pan-Canadian Oncology Drug Review

Final Clinical Guidance Report

Erratum: This is a revised Final Clinical Guidance Report which supersedes the Final Clinical Guidance Report for this drug and indication dated June 21, 2016. The revision does not impact the Final Economic Guidance Report. The revision was made to align the patient population critically appraised by the review team with the patient population in the pivotal trial (ASPIRE).

Carfilzomib (Kyprolis) for Multiple Myeloma

November 11, 2016

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of carfilzomib in combination with lenalidomide and dexamethasone on patient outcomes in the treatment of adult patients with multiple myeloma following at least one prior therapy.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one trial, ASPIRE, which was an open label randomized controlled trial that randomized 792 patients with relapsed multiple myeloma to receive carfilzomib plus lenalidomide plus dexamethasone (n=396) or lenalidomide plus dexamethasone (n=396). Carfilzomib was given up to cycle 18. In both groups, lenalidomide and dexamethasone were given until disease progression, withdrawal of consent, or occurrence of unacceptable toxic effects. Baseline patient characteristics are listed in Table 7 and were generally well balanced across groups.

The median age of patients in the ASPIRE study was 64.0 years and nearly 30% of patients in both arms were over the age 70. The majority of patients in the trial had and Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 (42.9%) or 1 (47.6%) while 9.5% of patients in both groups had an ECOG PS of 2. Patients also had received a median of 2 previous therapies. Overall, 65.8% had received bortezomib, 19.8% had received lenalidomide, and 56% had received prior transplant.

Patients previously treated with bortezomib were permitted entry into the trial provided they did not have disease progression during treatment. Patients previously treated with lenalidomide and dexamethasone were permitted entry provided they did not progress during the first three months of therapy, or at any time on therapy if it was the last regimen prior to study entry, or discontinued due to intolerance.

Efficacy

The primary outcome in the ASPIRE 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 31% reduction in the risk of progression or death during the study period. Median PFS was 26.3 vs. 17.6 months in the carfilzomib and control groups respectively (HR=0.69; 95%CI: 0.57-0.83, p=0.0001). For secondary outcomes, 24 month survival rates were 73.3% and 65.0% in the carfilzomib and control groups, respectively. Median OS was not reached in either arm.

Post-hoc subgroup analysis in patients ≥70 years was 23.8 months versus 16.0 months in the carfilzomib and control groups, respectively (HR=0.739 05%CI 0.513-1.065, p=0.0521). Additionally, there was no difference in OS, however, data were not yet mature.[1]

European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core Module (QLQ-C30) and Multiple Myeloma Module (QLQ-MY20) was used on day 1 of cycles 1, 3, 6, 12, and 18, and approximately 30 days after the last treatment to determine the impact of carfilzomib on patient reported outcomes. A minimally important difference (change of ≥5 points) was measured at cycle 12 for the global health status measure of HRQoL. Differences were not measured for the individual domains of

fatigue, nausea/vomiting, pain, physical functioning, role functioning, disease symptoms and side effects of treatment.

Harms

Treatment related deaths were similar between groups (6 and 8 patients each in the carfilzomib and control groups, respectively). Overall grade 3/4 adverse events were also similar between treatment groups (83.7% and 70.7% in the carfilzomib and control groups, respectively). Cardiac failure occurred in 3.8% and 1.8% of patients in the two arms respectively. In a post-hoc analysis among patient's ≥70 years, cardiac failure occurred in 8.7% and 1.8% of patients in the carfilzomib and control groups, respectively.

1.2.2 Additional Evidence

pCODR received input on carfilzomib (Kyprolis) in combination with lenalidomide and dexamethasone for previously treated multiple myeloma from one patient advocacy group, Myeloma Canada. Provincial Advisory group input was obtained from nine of the nine provinces participating in pCODR.

No supplemental question was identified during development of the review.

1.2.3 Interpretation and Guidance

Despite significant advancement in the treatment and life expectancy of patients with myeloma, it still remains an incurable disease. 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. Finding novel therapies that can improve life expectancy is a continued need. Carfilzomib plus lenalidomide and dexamethasone is a novel combination, and the first regimen to be compared with the standard second-line therapy of lenalidomide and dexamethasone, in the relapsed setting. Using newer chemotherapies in combination may lead to improvement in outcomes, as demonstrated in this review.[2]

Carfilzomib, lenalidomide and dexamethasone demonstrated statistically significant and clinically meaningful improvements in PFS. The benefit was observed across subgroups of patients. An overall survival benefit was also reported, however median OS had not yet been reached. It is not clear if the addition of carfilzomib to lenalidomide and dexamethasone results in improvement in health related quality of life. While a minimally important difference was measured at only week 12 of treatment, the consistently equal responses throughout the other timepoints of therapy would suggest that quality of life at the least remains the same in both arms of the ASPIRE trial.

Treatment related deaths and serious adverse events (SAE), grade 3 or higher, were similar in the carfilzomib arm compared to the control arm. The rate of cardiac failure was slightly increased with the addition of carfilzomib, however the significance of this is uncertain, and further data are necessary to determine the risk of cardiac toxicity with this regimen, particularly in the older patient population.[3]

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to carfilzomib, lenalidomide and low-dose dexamethasone, compared with lenalidomide and low dose 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 control. The adverse

event profiles were similar between the two groups. The current data also suggests that there may be an overall survival advantage, although the data needs time to mature, to clarify the magnitude of 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 was predominantly younger patients (median age 64 years old). Although the number of patients over the age of 70 included in this trial is small, the magnitude of benefit is similar to patients under the age of 70. There is some concern that there may be an increased risk of heart failure in older patients, but further study is necessary to clarify this risk.
- Although the study limited enrollment to patients with a CrCl of greater than or equal to 50 ml/min, use in patients with renal impairment would be a reasonable consideration. Carfilzomib is not renally excreted, and therefore, adding this drug to dose-adjusted lenalidomide would be appropriate.
- There are no efficacy or safety data for using this regimen in patients with an 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 2 or greater may be appropriate, and this would be consistent with standard practice with other myeloma therapies.
- This study was designed and accrued before maintenance therapy was common. How maintenance therapy would alter outcome is uncertain.
- This regimen is for patients with relapsed disease. Further data are necessary to clarify the role of this regimen in the first line setting.
- Patients must not have had disease progression during treatment with bortezomib or if previously treated with lenalidomide and dexamethasone patients must not have
    - discontinued therapy because of adverse effects,
    - disease progression during the first 3 months of treatment, or
    - progression at any time during treatment if lenalidomide plus dexamethasone was their most recent treatment.
    - If patients have received maintenance therapy, but they are not excluded by these criteria, they would be eligible for carfilzomib, lenalidomide, dexamethasone.
- The CGP recommends standard dose adjustments for carfilzomib, as per provincial guidelines. There was no clear scientific rationale to restrict dose adjustments to plus or minus 20% body weight.
- There is no evidence of benefit using carfilzomib beyond cycle 18 when combined with lenalidomide and dexamethasone.

2 CLINICAL GUIDANCE

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) 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) 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; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on carfilzomib (Kyprolis) for multiple myeloma and a summary of submitted Provincial Advisory Group Input on carfilzomib (Kyprolis) for multiple myeloma are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Multiple myeloma is an incurable plasma cell neoplasm and diagnosed based on the presence of 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. In 2015, it is estimated that 2700 Canadians will be diagnosed with myeloma and 1400 patients will die of this disease.[4] The median age at presentation is 69 years with a slightly higher incidence in males. Although there is significant heterogeneity within myeloma, the five-year survival for all patients is 48.5%.[5]

For asymptomatic disease, observation is appropriate and no therapy is required. For symptomatic disease, patients are primarily treated with anti-myeloma therapy. The three main classes of chemotherapy include alkylators (melphalan or cyclophosphamide), immunomodulatory drugs (thalidomide or lenalidomide), and proteasome inhibitors (bortezomib or carfilzomib). Various combinations of these drugs with steroids (prednisone or dexamethasone) have been proven to be highly effective for the treatment of multiple myeloma.[6] Initial therapy with chemotherapy may include induction prior to autologous stem cell transplant (for eligible candidates). Subsequent second-line therapy upon relapse may include a bortezomib-based or lenalidomide-based regimen,[7] depending on what regimen was used previously in first-line therapy.

Carfilzomib is a second generation proteasome inhibitor. It is an irreversible inhibitor which binds to a different site than bortezomib on the proteasome. Health Canada has approved carfilzomib in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

2.1.2 Objectives and Scope of pCODR Review

The objective of the review was to evaluate the efficacy and safety of carfilzomib in combination with lenalidomide and dexamethasone, for the treatment of patients with multiple myeloma following at least one prior therapy.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

One open label randomized controlled trial, ASPIRE, met the inclusion criteria of this systematic review.[2] The study randomized 792 patients with relapsed multiple myeloma to receive carfilzomib plus lenalidomide plus dexamethasone (n=396) or lenalidomide plus dexamethasone (n=396). Carfilzomib was given up to cycle 18. In both groups, lenalidomide and dexamethasone were given until disease progression, withdrawal of consent, or occurrence of unacceptable toxic effects. Patients with multiple myeloma were required to have relapsed or progressed on one to three prior treatments.[8] Patients previously treated with bortezomib were permitted entry into the trial provided they did not have disease progression during treatment. Patients previously treated with lenalidomide and dexamethasone were permitted entry provided they did not progress during the first three months of therapy, or at any time on therapy if it was the last regimen prior to study entry, or discontinued due to intolerance.

Baseline patient characteristics are listed in Table 7 and were generally well balanced across groups. The median age of patients in the ASPIRE study was 64.0 years and 90.5% of patients had an ECOG PS of 0 or 1. Seventy-five (9.5%) of patients in both groups had an ECOG PS of 2. Patients received a median of two previous regimens. Prior therapy received included bortezomib (65.8%), and lenalidomide (19.8%).[8] Fifty-six percent of patients had prior transplant. The primary outcome of the trial was progression-free survival (PFS) which was independently assessed. Secondary outcomes included overall survival (OS), overall response rate (ORR), disease control rate (DCR), duration of response (DoR), health-related quality of life (HrQoL), and safety. HrQoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life QuestionnaireCore Module (QLQ-C30) questionnaire and the Multiple Myeloma Module (QLQ-MY20).[9] All efficacy analyses were carried out in the intent-to-treat population while the safety analyses were conducted in the treated population only (n=781). Three analyses of PFS were planned, two interim and one final analysis. The first interim analysis was for administrative purposes to ensure adequate sample size or duration of follow-up to ensure timely achievement of the required PFS events. The second interim analysis was June 2014,[1] at this analysis as the monitoring boundary for benefit was met, the trial sponsor was able to consider filing the interim PRS data with regulatory agencies.[10]

Limitations/Sources of Biases

The ASPIRE study was open label, therefore investigators and patients were not blinded to treatment assignment. However, given carfilzomib is administered intravenously compared to oral administration of lenalidomide plus dexamethasone; blinding of patients to treatment assignment was not done, and although it was possible, it would have been difficult to implement. Although the primary outcome of PFS was independently reviewed, outcomes such as quality of life and reporting of adverse events are likely to be biased. The trial was stopped early as the primary objective was met at the second interim

analysis for comparison of treatment groups and no final analysis was available at the time of this review. The study completion date is expected October 2017. This has the potential to overestimate the true treatment effect of carfilzomib.

Results

The ASPIRE trial met its primary endpoint at the second interim analysis demonstrating a statistically significant longer independently assessed PFS in favour of the carfilzomib group with a 31% reduction in the risk of progression or death during the study period. Key outcomes reported at the interim analysis are shown in Table 1. Since the time of the reporting of the second interim analysis, no updated final analysis has been reported. The median PFS was 26.3 vs. 17.6 months in the two groups respectively (HR=0.69; 95%CI: 0.57-0.83, p=0.0001). Median OS had not been reached in either group at the interim analysis, although results suggested a positive trend in favour of carfilzomib. Twenty-four month survival rates were 73.3% and 65.0% in the carfilzomib and control groups, respectively. A post-hoc subgroup analysis in patients over the age of 70 (≥70 years) demonstrated results consistent with the overall population; the median PFS was 23.8 versus 16.0 months in the carfilzomib and control groups, respectively (HR=0.739, p=0.0521).[11] For this subgroup, there was no difference in OS, however, data were not yet mature.[1] Secondary endpoints were to be tested in a sequential approach; as OS did not cross the pre-specified boundary for superiority at the interim analysis, other secondary endpoints (i.e. ORR, HrQoL) were not formally tested. Therefore, all of the p-values reported are for descriptive purposes only and should be interpreted with caution. In the carfilzomib compared to control group, higher QLQ-C30 Global Health Status/HrQoL scores were reported over 18 cycles of treatment. The percentage of responders (to treatment) and improvement in score from baseline within treatment groups were in favour of the carfilzomib group.

Six treatment related deaths (occurring up to 30 days after the last dose of study treatment) occurred in the carfilzomib group and eight in the control group. Grade 3 or 4 adverse events occurred in more patients in the carfilzomib compared to the control group. Adverse events of interest included cardiac/thrombosis disorders and acute renal failure. Rates of peripheral neuropathy were similar between groups. Serious adverse events occurred in 59.9% and 54.0% of patients in the carfilzomib and control groups, respectively. In the subgroup of patients ≥70 years, adverse events of grade ≥3 that occurred >5% more frequently in the carfilzomib group compared to the control group, included: neutropenia (36.9% versus 23.2%), thrombocytopenia (20.4% versus 15.2%), hypokalemia (15.5% versus 6.3%),[11] and cardiac failure (8.7% versus 1.8%).[3]

Table 1: Key efficacy and harms outcomes reported at the primary analysis for the ASPIRE trial comparing carfilzomib in combination with lenalidomide plus dexamethasone vs. lenalidomide plus dexamethasone in patients with relapsed multiple myeloma[2]

Efficacy outcomes[**]					
Analysis date	**Study arms**	**OS, median (months)**	**PFS, median (months)**	**ORR**	**HrQoL[12]**
Interim analysis (June, 2014)	Carfilzomib, n=396 Control, n=396	Not reached Not reached HR=0.79	26.3 17.6 HR=0.69	87.1% 66.7%	EORTC QLQ-C30C LSM difference at cycle 12 (5.56; 95%CI: 2.42-8.71)[%], MCID was not reached at cycle 3, 6, and 18.

Efficacy outcomes*^					
Analysis date	**Study arms**	**OS, median (months)**	**PFS, median (months)**	**ORR**	**HrQoL[12]**
		95%CI: 0.63-0.99 p=0.04 *Prespecified stopping boundary of p = 0.0051 was not crossed, therefore not significant	95%CI: 0.57-0.83 p=0.0001	OR=3.472 95%CI: 2.41-5.00 p<0.0001 *Not significant given that OS did not meet its stopping boundary in the sequential analysis	Improved GHS in the carfilzomib group as compared with the control group, as indicated with higher QLQ-C30 GHS/QoL scores over 18 cycles of treatment p<0.001 *Not significant given that OS did not meet its stopping boundary in the sequential analysis

Harms Outcomes, n (%)		
	Carfilzomib, n=392	**Control, n=389**
Treatment related Deaths	6 (1.5)	8 (2.1)
Grade 3/4 AEs		
Overall Grade 3/4 AEs	**83.7%**	**80.7%**
Cardiac failure	15 (3.8)	7 (1.8)
Deep vein thrombosis	7 (1.8)	4 (1.0)
Ischemic heart disease	13 (3.3)	8 (2.1)
Pulmonary embolism	12 (3.1)	9 (2.3)
Dyspnea	11 (2.8)	7 (1.8)
Acute renal failure	13 (3.3)	12 (3.1)
Neutropenia	116 (29.6)	103 (26.5)
Thrombocytopenia	65 (16.6)	48 (12.3)
Peripheral neuropathy	10 (2.6)	12 (3.1)
SAEs[8]	235 (59.9)	210 (54.0)
WDAEs[8]	102 (26.0)	98 (25.2)

AE = adverse events; **CI** = confidence interval; **EORTC QLQ-C30** = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; **GHS** = global health status; **HR** = hazard ratio; **HrQoL** = health-related quality of life; **LSM** = least-squares mean; **MCID** = minimal clinically important difference; **OR** = odds ratio; **ORR** = overall response rate; **OS** = overall survival; **PFS** = progression free survival; **SAE** = serious adverse event; **WDAE** = withdrawal due to adverse event

*HR/OR <1 favours carfilzomib

^ Secondary endpoints were tested in a sequential approach, as OS did not cross the pre-specified boundary at the interim analysis, other secondary endpoints (i.e. ORR, HrQoL) were not formally tested and therefore, all of the p-values reported are for descriptive purposes only and should be interpreted with caution.

%Minimal clinically important difference was ≥5 points for EORTC QLQ-C30 between-group differences

Table 2. Assessment of generalizability of evidence for carfilzomib in multiple myeloma

Domain	Factor	Evidence	Generalizability Question	CGP Assessment
Population	Current maintenance therapy post stem cell transplant	PAG is seeking information on the generalizability of the trial results to patients who are on maintenance therapy with bortezomib or lenalidomide post stem cell transplant.	Do trial results apply to patients who are on maintenance therapy with bortezomib or lenalidomide?	This study was designed and accrued before maintenance therapy was common. How maintenance therapy would alter outcome is uncertain.
	Recommended dose adjustments not reflected in clinical practice	The trial protocol recommends maintaining dose for weight changes of less than 20%. PAG noted that this is different than standard practice with other chemotherapy where dose is adjusted for weight changes of more than 5% in each cycle.	Do trial results apply in Canadian clinical practice, where patients have dose adjustments for weight changes of more than 5% in each cycle?	Given the absence of clear scientific rationale to restrict dose adjustments to ±20% body weight, the CGP concluded that dose adjustments for carfilzomib be conducted as per provincial guidelines.
	Renal impairment	The trial excluded patients with renal impairment (creatinine clearance [CrCL] < 50 mL/min).	Does the exclusion of patients with renal impairment limit the interpretation of the trial results with respect to the target population?	Although the study limited enrollment to patients with a CrCl of ≥ 50 ml/min, use in patients with renal impairment would be a reasonable consideration. Carfilzomib is not renally excreted, and therefore, adding this drug to dose-adjusted lenalidomide would be appropriate.
	Age	Given that the median age of patients was 64 years with 50.4% of patients between the ages of 18 and 64 years, the Clinical Guidance Panel noted that this age group is not reflective of the clinical population which is older. There were no adjustments for starting dose by age.	Do trial results apply to an older population (i.e. 70 years and older)?	Based on the available evidence, the Clinical Guidance Panel concluded that although the number of patients over the age of 70 included in this trial is small, the magnitude of benefit is similar to patients under 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

Domain	Factor	Evidence	Generalizability Question	CGP Assessment
		A post-hoc analysis was conducted on patients from the ASPIRE trial to compare outcomes based on age (≥70 years). In total, 26% (103/396) and 29% (115/396) patients in the carfilzomib and control groups, respectively, were 70 years of age or older. Median treatment duration was 97.0 weeks for patients <70 years and was 74.0 weeks for patients ≥70 years. PFS was improved for patients treated with carfilzomib compared with control, with a 9 and 8 month improvement in PFS for the ITT population and patients ≥70 years. The median PFS for ITT population was 26.3 versus 17.6 months in the carfilzomib and control groups, respectively (HR=0.69 95%CI: 0.57-0.83, p=0.0001). Similarly, the median PFS for patients ≥70 years was 23.8 months versus 16.0 months in the carfilzomib and control groups, respectively (HR=0.739 95%CI 0.513-1.065, p=0.0521). The median duration of treatment of carfilzomib was 88 and 74 weeks for the ITT population and patients ≥70 years, respectively. Analyses of the patients aged 70 or older showed no OS difference between the treatment arms at this time. Subgroup OS data must however be interpreted with caution bearing in mind that OS data remain immature (42% information fraction) and the lack of power for comparisons of subgroups. Following a request for additional information, the submitter reported for treatment-emergent grade 3 or higher events in patients 70 years or older, there was a higher rate of neutropenia in the carfilzomib group and a lower rate of neutropenia in the control group when compared to the broader population. A higher rate of hypertension was also seen in the carfilzomib group in patients 70 years or older compared to the broader population. Similar rates to the broader population were seen for anemia, thrombocytopenia, cardiac or thrombosis disorders, and peripheral neuropathy. Palumbo et al (2015) reported adverse events of grade ≥3 that occurred >5% more frequently in the carfilzomib group compared to the control group in patients ≥70 years, included: neutropenia (36.9% versus 23.2%), thrombocytopenia (20.4% versus 15.2%), and hypokalemia (15.5% versus 6.3%). A Medscape Medical News release referencing Palumbo et al, reported a higher rate of grade ≥3 cardiac failure in the carfilzomib group compared to the control group for patients ≥70 years (8.7% vs 1.8%). Although the Medscape Medical News referenced Palumbo et al, the rate on cardiac failure was not reported in the abstract.		

Domain	Factor	Evidence	Generalizability Question	CGP Assessment
	Performance Status	Overall, 90.5% of patients had an ECOG PS of 0 or 1. Additionally, 10.1% and 8.8% of patients in the carfilzomib vs. lenalidomide/dexamethasone groups, respectively had an ECOG PS 2.	Do trial results apply to patients with an ECOG PS of 2 or great?	While data on the efficacy and safety of using carfilzomib in patients with an ECOG PS of >2 was not available, the CGP agreed that use of carfilzomib in this population may be appropriate. Given the data available and the manageable toxicity profile of carfilzomib/len/dex, 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.
Intervention	Carfilzomib beyond 18 cycles	Carfilzomib's product monograph indicates "Treatment may be continued until disease progression or until unacceptable toxicity occurs." Carfilzomib was discontinued after cycle 18 in the ASPIRE trial.	Do trial results apply to treatment with carfilzomib until disease progression? Beyond 18 cycles? Beyond disease progression?	The CGP concluded that there is no evidence of benefit using carfilzomib beyond cycle 18 when combined with lenalidomide and dexamethasone.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment
Outcomes	Surrogate Outcome	The primary outcome was progression-free survival (PFS).	Is PFS a validated surrogate for overall survival in relapsed refractory multiple myeloma?	While evidence is not available to verify the surrogacy of PFS for OS in multiple myeloma, the CGP agreed that PFS is an endpoint that is accepted within the clinical community for multiple myeloma and is a reasonable surrogate for OS. 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.

2.1.4 Comparison with Other Literature

Relevant literature identified jointly by the pCODR Clinical Guidance Panel and Methods Team and providing supporting information to the systematic review is summarized below. This information has not been systematically reviewed.

The pCODR Clinical Guidance Panel (CGP) identified cardiac related toxicities as emerging toxicities of concern with the use of carfilzomib. Based on this, relevant literature and regulatory information was searched.

The Canadian product monograph contains warnings and precautions, specifically: cardiac toxicities, pulmonary toxicities, hepatic failure, thrombotic microangiopathy, posterior reversible encephalopathy syndrome, hemorrhage, and venous thrombosis.[13]

The US Food and Drug Administration (FDA) has put out warnings and precautions for the following: cardiac toxicities including cardiac failure and myocardial infarction with fatal outcome, and myocardial ischemia; acute renal failure; tumor lysis syndrome; pulmonary toxicity including acute respiratory distress syndrome, acute respiratory failure, and acute diffuse infiltrative pulmonary disease; pulmonary hypertension; dyspnea; hypertension including hypertensive crisis; venous thrombosis; infusion reactions; thrombocytopenia; hepatic toxicity and hepatic failure; thrombotic thrombocytopenic purpura/hemolytic uremic syndrome; posterior reversible encephalopathy syndrome; embryo-fetal toxicity.[14]

As part of post-marketing requirements by the FDA, a randomized clinical trial is being conducted in patients receiving carfilzomib to identify and characterize the cardiac toxicities associated with carfilzomib. This is a cardiac sub-trial within the ongoing ENDEAVOR trial to identify and characterize cardiac and pulmonary toxicities.[15] The ENDEAVOR trial did not fit the inclusion criteria of this systematic review as carfilzomib was in combination with dexamethasone alone (no lenalidomide). The ENDEAVOR trial was an open-label, phase 3 randomized trial to evaluate the efficacy and safety of carfilzomib plus dexamethasone compared with bortezomib plus dexamethasone in patients with multiple myeloma whose disease had relapsed after one to three prior treatments. The study randomized 929 patients into carfilzomib plus dexamethasone group (n=464) and bortezomib plus dexamethasone (n=465).[16]

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.

Cardiac arrhythmias were reported in three patients in each arm. There was a higher incidence of cardiac failure (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 3.

Table 3. Treatment-emergent adverse events in the cardiopulmonary safety evaluable subgroup

Onyx Specific Search Strategy Preferred Term	Bortezomib + Dexamethasone N = 74, n (%)	Carfilzomib + Dexamethasone N = 74, n (%)
Cardiac Arrhythmias (SMQN)	3 (4.1)	3 (4.1)
Atrial fibrillation	1 (1.4)	1 (1.4)
Extrasystoles	0	2 (2.7)
Sinus bradycardia	0	1 (1.4)
Tachyarrhythmia	1 (1.4)	0
Ventricular arrhythmia	1 (1.4)	0
Cardiac failure (SMQN)	3 (4.1)	8 (10.8)
Ejection fraction decreased	2 (2.7)	4 (5.4)
Cardiac failure	1 (1.4)	3 (4.1)
Cardiac failure acute	0	1 (1.4)
Cardiac failure chronic	0	1 (1.4)
Right ventricular failure	1 (1.4)	0
Ischaemic Heart Disease (SMQN)	2 (2.7)	0
Acute myocardial infarction	1 (1.4)	0
Stress cardiomyopathy	1 (1.4)	0

SMQN = Standardised 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.
Adverse events were coded using MedDRA version 15.1. Subjects were counted only once for each Onyx specific search strategy and each preferred term.

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.

2.1.5 Summary of Supplemental Questions

No supplemental questions were identified for this submission.

2.1.6 Other Considerations

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 travel, exercise, volunteer, conduct household chores, fulfill family obligations, and spend time with family. Access to effective treatment for myeloma and improvement of quality of life were noted as very important for the majority of respondents. Dexamethasone and bortezomib were treatments used by many patients; other treatment included: lenalidomide, autologus stem cell transplant, melphalan, cyclophosphamide, thalidomide, and pomalidomide. Most patients experienced fatigue with treatment for myeloma; other treatment side effects included: neuropathy, pain, insomnia, stomach issues, nausea, shortness of breath, confusion, diarrhea, constipation, and skin rashes. According to Myeloma Canada, the majority of patients who have used carfilzomib rated their quality of life while taking carfilzomib between "3- *neither poor nor excellent*" to "5 - *excellent."* Common side effects experienced with carfilzomib included nausea, fever, pneumonia, and diarrhea. Myeloma Canada reported that the majority of respondents were willing to tolerate the side effects experienced with carfilzomib.

PAG Input

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:

- Indication creep into first-line treatment and for patients who have progressed on bortezomib or lenalidomide plus dexamethasone
- 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
- Intravenous infusion that is an add-on to current oral treatment
- Large prevalent patient population eligible for treatment

2.2 Interpretation and Guidance

Burden of Illness and Need:

In 2015, an estimated 2,700 patients were diagnosed with myeloma, and 1400 patients died of the disease.[4] 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. Finding novel therapies that can improve life expectancy is a continued need. Using newer chemotherapies in combination such as carfilzomib, lenalidomide and dexamethasone, may lead to improvement in outcomes, as demonstrated in this review.[2] This is a novel combination, and the first regimen to be compared with the standard second-line therapy of lenalidomide and dexamethasone, in the relapsed setting.

Effectiveness:

Progression-free Survival (PFS)—Primary Outcome:

At a pre-specified checkpoint, the median progression free survival favored the combination of carfilzomib, lenalidomide and dexamethasone compared to lenalidomide and dexamethasone (26.3 versus 17.6 months, respectively). This benefit was seen across subgroups. The absolute magnitude of benefit was 8.7 months, and would be considered clinically significant improvement based on the HR of 0.69 (CI: 0.57-0.83, p=0.0001).

Overall Survival (OS):

Although the study reports an overall survival benefit, the median OS had not been reached in either arm, and the analysis reported was not at a pre-specified checkpoint. Consequently, the data have not sufficiently matured to draw conclusions with respect to a survival benefit. However, a trend is noted favoring the carfilzomib, lenalidomide, and dexamethasone arm.

Quality of Life (QOL) analysis:

Health related quality of life data clearly shows no impairment in QOL in the carfilzomib, lenalidomide, and dexamethasone arm, compared to lenalidomide and dexamethasone. Whether the carfilzomib arm is associated with an improvement in QOL is uncertain. The minimal clinically important difference was met at the 12 week QOL assessment, and was not reached at all other time points. Bias in the unblinded randomization, and low reporting rates in the control arm later in the study confound the results. The consistently equal responses throughout the other timepoints of therapy would suggest the quality of life at the least remains the same in both arms of the ASPIRE trial.

Safety:

Toxicity:

Serious adverse events (SAE), grade 3 or higher, were similar in the carfilzomib arm compared to the control arm (59.9% versus 54%). Higher rates of grade three or higher AE`s for pneumonia, hypokalemia, and hypertension are noted in the carfilzomib group compared with the control group, but the clinical significance of these differences are uncertain. There was no major difference in peripheral neuropathy or secondary primary malignancies reported between the two groups. The rate of venous and arterial thrombotic events are slightly higher in the carfilzomib group. Further follow-up will be necessary to determine the clinical significance of these differences.

Of particular interest is the rate of heart failure. The carfilzomib arm had a heart failure rate of 3.8% for grade 3 or greater events, compared to 1.8% in the lenalidomide and dexamethasone group. This rate of heart failure in patients treated with carfilzomib appear to be similar to results of the ENDEAVOR trial comparing, carfilzomib and dexamethasone, and bortezomib and dexamethasone.[17] It is notable that the ENDEAVOR trial did not fit the inclusion criteria of the current systematic review and a separate pCODR review would be required of the data within this trial to make a conclusion on the safety and efficacy of using carfilzomib and dexamethasone. 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. The significance of this is uncertain, and further data are necessary to determine the risk of cardiac toxicity with this regimen, particularly in the older patient population.[3]

Death:

The rate of treatment related deaths in both arms of the ASPIRE trial is similar (1.5% in the carfilzomib arm, and 2.1% in the control arm). Adding carfilzomib to lenalidomide does not significantly increase the rate of treatment related deaths.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to carfilzomib, lenalidomide and low-dose dexamethasone, compared with lenalidomide and low dose 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 control. The adverse event profiles were similar between the two groups. The current data also suggests that there may be an overall survival advantage, although the data needs time to mature, to clarify the magnitude of 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 was predominantly younger patients (median age 64 years old). Although the number of patients over the age of 70 included in this trial is small, the magnitude of benefit is similar to patients under the age of 70. 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.
- Although the study limited enrollment to patients with a CrCl of greater than or equal to 50 ml/min, use in patients with renal impairment would be a reasonable consideration.

Carfilzomib is not renally excreted, and therefore, adding this drug to dose-adjusted lenalidomide would be appropriate.

- There are no efficacy or safety data for using this regimen in patients with an 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 2 or greater may be appropriate, and this would be consistent with standard practice with other myeloma therapies.
- This study was designed and accrued before maintenance therapy was common. How maintenance therapy would alter outcome is uncertain.
- This regimen if for patients with relapsed disease. Further data are necessary to clarify the role of this regimen in the first line setting.
- Patients must not have had disease progression during treatment with bortezomib or if previously treated with lenalidomide and dexamethasone patients must not have
    - discontinued therapy because of adverse effects,
    - disease progression during the first 3 months of treatment, or
    - progression at any time during treatment if lenalidomide plus dexamethasone was their most recent treatment.
    - If patients have received maintenance therapy, but they are not excluded by these criteria, they would be eligible for carfilzomib, lenalidomide, dexamethasone.
- The CGP recommends standard dose adjustments for carfilzomib, as per provincial guidelines. There was no clear scientific rationale to restrict dose adjustments to plus or minus 20% body weight.
- There is no evidence of benefit using carfilzomib beyond cycle 18 when combined with lenalidomide and dexamethasone.

3 BACKGROUND CLINICAL INFORMATION

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

3.1 Description of the Condition

Multiple myeloma is an incurable plasma cell neoplasm that makes up 1.3% of all new cancers in Canada.[4] In 2015, it is estimated that 2700 Canadians will be diagnosed with myeloma, and 1400 patients will die of this disease. The median age at presentation is 69 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%.[5]

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.[7]

3.2 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.[6] 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.[7] 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.[18] 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.[19] More recently, Lenalidomide and dexamethasone as continuous therapy proved to be a better tolerated regimen with an improved overall survival compared to melphalan, prednisone and thalidomide.[20] 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.[7] 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.

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.[21] 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 vs. 9.4 months; HR 0.53, $p<0.0001$).[17] These benefits included patients previously treated with bortezomib. Further follow-up is necessary to determine if this translates to an overall survival advantage. Another study in the relapsed setting compared carfilzomib in combination with lenalidomide and dexamethasone, versus lenalidomide and dexamethasone.[12] This triplet therapy was associated with an improvement in progression free survival and overall survival. The efficacy and safety of this regimen will be the focus of this review.

3.3 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.

3.4 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.[17] 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 triplet therapy if chemotherapy-sensitive disease is demonstrated on the most recent line of therapy.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group provided input on carfilzomib in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma following one prior treatment failure.

Myeloma Canada conducted an online survey from September 16, 2015 to October 8, 2015. The survey was directed to myeloma patients and caregivers about the impact of myeloma on their lives and the effect of treatments on their myeloma. It included specific questions directed to patients who have used carfilzomib to treat their myeloma.

A total of 599 responded completed the survey: 559 from Canada, 39 from the United States, and 1 from New Zealand. Canadian respondents represented each province and the Yukon; there were no responses from Nunavut or the Northwest Territories. Among the 599 respondents, 463 were individuals living with myeloma and 136 were caregivers. A total of 46 respondents are using or had used carfilzomib.

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 travel, exercise, volunteer, conduct household chores, fulfill family obligations, and spend time with family. Access to effective treatment for myeloma and improvement of quality of life were noted as very important for the majority of respondents. Dexamethasone and bortezomib were treatments used by many patients; other treatment included: lenalidomide, autologus stem cell transplant, melphalan, cyclophosphamide, thalidomide, and pomalidomide. Most patients experienced fatigue with treatment for myeloma; other treatment side effects included: neuropathy, pain, insomnia, stomach issues, nausea, shortness of breath, confusion, diarrhea, constipation, and skin rashes. According to Myeloma Canada, the majority of patients who have used carfilzomib rated their quality of life while taking carfilzomib between "3- *neither poor nor excellent*" to "5 - *excellent."* Common side effects experienced with carfilzomib included nausea, fever, pneumonia, and diarrhea. Myeloma Canada reported that the majority of respondents were willing to tolerate the side effects experienced with carfilzomib.

Please see below for a summary of specific input received from the patient advocacy group. Quotes are reproduced as they appeared in the survey, 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.

4.1 Condition and Current Therapy Information

4.1.1 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. Other aspects of myeloma noted by Myeloma Canada included mood/emotional issues and stomach issues including diarrhea, nausea, gastrointestinal. The results collected from the respondents are reproduced below.

How important it is to control various aspects of myeloma? Respondents rated on a scale of 1-5.							
	1 - Not important	2	3	4	5 - Very important	N/A	Total
Infections	1.91% 10	2.49% 13	4.40% 23	6.50% 34	82.60% 432	2.10% 11	523
Kidney problems	2.52% 13	1.94% 10	4.26% 22	10.27% 53	77.33% 399	3.68% 19	516
Pain	1.16% 6	3.09% 16	7.35% 38	18.57% 96	67.50% 349	2.32% 12	517
Mobility	1.54% 8	1.93% 10	7.72% 40	19.88% 103	66.41% 344	2.51% 13	518
Neuropathy	1.37% 7	2.35% 12	7.63% 39	21.72% 111	64.58% 330	2.35% 12	511
Fatigue	0.58% 3	2.53% 13	10.70% 55	25.68% 132	59.14% 304	1.36% 7	514
Shortness of breath	1.95% 10	3.89% 20	11.67% 60	22.76% 117	57.20% 294	2.53% 13	514
N/A = not available							

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 travel, exercise, volunteer, conduct household chores, fulfill family obligations, and spend time with family.

How much symptoms associated with myeloma impact or limit day-to-day activity and quality of life? Respondents rated on a scale of 1-5.							
	1 - Not at all	2	3	4	5 - Significant impact	N/A	Total
Ability to work	8.38% 44	12.38% 65	14.29% 75	13.14% 69	39.24% 206	12.57% 66	525
Ability to travel	9.92% 52	15.84% 83	20.61% 108	23.66% 124	28.63% 150	1.34% 7	524
Ability to exercise	7.27% 38	17.59% 92	25.43% 133	24.67% 129	24.28% 127	0.76% 4	523
Ability to volunteer	13.33% 70	16.00% 84	22.67% 119	20.19% 106	20.19% 106	7.62% 40	525
Ability to conduct household chores	11.83% 62	20.61% 108	30.73% 161	19.47% 102	16.22% 85	1.15% 6	524
Ability to fulfill family obligations	15.27% 80	20.23% 106	28.63% 150	19.08% 100	14.50% 76	2.29% 12	524
Ability to spend time with family and friends	18.74% 98	22.94% 120	27.92% 146	16.44% 86	13.00% 68	0.96% 5	523
N/A = not available							

Myeloma Canada indicated the level of impact varies depending on how long the patient has been diagnosed, whether or not he or she has had treatment and whether symptoms are under control. Below were some of the key responses reported to help illustrate the impact:

> *"All of the above, if affected by MM, change the quality of life for both patient and caregiver."*

"I am presently in remission so am delighted to be doing as much as possible at his time."

"Things are always more significant post chemo."

4.1.2 Patients' Experiences with Current Therapy for Multiple Myeloma

According to Myeloma Canada, almost all respondents (97% out of 491 respondents) rated access to effective treatment for myeloma as "*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 (88% out of 509 respondents) rated this as "*5 - very important*." Most respondents (88% out of 508 respondents) reported that improvement of quality of life was a "*very important*" consideration with any treatment for myeloma.

According to Myeloma Canada, almost 20% of respondents (68 out of 349 respondents) reported hardships which included: delays in treatment, more treatment options needed, cost, and not able to access clinical trials. Side effects and fear of treatment were other hardship expressed by respondents (n=1, n=1 respectively). Myeloma Canada noted that most respondents (81% out of 349 respondents) indicated that they did not experience hardships, were not aware of hardships, or so far are not experiencing hardship in accessing treatment.

Other than carfilzomib, respondents (N=506) were asked to identify treatment used to treat their myeloma. Many respondents identified dexamethasone and bortezomib as treatment used to treat their myeloma. Other treatments included: lenalidomide, autologus stem cell transplant, melphalan, cyclophosphamide, thalidomide, and pomalidomide.

Other than carfilzomib, select treatments that have been used to treat myeloma. Respondents selected all that applied.

Treatment	%	# of Respondents
dexamethasone (Decadron®)	82%	413
bortezomib (Velcade®)	73%	370
lenalidomide (Revlimid®)	66%	332
autologus stem cell transplant	65%	327
melphalan (Alkeran®)	43%	220
cyclophosphamide (Cytoxan®)	41%	207
thalidomide (Thalidomid®)	22%	109
pomalidomide (Pomalyst®)	18%	89

Most respondents reported experiencing fatigue with treatment for myeloma. Other side effects experienced with treatment for myeloma included: neuropathy, pain, insomnia, stomach issues, nausea, shortness of breath, and confusion.

What side effects experienced with treatment for myeloma? Respondents selected all that applied.		
Side Effect	%	# of Respondents
Fatigue	89	447
Neuropathy	60	304
Pain	43	219
Insomnia	57	287
Stomach Issues	49	248
Nausea	48	240
Shortness of Breath	43	215
Confusion	32	164
Does not apply to me as I have yet to be treated	2	11
I don't know or can't remember	1	4

Additional side effects listed by respondents included: stomach issues (e.g., diarrhea, constipation) (n=32), and skin rashes (n=12).

4.1.3 Impact of Multiple Myeloma and Current Therapy on Caregivers

Among the 599 respondents, 136 were caregivers. Myeloma Canada noted that more than 136 respondents answered questions directed to caregivers and indicated that these respondents were assumed to be patients.

Myeloma Canada asked caregivers 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 respondents, some of which were patients, indicated their ability to travel was most affected, followed by ability to work, spend time with family and friends, volunteer, fulfill family obligations, exercise, and conduct household chores.

When asked about challenges caregivers face as a result of the side effect of treatment, respondents, some of which were patients (N=148), indicated having experienced emotional issues such as feelings of helplessness, anxiety/worry, stress and depression (n=55). Other respondents noted having experienced more chores around the home and less time to do their own things (n=22). Some commented on the challenge of dealing with the patient's mood swings (n=14).Other challenges included: tiredness/fatigue, work was affected, food preparation (i.e., patient would not eat, or required different meals, food smells were an issue), and financial burden. A total of 27 respondents indicated experiencing no challenges as a result of the side effect of treatments and 10 respondents replied N/A to the question.

Below are quotes expressed by caregivers:

"I get worn down with all the side effects. It never ends. I have to keep the records, ask the questions, fill the prescriptions, be alert to infections, ask for test results, chart the test results, go to peer group, delay vacations and give my life over to taking care of my spouse. I'm not complaining, but retirement wasn't meant to be like this. My spouse does what he can, and at times that isn't a lot. Our MM peer support groups gets me through and without it I would be less effective and my spouse would not be treated so well."

"Extra burden both financially and not being able to have a family quality of life . the longer the cancer the less support."

"The illness has caused serious damage and my husband is no longer able to help me around the house. The treatments has saved his life but the desease has altered the quality of life for the worst."

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Carfilzomib

[Among the patients who have no experience with carfilzomib, most respondents (82%; n= 431) indicated that it was "*extremely important*" that the treatment bring improvement in their physical condition (i.e., increase in energy, improve mobility, reduction of pain, improved resistance to infections) if they were to consider a new treatment for their myeloma. The majority of these respondents (90%; n=436) indicated that the expected benefit (i.e., lack of disease progression) of the treatment was "*extremely important*." Myeloma Canada reported that 87% of respondents (n=436) 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 (i.e., nausea, diarrhea, fever, shortness of breath, constipation, anemia, and neuropathy). A total of 10% of respondents indicated that they were willing to tolerate significant side effects, while 6% of respondents indicated that they were not willing to tolerate side effects (N=437).

According to Myeloma Canada, there were 46 respondents who are using or had used carfilzomib. Myeloma Canada noted that not all respondents who responded "yes" to using carfilzomib, answered all the questions related to the use of carfilzomib. It was reported that less than half patients who have used carfilzomib (45% out of 42 respondents) reported that carfilzomib was very effective in controlling their myeloma.

When asked to rate on a scale of 1-5 (where 1 =completely intolerable and 5=very tolerable), more than half patients who have used carfilzomib (57% out of 42 respondents) rated side effects of carfilzomib as 4 or 5. Common side effects experienced with carfilzomib were also rated below:

What are the common side effects experienced with carfilzomib? Respondents rated on a scale of 1-5.							
	1 - Completely intolerable	2	3	4	5 - Very tolerable	N/A	Total
Nausea	5.71% 2	0.00% 0	17.14% 6	22.86% 8	28.57% 10	25.71% 9	35
Fever	6.06% 2	6.06% 2	6.06% 2	15.15% 5	24.24% 8	42.42% 14	33
Pneumonia	8.82% 3	5.88% 2	5.88% 2	8.82% 3	20.59% 7	50.00% 17	34
Diarrhea	9.09% 3	9.09% 3	15.15% 5	15.15% 5	21.21% 7	30.30% 10	33
Shortness of breath	8.11% 3	10.81% 4	24.32% 9	10.81% 4	24.32% 9	21.62% 8	37
Neutropenia (low white blood cell count)	6.06% 2	12.12% 4	24.24% 8	24.24% 8	15.15% 5	18.18% 6	33
Anemia (low red blood cell count)	5.88% 2	11.76% 4	29.41% 10	32.35% 11	8.82% 3	11.76% 4	34
Thrombocytopenia (low platelet count)	8.57% 3	20.00% 7	17.14% 6	22.86% 8	14.29% 5	17.14% 6	35
Fatigue	5.13% 2	23.08% 9	33.33% 13	25.64% 10	7.69% 3	5.13% 2	39
N/A = not available							

According to Myeloma Canada, when respondents (N=42) were asked to rate on a scale of 1-5 (where 1=poor quality of life and 5 =excellent quality of life), the majority of patients who have used carfilzomib rated quality of life while taking carfilzomib as 3 or higher, while half of respondents rated quality of life while taking carfilzomib as 4 or higher.

When asked open-ended questions about how carfilzomib changes or is expected to change long-term health and wellbeing, or to include anything else about carfilzomib. Myeloma Canada reported that 49% (n=17) of respondents expressed that they have had a positive result with the treatment, of those respondents, two were able to follow the treatment with a stem cell transplant and one is no longer on treatment and the other is "now in remission". In addition, 31% (n=11) of respondents indicated their anticipation for extended life or remission, while 14% (n=5) were not sure yet.

One respondent stated the following:

"Carfilzomib has extended my life by approx. 15 months. These are 15 months that I would not have without this drug. This time was spent enjoying life to the fullest possible. Unfortunately, I have relapsed once again. Like all MM patients, I am now trying another drug combination, hoping it proves to be effective."

Some respondents also commented on the need for patient access to carfilzomib (n=5). There were a small number of respondents who commented on the administration (oral or injection vs infusion) (n=3).

Two respondents reported that they are no longer on the treatment, and two respondents reported that the treatment did not work. One respondent stopped treatment because of side effects.

Illustrative quotes provided by Myeloma Canada were the following:

"It made a huge difference in my life specially they had given me 1 month to live & now it's been over 3 years with this medication & still tolerating it extremely well and I recommend it to all myeloma patients."

> *"…The only issue is the twice weekly IV administration, however this is soon to change to once weekly which will help with QOL and ability to work/travel etc. At least the IV infusion is quick, only 10 minutes. So patients can be in an out within 1 hour is all goes well."*

4.3 Additional Information

N/A

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for carfilzomib (Kyprolis) for multiple myeloma. 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 CADTH website (www.cadth.ca/pcodr).

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:

- Indication creep into first-line treatment and for patients who have progressed on bortezomib or lenalidomide plus dexamethasone
- 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
- Intravenous infusion that is an add-on to current oral treatment
- Large prevalent patient population eligible for treatment

Please see below for more details.

5.1 Factors Related to Comparators

PAG noted that lenalidomide plus dexamethasone is the standard of care for previously treated multiple myeloma and is funded in all provinces.

5.2 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.

PAG noted that patients in the ASPIRE trial were previously treated with bortezomib or treated with lenalidomide plus dexamethasone but did not have disease progression. PAG is seeking clarity on the group of patients eligible for treatment with carfilzomib and information on the generalizability of the trial results to patients who are on maintenance therapy with bortezomib or lenalidomide post stem cell transplant.

PAG is seeking guidance on when patients would be deemed progressive on or refractory to bortezomib and be eligible for carfilzomib, as patients who progressed on bortezomib were excluded from the trial.

PAG noted that lenalidomide plus dexamethasone in first-line treatment for patients ineligible for stem cell transplant is undergoing pCODR review at the time of this PAG input. PAG indicated there will likely be interest from clinicians and patients to use carfilzomib for patients who have progressed on first-line treatment with lenalidomide

plus dexamethasone or upfront in the first-line setting as data is emerging for use of carfilzomib in first-line treatment, recognizing that data may not be available yet.

PAG also indicated that there may be interest to use carfilzomib monotherapy or use carfilzomib in combination with pomalidomide plus dexamethasone for patients who have progressed on lenalidomide plus dexamethasone. However, PAG recognizes that these treatment regimens would be out of scope of this review.

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.

5.3 Factors Related to Accessibility

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.

Also, the multiple changes in dosing (e.g. dose escalation after cycle 1, decrease frequency of doses after cycle 12, and different dose adjustment for weight changes) may be a challenge for implementation.

The manufacturer recommends maintaining dose for weight changes of less than 20%. PAG noted that this is different than standard practice with other chemotherapy where dose is adjusted for weight changes of more than 5% in each cycle. PAG is seeking further information on the dose adjustments and treatment discontinuation.

It was noted that carfilzomib is administered for 18 cycles while lenalidomide plus dexamethasone is administered until disease progression. This may cause confusion for treatment centers and patients.

In addition, the dosing schedule may be confusing for some patients, resulting in missed doses.

5.4 Factors Related to Dosing

The addition of carfilzomib to the current oral therapy 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.

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 add-on 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 the cost of bortezomib has been significantly reduced with generic products being available and bortezomib re-treatment would be less expensive than carfilzomib for treatment in the second-line and beyond.

5.5 Factors Related to Implementation Costs

As carfilzomib is an intravenous infusion that is an add-on to an oral treatment regimen, PAG noted that an intravenous infusion may not be as acceptable or as accessible geographically as oral therapy for some patients.

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.

5.6 Other Factors

The cost of carfilzomib will be a barrier to implementation.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of carfilzomib in combination with lenalidomide and dexamethasone, for the treatment of patients with multiple myeloma following at least one prior therapy.

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 below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 4. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Randomized controlled trials	Patients with multiple myeloma who have received at least one prior therapy **Subgroups:** Prior therapies Relapsed disease Prior transplant	Carfilzomib in combination with lenalidomide and dexamethasone	Regimens including the following drugs: Immunomodulatory Drugs (e.g. lenalidomide, thalidomide, pomalidomide) Proteasome Inhibitors (e.g. bortezomib) Chemotherapy (e.g. cyclophosphamide) Dexamethasone	**OS** **PFS** **HrQoL** **TTP** DOR ORR SAE **AE** WDAE Death **AEs of Interest:** Cardiac disorders (e.g. thrombosis) 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

* *Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

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 to Present) with in-process records & daily updates via Ovid; Embase (1974 to 2015 December 22) 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 May 5, 2016.

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), the European Society for Medical Oncology (ESMO) 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:

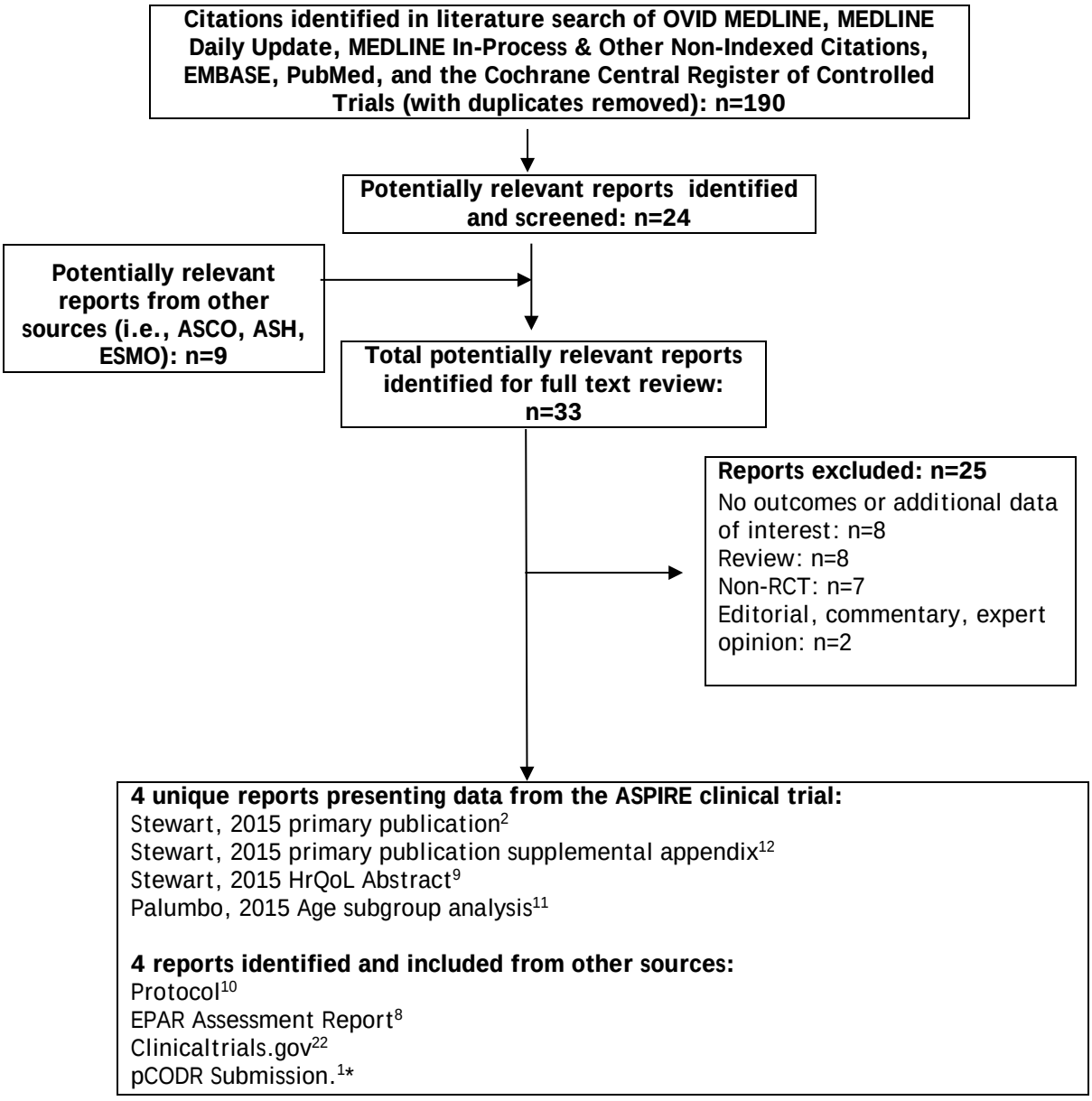
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental issues.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information, the interpretation of the systematic review and wrote guidance and conclusions for the report.
- The 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 24 potentially relevant reports identified for full text review, eight studies were included in the pCODR systematic review[1,2,8-12,22] and 25 studies were excluded. Reports were excluded because they were: reports that did not report outcomes or additional data of interest; reviews; not randomized controlled trials; or editorial/commentary/expert opinion.

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of Studies



**Note: Additional data related to the ASPIRE study were also obtained through requests to the Submitter by pCODR.*

6.3.2 Summary of Included Studies

One clinical trial, the ASPIRE trial, met the inclusion criteria for this systematic review. The key characteristics of this trial are summarized in Table 5 and specific features of trial quality are summarized in Table 6.

6.3.2.1 Detailed Trial Characteristics

Table 5. Summary of trial characteristics of the included study (ASPIRE)

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes[10,22]
NCT01080391 ASPIRE Open label phase 3 RCT Patient Enrollment: 14 July 2010 to 15 Mar 2012[22] Data cut-off date: 16 June 2014 Estimated Study Completion Date: October 2017 Randomized: n = 792 Treated: n = 781[12] Funded by: Onyx Pharmaceuticals	**Key Inclusion Criteria:** Adults with relapsed multiple myeloma and measurable disease who had received one to three prior treatments ECOG PS 0-2 Documented relapse or progressive disease on or after any regimen (subjects refractory to the most recent line of therapy are eligible)[10] Adequate hepatic, hematologic, and renal function (creatinine clearance, ≥50 ml per minute) at screening **Exclusion Criteria:** If previously treated with bortezomib, progression during treatment If previously treated with lenalidomide and dexamethasone: • Progression during the first 3 months of initiating treatment • Any progression during treatment if the len/dex regimen was the most recent line of therapy Discontinuation of previous lenalidomide or dexamethasone due to intolerance Note: patients who are intolerant to bortezomib are not excluded 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	**Intervention:** Carfilzomib + lenalidomide + low-dose dexamethasone **Comparator:** Lenalidomide + low-dose dexamethasone Carfilzomib in 10-minute infusion on days 1, 2, 8, 9, 15, and 16 (starting dose, 20 mg/m^2 on days 1 and 2 of cycle 1; target dose, 27 mg/m^2 thereafter) during cycles 1 through 12 and on days 1, 2, 15, and 16 during cycles 13 through 18, after which carfilzomib was discontinued Lenalidomide (25 mg) was given on days 1 through 21 Dexamethasone (40 mg) was administered on days 1, 8, 15, and 22 Lenalidomide and dexamethasone was continued beyond cycle 18 until withdrawal of consent, disease progression, or the occurrence of unacceptable toxic effects	**Primary:** PFS **Secondary:** OS, ORR^, DoR, DCR, HrQOL, safety **Exploratory:** Clinical benefit rate&, TTP, TTNT, HrQoL subscales

^Rate of overall response (partial response or better)
&Best response of minimal response or better
Abbreviations: **DCR** = disease control rate; **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; **TTNT** = time to next treatment; **TTP** = time to progression

a) Trials

One open label randomized controlled trial, ASPIRE, met the inclusion criteria of this systematic review.[2] ASPIRE was a phase III trial which randomized patients with relapsed multiple myeloma to carfilzomib with lenalidomide and dexamethasone or lenalidomide and dexamethasone alone. This trial was conducted in 129 centres in 20 countries located in North America (including Canada), Europe, and Israel. The ASPIRE study was terminated early as the primary objective was met at the interim analysis.

Key eligibility criteria for screened patients have been listed in Table 5. Briefly, patients with multiple myeloma were required to have relapsed or progressed on one to three prior treatments.[8] Other inclusion criteria included performance status (ECOG PS 0-2), and adequate hepatic, hematologic, and renal function. Patients with primary refractory disease were not eligible for the study; refractory to a therapy was defined as patients who met any of the following three criteria: 1) nonresponsive (< minimal response) to any regimen; progression during any regimen; or progression within 60 days of completion of any regimen.[1] Patients previously treated with bortezomib were permitted entry into the trial provided they did not have disease progression during treatment. However, patients with intolerance to bortezomib were allowed entry into the trial. Patients previously treated with lenalidomide and dexamethasone were permitted entry provided they did not progress during the first three months of therapy (90 days), or at any time on therapy if it was the last regimen prior to study entry, or discontinued due to intolerance.[8]

The ASPIRE trial randomized patients in a 1:1 ratio between two treatment groups with an interactive voice-response system. Central stratified randomization procedures were used, randomization was stratified by B_2 microglobulin levels, prior bortezomib exposure and prior lenalidomide exposure. Baseline patient characteristics are listed in Table 7.

The primary outcome was progression-free survival (PFS) defined as the time from randomization (using International Myeloma Working Group (IMWG) Uniform Response Criteria) or death. Disease assessment was performed on day 1 of each 28-day cycle. For patients who did not have disease progression during treatment, patients were followed for disease status and survival every 3 months for up to 1 year and for survival every 6 months thereafter. The hypothesis of the trial was that the addition of carfilzomib to lenalidomide and dexamethasone would increase PFS and is superior compared to lenalidomide and dexamethasone alone. The estimated sample size requirements for the trial was 780 patients (526 events) to provide 90% power, more detail is listed in Table 6.

Secondary outcomes included overall survival (OS), overall response rate (ORR), duration of response (DoR), disease control rate (DCR), health-related quality of life (HrQoL), and safety. Treatment response and disease progression were evaluated by local investigators and an independent review committee (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 Multiple Myeloma Module (QLQ-MY20).[9] 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 (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties).[23] 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 4.0.

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. An independent committee periodically reviewed unblinded safety data. Outcomes determined by the IRC

were the primary data source for analyses while outcomes based on the local investigators were supplemental secondary analyses.[10] The trial was designed by the first (Stewart AK), second (Rajkumar SV), next-to-last (Moreau P), and last (Palumbo A) authors and the sponsor (Onyx Pharmaceuticals). Data collection and analysis was performed by the sponsor.

Table 6: Selected quality features of the included ASPIRE trial comparing carfilzomib in combination with lenalidomide plus dexamethasone vs. lenalidomide plus dexamethasone in patients with relapsed multiple myeloma

Trial	Treatment vs. Comparator	Primary Outcome	Required Sample Size[10]	Sample Size	Randomization Method[10]	Allocation Concealment	Blinding	ITT analysis	Final Analysis	Early Termination	Ethics Approval
ASPIRE	CLd vs. Ld	PFS	780[A] patients required for 526 progression events to provide 90% power to detect a 25% reduction in the risk of disease progression or death (HR=0.75 , median PFS of 14.9 vs. 11.2 months) at a one-sided overall significance level of 0.025	396 vs. 396	Central IVRS, stratified using blocked scheme[B]	No	Open-label study Response and disease progression determined by IRC blinded and local investigator	Yes[C]	No	Yes	Yes

[A]Original design had the planned sample size of 700 subjects to achieve the required PFS events within 36 months of study initiation, as a result of the 1st interim analysis the sample size was increased[8]
[B]Stratified by B_2 microglobulin levels, prior bortezomib exposure, prior lenalidomide exposure
[C]Three analyses of progression-free survival were planned: 2 interim analyses and 1 final analysis. The first interim analysis occurred in December 2011 only for administrative purposes for blinded re-evaluation of sample size. The second interim analysis was planned when 80% of planned total events were observed. At this interim analysis, the IDMC recommended stopping the study for efficacy but to continue for safety and OS monitoring. If there was a significant between-group difference in PFS at the interim analysis, secondary endpoints were to be sequentially tested in the order of OS, ORR, and HrQoL.[8]

Abbreviations: **CLd** = carfilzomib + lenalidomide + dexamethasone; **HR** = hazard ratio; **HrQoL** = health-related quality of life; **IDMC** = Independent Data Monitoring Committee; **IRC** = Independent Review Committee; **IVRS** = Interactive Voice Recognition System; **ORR** = overall response rate; **OS** = overall survival; **PFS** = progression free survival; **Ld** = lenalidomide + dexamethasone

b) Populations

A total of 792 patients were randomized in the ASPIRE trial. Baseline characteristics were well balanced between the two groups, including age, gender, ECOG PS, high risk genetic mutations and baseline ISS stage III disease.[8] Geographic region included Europe (74.5%), North America (21.6%), and rest of world (3.9%). The median age of patients in the ASPIRE study was 64.0 years and 90.5% of patients had an ECOG PS of 0 or 1. The median time since diagnosis was 3.1 years in the ASPIRE trial which was also similar by treatment arm (range: 0.4-27.3).[12] Patients received a median of two previous regimens. Fifty-six percent of patients had prior transplant. Prior therapy received included bortezomib

(65.8%) and lenalidomide (19.8%).[8] Baseline characteristics including a breakdown of prior therapies are summarized in Table 7 and 8, respectively.

Table 7. Baseline Patient Characteristics of all randomized patients in the ASPIRE trial[12]

Characteristic	Carfilzomib n=396	Control n=396	Total (N=792)
Age			
Median (range), year	64.0 (38.0-87.0)	65.0 (31.0-91.0)	64.0 (31.0-91.0)
18-64, n (%)	211 (53.3)	188 (47.5)	399 (50.4)
65-74, n (%)	142 (35.9)	155 (39.1)	297 (37.5)
≥75, n (%)	43 (10.9)	53 (13.4)	96 (12.1)
Sex			
Male, n (%)	215 (54.3)	232 (58.6)	447 (56.4)
Race			
White	377 (95.2)	377 (95.2)	754 (95.2)
Black	12 (3.0)	11 (2.8)	23 (2.9)
Asian^	1 (0.3)	3 (0.8)	4 (0.5)
Other	6 (1.5)	5 (1.3)	11 (1.4)
ECOG PS			
0	165 (41.7)	175 (44.2)	340 (42.9)
1	191 (48.2)	186 (47.0)	377 (47.6)
2	40 (10.1)	35 (8.8)	75 (9.5)
Disease stage at initial diagnosis			
I or II	163 (41.2)	168 (42.4)	331 (41.8)
III	185 (46.7)	161 (40.7)	346 (43.7)
Unknown	48 (12.1)	67 (16.9)	115 (14.5)
Serum β_2-microglobulin			
<2.5 mg/liter	77 (19.4)	77 (19.4)	154 (19.4)
≥2.5 mg/liter	319 (80.6)	319 (80.6)	638 (80.6)
Cytogenetics at study entry			
High-risk+, n/N (%)	48/396 (12.1)	52/396 (13.1)	100/792 (12.6)
Presence of neuropathy			
No	252 (63.6)	259 (65.4)	511 (64.5)
Yes			
Grade 1	114 (28.8)	106 (26.8)	220 (27.8)
Grade ≥2	22 (5.6)	24 (6.1)	46 (5.8)
Missing Grade	8 (2.0)	7 (1.8)	15 (1.9)

^Includes Asian, Native Hawaiian, or other Pacific Islander
+The high-risk group consisted of patients with the genetic subtypes t(4;14), t(14;16), or deletion 17p in 60% or more of plasma cells based on central review of bone marrow sample obtained at study entry
Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status

Table 8. Prior Therapy Characteristics of all randomized patients in the ASPIRE trial[8]

	CRd (n = 396)	Rd (n = 396)	Total (N = 792)
Subjects with[a]			
Prior systemic therapy for multiple myeloma	396 (100.0%)	396 (100.0%)	792 (100.0%)
Prior transplant	217 (54.8%)	229 (57.8%)	446 (56.3%)
Prior radiotherapy for multiple myeloma	79 (19.9%)	90 (22.7%)	169 (21.3%)
Prior surgery for multiple myeloma	52 (13.1%)	44 (11.1%)	96 (12.1%)
Number of Prior Regimens			
N	396	396	792
Median (Min, Max)	2.0 (1, 4)	2.0 (1, 4)	2.0 (1, 4)
1	184 (46.5%)	157 (39.6%)	341 (43.1%)
2	120 (30.3%)	139 (35.1%)	259 (32.7%)
3	91 (23.0%)	99 (25.0%)	190 (24.0%)
4	1 (0.3%)	1 (0.3%)	2 (0.3%)
Number of Unique Anti-Myeloma Agents			
N	396	396	792
Median (Min, Max)	5.0 (1, 11)	5.0 (1, 15)	5.0 (1, 15)
Time Since Last Prior Regimen (Months)			
N	377	376	753
Median (Min, Max)	11.6 (0.0, 113.1)	10.7 (0.5, 243.4)	11.0 (0.0, 243.4)
Refractory to Last Prior Regimen	110 (27.8%)	119 (30.1%)	229 (28.9%)
Nonresponsive (< MR) to last prior regimen	48 (12.1%)	59 (14.9%)	107 (13.5%)
Progression during last prior regimen	46 (11.6%)	45 (11.4%)	91 (11.5%)
Progression within 60 days of completion of last prior regimen	44 (11.1%)	50 (12.6%)	94 (11.9%)
Refractory to			
Bortezomib in any prior regimen	60 (15.2%)	58 (14.6%)	118 (14.9%)
Nonresponsive (< MR) to any regimen	20 (5.1%)	27 (6.8%)	47 (5.9%)
Progression during any regimen[b]	20 (5.1%)	11 (2.8%)	31 (3.9%)
Progression within 60 days of completion of any regimen	32 (8.1%)	26 (6.6%)	58 (7.3%)
Lenalidomide in any prior regimen	29 (7.3%)	28 (7.1%)	57 (7.2%)
Bortezomib and an IMiD in any prior regimen	24 (6.1%)	27 (6.8%)	51 (6.4%)
Prior Therapy Received			
Bortezomib	261 (65.9%)	260 (65.7%)	521 (65.8%)
Lenalidomide	79 (19.9%)	78 (19.7%)	157 (19.8%)
Thalidomide	176 (44.4%)	171 (43.2%)	347 (43.8%)
Pomalidomide	0	0	0
IMiD	233 (58.8%)	229 (57.8%)	462 (58.3%)
Bortezomib and IMiD	146 (36.9%)	139 (35.1%)	285 (36.0%)
Corticosteroids	389 (98.2%)	387 (97.7%)	776 (98.0%)
Anthracycline	149 (37.6%)	136 (34.3%)	285 (36.0%)
Alkylators	340 (85.9%)	349 (88.1%)	689 (87.0%)
Received in Last Prior Regimen			
Bortezomib	194 (49.0%)	174 (43.9%)	368 (46.5%)
Lenalidomide	49 (12.4%)	50 (12.6%)	99 (12.5%)

[a]Subjects could be counted in more than 1 category
[b]Although these subjects were reported as having progression during a bortezomib-containing regimen, the progression date occurred after bortezomib had been stopped and all these subjects were eligible for enrollment
CRd = carfilzomib/Revlimid (lenalidomide)/dexamethasone arm; **IMiD** = immunomodulatory drug (thalidomide, lenalidomide, pomalidomide); **ITT** = intention-to-treat; **MR** = minimal response; **Rd** = Revlimid (lenalidomide)/dexamethasone arm

c) Interventions

Of the 792 patients in the ASPIRE trial, 392 patients and 389 patients received the allocated intervention in the carfilzomib and control arms, respectively. Carfilzomib was administered on day 1, 2, 8, 9, 15 and 16 (starting dose of 20 mg/m^2 on days 1 and 2 of cycle 1; target dose of 27 mg/m^2 thereafter) during cycles 1 through 12 and on days 1, 2, 15, and 16 cycles 13 through 18, after which carfilzomib was discontinued. The dose of carfilzomib was escalated to the target dose of 27 mg/m^2 in 382 patients (97.4%).[8] In both groups, lenalidomide was administered at 25 mg on days 1 through 21 and dexamethasone at 40 mg was administered on days 1, 8, 15, and 22. Beyond cycle 18, patients in both groups only received lenalidomide and dexamethasone until withdrawal of consent, disease progression, or the occurrence of unacceptable toxic effects. Pre-treatment and post-treatment intravenous hydration was required during cycle 1. Patients also received protocol-specified, required concomitant medications of antiviral and antithrombotic prophylaxis. Optional prophylaxis medications were allowed (i.e. oral thrush, diarrhea). Palliative radiation for pain management was permitted.[10]

Does adjustments did not need to be made for weight gains/losses of ≤20%.[10] Dose reduction for carfilzomib and lenalidomide for toxicity management were allowed in specified decrements. For the starting dose of 20 mg/m^2 of carfilzomib, the dose could be reduced to 15 mg/m^2 then 11 mg/m^2. For the target dose of 27 mg/m^2 of carfilzomib, the dose could be reduced to 20 mg/m^2, 15 mg/m^2, and then 11 mg/m^2. The lenalidomide dose reduction protocol was 15 mg, 10 mg, and then 5 mg. In addition to dose reductions, carfilzomib and lenalidomide could be interrupted in the event of a treatment-related toxicity. Provided a reduced dose is well tolerated, at the investigator's discretion, patients could be re-challenged with the dose level prior to reduction at the start of the next cycle. Details of extent of exposure to treatment are in Table 9.

Table 9: Extent of exposure to treatment[8]

	Carfilzomib (n=392)			Control (n=389)	
	Carfilzomib	Lenalidomide	Dexamethasone	Lenalidomide	Dexamethasone
Treatment duration (weeks)[2]					
	88.0 weeks			57.0 weeks	
Median	70.29	85.00	79.36	56.21	47.86
Range	0.1-91.4	0.1-184.0	0.1-177.1	0.4-200.7	0.1-200.1
# of cycles^ (median)	18.0	21.0	20.0	14.0	12.0
Relative dose intensity (%)					
Median	96.22	91.03	94.54	91.90	95.39
Range	35.2-112.6	19.4-101.3	30.7-103.3	19.3-101.2	32.1-112.0
Subjects on treatment in each cycle (%)					
Cycle 6	86.5	87.5	86.2	79.2	76.9
Cycle 12	71.2	68.9	68.1	57.8	53.7
Cycle 18	61.0	58.7	57.7	42.2	38.8
Cycle 24	0	45.2	41.8	31.6	29.0
Dose modifications,[1] n (%)					
Any dose modifications	273 (69.6)	301 (76.8)	255 (65.1)	264 (67.9)	203 (52.2)
Dose reductions	53 (13.5)	179 (45.7)	150 (38.3)	165 (42.4)	129 (33.2)
Dose interruptions	9 (2.3)	NA	NA	NA	NA
Dose increase to prior level	382 (97.4)	NA	NA	NA	NA

^Number of cycles started; NA = not available
Notes: Patients were still on protocol treatment as long as at least one of the specified drugs in the regimen is being administered.

d) *Patient Disposition*

The duration of the study was 3 years and 11 months.[8] Four patients in the carfilzomib group and seven patients in the control group did not receive the study intervention. As of the data cut-off date (June 2014), 118 patients (30.1%) and 86 (22.1%) of patients in the carfilzomib and control groups, respectively were continuing treatment. [8]

A total of 305 (38.1%) patients had died at the time of the data cut-off.[8] Thirty (7.7%) and 33 (8.5%) patients in the carfilzomib and control groups, respectively died during treatment or within 30 days after receiving the last dose of study treatment. Discontinuation rates were 69.2% and 76.5% in the carfilzomib and control groups, respectively, with disease progression being the most common reason for discontinuation in both treatment groups. As seen in Table 10, 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 control with the exception of protocol violation and other reasons.

Table 10. Patient Disposition at the time of primary data analysis[8]

Category	Carfilzomib, n (%)	Control, n (%)
Randomized	396 (100)	396 (100)
Received treatment, n (%)	392 (98.9)	389 (98.2)
Efficacy (ITT) analysis, n (%)	396 (100)	396 (100)
Safety analysis, n (%)	392 (98.9)	389 (98.2)
Discontinued treatment, n (%)	274 (69.2)	303 (76.5)
• Disease progression	156 (39.4)	195 (49.2)
• AEs	60 (15.2)	69 (17.4)
• Withdrew consent	7 (1.77)	11 (2.78)
• Protocol violation	2 (0.50)	1 (0.25)
• Other[%]	49 (12.4)	27 (6.81)
• Lost to follow-up[2]	3 (0.76)	4 (1.0)

[%]Other reasons included 'patient decision/too frequent visits but agree to follow-up', 'completed therapy (18 cycles of carfilzomib)/good response to study treatment/transplant/new therapy', and 'multiple adverse events/poor quality of life'. Where multiple adverse events denotes that the site could not attribute a reason to one particular adverse event. The most common other reason in both treatment arms was 'patient decision/too frequent visits but agree to follow-up', reported in 24 and 16 patients in the carfilzomib and control arms, respectively.

e) *Limitations/Sources of Bias*

- The trial was open label and therefore investigators and patients were not blinded to treatment assignment. Given that carfilzomib is administered intravenously, blinding was not conducted. 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). Patients in the carfilzomib arm may have been more likely to adhere to experimental therapy and investigators may have been more likely to discontinue treatment in the standard therapy arm.
- Furthermore, in open-label trials, the assessment of subjective measures, such as HrQoL, and the reporting of adverse events are likely to be biased. Although survival is 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.

- The trial was terminated early as the primary objective was met at the interim analysis. This has the potential to overestimate the true treatment effect of carfilzomib compared to the control.
- Pre-specified secondary endpoints were to be tested sequentially; OS did not cross the pre-specified boundary at the interim analysis, other secondary endpoints (e.g. ORR, HrQoL) were not formally tested. The p-values reported were noted for descriptive purposely only.
- 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.
- In addition to concerns around allocation concealment, the validity of HrQoL outcomes in the ASPIRE trial was impaired by the lower completion rates of questions in the control than the carfilzomib group at each cycle. Thus, the lower compliance to HrQoL questionnaires in the control group could bias results in favour of carfilzomib.
- A total of four patients (two in each group) had an important protocol deviation which resulted in exclusion from the per protocol population. A total of 151 (19.1%) patients had other important protocol deviation including, in order of frequency: deviations to drug administration routine, corticosteroids for non-malignant conditions at a given dose were not permitted per protocol, remained on study after confirmed disease progression, randomized to the wrong strata and analyzed according to their assigned stratum, deviations related to inclusion/exclusion criteria, received higher than prescribed doses of dexamethasone, and continued to receive carfilzomib after cycle 18, day 16. It is not clear what the magnitude or direction of the bias may have been due to these protocol deviations.
- Five amendments to the protocol occurred over the course of the trial.[8] After 235 patients (30%) were enrolled a minor administrative amendment occurred: reordering secondary endpoints and clarifications for disease outcome grading by investigators to be consistent within the protocol in the protocol synopsis, statistical methods, and efficacy analysis. Another clarification amendment occurred which applied to the remaining 70% of patients, this included increasing the window for demonstrating measurable disease by central laboratory analyses to account for challenges in the logistics of trans-country sample shipment followed by analysis and review. Additional changes included clarification of definitions, techniques, and criteria. 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.
- 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 reported at the primary interim analysis (June 2014) are shown in Table 1. Secondary endpoints were tested in a sequential approach, as OS did not cross the pre-specified boundary at the interim analysis, other secondary endpoints (i.e. ORR, HrQoL) were not formally tested and therefore, all of the p-values reported are for descriptive purposes only and should be interpreted with caution.

Table 1: Key efficacy and harms outcomes reported at the primary analysis for the ASPIRE trial comparing carfilzomib in combination with lenalidomide plus dexamethasone vs. lenalidomide plus dexamethasone in patients with relapsed multiple myeloma[2]

Efficacy outcomes*					
Analysis date	**Study arms**	**OS, median (months)**	**PFS, median (months)**	**ORR**	**HrQoL[12]**
Interim analysis (June, 2014)	Carfilzomib, n=396 Control, n=396	Not reached Not reached HR=0.79 95%CI: 0.63-0.99 p=0.04 * Prespecified stopping boundary of p = 0.0051 was not crossed, therefore not significant	26.3 17.6 HR=0.69 95%CI: 0.57-0.83 p=0.0001	87.1% 66.7% OR=3.472 95%CI: 2.41-5.00 p<0.0001 *Not significant given that OS did not meet its stopping boundary in the sequential analysis	EORTC QLQ-C30C LSM difference at cycle 12 (5.56; 95%CI: 2.42-8.71)%, MCID was not reached at cycle 3, 6, and 18. Improved GHS in the carfilzomib group as compared with the control group, as indicated with higher QLQ-C30 GHS/QoL scores over 18 cycles of treatment p<0.001 *Not significant given that OS did not meet its stopping boundary in the sequential analysis

Harms Outcomes, n (%)		
	Carfilzomib, n=392	**Control, n=389**
Treatment related Deaths	6 (1.5)	8 (2.1)
Grade 3/4 AEs		
Overall Grade 3/4 AE's	83.7%	80.7%
Cardiac failure	15 (3.8)	7 (1.8)
Deep vein thrombosis	7 (1.8)	4 (1.0)
Ischemic heart disease	13 (3.3)	8 (2.1)
Pulmonary embolism	12 (3.1)	9 (2.3)
Dyspnea	11 (2.8)	7 (1.8)
Acute renal failure	13 (3.3)	12 (3.1)
Neutropenia	116 (29.6)	103 (26.5)
Thrombocytopenia	65 (16.6)	48 (12.3)
Peripheral neuropathy	10 (2.6)	12 (3.1)
SAEs[8]	235 (59.9)	210 (54.0)
WDAEs[8]	102 (26.0)	98 (25.2)

AE = adverse events; **CI** = confidence interval; **EORTC QLQ-C30** = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; **GHS** = global health status; **HR** = hazard ratio; **HrQoL** = health-related quality of life; **LSM** = least-squares mean; **MCID** = minimal clinically important difference; **OR** = odds ratio; **ORR** = overall response rate; **OS** = overall survival; **PFS** = progression free survival; **SAE** = serious adverse event; **WDAE** = withdrawal due to adverse event

*HR/OR <1 favours carfilzomib

%Minimal clinically important difference was ≥5 points for EORTC QLQ-C30 between-group differences

a) Efficacy Outcomes

In the ASPIRE study, the median duration of follow-up among surviving patients was 32.3 months in the carfilzomib group and 31.5 months in the control group.

Overall Survival

Overall survival (OS) was defined as the duration from the date of randomization to the date of death due to any cause. As of the data cut-off, a total of 305 (38.5%) deaths occurred (143 in the carfilzomib group and 162 in the control group) of the 510 pre-specified events required for the final analysis. OS did not cross the pre-specified early stopping boundary for the interim analysis, however, results suggested a positive trend in favour of carfilzomib.[8] Twenty-four month survival rates were 73.3% and 65.0% in the carfilzomib and control groups, respectively. At 12, 18, 24, 30 and 36 months, there was a higher survival rate for the carfilzomib group compared with the control group; however, the median was not reached on either arm and these additional analyses were not pre-specified.[1] At the updated 120 days safety data-cut off, survival rates at 39 and 42 months were higher in the carfilzomib compared to control group.[1] According to the European public assessment report (EPAR) for carfilzomib, although the interim analysis suggest a trend in OS benefit, the data are still immature. In addition, the subgroup analyses of OS did not reveal an unexpected results, considering the limited sample size of some subsets.[8] The EPAR report did not provide further details on what would pertain to unexpected results.

Analyses of the patients aged ≥70 showed no OS difference between the treatment groups at this time. Subgroup OS data must however be interpreted with caution bearing in mind that OS data remain immature (42% information fraction) and the lack of power for comparisons of subgroups.[1]

Progression-free Survival – Primary Outcome of ASPIRE

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, whichever was earlier. This was determined by independent review committee (IRC) using the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma. As of the data cut-off, 431 PFS events had occurred (207 in the carfilzomib group and 224 in the control group). The ASPIRE trial met its primary objective at this pre-planned interim analysis which showed improved PFS when carfilzomib was administered with lenalidomide and dexamethasone. The median PFS was 26.3 compared to 17.6 months in the carfilzomib and control groups, respectively (HR=0.69, 95%CI: 0.57-0.83, p=0.0001). At the updated 120 days safety data-cut off, the median PFS was 26.1 and 16.6 months for the carfilzomib and control groups, respectively.[1]

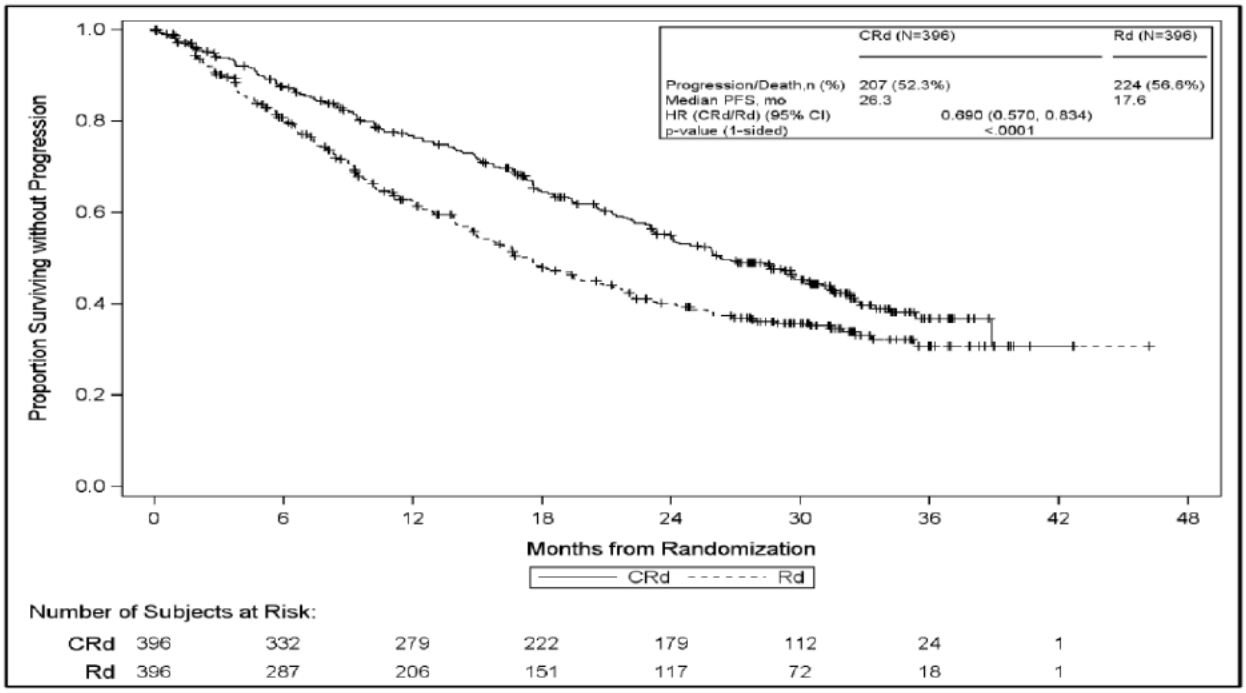


Figure 2: PFS Analysis of ASPIRE trial by treatment arm
Source: EPAR Report[8]

An improvement was observed (either statistically significant or a trend towards the carfilzomib group with treatment HRs <1 but confidence limits including 1) in all patient subgroups: sex, age, cytogenetic risk at study entry, β_2-microglobulin, geographic region, peripheral neuropathy at baseline, previous treatment with bortezomib, previous treatment with lenalidomide, disease nonresponsive to bortezomib in any previous regimen, disease refractory to immunomodulatory agent in any previous regimen, and disease nonresponsive to bortezomib and refractory to immunomodulatory agent in any previous regimen.

Table 11 presents descriptive statistics and HR (95%CI) estimates for PFS in protocol defined subgroups for the ASPIRE trial.

Table 11: Subgroup data for PFS[8]

	Carfilzomib		Control		
Subgroup	n	Median PFS (months)	n	Median PFS (months)	PFS HR (95%CI)
Prior Transplant					
Yes	217	26.3	229	17.8	0.678 (0.526-0.873)
No	179	26.4	167	16.6	0.760 (0.571-1.011)
Received any prior bortezomib					
Yes	261	24.4	260	16.6	0.699 (0.556-0.879)
No	135	30.3	136	18.2	0.726 (0.518-1.018)
Received any prior lenalidomide					
Yes	79	19.4	78	13.9	0.796 (0.522-1.215)
No	317	28.7	318	17.7	0.685 (0.554-0.847)
Refractory to prior bortezomib					
Yes	60	22.3	58	19.4	0.799 (0.492-1.297)
No	336	28.6	338	16.8	0.696 (0.566-0.855)
Refractory to prior lenalidomide					

	Carfilzomib		Control		
Subgroup	n	Median PFS (months)	n	Median PFS (months)	PFS HR (95%CI)
Yes	29	11.3	28	9.0	0.637 (0.333-1.219)
No	367	28.6	368	17.8	0.702 (0.576-0.856)
Double refractory to bortezomib and IMiD					
Yes	24	14.9	27	9.3	0.889 (0.447-1.768)
No	372	28.7	369	17.6	0.699 (0.574-0.852)
Age*[11]					
<70 years	293	28.6	281	17.6	0.668 (NR)
≥70 years	103	23.8	115	16.0	0.739 (NR)
*Post-hoc analysis HR = hazard ratio; IMiD = immunomodulatory drug; NR = not reported; PFS = progression free survival					

Time to Progression[8]

Time to progression (TTP) was an exploratory endpoint and defined as the duration in months from the date of randomization to the date of documented disease progression. As of the data cut-off, a total of 42.4% and 50.5% of patients in the carfilzomib and control groups, respectively, had progression of multiple myeloma. Among patients who had disease progression, the overall median TTP was 31.4 months (95%CI: 26.4 to not estimable) and 19.4 months (95%CI: 16.6-23.2) in the carfilzomib and control groups, respectively.

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.[12] ORR was 87.1% and 66.7% in the carfilzomib and control groups, respectively. Table 12 presents further details of response and response by subgroups.

Table 12: Overall response rate data by IRC-assessment for the ASPIRE trial

Characteristic	Carfilzomib n=396	Control n=396
Best response, n (%)		
Complete response or better	126 (31.8)	37 (9.3)
• Stringent complete response	56 (14.1)	17 (4.3)
• Complete response	70 (17.7)	20 (5.1)
Very good partial response[8]	151 (38.1)	123 (31.1)
Stable or progressive disease	14 (3.5)	59 (14.9)
Overall Response Rate, % (95%CI)	87.1 (83.4-90.3)	66.7 (61.8-71.3)
Overall Response Rate, OR[8]	OR=3.472 (95%CI:2.411-5.001), p<0.0001	
Overall Response Rate by Subgroups[8]		
Received any prior bortezomib		
• Yes	86.2 (81.4-90.1)	63.5 (57.3-69.3)
• No	88.9 (82.3-93.6)	72.8 (64.5-80.1)
Received any prior lenalidomide		
• Yes	81.0 (70.6-89.0)	50.0 (38.5-61.5)

Characteristic	Carfilzomib n=396	Control n=396
Best response, n (%)		
• No	88.6 (84.6-91.9)	70.8 (65.4-75.7)
Refractory to prior bortezomib		
• Yes	80.0 (67.7-89.2)	60.3 (46.6-73.0)
• No	88.4 (84.5-91.6)	67.8 (62.5-72.7)
Refractory to prior lenalidomide		
• Yes	69.0 (49.2-84.7)	25.0 (10.7-44.9)
• No	NR	NR
Time to response, mean (months)	1.6	2.3
Time to response, median (months)	1.0	1.0

Note: International Myeloma Working Group uniform response criteria
Stringent Complete Response: CR as defined below 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
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)
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

Duration of Response

Duration of response (DoR) was a secondary endpoint and calculated for patients achieving a partial response or better. 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.[12] The median DoR as determined by IRC was 28.6 and 21.2 months in the carfilzomib and control groups, respectively.

Health-related Quality of Life

Health-related quality of life (HrQoL) was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Module QLQ-C30) and the Multiple Myeloma Module (QLQ-MY20). Seven pre-specified subscales were assessed in the exploratory analysis: QLQ-C30 Fatigue, Nausea/Vomiting, Pain, Physical Functioning, Role Functioning, QLQ-MY20 Side Effects of Treatment and Disease Symptom Scale.[9] The QLQ-C30 was assessed on day 1 of cycles 1, 3, 6, 12, and 18, and approximately 30 days after the last treatment. Scores were compared between groups with the use of a repeated-measures mixed-effects model with the assumption of missing at random (MAR). The minimal clinically important difference (MCID) for between-group differences for the EORTC QLQ-C30 Global Health Status and Quality of Life scale was ≥5 points. Percentage of responders (defined as ≥10-point improvement from baseline for Global Health Status/QoL at each cycle and all time points) were compared between groups.[9] Sensitivity analyses were performed to estimate the impact of missing data on the results and were reported

to confirm the findings of the main analysis. Reasons for noncompliance to the EORTC QLQ-C30 questionnaire were not collected in the trial.[1]

The number of patients with at least one assessment at cycles 1, 3, 6, 12, and 18 was 365 (92.2%) and 348 (87.9%) patients in the carfilzomib and control groups, respectively. At cycle 18, 47.3% of patients completed the QLQ-C30 questionnaire.[8] At each cycle, a higher proportion of patients in the carfilzomib group compared to the control group completed the questionnaire. The largest difference was at cycle 18 with 57.3% versus 37.4% of patients in the carfilzomib and control groups, respectively. Given that more patients progressed in the control group than the carfilzomib group, the difference in QLQ-C30 completion rates was to be expected. At the end of treatment visit, 47.7% and 48.5% of patients in the carfilzomib and control groups, respectively, completed QLQ-C30 questionnaires.[1]

It was reported that there was no difference between treatment arms for the domains of fatigue, nausea/vomiting, pain, physical functioning, role functioning, disease symptoms and side effects of treatment.[9] The treatment difference over time for HrQoL is presented in Table 13. Overall, the mixed-effects model suggested patients reported improved global health status with higher QLQ-C30 Global Health Status/QoL scores over 18 cycles of treatment ($p<0.001$). The MCID was met at cycle 12 (5.56) and approached at cycle 18 (4.81) when comparing carfilzomib to the control group. Similarly, a higher percentage of patients met the responder definition for the carfilzomib compared to control group for all time points, this was statistically significant at cycle 12 (19.9% vs. 12.4%) and 18 (17.7% vs. 10.6%).[9]

Table 13: HrQoL treatment effect least-squares mean estimates[12]

	Mean Estimate				
Visit	Carfilzomib	Control	Difference[&] (SE)	95%CI	p-value
Cycle 3, day 1	60.44	57.23	3.20 (1.369)	0.52-5.89	0.019
Cycle 6, day 1	62.64	59.30	3.34 (1.443)	0.51-6.17	0.021
Cycle 12, day 1	62.32	56.75	5.56 (1.605)	2.42-8.71	<0.001
Cycle 18, day 1	63.35	58.54	4.81 (1.793)	1.29-8.33	0.007

[&]Carfilzomib-Control
Notes: SE = standard error
P value for overall treatment effect: <0.001
The mixed model for repeated measurements model included the fixed, categorical effects of treatment, visit, and treatment by visit; the fixed, continuous covariates of baseline health-related quality-of-life score and baseline score by visit, as well as the randomization stratification factors: β2- microglobulin levels (< versus ≥ 2.5 mg/L), prior bortezomib (no versus yes), and prior lenalidomide (no versus yes) as fixed factors. Random subject effect was modeled using within subject error correlation structure. CI denotes confidence interval, SE denotes standard of error.

A request to the submitter indicated that changes from baseline within each treatment group using least-squares mean estimates from mixed models repeated measures, reported statistically significant improvements in global health status and QoL in the carfilzomib group at cycles 6, 12, and 18 and deterioration in the control group at cycles 3 and 12.[1]

Post-progression Therapy

Post-progression therapy was not predefined in the review protocol. A total of 38.1% and 46.5% of patients in the carfilzomib and control groups started a new anti-myeloma treatment by the time of the data cut-off.[8] The median time from randomization to new treatment was 17.3 and 12.1 months in the carfilzomib and control groups, respectively.[8] Of the safety population, 112 (28.5%)

and 164 (42.2%) patients received antineoplastic agents.[1] The most frequent antineoplastic agents received in the carfilzomib and control groups, respectively, were: bortezomib (13.0% and 25.7%), cyclophosphamide (12.8% and 16.7%), and doxorubicin (4.6% and 4.9%) Nine and eight patients in the carfilzomib and control groups, respectively, received carfilzomib as a new anti-myeloma therapy.[1] There was no documentation in the protocol regarding permitting or prohibiting cross-over.

b) Harms Outcomes

The ASPIRE trial provided data on the harm outcomes of interest. Harms data are summarized in Table 13. No statistical comparisons of the rates of adverse events (AEs) between trial arms were reported in the trial. All patients who received at least one dose of study treatment were included in analyses of safety, 392 patients in the carfilzomib group and 389 in the control group.

Deaths

A total of 7.7% and 8.5% of patients in the carfilzomib and control groups, respectively, died during treatment or within 30 days of receiving the last dose of study treatment. Overall, 14 deaths were reported as treatment-related, 6 occurred in the carfilzomib group and 8 in the control group. No deaths were considered by the investigators to be related specifically to carfilzomib alone.[8] Two of the deaths in the carfilzomib group were considered to be related both to carfilzomib and lenalidomide (events of hemorrhage intracranial and cardiac arrest)[8] and eight of the deaths (events of septic shock, sepsis, hepatic infection, respiratory failure, pulmonary embolism, myelodysplastic, acute coronary syndrome, and acute renal failure) in the control group were considered to be related to the study treatment.[8]

Serious Adverse Events

Overall, there were 235 (59.9%) and 210 (54.0%) patients in the carfilzomib and control groups, respectively who had at least one serious adverse event (SAE).[8] The most common SAEs in the carfilzomib group were pneumonia (14.3%), respiratory tract infection (3.8%) and pyrexia (3.6%). The most common SAEs in the control group were pneumonia (11.1%), anaemia (2.6%), pyrexia (2.3%), and diarrhea (2.3%).[8] SAE incidence by treatment cycle (cycles 1-6, 7-12, 13-18, and ≥18) was reported in the ASPIRE trial. Incidence rates were higher in the carfilzomib group compared to the control group from cycles 1-18, when carfilzomib was administered. Beyond cycle 18, the control group experienced a higher rate of SAEs compared to the carfilzomib group (29.6% versus 23.3%).[12] The incidence of cardiac failure and ischemic heart disease by cycle category was similar for both treatment arms.

A post-hoc analysis of patients from the ASPIRE trial to compare outcomes based on age (<70 years and ≥70 years), demonstrated a higher rate of treatment-emergent grade 3 or higher events in patients ≥ 70 years.[1] The submitter noted, there was a higher rate of neutropenia in the carfilzomib group and a lower rate of neutropenia in the control group when compared to the broader population. A higher rate of hypertension was also seen in the carfilzomib group in patients 70 years or older compared to the broader population. Similar rates to the broader population were seen for anemia, thrombocytopenia, cardiac or thrombosis disorders, and peripheral neuropathy.

Adverse events of grade ≥3 that occurred >5% more frequently in the carfilzomib group compared to the control group in patients ≥70 years, included: neutropenia (36.9% versus 23.2%), thrombocytopenia (20.4% versus 15.2%), hypokalemia (15.5% versus 6.3%),[11] and cardiac failure (8.7% versus 1.8%).[3]

Adverse Events of Interest

Cardiac disorders

Overall, cardiac disorders occurred in 85 (21.7%) and 72 (18.5%) patients in the carfilzomib and control groups, respectively.[8] There were higher rates of grade ≥3: hypertension (4.3% in the carfilzomib and 1.8% in the control group), cardiac failure (grouped term; 3.8% in the carfilzomib group and 1.8% in the control group), and ischemic heart disease (grouped term; 3.3% and 2.1%) in the carfilzomib compared to control group. Seven deaths occurred due to cardiac failure (3 in the carfilzomib group and 4 in the control group), five deaths occurred due to ischemic heart disease (3 and 2), one death each due to circulatory collapse, left ventricular dysfunction (both in carfilzomib), and arrhythmia (control).[8]

Vascular disorders

Vascular disorders occurred in 148 (37.8%) and 98 (25.2%) patients in the carfilzomib and control groups, respectively.[8] There were higher rates of grade ≥3 deep vein thrombosis (1.8% and 1.0%) and grade ≥3 pulmonary embolism (3.1% and 2.3%).

Hematological toxicity

There was an increase in the frequency and severity of neutropenia and thrombocytopenia for the carfilzomib compared to control group. The frequencies for all-grade neutropenia were 37.8% versus 33.7%, for the carfilzomib compared to the control group, and of grade 3/4 were 29.6% versus 26.5%, respectively. Similarly, the frequencies for all-grade thrombocytopenia were 29.1% and 22.6%, for the carfilzomib compared to the control group, and of grade 3/4 were 16.6% and 12.3%, respectively. SAEs were higher in the carfilzomib compared to control groups for anemia (2.0% versus 2.6%), febrile neutropenia (2.0% versus 1.0%), thrombocytopenia (1.5% versus 0.8%), and neutropenia (1.0% versus 1.3%).[8]

Neuropathy

Overall, there was no increase in the frequency or severity of peripheral neuropathy for the carfilzomib group compared to the control group. The incidence of peripheral neuropathy was similar between the carfilzomib and control groups (17.1% and 17.0% respectively). Rates of grade 3 or higher peripheral neuropathy were 2.6% and 3.1% in the carfilzomib and control groups, respectively.

Infections[8]

Infections and infestations occurred in 310 (79.1%) and 270 (69.4%) patients in the carfilzomib and control groups, respectively. These included upper respiratory tract infections (URTI), nasopharyngitis, bronchitis, pneumonia, and respiratory tract infection. The most common cause of on-study death in the ASPIRE trial were infections (9 in the carfilzomib group and 10 in the control group). These included 8 deaths due to sepsis/septic shock (4 in the carfilzomib group and 4 in the control group), 7 due to pneumonia / bronchopneumonia (3 and 4), and other deaths due to: URTI and endocarditis (carfilzomib), urosepsis and hepatic infection (control).

Hepatic toxicity[8]

The incidence of hepatic failure, fibrosis and cirrhosis and other liver damage related conditions was reported in 2.0% and 0.5% of patients in the carfilzomib and control groups, respectively. Similar rates of grade 3 or higher hepatic events were observed with 0.5% and 0.3% of patients in the carfilzomib and control groups, respectively.

Renal toxicity

Renal and urinary disorders occurred in 61 (15.6%) and 53 (13.6%) patients in the carfilzomib and control groups, respectively.[8] Grade 3 or higher acute renal failure was similar between treatment arms (grouped term; 3.3% in the carfilzomib group and 3.1% in the control group).

Pulmonary disorders

Respiratory, thoracic and mediastinal disorders occurred in 218 (55.6%) and 162 (41.6%) patients in the carfilzomib and control groups, respectively.[8] Rates of grade 3 or higher AEs were higher in the carfilzomib group compared to control group for upper respiratory tract infections (1.8 versus 1.0%) and dyspnea (2.8% versus 1.8%). Pulmonary oedema occurred in 4 patients in the carfilzomib group and no patients in the control group.[8]

Second Primary Malignancy[8]

The rate of second primary malignancy (SPM) was 3.8% and 4.1% in the carfilzomib and control groups, respectively. Both groups had an incidence of grade 3 or higher SPM of 1.8%. The five most frequently reported SPM were myelodysplastic syndrome, acute myeloid leukemia, colon cancer, colorectal cancer, and malignant hepatic neoplasm.

Withdrawal due to adverse events[8]

Overall, 102 (26.0%) and 98 (25.2%) patients in the carfilzomib and control groups, respectively, had an AE leading to discontinuation of study treatment. The most common AEs leading to discontinuation of any study drug in either arm included thrombocytopenia, insomnia, neutropenia, anemia, pneumonia, and URTI.

Table 14: Summary of Key Harms Outcomes in the ASPIRE trial

Treatment Arm	Carfilzomib n=392	Control n=389
Grade 3 or Higher Adverse Events (AE)[12]		
Hematologic AE, n (%)		
Anemia	70 (17.9)	67 (17.2)
Neutropenia	116 (29.6)	103 (26.5)
Thrombocytopenia	65 (16.6)	48 (12.3)
Non-hematologic AE, n (%)		
Diarrhea	15 (3.8)	16 (4.1)
Fatigue	30 (7.7)	25 (6.4)
Cough	1 (0.3)	0
Pyrexia	7 (1.8)	2 (0.5)
Upper respiratory tract infection	7 (1.8)	4 (1.0)
Hypokalemia	37 (9.4)	19 (4.9)
Muscle spasms	4 (1.0)	3 (0.8)
Peripheral edema	5 (1.3)	2 (0.5)
Nasopharyngitis	1 (0.3)	0
Constipation	1 (0.3)	2 (0.5)
Back Pain	5 (1.3)	8 (2.1)
Other AEs of interest, n (%)		
Dyspnea	11 (2.8)	7 (1.8)
Peripheral neuropathy[%]	10 (2.6)	12 (3.1)
Hypertension	17 (4.3)	7 (1.8)
Acute renal failure[^]	13 (3.3)	12 (3.1)
Elevated creatinine	4 (1.0)	1 (0.3)
Cardiac Failure[&]	15 (3.8)	7 (1.8)

Treatment Arm	Carfilzomib n=392	Control n=389
Grade 3 or Higher Adverse Events (AE)[12]		
Deep vein thrombosis	7 (1.8)	4 (1.0)
Ischemic heart disease*	13 (3.3)	8 (2.1)
Pulmonary embolism	12 (3.1)	9 (2.3)
Second primary malignancy+	9 (2.3)	11 (2.8)
Serious Adverse Event (SAE) occurring in ≥1% of Patients[8]		
At least one SAE, n (%)	235 (59.9)	210 (54.0)
Pneumonia	56 (14.3)	43 (11.1)
Respiratory Tract Infection	15 (3.8)	6 (1.5)
Pyrexia	14 (3.6)	9 (2.3)
Pulmonary Embolism	12 (3.1)	8 (2.1)
Deep Vein Thrombosis	9 (2.3)	6 (1.5)
Febrile Neutropenia	8 (2.0)	4 (1.0)
Acute Renal Failure	6 (1.5)	4 (1.0)
Atrial Fibrillation	6 (1.5)	7 (1.8)
Myocardial Infarction	6 (1.5)	2 (0.5)
Thrombocytopenia	6 (1.5)	3 (0.8)
Congestive Cardiac Failure	5 (1.3)	4 (1.0)
Acute Myocardial Infarction	4 (1.0)	1 (0.3)
Neutropenia	4 (1.0)	5 (1.3)
Cardiac Failure	4 (1.0)	3 (0.8)
Gastroenteritis	4 (.10)	4 (1.0)
Sepsis	4 (1.0)	4 (1.0)

Note: AEs listed for those reported in at least 20% of patients in either group or of clinical relevance.
%Included (in descending order of frequency) peripheral neuropathy, peripheral sensory neuropathy, polyneuropathy, neuralgia, peripheral motor neuropathy, sensorimotor disorder, sensory loss, and toxic neuropathy.
^Included (in descending order of frequency) acute renal failure, renal failure, renal impairment, azotemia, oliguria, anuria, toxic nephropathy, and prerenal failure.
&included (in descending order of frequency) cardiac failure, congestive cardiac failure, pulmonary edema, hepatic congestion, cardiopulmonary failure, acute pulmonary edema, acute cardiac failure, and right ventricular failure.
*(in descending order of frequency) angina pectoris, myocardial infarction, acute myocardial infarction, increased blood creatinine phosphokinase, coronary artery disease, myocardial ischemia, coronary artery occlusion, increased troponin, increased troponin T, acute coronary syndrome, abnormal cardiac stress test, cardiomyopathy stress, unstable angina, coronary artery stenosis, abnormal electrocardiogram ST-T segment, and abnormal electrocardiogram T wave.
+included (in descending order of frequency) myelodysplastic syndrome, acute myeloid leukemia, colon cancer, colorectal cancer, malignant hepatic neoplasm, acute lymphoblastic leukemia, adenocarcinoma, gastrointestinal neoplasm, gastrointestinal stromal tumor, malignant melanoma, malignant neoplasm of pleura, metastatic pancreatic carcinoma, non-small cell lung cancer, pancreatic adenocarcinoma, rectal cancer, and transitional cell carcinoma.

6.4 Ongoing Trials

None were identified.

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR 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.

The Myeloma Clinical Guidance Panel is comprised of three hematologists .The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

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 November 2015, **Embase** 1974 to 2015 December 22, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

#	Searches	Results
1	(carfilzomib* or kyprolis* or PR171 or PR 171 or 868540-17-4 or 72X6E3J5AR).ti,ab,rn,nm,hw,ot,kf.	2103
2	exp Multiple Myeloma/	93099
3	(myelom* or kahler disease or morbus kahler).ti,ab.	124387
4	(plasma adj2 (Cancer* or neoplasm* or oncolog* or tumor* or tumour* or leukemia* or leukaemia*)).ti,ab.	11937
5	2 or 3 or 4	155727
6	1 and 5	1637
7	6 use pmez	307
8	6 use cctr	10
9	*carfilzomib/	472
10	(carfilzomib* or kyprolis* or PR171 or PR 171).ti,ab.	1348
11	9 or 10	1367
12	Multiple Myeloma/	92584
13	(myelom* or kahler disease or morbus kahler).ti,ab.	124387
14	(plasma adj2 (Cancer* or neoplasm* or oncolog* or tumor* or tumour* or leukemia* or leukaemia*)).ti,ab.	11937
15	12 or 13 or 14	155603
16	11 and 15	1081
17	16 use oemezd	805
18	7 or 8 or 17	1122
19	(Randomized Controlled Trial or Controlled Clinical Trial).pt.	945392
20	Randomized Controlled Trial/	812109
21	Randomized Controlled Trials as Topic/	137059

22	"Randomized Controlled Trial (topic)"/	87516
23	Controlled Clinical Trial/	483546
24	Controlled Clinical Trials as Topic/	9576
25	"Controlled Clinical Trial (topic)"/	5536
26	Randomization/	176630
27	Random Allocation/	170484
28	Double-Blind Method/	340434
29	Double Blind Procedure/	127190
30	Double-Blind Studies/	225563
31	Single-Blind Method/	54470
32	Single Blind Procedure/	21185
33	Single-Blind Studies/	55908
34	Placebos/	280162
35	Placebo/	279888
36	Control Groups/	86227
37	Control Group/	86139
38	(random* or sham or placebo*).ti,ab,hw.	3104233
39	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	631280
40	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	1688
41	(control* adj3 (study or studies or trial*)).ti,ab.	1019963
42	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.	73774
43	allocated.ti,ab,hw.	130621
44	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.	75830
45	or/19-44	3909122
46	18 and 45	167
47	limit 46 to english language	162
48	remove duplicates from 47	137

2. **Literature search via PubMed**
A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#4	Search **#2 AND #3** Filters: **English**	5
#3	Search **randomized controlled trial[pt] OR randomized controlled trials as topic[mh] OR random allocation [mh] OR double-blind method[mh] OR single-blind method[mh] OR random*[tw] OR "Placebos"[Mesh] OR placebo[tiab] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw] OR dumm*[tw])) OR Controlled clinical trial[pt] OR controlled clinical trials as topic[mh] OR clinical trial[pt] OR clinical trials as topic[mh] OR "clinical trial"[tiab] OR evaluation studies[pt] OR evaluation studies as Topic[mh] OR control[tiab] OR controlled[tiab] OR volunteer[tiab] OR volunteers[tiab] OR open label*[tiab] OR nonrandom*[tiab] OR non random*[tiab] OR quasirandom*[tiab] OR Observational stud*[tiab] OR Cohort studies[Mesh] OR cohort[tiab] OR cohorts[tiab] OR Longitudinal studies[Mesh] OR longitudinal[tiab] OR Prospective studies[Mesh] OR prospective[tiab] OR Follow-up studies[Mesh] OR follow up stud*[tiab] OR followup stud*[tiab] OR Retrospective studies[Mesh] OR retrospective[tiab] OR Population based stud*[tiab] OR Population based analy*[tiab] OR Population study[tiab] OR Population studies[tiab] OR descriptive stud*[tiab] OR Multidimensional stud*[tiab] OR "Comparative Study"[Publication Type] OR Comparative study[tiab] OR comparative studies[tiab] OR Validation Studies[pt] OR Case-control studies[Mesh] OR case control*[tiab] OR case series[tiab] OR case comparison*[tiab] OR Case history[tiab] OR Case histories[tiab]** Filters: **English**	5983134
#2	Search **#1 AND publisher[sb]** Filters: **English**	15
#1	Search **(carfilzomib[Supplementary Concept] OR Carfilzomib*[tiab] OR kyprolis*[tiab] OR PR171[tiab] OR PR 171[tiab] OR 868540-17-4[rn] OR 72X6E3J5AR[rn]) AND (Myelom*[tiab] OR Kahler disease[tiab] OR morbus kahler[tiab] OR (plasma[tiab] AND (Cancer*[tiab] OR neoplasm* [tiab] OR tumor*[tiab] OR tumour*[tiab] OR oncolog*[tiab] OR leukemia*[tiab] OR leukaemia*[tiab]))))**	278

3. **Cochrane Central Register of Controlled Trials (Central)**
Searched via Ovid

4. **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 terms: Kyprolis, carfilzomib

Select international agencies including:

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

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

Search terms: Kyprolis, carfilzomib

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

European Society for Medical Oncology (ESMO)
http://www.esmo.org/

American Society of Hematology (ASH)
http://www.hematology.org/

Search terms: Kyprolis, carfilzomib/ last 5 years

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