEAVOR trial (8.2% and 2.9%). Ischemic heart disease was reported in two patients in the bortezomib plus dexamethasone group and none in the carfilzomib plus dexamethasone group. Hypertension was reported in 20.3% versus 8.1% of patients in the carfilzomib plus dexamethasone and bortezomib plus dexamethasone groups, respectively. Overall, there were higher rates of treatment-emergent adverse events within the system organ class of respiratory, thoracic, mediastinal disorders in the carfilzomib plus dexamethasone group compared with the bortezomib plus dexamethasone group (41.9% versus 33.8%).

Cardiac related treatment-emergent adverse events are reported in Table 17 below.

Table 17: Treatment-emergent adverse events in the cardiopulmonary safety evaluable subgroup

Onyx Specific Search Strategy Preferred Term	Carfilzomib + Dexamethasone N = 74, n (%)	Bortezomib + Dexamethasone N = 74, n (%)
Cardiac Arrhythmias (SMQN)	3 (4.1)	3 (4.1)
Atrial fibrillation	1 (1.4)	1 (1.4)
Extrasystoles	2 (2.7)	0
Sinus bradycardia	1 (1.4)	0
Tachyarrhythmia	0	1 (1.4)
Ventricular arrhythmia	0	1 (1.4)

Onyx Specific Search Strategy Preferred Term	Carfilzomib + Dexamethasone N = 74, n (%)	Bortezomib + Dexamethasone N = 74, n (%)
Cardiac failure (SMQN)	8 (10.8)	3 (4.1)
Ejection fraction decreased	4 (5.4)	2 (2.7)
Cardiac failure	3 (4.1)	1 (1.4)
Cardiac failure acute	1 (1.4)	0
Cardiac failure chronic	1 (1.4)	0
Right ventricular failure	0	1 (1.4)
Ischaemic Heart Disease (SMQN)	0	2 (2.7)
Acute myocardial infarction	0	1 (1.4)
Stress cardiomyopathy	0	1 (1.4)
SMQN = Standardized MedDRA Query, narrow scope Only subjects who received at least 1 dose of any study-specific treatment are included. Treatment-emergent adverse events were defined, as any adverse event with an onset data from the first dose through 30 days after the last dose of any study drug.		

Source: Rusell, ¹⁷ pCODR review.⁶

There was no statistically significant association found between the protocol-defined significant reduction in LVEF and cardiac adverse events (OR=2.68; 95%CI: 0.14=160.09). The proportion of patients who had a cardiac adverse event who also had a significant reduction in LVEF was low, with one patient in each group. There was a higher proportion of patients who had clinically relevant changes in echocardiogram assessments in the carfilzomib plus dexamethasone versus bortezomib plus dexamethasone group (10.7% (n=8) versus 7.9% (n=6)). All eight patients in the carfilzomib plus dexamethasone group were considered to have clinical adverse event data suggestive of an associated clinical outcome, particularly pulmonary hypertension-type outcome and cardiac failure-type outcome. Discontinuation due to deaths or adverse events was higher in the carfilzomib plus dexamethasone group compared with the bortezomib plus dexamethasone group (22.7% versus 11.8%). Eight of these subjects discontinued due to cardiac-related adverse events. No patient in the sub study had a fatal cardiac adverse event.

The authors concluded that, despite increased rates of cardiac failure adverse events, the sub study did not reveal an elevated risk with carfilzomib compared to bortezomib of left ventricular dysfunction based on LVEF changes over time. Although 151 patients enrolled, there were very low event rates which limits conclusions that can be drawn. Furthermore, the analysis was exploratory in nature and the power to detect treatment differences in this sub study could not be determined and was not considered in the sample size calculation. The results in this study should therefore be considered as hypothesis generating. However, the safety profile (cardiac in nature) of carfilzomib in this study was similar to that seen in the ASPIRE study. Baseline characteristics of patients treated with carfilzomib in this sub study compared with the ASPIRE study, showed a higher proportion of patients who had prior therapy with lenalidomide (42% versus 11%) and were refractory to their last prior regimen (38% versus 28%). Overall, rates of cardiac events in the carfilzomib plus dexamethasone group were similar to those observed for patients treated with carfilzomib plus lenalidomide plus dexamethasone in the ASPIRE trial.⁶

Withdrawal due to adverse events

Discontinuation of study treatments due to adverse events were reported in 65 (14%) patients and 73 (16%) in carfilzomib and bortezomib groups, respectively.¹ Adverse events leading to discontinuation of the treatment and occurring in $\geq 1\%$ of patients in either treatment group included dyspnea (Cd versus Bd: 0.2% versus 1.1%); fatigue (0.2% versus 1.3%); peripheral neuropathy (0 versus 2.2%).¹

Table 18: SAEs (all grades, $\geq 1\%$ in either treatment group)

Preferred term	Cd (n=463)	Bd (n=456)
	n (%)	
Any SAEs	223 (48.2)	162 (35.5)
Pneumonia	28 (6.0)	39 (8.6)
Pyrexia	15 (3.2)	3 (0.7)
Dyspnoea	14 (3.0)	1 (0.2)
Pulmonary embolism	10 (2.2)	3 (0.7)
Cardiac failure	8 (1.7)	3 (0.7)
Acute renal failure	8 (1.7)	5 (1.1)
Upper respiratory tract infection	7 (1.5)	3 (0.7)
Bronchopneumonia	6 (1.3)	0
Sepsis	6 (1.3)	3 (0.7)
Atrial fibrillation	5 (1.1)	4 (0.9)
Back pain	5 (1.1)	2 (0.4)
Diarrhoea	5 (1.1)	9 (2.0)
Respiratory tract infection	5 (1.1)	5 (1.1)
Urinary tract infection	5 (1.1)	4 (0.9)
Vomiting	5 (1.1)	2 (0.4)
Thrombocytopenia	4 (0.9)	6 (1.3)
Hypercalcaemia	0	5 (1.1)

Bd = bortezomib plus dexamethasone; Cd = carfilzomib plus dexamethasone; SAE = serious adverse events.
Source: HC module 2.7.4, ⁴ Dimopoulos 2016.¹

Table 19: Treatment-Emergent \geq Grade 3 AEs ($\geq 2\%$ in either arm)

Preferred Term	Cd (N = 463) n (%)	Bd (N = 456) n (%)
Number of subjects reporting AEs	339 (73.2)	305 (66.9)
Anemia	67 (14.5)	45 (9.9)
Thrombocytopenia	39 (8.4)	43 (9.4)
Hypertension	41 (8.9)	12 (2.6)
Peripheral neuropathy ^a	10 (2.2)	37 (8.1)
Pneumonia	32 (6.9)	36 (7.9)
Diarrhoea	16 (3.5)	34 (7.5)
Fatigue	25 (5.4)	32 (7.0)
Dyspnea	25 (5.4)	10 (2.2)
Platelet count decreased	17 (3.7)	24 (5.3)
Cardiac failure ^a	22 (4.8)	8 (1.8)
Lymphopenia	20 (4.3)	12 (2.6)
Acute renal failure ^a	19(4.1)	12 (2.6)
Hyperglycaemia	18 (3.9)	16 (3.5)

Preferred Term	Cd (N =463) n (%)	Bd (N = 456) n (%)
Asthenia	16 (3.5)	14 (3.1)
Hypokalemia	7 (1.5)	13 (2.9)
Hypophosphataemia	11 (2.4)	5 (1.1)
Pyrexia	11 (2.4)	3 (0.7)
Neutropenia	10 (2.2)	10 (2.2)
Bone pain	10 (2.2)	6 (1.3)
Hyponatremia	10 (2.2)	6 (1.3)
Bronchitis	10 (2.2)	4 (0.9)

AE = adverse event; ; Bd = bortezomib plus dexamethasone, Cd = carfilzomib and dexamethasone

Notes: Bold text indicates the AEs of interest.

^a reported in grouped or broader terms

Source: HC module 2.7.4, ⁴ and Dimopoulos 2016,¹

6.4 Ongoing Trials

An ongoing phase II RCT³¹ was found to compare low dose of carfilzomib plus dexamethasone with high dose of carfilzomib plus dexamethasone in treating patients with relapsed or refractory multiple myeloma (NSC-756640, NCT01903811³¹). The study was sponsored by Southwest Oncology Group and collaborated with National Cancer Institute (NCI). This phase II RCT was an open-label, crossover RCT conducting in 459 study sites in USA. It was started in 2013 and estimated to be completed in February 2018 (Table 20). The actual dosage (low or high dose) of carfilzomib was not described in the available clinical trial site.³¹ The objective of this RCT was to compare low dose of carfilzomib plus dexamethasone with high dose of carfilzomib plus dexamethasone in treating patients with relapsed or refractory multiple myeloma.³¹ No published data on this study was found at this time. The main characteristics of the study design were summarized in Table 20 below.

Table 20: Main study design characteristics (NCT01903811)

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
<p>NCT01903811 S1304 (Ongoing study, estimated complete date: Feb. 2018)³¹</p> <p>Open label Crossover assignment phase II RCT</p> <p>459 study locations in USA</p> <p>Randomized size (N): Not available</p> <p>Funded by Southwest Oncology Group and collaborated with National Cancer Institute (NCI).</p>	<p>Key Inclusion Criteria: <u>Registration Step 1 (initial):</u> Adults with relapsed or refractory multiple myeloma and measurable disease who had received one prior treatments; Must have not received carfilzomib treatment)</p> <p>Zubrod performance status 0-2</p> <p>Adequate hepatic, hematologic, and renal function (CrCl: $\geq \geq 30$ ml/min within 14 days prior to registration</p> <p><u>Registration step 2 (crossover):</u> Patient must have been eligible for and initially randomized to Arm 1 (low dose carfilzomib), begun cycle 2 of treatment, and progressed prior to completing 12 cycles of protocol therapy</p> <p>At least 14 days and no more than 28 days must have elapsed between the last day of treatment on Arm 1 and registration to Arm 3</p> <p>Patients must have recovered from all non-hematologic toxicities to \leq grade 2 and from all hematologic toxicities to \leq grade 3 prior to registration</p>	<p>Intervention: Carfilzomib + dexamethasone (Cd) (Arm 1 versus Arm 2)</p> <p><u>Arm 1: low dose carfilzomib +dexamethasone</u></p> <p>Patients receive dexamethasone IV and low-dose carfilzomib IV on days 1, 2, 8, 9, 15, and 16.</p> <p><u>Arm 2: high dose carfilzomib +dexamethasone</u></p> <p>Patients receive dexamethasone IV and high-dose carfilzomib IV on days 1, 2, 8, 9, 15, and 16.</p> <p>Note that for the first course of treatment on both arms carfilzomib is given at a reduced rate to assess toxicity.</p> <p>In both arms, treatment repeats every 28 days for up to 12 courses in the absence of disease progression or unacceptable toxicity.</p> <p>After completion of study treatment, patients are followed up every 3 months for 3 years from initial registration.</p>	<p>Primary: PFS</p> <p>Secondary: RR OS</p> <p>Others molecular variability in MM cells (bone marrow relapse sites)</p> <p>PET scanning in assessing disease burden and as a tool to assess treatment response</p> <p>LVEF</p>

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
	<p>Patients must have begun cycle 2 (carfilzomib - 27 mg/m²) and must not have received any dose reduction for toxicity in the last cycle of treatment, immediately preceding progression</p> <p>Key Exclusion Criteria: Patients with significant neuropathy (Grade 2)</p> <p>Patients with ejection fraction decrease > 10% from baseline (as determined by ECHO)</p>		
<p>Abbreviations: CrCl = creatinine clearance; LVEF = left ventricular ejection fraction; OS = overall survival; PET = positron emission tomography; PFS = progression free survival; RCT = randomized controlled trial;</p> <p>Source: ClinicalTrials.gov ³¹ https://clinicaltrials.gov/ct2/show/NCT01903811</p>			

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 COMPARISON WITH OTHER LITERATURE

Given the issuance of a final pERC recommendation on the results of the ASPIRE trial ⁶, conducted in patients with relapsed or refractory multiple myeloma who received 1 – 3 prior lines of therapies, the pCODR review team considered whether there were important similarities or differences in the patient population included in the ASPIRE versus ENDEAVOR trials. Both studies were conducted in relapsed or refractory patients multiple myeloma who received 1 – 3 prior lines of therapies. The ASPIRE study was reviewed by pCODR in June 2016.⁶ It is important to note that the information presented below was not done in an effort to make an indirect comparison, rather, the intent was to present the data to demonstrate where there may be important differences in the trial characteristics that could explain the variation in response observed.

Table 21: Comparison of Study ENDEAVOR with study ASPIRE

	ENDEAVOR	ASPIRE ⁶
Study design	<p>Open label phase 3 RCT</p> <p>Patient Enrollment: June 20, 2012 to June 30, 2014. ^{1,21}</p> <p>Data cut-off date: 10 November 2014 ⁴</p> <p>Estimated completion date: Dec. 2018</p> <p>Randomized: n = 929 Treated: n = 919 ¹</p>	<p>Open label phase 3 RCT</p> <p>Patient Enrollment: 14 July 2010 to 15 Mar 2012</p> <p>Data cut-off date: 16 June 2014</p> <p>Estimated Completion Date: Oct. 2017</p> <p>Randomized: n = 792 Treated: n = 781</p>
Key Inclusion Criteria	<p>Adults with relapsed or refractory MM who had received 1 – 3 three lines of prior treatments.</p> <p>ECOG PS 0-2</p> <p>Adequate hepatic, hematologic, and renal function (CrCl: \geq 15 mL/min) at screening</p> <p>Exclusion Criteria: ^{1,21} Significant neuropathy (Grade 2 with pain, grade 3 to 4 peripheral neuropathy within 14 days before randomisation,</p> <p>Myocardial infarction within 4-month before randomisation, or New York Heart Association class III or IV heart failure</p>	<p>Adults with relapsed /refractory to most recent line of therapy MM who had received 1 – 3 lines of prior treatments</p> <p>ECOG PS 0-2</p> <p>Adequate hepatic, hematologic, and renal function (creatinine clearance, \geq50 ml per minute) at screening</p> <p>Exclusion Criteria: If previously treated with bortezomib, progression during treatment; If previously treated with lenalidomide and dexamethasone</p> <p>Had grade 3 or 4 peripheral neuropathy (or grade 2 with pain) within 14 days of randomization or New York Heart Association class III or IV heart failure</p>
Intervention/comparator	<p>Intervention: Carfilzomib + dexamethasone (Cd)</p> <p>Carfilzomib 20 mg/m² on days 1 and 2 of cycle 1; 56 mg/m² given thereafter;</p> <p>Dexamethasone: 20 mg</p> <p>Comparator:</p>	<p>Intervention: Carfilzomib + lenalidomide + dexamethasone (CLd)</p> <p>Carfilzomib 20 mg/m² on days 1 and 2 of cycle 1; 27 mg/m² thereafter from cyle 2 through 18, after which carfilzomib was discontinued.</p> <p>Lenalidomide (25 mg)</p> <p>Comparator:</p>

	ENDEAVOR			ASPIRE ⁶		
	Bortezomib + dexamethasone (Bd) Bortezomib: 1-3 mg/m ² Dexamethasone: 20 mg			Lenalidomide + dexamethasone (Ld) Lenalidomide (25 mg) Dexamethasone (40 mg)		
Primary outcome	PFS			PFS		
Exposure of treatment, Median (weeks)	Carfilzomib: Bortezomib:	Cd: 40 NA	Bd NA 27	Carfilzomib: Lenalidomide:	CLd: 70 85	Ld NA 56
PFS	Cd		Bd	CLd:	Ld	
median (months) (95% CI)	18.7 (15.6-NE)		9.4 (8.4-10.4)	26.3	17.6	
HR (95%CI), p	0.53 (0.44, 0.65); p<0.0001 1			0.69 (0.57, 0.83) P = 0.0001		

Bd = Bortezomib + dexamethasone; Cd = Carfilzomib + dexamethasone; CLd = Carfilzomib + lenalidomide + dexamethasone; IV= intra venous; Ld = Lenalidomide + dexamethasone; MM = multiple myeloma; NA = not applicable; NR = not reported; SC= subcutaneous;

Table 22: Comparison of Key Baseline Characteristics of study ENDEAVOR and ASPIRE

	ENDEAVOR		ASPIRE ⁶	
	Cd (n=464)	Bd (n=465)	CLd (n=396)	Ld (n=396)
Age (years)				
Median (range)	65 (35-89)	65 (30, 88)	64.0 (38.0, 87.0)	65.0 (31.0, 91.0)
<65	223 (48)	210 (45)	211 (53.3)	188 (47.5)
65-74	164 (35)	189 (41)	142 (35.9)	155 (39.1)
≥75	77 (17)	66 (14)	43 (10.9)	53 (13.4)
Sex				
Male	240 (52)	229 (49)	215 (54.3)	232 (58.6)
ECOG performance status				
0	221 (48)	232 (50)	165 (41.7)	175 (44.2)
1	211 (45)	203 (44)	191 (48.2)	186 (47.0)
2	32 (7)	30 (6)	40 (10.1)	35 (8.8)
ISS stage				
I	205 (44)	204 (44)	64 (16.2)	74 (18.7)
II-III	259 (56)	261 (56)	284 (71.7)	255 (64.4)
Cytogenetics				
High risk	97 (21)	113 (24)	48 (12.1)	52 (13.1)
Race				
White	348 (75)	353 (76)	377 (95.2)	377 (95.2)
Black	8 (2)	9 (2)	12 (3.0)	11 (2.8)
Asian	58 (13)	57 (12)	1 (0.3)	3 (0.8)
CrCL ml/min)				
>15 to < 50	85(18)	99(21%)	0	0
Previous regimens				
One	232 (50)	232 (50)	184 (46.5)	157 (39.6)
Two	157 (34)	145 (31)	120 (30.3)	139 (35.1)
Three	75 (16)	87 (19)	91 (23.0)	99 (25.0)
History of peripheral neuropathy				
No	249 (54)	221 (48)	252 (63.6)	259 (65.4)
Yes	215 (46)	244 (52)	144 (36.4)	137 (34.6)

	ENDEAVOR		ASPIRE ⁶	
	Cd (n=464)	Bd (n=465)	CLd (n=396)	Ld (n=396)
Ongoing peripheral neuropathy at screening				
Grade 1	133 (29)	159 (34)	114 (28.8)	106 (26.8)
Grade 2	10 (2)	10 (2)	22 (5.6)	24 (6.1)
Previous proteasome inhibitor treatment†				
Carfilzomib	2 (<1)	1 (<1)	NR	NR
Bortezomib	250 (54)	252 (54)	261(65.9)	260 (65.7)
None	212 (46)	212 (46)	NR	NR
Previous immunomodulatory agent treatment				
Lenalidomide	177 (38)	177 (38)	79 (19.9)	78 (19.7)
Thalidomide	211 (45)	247 (53)	176 (44.4)	171 (43.2)
Refractory to prior regimen				
Bortezomib	15 (3.2)	19 (4.1)	60 (15.2)	58(14.6)
Lenalidomide	NR	NR	29(7.3)	28(7.1)
Received in last prior regimen				
Bortezomib	NR	NR	194 (49.0)	174 (43.9)
Thalidomide	NR	NR	49 (12.4)	50(12.6)
Refractory to last prior regimen				
	184 (39.7)	188 (40.4)	110 (27.8)	119 (30.1)

Bd = Bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CLd = Carfilzomib + lenalidomide + dexamethasone; CrCL = Creatinine Clearance; ECOG=Eastern Cooperative Oncology Group; ISS=International Staging System; Ld = Lenalidomide + dexamethasone.

Note: data presented as n(%), unless specified otherwise.

Source: Dimopoulos 2016.¹ pCODR report ⁶

Differences were noted in the inclusion criteria and baseline characteristics of the ENDEAVOR and ASPIRE studies (Table 21 and Table 22:). The main observed differences in the baseline demographics and patients characteristics were as follow: nearly 20% patients in ENDEAVOR had CrCL < 50 ml/min; numerically, more patients in ENDEAVOR had ISS stages I and II-III disease, high cytogenetics risk, history of peripheral neuropathy and received prior immunomodulatory agent treatment (lenalidomide and thalidomide). Numerically more female and Asian patients were included in ENDEAVOR than that in the ASPIRE study; however, more patients in ENDEAVOR were in ECOG 0. Few patients received 3 prior lines of treatments including bortezomib in ENDEAVOR than that in ASPIRE (Table 21 and Table 22:).

Difference were also noticed in the magnitude of response seen in terms of the PFS. Observed PFS in ENDEAVOR was much shorter than that in ASPIRE study (Intervention versus comparator: 18.7 versus 9.4 in ENDEAVOR and 26.3 versus 17.6 in ASPIRE respectively), although the absolute magnitude of difference was the same between the two studies (9.3 month) and the HRs in the two studies were similar (Table 21). It is unknown whether the observed differences of PFS between the two studies were caused or related to the differences of the baseline characteristics of patients included in the two studies mentioned. Notable, there may be other unknown confounders that may be resulting in difference between trials.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lymphoma/Myeloma Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on carfilzomib (Kyprolis) for multiple myeloma. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials August 2016, Embase 1974 to 2016 September 14, Limits: English, 5 years for conference abstracts, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

2. Search Strategy:

Search Strategy:

#	Searches	Results
1	(carfilzomib* or kyprolis* or PR171 or PR 171 or 868540-17-4 or 72X6E3J5AR).ti,ab,rm,nm,hw,ot,kf.	2624
2	exp Multiple Myeloma/	98380
3	(myelom* or kahler disease or morbus kahler).ti,ab,kf.	132864
4	((plasma or plasmacytic or plasmocytic or plasmocyte) adj2 (cancer* or malignant or malignancy or neoplasm* or oncolog* or tumor* or tumour* or leukemia* or leukaemia*)).ti,ab,kf.	15811
5	2 or 3 or 4	164852
6	1 and 5	2025
7	6 use ppez	380
8	6 use cctr	23
9	*carfilzomib/	572
10	(carfilzomib* or kyprolis* or PR171 or PR 171).ti,ab,kw.	1765
11	9 or 10	1787
12	Multiple Myeloma/ or Plasma Cell Leukemia/	99031
13	(myelom* or kahler disease or morbus kahler).ti,ab,kw.	133605
14	((plasma or plasmacytic or plasmocytic or plasmocyte) adj2 (cancer* or malignant or malignancy or neoplasm* or oncolog* or tumor* or tumour* or leukemia* or leukaemia*)).ti,ab,kw.	15951
15	12 or 13 or 14	165724
16	11 and 15	1402
17	16 use oomezd	11039
18	conference abstract.pt.	2339159
19	17 and 18	624

20	limit 19 to yr="2011-Current"	563
21	17 not 18	415
22	7 or 8 or 21	1066
23	limit 22 to english language	1027
24	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt.	1004306
25	Randomized Controlled Trial/	981498
26	exp Randomized Controlled Trials as Topic/	263854
27	"Randomized Controlled Trial (topic)"/	129379
28	Controlled Clinical Trial/	564527
29	exp Controlled Clinical Trials as Topic/	275613
30	"Controlled Clinical Trial (topic)"/	10827
31	Randomization/	203206
32	Random Allocation/	199340
33	Double-Blind Method/	391474
34	Double Blind Procedure/	139967
35	Double-Blind Studies/	257465
36	Single-Blind Method/	69321
37	Single Blind Procedure/	28800
38	Single-Blind Studies/	70771
39	Placebos/	330945
40	Placebo/	330761
41	Control Groups/	269930
42	Control Group/	269834
43	(random* or sham or placebo*).ti,ab,hw,kf,kw.	3574484
44	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	705576
45	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	2190
46	(control* adj3 (study or studies or trial*)).ti,ab,kf,kw.	1294099
47	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	86448
48	allocated.ti,ab,hw.	151241
49	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	93450

50	or/24-49	4194389
51	23 and 50	231
52	remove duplicates from 51	197
53	23 not 50	1109
54	remove duplicates from 53	845
55	limit 20 to english language	472
56	remove duplicates from 55	451

2. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
<http://www.clinicaltrials.gov/>

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
<http://www.canadiancancertrials.ca/>

Search: Carfilzomib

Select international agencies including:

Food and Drug Administration (FDA):
<http://www.fda.gov/>

European Medicines Agency (EMA):
<http://www.ema.europa.eu/>

Search: Carfilzomib

Conference abstracts:

American Society of Clinical Oncology (ASCO)

<http://www.asco.org/>

American Society of Hematology

<http://www.hematology.org/>

Search: Carfilzomib - last 5 years

REFERENCES

1. Dimopoulos MA, Moreau P, Palumbo A, Joshua D, Pour L, Hájek R, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol.* 2016 Jan;17(1):27-38.
2. Mateos MV, Knop S, Femand JP, Hajek R, Ludwig H, Feng S, et al. Efficacy and safety of carfilzomib and dexamethasone (KD) vs bortezomib and dexamethasone (Vd) in patients with relapsed multiple myeloma by prior autologous stem cells transplantation: Secondary analysis from the phase 3 endeavor study (NCT01568866) [abstract]. *Bone Marrow Transplant.* 2016;51:S17-S18. (Presented at 42nd Annual Meeting of the European Society for Blood and Marrow Transplantation, EBMT 2016; 2016 April 3-6; Valencia, Spain).
3. Osterweil N. Carfilzomib/dex doubles PFS of relapsed myeloma. *Oncology Practice (Oncology Report)* [Internet]. 2015 Jun [cited 2017 Jan 9];11(7):4-5. Available from: [http://www.oncologypractice.com/?id=4475&tx_ttnews\[tt_news\]=409177&cHash=b9d048320ead53a0f9942d68aa216f1](http://www.oncologypractice.com/?id=4475&tx_ttnews[tt_news]=409177&cHash=b9d048320ead53a0f9942d68aa216f1)
4. pan-Canadian Oncology Drug Review manufacturer submission. Drug name: ^{Pr}Kyprolis™ (carfilzomib for injection) 60 mg per vial. Company: Amgen Canada, Inc. Mississauga (ON): Amgen Canada Inc.; 2016 Sep 9.
5. Amgen powerpoint presentation on ENDEAVOR trial for pCODR checkpoint meeting [additional manufacturer's information]. Mississauga (ON): Amgen Canada Inc.; 2016 Nov 1.
6. pan-Canadian Oncology Drug Review final clinical guidance report: carfilzomib (Kyprolis) for multiple myeloma [Internet]. Toronto (ON): CADTH pan-Canadian Oncology Drug Review; 2016 Jun 21. [cited 2016 Oct 24]. Available from: https://www.cadth.ca/sites/default/files/pcodr/pcodr_carfilzomib_kyprolis_mm_fn_cgr.pdf
7. Multiple myeloma statistics [Internet]. Toronto: Canadian Cancer Society; 2016. [cited 2017 Jan 10]. Available from: <http://www.cancer.ca/en/cancer-information/cancer-type/multiple-myeloma/statistics/?region=bc>
8. Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Spicka I, Oriol A, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med.* 2015 Jan 8;372(2):142-52.
9. Palumbo A, Stewart AK, Rajkumar SV, Masszi T, Spicka I, Oriol A, et al. Efficacy and safety of carfilzomib, lenalidomide, and dexamethasone (KRd) vs lenalidomide and dexamethasone (Rd) in patients (pts) with relapsed multiple myeloma (RMM) based on age: Secondary analysis from the phase 3 study aspire (nct01080391) [abstract]. *Clinical Lymphoma, Myeloma and Leukemia Conference: 15th International Myeloma Workshop Rome Italy Conference Start: 20150923 Conference End: 20150926 Conference Publication: (var pagings) 15 ()(pp e75-e76), 2015 Date of Publication: September 2015. 2015. (Presented at 20150923;- 20150926. Conference Publication: (var.pagings). 15 ()(pp e75-e76), 2015. Date of Publication: September 2015).*
10. Hajek R, Russell SD, Lyon A, Lenihan D, Moreau P, Joshua D, et al. A substudy of the phase 3 ENDEAVOR study: Serial echocardiographic assessment of patients with relapsed multiple myeloma(RMM) receiving carfilzomib plus dexamethasone or bortezomib plus dexamethasone [Internet]. Poster presented at: 21st Congress of the European Hematology Association. 2016 Jun 11; Copenhagen (Netherlands). [cited 2017 Jan 10]. Available from:

<http://learningcenter.ehaweb.org/eha/2016/21st/133552/roman.hajek.a.substudy.of.the.phase.3.endeavor.study.serial.echocardiographic.html?f=m3>

11. Moreau P, Pylypenko H, Grosicki S, Karamanesht I, Leleu X, Grishunina M, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. *Lancet Oncol*. 2011 May;12(5):431-40.
12. Bringhen S, Larocca A, Rossi D, Cavalli M, Genuardi M, Ria R, et al. Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. *Blood*. 2010 Dec 2;116(23):4745-53.
13. Dimopoulos MA, Moreau P, Palumbo A, Joshua DE, Pour L, Hajek R, et al. Carfilzomib and dexamethasone (Kd) vs bortezomib and dexamethasone (Vd) in patients (pts) with relapsed multiple myeloma (RMM): Results from the phase III study ENDEAVOR. *J Clin Oncol* [Internet]. 2015 May 29 [cited 2016 Sep 29];33(15 Suppl 1). Available from: http://meeting.ascopubs.org/cgi/content/abstract/33/15_suppl/8509?sid=76b1df25-6917-4895-9643-580275df43c5 (Presented at 2015 ASCO Annual Meeting; 2015 May 29 - Jun 2; Chicago, IL).
14. National Cancer Institute. Surveillance, epidemiology, and end results program [Internet]. 2017. [cited 2016 Jan 23]. Available from: <https://seer.cancer.gov/>
15. Palumbo A, Anderson K. Multiple myeloma. *N Engl J Med*. 2011 Mar 17;364(11):1046-60.
16. National Cancer Institute. Surveillance, epidemiology, and end results program [Internet]. 2017. [cited 2016 Jan 23]. Available from: <https://seer.cancer.gov/>
17. Russell SD, Lyon A, Lenihan DJ, Moreau P, Joshua D, Chng WJ, et al. Serial echocardiographic assessment of patients (PTS) with relapsed multiple myeloma (RMM) receiving carfilzomib and dexamethasone (KD) vs bortezomib and dexamethasone (VD): A substudy of the phase 3 endeavor trial (NCT01568866) [abstract]. *Blood* [Internet]. 2015;126(23):4250. Available from: <http://www.bloodjournal.org/content/126/23/4250> (Presented at 57th Annual Meeting of the American Society of Hematology, ASH 2015; 2015 Dec 3-6; Orlando, FL).
18. Palumbo A, Dimopoulos MA, Moreau P, Chng WJ, Goldschmidt H, Hajek R, et al. Carfilzomib and dexamethasone vs bortezomib and dexamethasone in patients with relapsed multiple myeloma: Results of the phase 3 study endeavor (NCT01568866) according to age subgroup [abstract]. *Blood* [Internet]. 2015 [cited 2016 Oct 4];126(23). Available from: <http://www.bloodjournal.org/content/126/23/1844> (Presented at 57th Annual Meeting of the American Society of Hematology, ASH 2015; 2015 Dec 5-8; Orlando, FL).
19. Chng WJ, Goldschmidt H, Dimopoulos MA, Moreau P, Joshua D, Palumbo A, et al. Efficacy and safety of carfilzomib and dexamethasone vs bortezomib and dexamethasone in patients with relapsed multiple myeloma based on cytogenetic risk status: Subgroup analysis from the phase 3 study endeavor (NCT01568866) [abstract]. *Blood* [Internet]. 2015 [cited 2017 Jan 9];126(23):30. Available from: <http://www.bloodjournal.org/content/126/23/30> (Presented at 57th Annual Meeting of the American Society of Hematology, ASH 2015 San Diego, CA; Dec 3-6, 2016).
20. Dimopoulos M, Moreau P, Palumbo A, Joshua D, Pour L, Hajek R, et al. Carfilzomib and dexamethasone improves progressionfree survival and response rates vs bortezomib and dexamethasone in patients (PTS) with relapsed multiple myeloma (RMM): the phase 3 study endeavor [abstract]. *Haematologica*. 2015;100:336. (Presented at 20th Congress of the European Hematology Association; 2015 June 11-15; Vienna, Austria).

21. Onyx Pharmaceuticals. Phase 3 study with carfilzomib and dexamethasone versus bortezomib and dexamethasone for relapsed multiple myeloma patients (ENDEAVOR). 2012 Mar 28 [cited 2016 Oct 4; updated 2015 Dec 14]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: <https://clinicaltrials.gov/ct2/show/NCT01568866> Identifier: NCT01568866.
22. Fayers PM, Aaronsen NK, Bjordal K, Groenvold M, Curran D, Bottomley A. The EORTC QLQ-C30 scoring manual [Internet]. 3rd ed. Brussels (BE): European Organisation for Research and Treatment of Cancer; 2001. [cited 2016 Oct 5]. Available from: <http://www.eortc.be/qol/files/SCManualQLQ-C30.pdf>
23. Stewart AK, Rajkumar SV, Moreau P, Palumbo A. Randomized, multicenter, phase 3 study comparing carfilzomib, lenalidomide, and dexamethasone (CRd) vs lenalidomide and dexamethasone (Rd) in subjects with relapsed multiple myeloma [protocol]. Emeryville (CA): Onyx Therapeutics; 2010 Feb 5.
24. Stewart AK, Rajkumar SV, Moreau P, Palumbo A. Randomized, multicenter, phase 3 study comparing carfilzomib, lenalidomide, and dexamethasone (CRd) vs lenalidomide and dexamethasone (Rd) in subjects with relapsed multiple myeloma [protocol]. Emeryville (CA): Onyx Therapeutics; 2010 Feb 5.
25. Papadopoulos KP, Siegel DS, Vesole DH, Lee P, Rosen ST, Zojwalla N, et al. Phase I study of 30-minute infusion of carfilzomib as single agent or in combination with low-dose dexamethasone in patients with relapsed and/or refractory multiple myeloma. *J Clin Oncol* [Internet]. 2015 Mar 1 [cited 2016 Oct 12];33(7):732-9. Available from: <http://ascopubs.org/doi/full/10.1200/JCO.2013.52.3522>
26. Siegel DS, Martin T, Wang M, Vij R, Jakubowiak AJ, Lonial S, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. *Blood* [Internet]. 2012 Oct 4 [cited 2017 Jan 4];120(14):2817-25. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4123387>
27. Amgen response to pCODR checkpoint meeting questions on the submission of carfilzomib (Kyprolis) for multiple myeloma [additional manufacturer's information]. Mississauga (ON): Amgen Canada Inc.; 2016 Nov 1.
28. Restricted maximum likelihood [Internet]. [San Francisco (CA)]: Wikipedia; 2016. [cited 2017 Jan 5]. Available from: https://en.wikipedia.org/wiki/Restricted_maximum_likelihood
29. Yost KJ, Cella D, Chawla A, Holmgren E, Eton DT, Ayanian JZ, et al. Minimally important differences were estimated for the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) instrument using a combination of distribution- and anchor-based approaches. *J Clin Epidemiol*. 2005 Dec;58(12):1241-51.
30. pCODR checkpoint meeting follow up on the submission of carfilzomib (kyprolis) for multiple myeloma - (pCODR 10084). Toronto (ON): CADTH pan-Canadian Oncology Drug Review; 2016.
31. S1304, Carfilzomib and dexamethasone for treating patients with relapsed or refractory myeloma. 2016 Oct 6 [cited 2017 Jan 24]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: <https://clinicaltrials.gov/ct2/show/NCT01903811> Identifier: NCT01903811.