CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Pomalidomide (Pomalyst) Bortezomib for Multiple Myeloma

September 18, 2019

DISCLAIMER

Not a Substitute for Professional Advice

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

Liability

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

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

FUNDING

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

INQUIRIES

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

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

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

TABLE OF CONTENTS

List of Abbreviations

AE(s)	Adverse Events
CI	Confidence interval
CGP	Clinical Guidance Panel
CyBorD	Cyclophosphamide + bortezomib + dexamethasone
DOR	Duration of Response
DLd	Daratumumab + lenalidomide + dexamethasone
DVd	Daratumumab + bortezomib + dexamethasone
ELd	Elotuzumab + lenalidomide + dexamethasone
HR	Hazard ratio
HRQoL	Health related quality of life
ILd	Ixazomib + lenalidomide + dexamethasone
Kd	Carfilzomib + dexamethasone
CLd	Carfilzomib + lenalidomide + dexamethasone
Ld	Lenalidomide + dexamethasone
MM	Multiple Myeloma
NMA	Network meta-analysis
ORR	Overall response rate
OS	Overall survival
pCODR	pan-Canadian Oncology Drug Review
PVd	Pomalidomide + Bortezomib + dexamethasone
PFS	Progression free survival
V	Bortezomib
VCD	Cyclophosphamide + bortezomib + dexamethasone
VLd	Bortezomib + lenalidomide + dexamethasone
Vd	Bortezomib + dexamethasone

1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding pomalidomide (Pomalyst) in combination with bortezomib and dexamethasone for multiple myeloma (MM).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 pomalidomide (Pomalyst) in combination with bortezomib and dexamethasone for multiple myeloma (MM) conducted by the Lymphoma/Myeloma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; 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. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on pomalidomide (Pomalyst) in combination with bortezomib and dexamethasone for multiple myeloma (MM), a summary of submitted Provincial Advisory Group Input pomalidomide (Pomalyst) in combination with bortezomib and dexamethasone for multiple myeloma (MM), and a summary of submitted Registered Clinician Input on pomalidomide (Pomalyst) in combination with bortezomib and dexamethasone for multiple myeloma (MM), and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

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

Pomalidomide is an immunomodulatory agent with antineoplastic activity. Pomalidomide has the following pCODR requested reimbursement criteria: Pomalidomide in combination with dexamethasone and bortezomib for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least one prior treatment regimen including lenalidomide. Health Canada has issued marketing authorisation for pomalidomide (Pomalyst) in combination with dexamethasone and bortezomib for the treatment of adult patients with multiple myeloma (MM) who have received at least one prior treatment regimen that included lenalidomide. Note that the Health Canada approved indication differs slightly from the reimbursement criteria, in that it does not specify that patients must be ‘relapsed or refractory’.

The recommended daily dose of pomalidomide is 4 mg once daily (days 1-14 for each 21-day cycle until disease progression); dexamethasone is recommended at 20 mg orally once daily (in patients > 75 years of age reduce dose to 10 mg) (cycles 1 – 8: days 1,2,4,5,8,9,11, and 12 of a 21-day cycle; cycle 9 onwards: days 1,2,8, and 9 of a 21-day cycle until disease progression; bortezomib is recommended at 1.3 mg/m2 intravenous or subcutaneous (cycles 1-8: days 1,4,8, and 11 of a 21-day cycle; cycle 9 onwards: Days 1 and 8 of 21-day cycle until disease progression).

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one trial, OPTIMISMM which is an ongoing, international, multi-centre, phase 3, open-label, randomized controlled trial that randomized 559 patients with relapsed multiple myeloma who had received prior lenalidomide to receive pomalidomide bortezomib plus dexamethasone (n=281) or bortezomib plus dexamethasone (n=278). No treatment crossover was permitted.

Patients were eligible for enrollment if they met the following criteria: aged ≥ 18 years, diagnosis of multiple myeloma and measurable disease, received one to three prior regimens, including a lenalidomide-containing regimen for at least two consecutive cycles, and had an ECOG performance status of 0-2. Patients previously treated with bortezomib were permitted entry into the trial provided they did not have disease progression during treatment or within 60 days of the last dose of bortezomib. Patients who progressed on or within 60 days of a once-weekly bortezomib schedule or on a lower dose of bortezomib were included in the trial and were defined as the bortezomib-refractory patient population in this trial.

Patients who were enrolled in the trial were treated with PVd (pomalidomide 4 mg orally on days 1-14 of each 21-day cycle, dexamethasone 20 mg orally (10 mg if over age 75) on days 1, 2, 4, 5, 8, 9, 11, 12 of each 21-day cycle (cycles 1-8), then on days 1, 2, 8, 9 of each 21-day cycle (cycle 9 onwards), bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11 of each 21-day cycle (cycles 1-8), then days 1 and 8 of each 21-day cycle (cycle 9 onwards)), or Vd (same doses). In both groups, study drugs were given until disease progression, withdrawal of consent, or occurrence of unacceptable toxic effects.

Baseline patient characteristics were generally well balanced across treatment groups. The median age of patients in the OPTIMISMM study was 68.0 years and median time since diagnosis was 4.2 years. A total of 94% of patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

Patients received a median of two previous regimens. Overall, 100% of patients had received lenalidomide (70% were refractory to lenalidomide); 71.5% and 73% in the pomalidomide and control arms, respectively had received prior bortezomib. A total of 57% and 59% in the pomalidomide and control arms, respectively had received prior stem cell transplantation.

The estimated sample size requirements for the trial was 544 patients (320 PFS events) to provide 80% power and 2-sided alpha of 0.05. The sample size was amended to perform the final PFS analysis based on 320 events rather than 381 events based on phase 3 trials that showed that the PFS of the Vd arm was shorter than expected in patients who have previously received lenalidomide.[1] More detail is listed in Table 6.3

Efficacy[1]

For the primary endpoint PFS assessed by independent review (censoring rule according to FDA guidelines), this pCODR review reports on the protocol defined final analysis (Nov 26, 2017 data cut-off). In addition, for PFS assessed by investigator (censoring rule according to EMA guidelines) an updated PFS analysis (Sep 15, 2018) is reported, which aligns with the data used in the submitted economic model. For the prespecified secondary endpoint OS one preplanned interim analysis at the time of the final PFS analyses (Nov 26, 2017) and one updated analysis (Sep 15, 2018) are reported. A final OS analysis is projected to occur in the third quarter of 2021.[2]

The study met its primary endpoint with a statistically significantly longer PFS in favour of the pomalidomide group, with a reduction in the risk of progression or death during the study period. As of the protocol defined final PFS analysis (data cut-off: Oct 26, 2017; median follow up 15.9 months), median PFS was 11.2 vs. 7.1 months in the pomalidomide bortezomib dexamethasone and bortezomib dexamethasone arms, respectively (HR=0.61; 95%CI: 0.49-0.77, *P*=0.0001). As of the updated data cut-off (Sep 15, 2018) (median follow up 26.2 months) [2], a total of 339 PFS events had occurred. The median PFS was 10.9 months (95% CI: 9.5, 13.6) in the PVd arm and 6.9 months (95% CI: 5.6, 8.2) in the Vd arm HR=0.62, 95%CI: 0.50, 0.76, two sided *P* <0.001).[3]

The key secondary outcome, overall response rate (partial response or better according to IMWG criteria), was 82.2% and 50% in the pomalidomide bortezomib dexamethasone and bortezomib dexamethasone arms, respectively; odds ratio 5.02 (95% CI 3.35-7.52); P<0.001. The overall survival (OS) analysis at the first interim analysis for OS (October 26, 2017 data cut-off) was immature and did not cross the pre-specified early stopping boundary for the interim analysis. The OS difference between treatment arms resulted in a HR of 0.98 (95% CI: 0.73, 1.32) *P* = 0.89. As of an updated OS analysis at the September 15, 2018 data cut-off with a median follow up of 26.2 months, a total of 242 OS events had occurred (43.3%). There were 116/281 deaths with a median OS duration of 40.54 months (95% CI: 29.83, not evaluable) in the PVd arm and 126/278 deaths with a median OS of 30.46 months (95% CI: 24.61, 35.94) in the Vd arm HR=0.91, 95%CI: 0.70, 1.18, two sided *P*=0.476). [2]

Pre-specified, yet exploratory subgroup analyses for lenalidomide refractory disease, age and other demographic characteristics reveal a consistent benefit to pomalidomide bortezomib and dexamethasone as compared to bortezomib and dexamethasone.

Health related quality of life analyses were exploratory. The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core Module (QLQ-C30), the Multiple Myeloma Module (QLQ-MY20) and the EQ-5D-3L were used to determine the impact of pomalidomide bortezomib dexamethasone on patient reported outcomes as compared to bortezomib dexamethasone. A minimally important difference (change of ≥10 points) was measured for the global health status/QOL domain. Generally, in both arms the global health status/QoL domain did not change over time, or between arms at any point in time. There were no statistical differences between treatments at any cycle on the global health status/QoL domain.

Harms[1]

Twenty-seven (9.7%) patients in the pomalidomide arm and 12 patients (4.4%) in the control arm died during treatment period or within 28 days after receiving the last dose of study treatment. Discontinuation rates were (65.8%) in the pomalidomide arm and (80.9%) in the control arm, with disease progression being the most common reason for discontinuation in both treatment groups.

At least one treatment emergent adverse event (TEAE) occurred in 277/278 (99.6%) and 264/270 (97.8%) patients in the PVd and Vd arms, respectively.[2] At least one TEAE related to any study drug occurred in 267/278 (96.0%) and 226/270 (83.7%) patients in the PVd and Vd arms, respectively. Of these, grade 3 or 4 TEAEs 215/278 (77.3%) versus 126/270 (46.7%) occurred in the PVd arm and Vd arm, respectively.

More patients in the PVd arm experienced at least one grade 3 or 4 TEAE: 251/278 (90.3%) patients in the PVd arm and 190/270 (70.4%) patients in the Vd arm. Similarly, there were more serious TEAE in the PVd arm 159/278 (57.2%) than the Vd arm 114/270 (42.2%).

There were more TEAEs leading to dose reduction of any study drug in the PVd arm 200/278 (71.9%) in the Vd arm 139/270 (51.5%) and TEAEs leading to interruption of any study drug (87.8% versus 67%).

The most common treatment related adverse events were infections and infestations (all grade); these occurred in 223/278 (80.2%) and 175/270 (64.8%) patients in the PVd and Vd arms, respectively.[2] Grade 3 or 4 infections occurred in 86/278 (30.9%) of PVd patients, and 48/270 (17.8%) of Vd patients.[1] It was reported that those patients with infections did not have febrile neutropenia. The most common hematologic adverse event was neutropenia. All-grade neutropenia occurred in 130/278 (46.8%) patients in the PVd arm and 29/270 (10.7%), patients in the Vd arm.[2] Grade 3/4 neutropenia occurred in 41.7% and 8.5% of patients in the PVd and Vd arms, respectively.[1] All-grade thrombocytopenia occurred in 102/278 (36.7%) patients in the PVd arm and 103/270 (38.1%), patients in the Vd arm. Grade 3/4 thrombocytopenia occurred in 27.3% and 29.3% of patients in the PVd and Vd arms, respectively.[1] The incidence of all grade peripheral sensory neuropathy occurred in 133 (47.8%) patients in the PVd arm and 100 (37.1%) in the Vd arm. Pulmonary embolism (grade 3 or 4) occurred in 11/278 (4.0%) and 1/270 (0.4%) of the PVd and Vd arms, respectively.[1]

There were 159 (57.2%) and 114 (42.2%) patients in the pomalidomide and control arms, respectively who had at least one serious adverse event. The most common serious adverse event was pneumonia, which occurred 32 (11.5%) in the pomalidomide arm and 17 (6.3%) in the control arm.[2]

Limitations

- The trial was open-label and therefore, investigators and patients were not blinded to treatment assignment. Therefore, the trial may be at risk for biases related to blinding that can affect the internal validity.
- Pre-specified secondary endpoints were tested sequentially (PFS, then ORR then OS); the OS data did not meet the pre-specified superiority boundary. The OS data was not mature at the time of the interim analysis for the OS data (the OS interim analysis coinciding with the final PFS analysis). The other secondary end points (duration of response and safety) as well as some exploratory end points were presented at the time of final PFS analysis, but without multiplicity adjustment. Therefore, the p-values reported were noted for descriptive purposely only. The lack of adjustment for multiplicity control limits the interpretation of these end points.
- Pre-specified subgroup analyses were exploratory in nature (including, for example, patients who were lenalidomide refractory) and therefore not adjusted for multiplicity, adequately powered, nor included in the statistical hierarchy. The interpretation of results for subgroup analyses is therefore limited. Additionally, the interpretation of any differences in end points in subgroups is limited because of the small number of patients in the subgroups.
- HRQoL end points were exploratory, and were not adequately powered, included in the statistical hierarchy or adjusted for multiplicity. Therefore, any interpretation of HRQoL end points is limited. Additionally, the lower compliance to HRQoL questionnaires in the control group could bias results in favour of pomalidomide.

Table 1.1: Highlights of Key Outcomes in the OPTIMISMM trial[2]

	OPTIMISMM	
	PVd n=281	Vd n=278
Primary Outcome, median PFS months – Nov 26, 2017 data cut (95% CI)	11.20 (95%CI: 9.66 – 13.73)	7.10 (95%CI: 5.88 – 8.48)
HR (95%CI)	HR=0.61 95%CI: 0.49-0.77	
p-value	*P* <0.0001	
Key Secondary Outcome, median ORR	231/281 (82.2%)	139/278 (50.0%)
OR (95%CI)	5.02 (95%CI: 3.35-7.52)	
p-value	*P* <0.001	
Key Secondary Outcome, median OS as of Oct 6, 2017 (data not mature) months (95% CI)	Not reached	31.24 (95% CI: 27.01, NE)
HR (95%CI)	HR=0.98 (95%CI: 0.73-1.32)	
p-value	*P*=0.894 Pre-specified stopping boundary of p = 0.031 was not crossed, therefore not significant.	
Key Secondary Outcome, median OS as of Sept 15, 2018 (data not mature) months (95% CI)	40.54 (95% CI: 29.83, NE)	30.46 (95% CI: 24.61, 35.94)
HR (95%CI)	HR=0.91 (95% CI: 0.70, 1.18)	
p-value	*P*=0.476[2]	
HrQoL		
Difference (95%CI)	**No difference**	**No difference**
Harms Outcome, n (%)	PVd n=278	Vd n=270
Grade ≥3	251 (90.3)	190 (70.4)
TRAE	277 (99.6%)	264 (97.8%)
WDAE	31 (11.2)	50 (18.5)

AE = adverse event, **CI** = confidence interval, **HR** = hazard ratio, **HRQoL** = health-related quality of life, **NE = not estimable, NR** = not reported, **SD** = standard deviation, **TRAE** = treatment-related adverse event, **WDAE** = withdrawal due to adverse event
*HR < 1 favours PVd arm

1.2.2 Additional Evidence

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

Patient Advocacy Group Input

One patient input was provided to pCODR through a patient advocacy group submission from Myeloma Canada (MC) for pomalidomide in combination with dexamethasone and bortezomib (PVd) for relapsed or refractory multiple myeloma (RRMM).

From a patient's perspective, infections were the most important aspect of myeloma to control. MM symptoms had a relatively high impact on daily life and most notably impacted patients' ability to work. Patients regarded the maintenance of quality of life as the most desirable treatment goal, followed by management/minimization of side effects. Dexamethasone, bortezomib and lenalidomide were the most frequently cited therapies experienced by patients. Frequent side effects included fatigue, neuropathy, insomnia,

gastrointestinal problems and shortness of breath. Almost all respondents considered access to effective treatments for MM to be crucial, and three quarters did not report any issues with accessing treatment. Additionally, most patients believed treatment choice based on side effects was highly important. Most respondents had concerns about financial implications, with drug and parking costs being the most frequently cited. Patients had a generally positive outlook towards treatment with Vd and appreciated its effectiveness and low toxicity, allowing them to maintain a good quality of life.

Treatment with PVd was similarly rated by patients, but slightly lower quality of life, side effect tolerability and overall satisfaction were noted (the low number of respondents in each group precludes any formal comparison). A majority of patients that received PVd stated an improvement in disease control followed by /remission and improved side effects whereas less than half expressed quality of life was fulfilled with PVd. Side effects deemed completely intolerable were infections/pneumonia, pain and diarrhea.

Caregivers of MM patients taking PVd experienced challenges with managing side effects, which largely impacted their ability to travel and to volunteer.

Provincial Advisory Group (PAG) Input

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

Clinical factors:

- Clarity on patients who would eligible for treatment
- Sequencing of currently available treatment and upcoming treatments

Economic factors:

- Additional healthcare resources for drug preparation and toxicity management

Registered Clinician Input

A total of four clinicians, an individual input from one clinician from Cancer Care Ontario, and a joint clinician input reporting the perspective of three clinicians belonging to the Myeloma Canada Research Network (MCRN) was submitted to pCODR for pomalidomide in combination with dexamethasone and bortezomib (PVd) for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior treatment regimen including lenalidomide. A summary of the input is provided below.

There are several options for relapsing multiple myeloma patients, which introduces challenges in treatment selection but also opportunities for treatment personalization. Relevant comparators include carfilzomib plus dexamethasone and the combination of daratumumab, bortezomib and dexamethasone. Clinicians reported that PVd has several notable advantages compared with available treatments including lower toxicity and easier administration, in addition to good survival benefits. In terms of sequencing, PVd could be given in the third-line setting after daratumumab-containing regimens, or second-line in patients who experience challenges with long-term intravenous therapies or have certain comorbidities or contraindications. Most clinicians believed it would be an addition to and not a replacement for existing therapies.

Summary of Supplemental Questions

The Submitter provided a network meta-analysis (NMA) to evaluate the relative efficacy and safety of pomalidomide in combination with bortezomib and low dose of dexamethasone (PVd) in comparison to other treatment options among adult patients with RRMM. The following five therapies were included in the NMA: bortezomib dexamethasone (Vd), Carfilzomib dexamethasone (Kd), Bortezomib cyclophosphamide dexamethasone (Vcd), Daratumumab, bortezomib and dexamethasone (Dvd) and panobinostat, bortezomib and dexamethasone (PanVd). Although PANVd was included in the NMA, it was not identified as relevant comparator for this pCODR review as it is currently not publicly funded in the target population. This pCODR review reports results for the PFS and OS outcomes (see section 7 for detailed results for the ITT, lenalidomide exposed, lenalidomide-refractory, and immunomodulatory exposed populations). The pCODR Methods Team noted that due to concerns of a lack of risk of bias assessment performed, there may be poor quality studies included in the NMA. The validity of the NMA is based on three assumptions (i.e., similarity, homogeneity, and consistency) which were assessed in this review. There was significant heterogeneity present on ISS stage at baseline, the number of prior therapies and PFS definition across studies. In addition, the proportion of patients with prior exposure to lenalidomide varied across the included trials in the evidence network. Specifically, the OPTIMISM MM-007 trial included 100% of patients with prior lenalidomide exposure in comparison to the other trials which included a very small proportion. Thus, the homogeneity assumption was violated. The Submitter outlined that the CASTOR trial presented a significant difference in the Vd arm design which has a fixed schedule, with a maximum medication time of 24 weeks when compared to other included trials: Kropff 2017[4], ENDEAVOR[5], PANORAMA-1[6] and MM-007[7] which relied on continuous treatment over the trial duration. Thus, the similarity assumption was violated. Due to a lack of a closed loop in the evidence network, the consistency between direct and indirect comparisons could not be assessed. Other outcomes of interest (e.g., health related quality of life and safety) were not explored in the NMA. Finally, the submitted systematic literature review and NMA were completed by external consultancy groups hired by the Submitter. As a result, the information provided in the reports should be viewed considering this potential conflict of interest and lack of peer-review. Based on the aforementioned limitations, the comparative efficacy estimates may be biased. Thus, the certainty in the results reported for PFS and OS is limited and should be interpreted with caution.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 1.2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 1.2: Assessment of generalizability of evidence for pomalidomide in combination with bortezomib and dexamethasone for RRMM

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(OPTIMISMM trial)[7]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="2">Population</td><td>Performance status</td><td>Patients were enrolled in the trial if they had an ECOG status of 0, 1 or 2.
The majority of patients (94%) had ECOG score of 0 or 1 in both treatment groups. A minority of patients had an ECOG PS of 2.

<table>
<tr><td colspan="3">ECOG score, n (%)</td></tr>
<tr><td></td><td>Pomalidomide bortezomib dexamethasone n= 281</td><td>Bortezomib dexamethasone n=278</td></tr>
<tr><td>0</td><td>149/281 (53%)</td><td>137/278 (49%)</td></tr>
<tr><td>1</td><td>121/281 (43%)</td><td>119/278 (43%)</td></tr>
<tr><td>2</td><td>11/281 (4%)</td><td>22/278 (8%)</td></tr>
</table></td><td>Are the trial results generalizable to patients with an ECOG score of 2 or higher?</td><td>Most patients included in the trial had ECOG equal or ≤ 2. This aligns with the patient population seen in Canadian clinical practice.
The benefit for patients with ECOG ≥ 2 cannot be concluded, based on the small subgroup of patients with ECOG 2 and the exclusion of patients with ECOG > 2 in the OPTIMISMM trial. However, it would be reasonable to expand the pomalidomide triplet combination therapy to patients with disease related ECOG ≥ 2 at the discretion of the treating physician. This would be consistent with standard practice with other myeloma therapies. Disease related symptoms from multiple myeloma may improve with reduction of disease burden. If that symptom is a fracture, or symptomatic anemia, then ECOG can drop to 3 very easily. Myeloma often responds to therapy, and as hemoglobin can rise, or pain settles from fracture, patients' performance status can likewise improve with treatment.</td></tr>
<tr><td>Age</td><td>Patients were enrolled in the trial if they were >18 years old.
<table>
<tr><td colspan="3">Age group, n (%)</td></tr>
<tr><td></td><td>Pomalidomide bortezomib dexamethasone n= 281</td><td>Bortezomib dexamethasone n=278</td></tr>
<tr><td>Median</td><td>67 (IQR 60-73)</td><td>68 (IQR 59-73)</td></tr>
<tr><td>≤65</td><td>123/281 (44%)</td><td>120/278 (43%)</td></tr>
<tr><td>>65</td><td>237/281 (56%)</td><td>158/278 (57%)</td></tr>
<tr><td>≤75</td><td>235/281 (84%)</td><td>231/278 (83%)</td></tr>
<tr><td>>75</td><td>46/281 (16%)</td><td>47/278 (17%)</td></tr>
</table></td><td>Are the trial results generalizable to patients who are age 75 years or higher?</td><td>Most patients included in the trial were < 75 years old. This aligns with the patient population seen in Canadian clinical practice.
The benefit for patients who are older than 75 cannot be concluded, based on the small subgroup of patients in the trial. However, it would be reasonable to expand the pomalidomide triplet combination therapy to patients > 75 at the discretion of the treating physician. This would be consistent with standard practice with other myeloma therapies. The CGP acknowledged some concern</td></tr>
</table>

<table>
<tr><td></td><td></td><td>Subgroup analyses for age groups:
The trial results are reported by each age group (prespecified subgroup analysis, but exploratory in nature). For those >75 there were 28/46 progression free survival events in the PVd group and 25/47 in the Vd group; HR 0.78 (95% CI 0.46-1.32).</td><td></td><td>that there may be an increased risk of heart failure in older subjects, but further study is necessary to clarify this risk.</td></tr>
<tr><td></td><td>Number of prior lines of therapy</td><td>Patients were enrolled in the trial if they had received one to three prior regimens*.

<table>
<tr><td colspan="3">Number of prior lines of therapy n (%)</td></tr>
<tr><td></td><td>Pomalidomide bortezomib dexamethasone n= 281</td><td>Bortezomib dexamethasone n=278</td></tr>
<tr><td>1</td><td>98/281 (35%)</td><td>95/278 (34%)</td></tr>
<tr><td>2</td><td>118/281 (42%)</td><td>107/278 (39%)</td></tr>
<tr><td>≥3</td><td>65/281 (23%)</td><td>76/278 (27%)</td></tr>
<tr><td>> 3</td><td>1/281 (0.35%)</td><td>1/278 (0.35%)</td></tr>
<tr><td>Prior stem cell transplant</td><td>161/281 (57%)</td><td>163/278 (59%)</td></tr>
</table>
* Note: Induction with or without bone marrow transplantation and with or without maintenance therapy was considered to be one regimen.
Pre-specified subgroup analyses (exploratory in nature) for the number of prior lines of therapy:
• For those with 2 prior lines of therapy there were 74/117 progression free survival events in the PVd group and 67/104 in the Vd group; HR 0.67 (95% CI 0.48-0.94)
• For those with >2 prior lines of therapy there were 35/53 progression free survival events in the PVd group and 43/59 in the Vd group; HR 0.60 (95% CI 0.38-0.95)</td><td>Are the trial results generalizable to patients with more than 3 lines of therapy? (PAG question)</td><td>The benefit for patients with more than 3 lines of prior therapy cannot be concluded, based on the very small subgroup (i.e., including only one patient per arm). The CGP concluded that the trial results cannot be generalized to patients with more than 3 prior lines of therapy.</td></tr>
<tr><td></td><td>Type of prior therapy</td><td>Patients were enrolled in the trial if they had received one to three prior regimens*, including at least 2 consecutive cycles of lenalidomide.

All patients received prior immunomodulatory agents. Most patients received corticosteroids, alkylating agents, proteasome inhibitors.</td><td>Do the proportions of prior antimyeloma therapies received by patients in the trial limit the interpretation of the trial results with</td><td>All patients must have received lenalidomide as per trial inclusion criteria. The CGP agreed that the results of the trial are not generalizable to patients who have not received prior therapy with lenalidomide.
The CGP noted that the multiple</td></tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>Selected prior antimyeloma drugs[2]
<table><tr><th></th><th>Pomalidomide bortezomib dexamethasone n= 281</th><th>Bortezomib dexamethasone n=278</th></tr><tr><td>Thalidomide, lenalidomide and Corticosteroids</td><td>25.6%</td><td>24.5%</td></tr><tr><td>Lenalidomide and Proteasome Inhibitor</td><td>75.4%</td><td>76.6%</td></tr><tr><td>Lenalidomide and Bortezomib</td><td>71.5%</td><td>73.0%</td></tr><tr><td>Bortezomib and Dexamethasone</td><td>70.1%</td><td>71.9%</td></tr></table>* Note: Induction with or without bone marrow transplantation and with or without maintenance therapy was considered to be one regimen.</td>
<td>respect to the target population (e.g., Canadian clinical practice patients)?</td>
<td>myeloma landscape is rapidly evolving as new treatments are introduced in the first and subsequent lines. As a result, there may be differences in the proportion of prior antimyeloma therapies received between the OPTIMISMM trial and evolving Canadian clinical practice. However, the CGP felt that the results from the OPTIMISMM trial remain relevant in the Canadian context.</td>
</tr>
<tr>
<td></td>
<td>Lenalidomide non-refractory/ refractory</td>
<td>100% of patients had received prior lenalidomide, of whom, 69.9% were refractory to lenalidomide. About 30% of patients were lenalidomide non-refractory.
Prespecified subgroup analyses (exploratory by nature) were reported for those who are lenalidomide refractory:
• For those who were lenalidomide refractory, there was a median PFS of 9·53 months (95% CI 8·05–11·30) in the PVd arm and 5·59 months (95% CI 4·44–7·00) in the Vd arm (HR 0·65 [95% CI 0·50–0·84]; P=0·0008. This corresponded to 120/200 PFS events in the PVd group and 118/191 in the Vd group.</td>
<td>Are the trial results generalizable to the RRMM population that is non-refractory/refractory to lenalidomide?</td>
<td>The majority of the trial was in those patients with RRMM who are refractory to lenalidomide. Therefore, the CGP felt that results were most generalizable to this population.
A minority of patients in the trial were lenalidomide non-refractory. There is currently no established clinical definition for lenalidomide sensitivity and it is often determined at the discretion of the treating physician using slightly varying criteria. Therefore, it is difficult to determine if the patients in the lenalidomide non-refractory subgroup align with patients in clinical practice.

In Canadian clinical practice lenalidomide treatment is usually prescribed until disease progression or intolerance in newly diagnosed maintenance post-ASCT transplant eligible, newly diagnosed</td>
</tr>
</table>

				transplant ineligible, and relapsed/refractory multiple myeloma. Therefore, patients who have received lenalidomide and are lenalidomide non-refractory upon progression are very few. Subsequent therapy options for these patients are dependent on provincial funding.
	Bortezomib refractory	201/281 (71.5%) and 203/278 (73.0%) had received previous bortezomib and 24/281 (8.5%) and 32/278 (11.5%) were refractory to bortezomib in the PVd group and Vd group, respectively. There are no trial results specified for the subgroup of patients who were refractory to bortezomib.	Are the trial results generalizable to the RRMM population that is refractory to bortezomib?	Due to the small number of patients in the OPTIMISMM trial with bortezomib refractory disease, the CGP did not feel that the results were generalizable to that 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 the trial results apply to patients who are on maintenance therapy with bortezomib or lenalidomide?	This study did include lenalidomide maintenance and the CGP agrees that the results of the OPTIMISMM trial are generalizable to patients who have received prior lenalidomide maintenance therapy post stem cell transplant. There is no data from OPTIMISMM to guide care in individuals who received bortezomib maintenance therapy post-transplant. However, in both transplant and transplant ineligible settings, it is reasonable to apply the results of the OPTIMISMM study in bortezomib exposed patients, if patients are not refractory to bortezomib.
	Renal function	Patients with severe renal impairment (creatinine clearance < 30 mL/min) and receiving hemodialysis were excluded from the OPTIMISMM trial.	Does the exclusion of patients with severe renal impairment limit the interpretation of trial results with the respect to target population?	Although the study excluded patients with a CrCl of 30 ml/min (Cockcroft-Gault) and receiving hemodialysis, use of pomalidomide in patients with renal impairment may be a reasonable consideration in clinical practice. The product monograph does not provide dose adjustments for creatinine clearance $\geq$ 15 to < 60 ml/min as the pharmacokinetics are not significantly altered in this population as compared to those with normal renal function. There are dosing recommendations for patients with creatinine clearance < 30 mL/min

				and receiving hemodialysis.[8] Bortezomib dosing does not need to be adjusted as per the product monograph in renal dysfunction or hemodialysis.[9]
	Hepatic function	Patients with inadequate hepatic function were excluded (total bilirubin level > 1·5 × upper limit of normal; aspartate aminotransferase and alanine aminotransferase levels > 3 × upper limit of normal).	Does the exclusion of patients with inadequate hepatic function limit the interpretation of trial results with respect to target population?	Metabolism of pomalidomide is hepatic, via the cytochrome p450 system. It may be reasonable to allow clinicians to cautiously select patients with hepatic dysfunction prior to treatment to access this treatment, recognizing that such patients would have been ineligible for the key trial but might still benefit from this therapy. *A priori* pomalidomide dose reduction may be required depending on the severity of hepatic impairment, as per the product monograph.[8] Dose adjustment may be required for bortezomib in hepatic dysfunction according to elevated bilirubin or AST levels.[9]
	Other conditions	No evidence was identified within the current review to support the use of PVd in the following populations: Waldenstrom's macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome These conditions were not explicitly excluded from the OPTIMISMM trial; however, inclusion criteria required a diagnosis of multiple myeloma.	Is there evidence to support the use of PVd in patients with Waldenstrom's macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome?	There is insufficient evidence to know the effectiveness of PVd in patients with of Waldenstrom's macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome. The one exception would be plasma cell leukemia, as this is a rare disorder managed in the same fashion as myeloma. This regimen would be a reasonable treatment consideration in this circumstance.
Intervention	Bortezomib dose	The dose of bortezomib in the trial is different than the dose used in Canadian practice (e.g., given on a once weekly schedule for all cycles). The trial dose is 1.3 mg/m2 **twice** weekly and the dose used in Canadian clinical practice is 1.5 mg/m2 **once** weekly.	Is the dose of bortezomib generalizable to that used in Canadian practice?	Intravenous or prolonged twice weekly dosing of bortezomib may be associated with painful peripheral neuropathy. Hematologic and neurologic toxicities are reduced with subcutaneous and once weekly administration of bortezomib

				without sacrificing efficacy.[10] Subcutaneous administration once weekly is currently used in Canada for many bortezomib-containing regimens. In Canada for both VMP and CyBorD Bortezomib is given once weekly for a duration defined by provincial funding.
	Treatment intent	The intent of treatment in the trial was curative and/or palliative?	Are the results of the treatment generalizable to an alternative treatment intent? (i.e., if the trial is palliative in intent, could the therapy also be used in the adjuvant setting or vice versa?)	All therapy(s) in myeloma is palliative. There is no curative therapy.
Comparator	Bortezomib dexamethasone as comparator	The comparator in the OPTIMISMM trial was bortezomib plus dexamethasone. Bortezomib 1.3 mg/m^2 of body surface area was administered subcutaneously or intravenously on days 1,4,8,11 of cycle 1-8 and days 1 and 9 of cycle 9 and beyond. After a total of 15 patients in the PVd arm and 19 in the Vd arm who received bortezomib intravenously, bortezomib administration was changed to subcutaneous after a protocol amendment. Dexamethasone 20 mg orally was given if age 75 or less and 10 mg orally if over age 75 on days 1,2,4,5,8,9,11 and 12 of cycles 1-8 and days 1 and 8 of cycle 9 and beyond. Currently funded treatments for patients who have received at least one prior therapy containing lenalidomide are: (1) daratumumab in combination with bortezomib and dexamethasone, (2) carfilzomib in combination with dexamethasone, or (3) bortezomib, cyclophosphamide and dexamethasone. In order to assess the comparative efficacy of pomalidomide, bortezomib and dexamethasone compared with above therapies, the pCODR Methods Team reviewed one Submitter-provided ITC. Refer to section 7 for more details.	Are the findings of the OPTIMISMM trial generalizable to patients who may receive 1) daratumumab in combination with bortezomib and dexamethasone, (2) carfilzomib in combination with dexamethasone, or (3) bortezomib, cyclophosphamide and dexamethasone instead of bortezomib + dexamethasone?	Yes, the findings of the OPTIMISMM trial are generalizable to the three stated patient populations as long as these patients are not considered bortezomib refractory Per the CSR "Vd was selected as the control arm because this combination was a globally approved standard therapy for RRMM at the time the OPTIMISM trial was conducted. The approved Vd doses and schedule for relapsed or refractory MM was utilized in accordance with the US Prescribing Information and the European Union Summary of Product Characteristics" (Ref = CSR pg 48) The pCODR CGP and the provincial advisory group (PAG) noted that in Canadian clinical practice bortezomib plus dexamethasone is no longer used as it has been replaced by more effective triplet therapies. Due to the lack of randomized comparative data, there is no reliable estimate of the comparative efficacy of pomalidomide, bortezomib and dexamethasone compared with current

				comparators such as (1) daratumumab in combination with bortezomib and dexamethasone, (2) carfilzomib in combination with dexamethasone, or (3) bortezomib, cyclophosphamide and dexamethasone. The CGP suggested that, patient values and preferences, co-morbidities, treatment toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection in clinical practice. CGP believes pomalidomide, bortezomib and dexamethasone would be an addition to and not a replacement of existing therapies. Refer to section 7 for the complete critical appraisals of the Submitter-provided ITC.
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[11], and it is also consistent with other pCODR reviews in myeloma accepting this endpoint as clinically relevant.

1.2.4 Interpretation

Burden of Illness and Need

Multiple myeloma is an incurable plasma cell neoplasm representing 1.3% of all new cancers in Canada. In 2016, it is estimated that 2,700 Canadians were diagnosed with myeloma with 1,450 patients dying from myeloma. The median age at diagnosis is 70 years with a slight male preponderance. Although there is significant heterogeneity within myeloma, the age-standardized five-year net survival rate for Canadian patients between 2006-2008 (excluding Quebec) was 42%.[12]

With better understanding of the biology of multiple myeloma, it is now widely accepted that effective combination novel therapies should be embraced early and continuously while paying attention to the side effect profile. Alkylators, immunomodulatory agents (IMiD), proteasome inhibitors (PI), and monoclonal antibodies are the 4 main "currently" available/approved classes of chemotherapeutics in Canada. An agent from a different therapeutic class is often used in combination with an agent from another in conjunction with steroids such as dexamethasone to enhance efficacy.

Regardless of the choice and duration of initial therapy, myeloma will eventually relapse in the vast majority and further therapy will be required. There is no single clear choice of therapy (combination or sequencing) in relapsed and/or refractory myeloma. The choice of chemotherapy considers the: 1) outcomes with the regimens used in prior lines of therapy, 2) condition of the patient, 3) expected tolerance of adverse effects, 4) availability of treatment options, and 5) personal and geographical considerations. However, it is important to emphasize the need for options and flexibility in chemotherapeutic care from a patient-centred perspective.

Taken together, patients typically receive all possible available effective chemotherapeutic options sooner or later and in various combinations unless lost to early mortality. It is important to emphasize that the use of effective, superior and safe combination therapy early is preferred as opposed to "saving them for later". In general, the former approach leads to better PFS, OS and health-related quality of life (HRQOL).

Sequencing of therapy – the Canadian landscape

Excluding the participation in clinical trials and compassionate access to medications, the sequencing of therapy is highly dependent on provincial funding. Given the differences in provincial funding of various myeloma therapies, it is impossible to ascertain or recommend the optimal or preferred sequencing of therapy. However, clinicians and patients value more (as opposed to fewer) chemotherapeutic care options. As such, a chemotherapeutic sequence that enables more options is generally favoured.

Clinical Outcomes in Myeloma

Progression Free Survival (PFS) is considered a clinically important and valid primary endpoint in studies of myeloma therapy where an absolute improvement of >4-6 months is considered clinically meaningful from a patient's perspective. Overall survival (OS) remains an important endpoint in myeloma studies but the use of subsequent lines of therapy in this incurable malignancy often makes it difficult to discern an OS benefit from one line of therapy. Additionally, measurements of adverse events and health-related quality of life are critical in assessing potential benefits of therapy from a patient-centred perspective.

It is within this context that pomalidomide in combination with bortezomib and dexamethasone for relapsed myeloma is assessed at the Clinical Guidance Panel. Within the pCODR framework of reviews, the reviewers identified one Randomized Control Trial addressing the Submitter's request for funding.

Effectiveness

The identified randomized open labelled trial (OPTIMISMM) compared bortezomib, dexamethasone and pomalidomide (PVd) to bortezomib and dexamethasone (Vd) for patients with progression of myeloma following at least one prior treatment regimen including lenalidomide with PFS as the primary outcome. The population enrolled within the trial is currently considered to be reflective of patients within the Canadian context and notably the trial included patients who were refractory to lenalidomide (70% of the trial population).

Overall, this trial demonstrates a statistically and clinically significant improvement in PFS with the addition of pomalidomide to bortezomib and dexamethasone; PVd (HR=0.61; 95%CI: 0.49-0.77, P=0.0001) with a median follow-up of 15.9 months. There was 4.1 months median PFS advantage for the triple combination.

Pre-specified subgroup analyses were also in favor of the triple combination. Interestingly, the PFS2 (PFS after next line of therapy) was also in favor of the triple combination where the median PFS after next line of therapy was 22.44 months (95% CI 18.96 – not estimable) in the PVd arm and 16.95 months (95% CI: 14.69-21.09) in the Vd arm (HR=0.76, 95%CI: 0.59-0.99, P<0.041). In contrast, the trial did not demonstrate an OS benefit with PVd nor differences in HRQOL as measured by QLQ-C30, QLQ-MY20 and EQ5D scales.

Clinical Uncertainties

With the assumed increasing use of monoclonal antibody therapy: daratumumab (D), there is uncertainly on where the regimen of PVd would fit, especially where none of the patients within the trial had previously received daratumumab. Additionally, daratumumab is currently only funded as part of combination therapy (DRd or DVd) but not otherwise which may influence the sequence of therapy.

Another potential uncertainty relates to the definition of refractoriness to lenalidomide which follows the International Myeloma Working Group (IMWG) criteria. Individuals could be considered refractory to lenalidomide on a traditional maintenance dose of 5-15mg or refractory to lenalidomide on a generally considered therapeutic dose of 15-25mg. Nonetheless, an inspection of the total dose delivered and duration of therapy of lenalidomide, both randomized arms appeared balanced.

In addition, as clarified by the sponsor in the June 14, 2019 response to specific requests for additional information, 75% (75% on PVd and 77% on Vd) of the patients considered refractory to lenalidomide manifested their myeloma progression while receiving or within 60 days of receiving lenalidomide in combination with other agents (primary therapeutic refractoriness) and only 25% (25% on PVd and 23% on Vd) did so while receiving single agent lenalidomide (refractory to maintenance lenalidomide). Thus, the majority of patients considered refractory to lenalidomide manifested this treatment resistance while receiving a full therapeutic dose of lenalidomide.

Safety

The addition of pomalidomide to bortezomib and dexamethasone resulted in additional infectious risk, but this toxicity is manageable in clinical practice. There was no obvious

detrimental impact on HRQOL. Overall the CGP agreed that the safety of PVd seems manageable and consistent with the safety profile of pomalidomide with dexamethasone in later line of therapy.

Comparative Therapies considered

There are several recent drug therapies for relapsed myeloma that have been demonstrated in randomized trials to improve PFS. The following 2 trials are most pertinent in the current context:

- ENDEAVOR, where carfilzomib and dexamethasone has been compared to bortezomib and dexamethasone in a randomized trial in the relapsed setting. The proportion of patients who were refractory to lenalidomide was 27.4%.

- CASTOR, where daratumumab, bortezomib and dexamethasone has been compared to bortezomib and dexamethasone in a randomized trial in the relapsed setting. The proportion of patients who were refractory to lenalidomide was 28.3%.

- *69-72% of patients in the OPTIMISMM trial were refractory to lenalidomide.*

Direct randomized comparisons between these various regimens are unlikely to take place in the setting of relapsed myeloma. Consequently, network meta-analyses (NMA) are performed with an example of which is provided by the Submitter. The results are uncertain given the limitations of the available data. Ultimately, the NMA seeks to ascertain indirectly which agent(s) is superior. However, in the care of patients with myeloma, a "new" medication is not a replacement for another, rather an additional option for care.

1.3 Conclusions

The Clinical Guidance Panel concluded that there may be a net overall clinical benefit to pomalidomide in combination with bortezomib and dexamethasone (PVd) in the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

This is based on one high-quality randomized controlled trial that demonstrates a clinically and statistically significant benefit in progression-free survival as compared to the previous standard regimen of bortezomib and dexamethasone (Vd) with a manageable adverse event profile. For instance, PVd may be the preferred option by patients and/or clinicians who chose to avoid the long infusion times associated with daratumumab based therapy in the relapsed setting.

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

- Other drug combinations (DVd and KD) have been compared with bortezomib and dexamethasone to treat relapsed and refractory myeloma. Both regimens have been reviewed by pCODR and other drugs (e.g. panobinostat) which have not yet been reviewed by pCODR in this setting. Given the absence of direct comparisons, it is not clear that one of these agents is superior to another. A Network meta-analysis was submitted to help determine the comparative efficacy of PVd combination therapy compared to these relevant therapies. Several limitations were identified in the presented results and therefore caution must be used in interpreting these results as discussed.

- The evidence base is the strongest in those that are LEN-refractory and is most consistent with the circumstances in which Canadian physicians would consider PVd. In Canadian clinical practice lenalidomide treatment is usually prescribed until disease progression or intolerance in newly diagnosed maintenance post-ASCT transplant eligible, newly diagnosed transplant ineligible, and relapsed/refractory multiple myeloma. Therefore, patients for whom lenalidomide is no longer an option are clinically a very relevant population. None of the current standard of care regimens are specifically indicated in lenalidomide refractory patients.
- The OPTIMISMM trial evidence supporting PVd provides the best data on response and PFS using a triplet regiment in a majority lenalidomide-refractory population. Previous large studies have only included relatively small subsets of LEN-refractory patients.
- From a clinical and patient-centred perspective, a reasonable option is to make pomalidomide available to be combined with bortezomib and dexamethasone (PVd) as opposed to "saving it for last", using it as a later line of therapy as pomalidomide with dexamethasone +/- cyclophosphamide (currently funded).
- The CGP agreed that there is insufficient data to critically know the appropriate sequencing of these drugs in the first, second or subsequent line setting. This is compounded by differing provincial funding of drugs, including some provinces' requirement that certain specific agents such as daratumumab only be provided in combination with other specified agents. These province-specific requirements preclude identification of a common Canadian algorithm for sequencing myeloma treatment regimens.

Provincial Advisory Group's (PAG's) Implementation Questions:

1. PAG is seeking clarity on whether autologous stem cell transplant or maintenance lenalidomide would be considered as one line of prior therapy. Specifically, whether consistency with the carfilzomib recommendation would be appropriate.

   Response: Yes, autologous stem cell transplant with or without maintenance lenalidomide would be considered one line of therapy. The following regimens would be considered one line of therapy (depending on provincial funding criteria and access to medications based on individualized cases):
   i. CYBORD, ASCT (no maintenance lenalidomide);
   ii. CYBORD, ASCT (with maintenance lenalidomide);
   iii. CYBORD, ASCT, RvD (with maintenance lenalidomide);
   iv. CYBORD. Bortezomib (as maintenance therapy) ;
   v. Rd, R(d).

2. PAG noted that additional health care resources may be required to monitor and treat toxicities (e.g., neutropenia, thrombocytopenia, neuropathies). Some patients may require G-CSF while on pomalidomide combination therapy

   Response: It is not anticipated that additional health care resources will be required (beyond those that are typically required for comparator treatments) to monitor and treat toxicities (e.g., neutropenia, thrombocytopenia, neuropathies). It is important to recognize that if PVd is not used in earlier lines of therapy, that pomalidomide may be used later. The monitoring and treatments for side effects will be the same if used in earlier or later lines of therapy - contingent on mortality. The need for G-CSF while on pomalidomide combination therapy versus comparators is difficult to quantify because

its use varies by clinician. Clinical considerations for using G-CSF include if there is belief that the disease or the drug is causing the neutropenia, if the neutropenia is a clinical concern for the patient (e.g., the patient has neutropenia but has not had an infection), if one would prefer to attenuate the dosing and frequency of pomalidomide versus prescribing G-CSF, and the availability of grastofil (potentially less expensive biosimilar).

3. PAG noted the different dosing schedules for the three medications (two oral and one intravenous) may be difficult for patients and may lead to patient confusion. Processes would need to be in place, prior to implementation of pomalidomide + bortezomib + dexamethasone, to minimize dosing errors and patient confusion. PAG noted that familiarity with bortezomib and dexamethasone would be an enabler to implementation.

   Response: The CGP does not anticipate that the different dosing schedules for the three medications (two oral and one intravenous) will be difficult for patients or lead to dosing errors or patient confusion. The CGP noted that there are already processes in place for more complicated treatment schedules (e.g., KRD, RVD, DRd).

4. Given the multiple treatments that will be available, PAG is seeking guidance on the appropriate place in therapy of pomalidomide in combination with bortezomib and dexamethasone and sequencing of all treatments available. Sequencing of first and second-line therapies (e.g., carfilzomib-based, lenalidomide-based, daratumumab-based, and bortezomib-based regimens) for patients that are either eligible or ineligible for autologous stem cell transplant.

   Response: The CGP indicated that treatment sequencing varies depending on provincial funding and access. There is limited evidence to guide appropriate sequencing of treatments.

5. If pomalidomide + bortezomib + dexamethasone was available, what line of therapy would you prefer to use the pomalidomide triplet therapy?

   Response: The CGP emphasized that more treatment options are better given that this disease is not curable. If pomalidomide + bortezomib + dexamethasone was available, the CGP indicated that it would be valuable to have flexibility in the line of therapy that is selected given that line of therapy is dependent on provincial access to other active agents together with patient preferences. Three scenarios are outlined below that provide hypothetical examples of the complexity of the treatment sequencing, and how clinicians may maximize the lines of therapy available (ignoring potential patient access through clinical trials):

Scenario 1: Transplant Eligible

1st line: CYBORD, ASCT, LEN maintenance
2nd line: Daratumumab, bortezomib, dexamethasone. In principle, one could not use DRd with progression on LEN. If PVd was used here, on relapse, the patient would be refractory to LEN and bortezomib. This means the patient would not be able to access Daratumumab (not funded as a non-triplet, only in combination with either bortezomib or LEN). This would mean a loss of a line of therapy. Carfilzomib and dexamethasone (KD) as second line could be used; however, provinces may view carfilzomib (more potent PI as compared to bortezomib) refractory as bortezomib refractory, which again negates the potential to use Daratumumab.

3rd line: Kd. PVd cannot be used here because the patient would not be considered refractory to both bortezomib and carfilzomib.
4th line: By default, the clinician would use Pomolidomide/dexamethasone (+/- cyclophosphamide).

Scenario 2: Transplant Ineligible

1st line: LEN and Dex. The majority of patients and physicians prefer this option as 1st line)
2nd line: Daratumumab, bortezomib, dexamethasone.

The same scenario as above (transplant eligible) applies. PVd would therefore be used when clinicians and/or patients are willing to forgo future access to daratumumab (resulting in a loss of one therapeutic option).

Scenario 3: Transplant Ineligible

1st line: CYBORD and Bortezomib, Melphalan, and Prednisone (VMP) (fixed duration therapy)

2nd line: Daratumumab—bortezomib- dexamethasone or
Daratumumab—lenalidomide- dexamethasone or
Carfilzomib - dexamethasone or
PVd
3rd line: Dependent on the above choice in 2nd line.

This is the only scenario where a true choice of using PVd in an earlier line of therapy will not result in the loss of option of Dara triple or carfilzomib use in later lines.

6. In clinical practice, if pomalidomide + bortezomib + dexamethasone was available, when would you prefer to use pomalidomide over currently available novel triplet therapies?

   Response: The CGP indicated that all myeloma treatment options are considered additional treatment options, not replacements. This is because the disease is incurable and having more options has the potential to improve patient outcomes. The preference for PVd over other novel triplets (DRd, DVd, KRD) is nearly never as described above (see response to question 5). The only circumstance pertains to patient preference.

7. In clinical practice, can proteasome inhibitors (i.e., bortezomib, ixazomib, or carfilzomib) be used interchangeably for patients with relapsed/refractory multiple myeloma? If yes, what is the preferred proteasome inhibitor? Please comment on the preference considering patient preference, efficacy, safety, and administration.

   Response: The CGP indicated that from an efficacy perspective, carfilzomib would be considered superior to bortezomib and ixazomib, while bortezomib and ixazomib would be considered equivalent. Carfilzomib is considered to be “more toxic” compared to ixazomib and bortezomib; however, the toxicity profile is highly individualized. From a patient preference perspective, oral drugs are preferred over SC and SC over IV. Generally, the CGP indicated that proteasome inhibitors can be used interchangeably, however, when used without considering the provincial funding landscape, this may preclude patient access to other active

myeloma agents as discussed above (see response to question 5) (based on funding criteria, not clinical evidence).

2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

Multiple myeloma is an incurable plasma cell neoplasm that makes up 1.3% of all new cancers in Canada. In 2016, it is estimated that 2700 Canadians were diagnosed with myeloma, and 1450 patients died of this disease. The median age at presentation is 70 years old with a slightly higher incidence in males. Although there is significant heterogeneity within myeloma, the age-standardized five-year net survival rate for Canadian patients between 2006-2008 (excluding Quebec) was 42%.[12]

The diagnosis of myeloma is made based on excess clonal plasma cells in the bone marrow and/or very high levels of secreted monoclonal protein in the blood. 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. For some patients without end organ damage, observation is appropriate, and no therapy is initially required. Most patients are either symptomatic at diagnosis or are highly likely to soon develop symptoms; these patients require immediate therapy.[13]

Patients can be stratified into groups with differing prognosis based on clinical and laboratory parameters. The International Myeloma Working Group has most recently defined high-risk cytogenetic features of myeloma to include one or more of the following: FISH –detected t(4;14), t(14;16), t(14;20), del(17p), or gain(1q); non-hyperdiploid karyotype; high risk gene expression profile signature; and del(13) detected by conventional cytogenetics.[14] Other clinical features of high risk myeloma include elevated serum beta-2-microglobulin and LDH levels. The current, revised international staging system (R-ISS) for myeloma identifies three stages, the highest risk stage being those 10% of patients with Beta-2-microglobulin >/=5.5 mg/L and at least one of the following: elevated serum LDH, t(4;14), t(14;16), del(17p).[15]

To date there has not been definitive evidence from randomized trials that has identified a superior treatment strategy which differs based on patient risk stratification. While existing evidence suggests that proteasome inhibitors and newer immunomodulatory drugs partly overcome the adverse prognostic significance of high risk disease features, especially when used in combination, the same therapies are generally recommended for patients without high-risk disease features.[14] Nevertheless, some expert clinicians have interpreted the existing evidence to recommend treating patients differently based on cytogenetic profile, for example offering bortezomib rather than lenalidomide as maintenance therapy for patients with t(4;14) myeloma[16]; this practice is applied by some Canadian clinicians.

2.2 Accepted Clinical Practice

Systemic therapy is the primary modality of treatment. Alkylators (melphalan or cyclophosphamide), proteasome inhibitors (ixazomib, bortezomib or carfilzomib), immunomodulatory drugs (thalidomide, pomalidomide or lenalidomide) and corticosteroids (prednisone or dexamethasone) have proven to be highly effective therapies for myeloma, and the utilization of these drugs have improved survival of myeloma patients.[17] There is no consensus with respect to the optimal sequencing or combination of drugs that should be used.

For fit patients, an autologous stem cell transplant (ASCT) can be considered as part of the initial therapy of myeloma and substantially improves life expectancy. However, the toxicity of this treatment precludes its use in less fit patients. Choosing the appropriate patients for ASCT is at the discretion of the treating physician and approximately half of patients are transplant eligible. Prior to receiving high dose melphalan chemotherapy conditioning for the transplant, three or four cycles of systemic induction therapy is used to control the disease, improve the health of the patient, and clear the bone marrow to allow for easier stem cell collection. In Canada, induction is usually with bortezomib, cyclophosphamide and dexamethasone. Patients receive one or sometimes two cycles of high dose chemotherapy with stem cell rescue as part of front line treatment. Following stem cell transplant, further consolidation therapy is sometimes given; an indefinite course of maintenance therapy with lenalidomide or bortezomib is often given with the intent to prolong remission duration and survival.[18,19] The administration of induction therapy, high dose chemotherapy with autologous stem cell transplant, and post-transplant consolidation and/or maintenance therapy is all considered as being part of first-line treatment.

Current standard frontline systemic therapy regimens in Canada for transplant-ineligible patients include combinations of bortezomib with an alkylating agent (melphalan or cyclophosphamide) and a corticosteroid; or lenalidomide and dexamethasone.[20] While recent evidence supports the use of bortezomib, lenalidomide and dexamethasone as a standard 3-drug frontline regimen, this combination has only recently been evaluated by pCODR and is not yet routinely available in most jurisdictions.[21]

It seems generally that continuous therapy prolongs remission duration as compared to a more defined duration of therapy.[22] Many patients will therefore continue with frontline therapy until the disease demonstrates itself to be relapsed and/or refractory to the current treatment. Other patients will discontinue frontline therapy while still in remission, without the disease being demonstrably refractory to any drugs, in order to have a reprieve from the adverse effects of treatment.

Regardless of the choice and duration of initial therapy, myeloma will eventually relapse in the vast majority and further therapy will be required. There is no single clear choice of therapy in relapsed and/or refractory myeloma. The choice of agents used in this setting will depend on the outcomes with the regimens used in prior lines of therapy, the condition of the patient, the expected tolerance of adverse effects, and the availability of treatment options. Although patients are often not offered therapy with drugs that have been part of a regimen to which the disease has become refractory, there is evidence that combining such agents sometimes induces responses, particularly in the case of combining proteasome inhibitors and immunomodulatory drugs.[23]

2.3 Evidence-Based Considerations for a Funding Population

Pomalidomide in combination with dexamethasone (dex) and bortezomib is currently approved by Health Canada for use in adult patients with multiple myeloma (MM) who have received at least one prior treatment regimen that included lenalidomide.

The population studied in the key clinical trial under consideration here includes patients aged ≥ 18 years, with a diagnosis of multiple myeloma and measurable disease who had received one to three prior regimens, including a lenalidomide-containing regimen for at least two consecutive cycles, and who have an ECOG performance status of 0-2. Patients previously treated with bortezomib were permitted entry into the trial provided they did not have disease progression during treatment or within 60 days of the last dose of bortezomib. Overall, 100% of patients had received lenalidomide (70% were refractory to lenalidomide); 71.5% and 73% in the pomalidomide and control arms, respectively had received prior bortezomib. This trial provides evidence for patients who are lenalidomide refractory, which is a group of patients who have not been well represented in clinical trials. We are

reviewing the efficacy of the pomalidomide triplet combination in the entire population of patients that were enrolled in this clinical trial.

2.4 Other Patient Populations in Whom the Drug May Be Used

The combination of pomalidomide, dexamethasone, and bortezomib could potentially be considered as treatment for patients with an ECOG performance status of greater than 2; for those with creatinine clearance of 30 mL/min/1.73 m2; for those with hepatic dysfunction; and for patients who receive bortezomib at a dose of 1.5mg/m^2 once weekly.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient input was provided to pCODR through a patient advocacy group submission from Myeloma Canada (MC) for pomalidomide in combination with dexamethasone and bortezomib (PVd) for relapsed or refractory multiple myeloma (RRMM). Information was obtained via four online surveys:

Survey 1 included a total of 344 patients. Among these respondents, 238 were from Canada (representing each province, except New Brunswick and none of the respondents were from the territories), 104 were from the United States and 2 were from Israel.

Survey 2 included a total of 123 caregivers. Among these respondents, 82 were from Canada (representing each province, except New Brunswick, Prince-Edward-Island and none of the respondents were from the territories), 40 were from the United States and 1 was from Australia. Surveys 1 and 2 were conducted between August 15, 2016 and August 31, 2016. Survey details and related results were submitted to pCODR for both the carfilzomib (September 2016) and ixazomib (January 2017) reviews, (for RRMM) and were referred to by MC in their submission for the current review on PVd.

Table 3.1 Geographic location of respondents

Location	Survey 1	Survey 2
Canada	238	82
Unites States	104	40
Israel	2	0
Australia	0	1

Surveys 3 and 4 gathered experiences on the triple drug combination under review (PVd) as well as on bortezomib combined with dexamethasone (Vd). These surveys were available online from February 22 to March 26, 2019. In both surveys, respondents were patients, or the caregiver of a patient, with relapsed or refractory multiple myeloma (RRMM) who had received at least one prior treatment regimen. Overall, eight patients and nine caregivers had experience with PVd, while 36 patients and 13 caregivers had experience with Vd. Country of origin of respondents to Surveys 3 and 4 was not mentioned. Note that MC did not report the proportion of respondents who had RR MM (as opposed to newly diagnosed MM) at the time of the surveys (1-4).

Unless otherwise specified, the information in this report under sections: 3.1.1 Experiences Patients Have with Multiple Myeloma, 3.1.2 Patients' Experiences with Current Therapy for Multiple Myeloma are derived from the first MC survey directed to patients (Survey 1) and the information under section 3.1.3 Impact of Multiple Myeloma on Caregivers is based on the survey directed to caregivers (Survey 2). Note that experiences with "current" treatments (section 3.1.2) collected by these older surveys may no longer reflect the present situation (as of 2019). Information reported under section 3.2 Information about the Drug Being Reviewed was obtained from Survey 3 (patients) and Survey 4 (caregivers). Experiences with Vd taken from Survey 3 are briefly summarized in section 3.1.2.

In all open-ended questions, the responses have been grouped into categories with the percentage of responses indicated. In some cases, the total does not add up to 100% due to responses falling into more than one category (i.e., the total is more than 100% as respondents were able to select more than one answer).

From a patient's perspective, infections were the most important aspect of myeloma to control. MM symptoms had a relatively high impact on daily life and most notably impacted patients' ability to work. Patients regarded the maintenance of quality of life as the most desirable treatment goal, followed by management/minimization of side effects. Dexamethasone, bortezomib and lenalidomide were the most frequently cited therapies used by patients. Frequent side effects included fatigue, neuropathy, insomnia, gastrointestinal problems and shortness of breath. Almost all respondents considered access to effective treatments for MM to be crucial, and three quarters did not report any issues with accessing treatment. Additionally, most patients believed treatment choice based on side effects was highly important. Most respondents had concerns about financial implications, with drug and parking costs being the most frequently cited. Patients had a generally positive outlook towards treatment with Vd and appreciated its effectiveness and low toxicity, allowing them to maintain a good quality of life.

Treatment with PVd was similarly rated by patients, but slightly lower quality of life, side effect tolerability and overall satisfaction were noted (the low number of respondents in each group precludes any formal comparison). A majority of patients that received PVd stated an improvement in disease control followed by remission and improved side effects whereas less than half expressed quality of life was fulfilled with PVd. Side effects deemed completely intolerable were infections/pneumonia, pain and diarrhea.

Caregivers of patients with MM taking PVd experienced challenges with managing side effects, which largely impacted their ability to travel and to volunteer.

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

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Relapsed/Refractory Multiple Myeloma

The following survey responses were submitted for pCODR reviews on ixazomib and carfilzomib, two comparator drugs used for RRMM, and also apply to PVd according to MC. MC 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 MM. According to MC, infections were the most important aspect of myeloma to control, followed by kidney problems, pain, mobility, neuropathy, fatigue and shortness of breath. The results collected from the respondents are reproduced in Table 3.2**Error! Reference source not found.** below.

Table 3.2: Aspects of MM to Control

	1 - Not important	2	3	4	5 - Very important	N/A	Total
Infections	0.34% 1	1.34% 4	4.36% 13	10.40% 31	83.22% 248	0.34% 1	298
Kidney problems	2.01% 6	1.34% 4	3.68% 11	9.36% 28	80.60% 241	3.01% 9	299

	1 - Not important	2	3	4	5 - Very important	N/A	Total
Mobility	0.34% 1	1.01% 3	4.70% 14	21.14% 63	70.81% 211	2.01% 6	298
Pain	0.67% 2	1.67% 5	9.03% 27	20.07% 60	66.56% 199	2.01% 6	299
Fatigue	0.00% 0	1.71% 5	10.92% 32	20.48% 60	65.87% 193	1.02% 3	293
Neuropathy	0.33% 1	2.34% 7	9.70% 29	21.07% 63	64.55% 193	2.01% 6	299
Shortness of breath	1.01% 3	2.03% 6	13.85% 41	18.92% 56	62.16% 184	2.03% 6	296

The following survey responses also reflect the views of patients submitted for pCODR reviews on ixazomib and carfilzomib. When MC asked patient respondents to rate on a scale of 1 to 5, how much symptoms associated with MM impact or limit day-to-day activity and quality of life, patient respondents indicated that their ability to work was most affected, followed by the ability to exercise, travel, volunteer, concentrate, conduct household chores, fulfill family obligations, and spend time with family. Based on the responses below, MC expressed that symptoms associated with myeloma have a higher than neutral impact.

Table 3.3: Impact of MM Symptoms on Daily Life

Ability to:	1 - Not at all	2	3	4	5 - Significant impact	N/A	Total
Work	10.23% 31	14.19% 43	16.83% 51	14.19% 43	29.70% 90	14.85% 45	303
Exercise	8.61% 26	19.21% 58	24.17% 73	24.83% 75	21.85% 66	1.32% 4	302
Travel	13.25% 40	16.23% 49	27.15% 82	17.88% 54	24.17% 73	1.32% 4	302
Volunteer	16.33% 49	18.00% 54	23.33% 70	18.33% 55	19.00% 57	5.00% 15	300

Ability to:	1 - Not at all	2	3	4	5 - Significant impact	N/A	Total
Concentrate	12.67% 38	24.33% 73	23.00% 69	21.00% 63	17.33% 52	1.67% 5	300
Conduct household chores	14.62% 44	22.26% 67	29.24% 88	20.60% 62	12.62% 38	0.66% 2	301
Fulfill family obligations	18.94% 57	25.58% 77	27.91% 84	13.62% 41	11.96% 36	1.99% 6	301
Spend time with family and friends	22.85% 69	25.17% 76	24.83% 75	14.57% 44	11.92% 36	0.66% 2	302

The following are quotes reported by MC to illustrate the effect of MM on patients:

"Extra care when going out into the public to minimize the potential exposure to disease and germs - easier to get sick, takes longer to get better."

"My emotional well being is significantly impacted due to treatment which includes steroids."

"The impact is cyclical depending on where I am in my disease control, sometimes all of these things (the list above) see(m) very difficult and sometimes not as much."

"Diarrhea limits my day plan - have to plan around it all the time."

"Ability to work n/a as Retired, but often unable to do what I used to enjoy e.g. Woodworking, "outside chores".

Certainly could not have done my job - renovations, building etc."

3.1.2 Patients' Experiences with Current Therapy for Relapsed/Refractory MM

MC reported that 261 respondents to survey 1 indicated the following when asked "*what is important to you when it comes to treating your myeloma*":

- Maintain Quality of Life or normal life: 36%
- Manage/minimize side effects: 20%,
- Control the disease: 19%
- Access to effective treatments: 15%
- Control symptoms: 13%,
- Achieve or maintain remission: 7%
- Prolong survival: 7%
- Access to a skilled medical team: 6%
- To be cured: 5%
- Affordable treatments: 3%
- Disease status: 2%

- Maintain physical fitness: 1%
- Minimal use of drugs: 0.5%
- To feel hopeful: 0.5%.

Respondents (n=295) were asked to identify treatment(s) used to treat their myeloma. It is important to note that some respondents selected more than one answer. Also, survey results were reported in the context of a pCODR call for input on carfilzomib and were referred by MC for the present review. As a result, survey questions referring to "current" therapies excluded carfilzomib. Treatments that patients used included:

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

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

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

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

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

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

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

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

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

The yes responses included:

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

Complementing the aforementioned information from Survey 1 (2016), Survey 3 (2019) collected the experience of patients who had undergone or were undergoing Vd therapy. Fifty percent or more of the patients (N=24) considered that Vd fulfilled their expectations regarding improved quality of life, disease control, remission and prolonged life. However, only 33% had fewer side effects than expected and 43% were able to enjoy a normal life.

In terms of effectiveness, 29% of respondents (9 out of 31 patient respondents) to Survey 3 rated Vd as "not" effective or "fairly effective" and 71% rated it as "effective" to "extremely effective". Some patients commented about the burden of weekly (or more) hospital visits for bortezomib injections. Side effects from Vd (e.g., pain, fatigue, fever, low blood counts) were "tolerable" to "extremely tolerable" according to 86% of survey respondents and were managed by lifestyle changes. Patients were able to maintain their quality of life with only 3% rating it as "poor" throughout the treatment. Vd met the therapeutic expectations of 61% of respondents while 3% of patients were not satisfied; the remaining 35% provided a mixture of positive and negative comments:

- *"Didn't expect neuropathy"*
- *"The treatment sure helped in taking away the pain of myeloma and prepared me for my transplants."*
- *"Doing good since my first treatment"*
- *"I didn't know what to expect re. outcome but did achieve remission for about 18 mos"*
- *"Stopped responding to treatment after 3 cycles"*
- *"I had to fast before and after to help Val./Dex do the job for me"*
- *"It was good but was only effective for a little over a year."*

Overall, 66% of survey respondents (20 out of 31 respondents) felt that Vd has improved their health and well-being and 53% thought it improved their long-term health outlook.

3.1.3 Impact of RR MM and Current Therapy on Caregivers

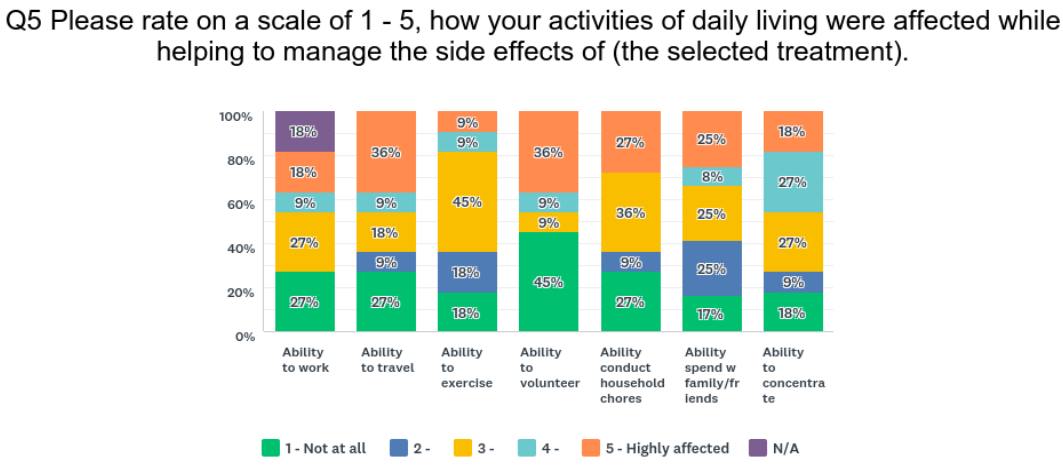
When MC asked caregiver respondents in Survey 2 to rate how much caring for someone with MM limits their day-to-day activity and quality of life, caregivers indicated that their ability to travel was most affected, followed by the ability to volunteer, spend time with family and friends, concentrate, fulfill family obligations, work, exercise, and conduct household chores. The total number of caregiver respondents for this answer ranged from 115 to 120.

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

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

Survey 3 provided more details around the perspective of caregivers specifically about Vd. Slightly more than half (54%) of caregivers (7 out of 13 caregiver respondents) experienced challenges with helping to manage side effects of Vd for the person under their care. Caregivers (N=11) rated the impact of the treatment on their activities of daily living. Figure 3.1 displays the proportion of caregivers who rated the impact on various activities on a scale of 1 (not at all) to 5 (highly affected). When considering all ratings above 1 as affecting daily living, the ability to travel and volunteer was rated as the activity most affected by Vd therapy, followed by the ability to conduct household chores and spend time with family and friends.

Figure 3.1: Impact of Vd on Caregiver Daily Activities



3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for Pomalidomide/Bortezomib/Dexamethasone (PVd)

Survey 3 asked patients (N=8) what would be their expectations regarding treatment with PVd. Responses were ranked from most important (1) to least (6) important. Quality of life, disease control and the enjoyment of a normal life were prioritized by most survey respondents. Table 3.4 presents the results for expectations regarding PVd

Table 3.4: Expectations Regarding PVd

Expectation	1 (most important)	2	3	4	5	6 (least important)	N/A
Improved quality of life	43%	0%	14%	43%	0%	0%	0%
Disease control	25%	13%	13%	13%	13%	13%	13%

Remission	13%	13%	25%	13%	13%	13%	13%
Prolonged life	0%	38%	25%	13%	13%	13%	0%
Fewer side effects than other treatments	0%	29%	14%	14%	14%	14%	14%
Enjoy a normal life	25%	0%	0%	13%	38%	25%	0%

3.2.2 Patient and Caregiver Experiences To Date with PVd

Patients (N=7) experienced treatment with PVd and answered whether their expectations regarding the treatment were fulfilled. The following proportions of patients answered "yes":

- Improved quality of life: 38%
- Disease control: 63%
- Remission: 50%
- Prolonged life: 25%
- Fewer side effects than other treatments: 50%
- Enjoy a normal life: 13%
- Other: 13%

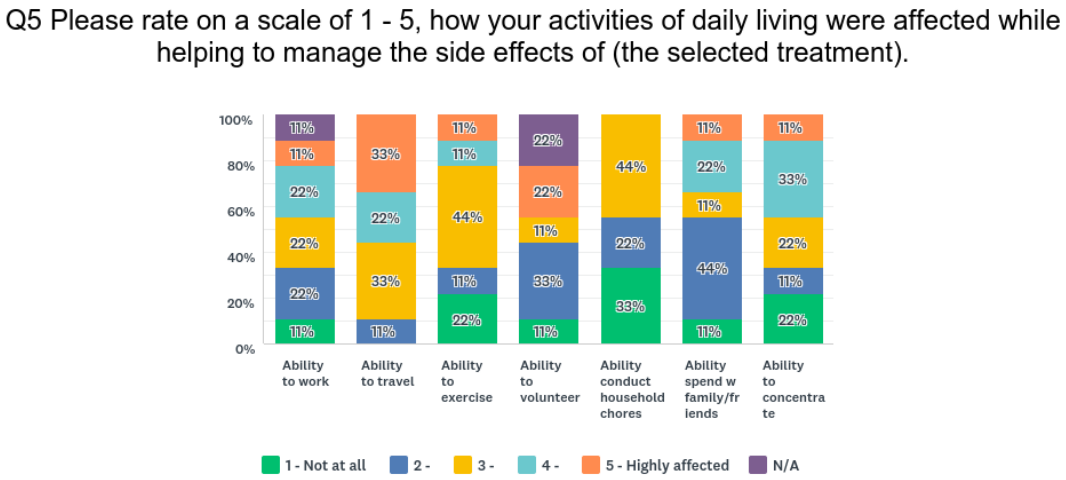
Patients (N=7) rated the effectiveness of PVd in controlling their MM. Fourteen percent of patients reported a rating of "not effective" and "fairly effective", 43% rated the treatment as "very effective" and 29% rated it as "extremely effective". When the seven respondents who used the treatment under review were asked if the administration of their treatment (oral vs. injection) had a negative effect, three (43%) responded "yes" and four (57%) responded "no". Survey respondents provided additional comments. Respondents included that they experienced "lots of nausea & diarrhea," "lack of energy for a couple days after treatment" in addition to sleep difficulties.

Patients (N=8) were asked to share their experiences regarding side effects of PVd. Thirty eight percent answered that the side effects were "somewhat intolerable" while 25% reported "tolerable", 25% reported "very tolerable", and 13% extremely tolerable side effects. In addition, patients reported the side effect rating of PVd. Most patients rated all side effects as at least "tolerable". Infections/pneumonia, pain and diarrhea were rated as completely intolerable by 13% of respondents. When asked to explain how they managed their side effects, respondents who used PVd reported either quitting treatment or using drugs such as Tylenol #3, Tylenol, morphine or lorazepam.

Patients rated their quality of life since starting PVd. Three patients (38%) reported "fair quality of life" while the rest deemed their quality of life "good" to "excellent". Eight respondents reported on whether their expectations were met with PVd treatment. PVd met therapeutic expectations of three (38%) patients while one (13%) was not satisfied. The remainder (four) answered with the following comments: "toe amputations", "not yet", "didn't work" and "total remission". In the same vein, half of the patients felt that PVd improved their health and well-being and their long-term health outlook.

Caregivers (N=9) also provided their perspective on PVd therapy. Two thirds experienced challenges with managing side effects experienced by the patients under their care. Caregivers rated the impact of the treatment on their activities of daily living. Figure 3.2 displays the proportion of caregivers who rated the impact of side effects on various activities on a scale of 1 (not at all) to 5 (highly affected). The ability to travel was rated as the activity most affected by PVd side effects.

Figure 3.2: Impact of PVd on Caregiver Daily Activities



3.3 Additional Information

None

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

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

Clinical factors:

- Clarity on patients who would eligible for treatment
- Sequencing of currently available treatment and upcoming treatments

Economic factors:

- Additional healthcare resources for drug preparation and toxicity management

Please see below for more details.

4.1 Currently Funded Treatments

Currently funded treatment options for previously treated multiple myeloma include carfilzomib/lenalidomide/dexamethasone, carfilzomib/dexamethasone, lenalidomide/dexamethasone, bortezomib, and pomalidomide/dexamethasone.

PAG noted that daratumumab (with lenalidomide/dexamethasone or bortezomib/dexamethasone) was recently reviewed at pCODR, for the treatment of patients with multiple myeloma who have received at least one prior therapy. Pomalidomide is under review at pCODR, in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

PAG noted that the comparator in the MM-007 trial was bortezomib/dexamethasone, which is not a relevant treatment option for previously treated multiple myeloma. PAG is seeking information on whether comparison data is available comparing pomalidomide combination therapy to carfilzomib/dexamethasone as well as daratumumab/bortezomib/dexamethasone.

4.2 Eligible Patient Population

PAG is seeking clarity on the patient population who would be eligible for treatment with pomalidomide/bortezomib/dexamethasone, if recommended for reimbursement:

- Patients who received more than 3 lines of prior therapy
- Patients with diagnosis of primary amyloidosis, as these patients were excluded from the MM-007 trial?

PAG is also seeking clarity on whether autologous stem cell transplant or maintenance lenalidomide would be considered as one line of prior therapy. Specifically, whether consistency with the carfilzomib recommendation would be appropriate.

If recommended for reimbursement, PAG noted the following groups of patients would need to be addressed on a time-limited basis:

- Patients currently treated with alternative relapsed/refractory regimens (e.g., pomalidomide/dexamethasone, bortezomib/dexamethasone, or triplet-based therapies such as carfilzomib/lenalidomide/dexamethasone,) but who have not yet progressed

4.3 Implementation Factors

PAG noted that additional health care resources may be required to monitor and treat toxicities (e.g., neutropenia, thrombocytopenia, neuropathies). Some patients may require G-CSF while on pomalidomide combination therapy. Additional pharmacy resources would be required for preparation of bortezomib and as pomalidomide is part of the controlled distribution program RevAid, this will have significant impact on pharmacy resources.

Bortezomib is dosed at 1.3 mg/m2 on days 1, 4, 8, 11 of each 21-day cycle (cycles 1-8), then days 1 and 8 of each 21-day cycle (cycle 9 onwards), until disease progression. Dexamethasone is dosed at 20 mg orally on days 1, 2, 4, 5, 8, 9, 11, 12 of each 21-day cycle (cycles 1-8), then on days 1, 2, 8, 9 of each 21-day cycle (cycle 9 onwards). PAG noted that the standard of care in most jurisdictions is to administer bortezomib subcutaneously and weekly to reduce neurotoxicity; as well as dexamethasone on the same days of bortezomib treatment. Some patients may not be able to tolerate the twice weekly bortezomib dose. If pomalidomide/bortezomib/dexamethasone is recommended for reimbursement, PAG is seeking guidance on the use of bortezomib and dexamethasone as per standard of care (i.e., weekly subcutaneous bortezomib and dexamethasone on the same days).

Although the availability of four different strengths is an enabler for ease of dose adjustments, PAG expressed concerns if all tablet strengths are the same price. The flat pricing would be a barrier as there would be added costs for dose modifications. For example, a patient on a 4mg daily dose may be dispensed the smaller tablet strengths, to allow for the possible need of dose reductions. However, this dispensing strategy would cost more than dispensing the 4mg tablets. There are also concerns with the potential for drug wastage for patients who may be dispensed the 4mg tablets but do not tolerate and then have dose reduced 1mg, 2 mg or 3mg prior to finishing the amount of 4mg tablets dispensed.

PAG noted that the prevalent number of patients with multiple myeloma who have received at least one prior line of therapy is significant. There will be a large budget impact and this is a barrier to implementation.

PAG noted that the cost of bortezomib has been significantly reduced with generic products being available and bortezomib re-treatment in second-line and beyond treatment settings would be an option in most provinces, particularly for patients who have already been previously treated with lenalidomide.

PAG noted the different dosing schedules for the three medications (two oral and one intravenous) may be difficult for patients and may lead to patient confusion. Processes would need to be in place, prior to implementation of pomalidomide/bortezomib/dexamethasone, to minimize dosing errors and patient confusion. PAG noted that familiarity with bortezomib and dexamethasone would be an enabler to implementation.

PAG noted that pomalidomide is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. As an oral option, chemotherapy chair time and nursing time would not be required. PAG identified the oral route of administration is an enabler to implementation.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.4 Sequencing and Priority of Treatments

Given the multiple treatments that will be available, PAG is seeking guidance on the appropriate place in therapy of pomalidomide in combination with bortezomib and dexamethasone and sequencing of all treatments available. In particular:

- Sequencing of first and second-line therapies (e.g., carfilzomib-based, lenalidomide-based, daratumumab-based, and bortezomib-based regimens) for patients that are either eligible or ineligible for autologous stem cell transplant
- Preference for proteasome inhibitor (i.e., bortezomib, carfilzomib, or ixazomib) and whether they are considered interchangeable

4.5 Companion Diagnostic testing

None identified.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

A total of four clinicians, an individual input from one clinician from Cancer Care Ontario, and a joint input reporting the perspective of three clinicians belonging to the Myeloma Canada Research Network (MCRN), submitted to pCODR for pomalidomide in combination with dexamethasone and bortezomib (PVd) for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior treatment regimen including lenalidomide. A summary of the input is provided below.

There are several options for relapsing multiple myeloma patients, which introduces challenges in treatment selection but also opportunities for treatment personalization. Relevant comparators include carfilzomib plus dexamethasone and the combination of daratumumab, bortezomib and dexamethasone. Clinicians reported that PVd has several notable advantages compared with available treatments including lower toxicity and easier administration, in addition to good survival benefits. In terms of sequencing, PVd could be given in the third-line setting after daratumumab-containing regimens, or second-line in patients who experience challenges with long-term intravenous therapies or have certain comorbidities or contraindications. Most clinicians believed it would be an addition to and not a replacement for existing therapies.

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

5.1 Current Treatment(s) for Relapsed/Refractory Multiple Myeloma

The clinician inputs indicated that there are currently several regimens for multiple myeloma (MM) patients relapsing after 1 to 3 prior regimens. These include carfilzomib + lenalidomide + dexamethasone (KRd), carfilzomib + dexamethasone (Kd), lenalidomide + dexamethasone (Rd), bortezomib + dexamethasone (Vd), and pomalidomide + dexamethasone (Pd). Access to daratumumab + lenalidomide + dexamethasone (DRd) and daratumumab + bortezomib + dexamethasone (DVd) is also expected shortly. While this introduces challenges in selecting the best treatment for a given patient, MM is a very heterogeneous disease with respect to biology (with at least seven different cytogenetic/molecular subtypes with different behaviours and in some instances drug class sensitivity), pace of disease (indolent or aggressive) and patient features (frailty, renal failure, limited mobility due to age, extensive skeletal destruction, social factors). One clinician from the joint submission added that pomalidomide is currently used in the third line setting but that there is a movement to use second line drugs earlier. Given the favourable data and convenience of pomalidomide plus bortezomib, this combination would be a desirable option for patients.

According to one of the clinicians, the best comparators would be Kd or DVd, both specifically for lenalidomide-refractory patients.

5.2 Eligible Patient Population

The clinicians indicated that the funding request can be extrapolated to clinical practice and corresponds to a growing need. One input mentioned that there has been a shift in the therapy in the first-line treatment of MM. Other clinicians explained that most patients receive upfront lenalidomide/dexamethasone or cyclophosphamide/bortezomib/dexamethasone (CyBorD) followed by stem cell transplant if eligible. Currently, almost all transplant-eligible patients are now progressing on lenalidomide maintenance, and around 75–80% of transplant-ineligible patients are progressing on Rd; these groups are not eligible for the best triplets, i.e., KRd and particularly DRd whose favourable results are unprecedented according to most clinicians. For the treatment under review, only prior lenalidomide exposure is mandatory. Not all trial

patients had experience with a proteasome inhibitor (e.g., bortezomib), which is not needed according to the funding request and aligns with real life practice. A clinician indicated that patients who previously received an autologous stem cell transplant (ASCT) would also be eligible for this treatment.

One clinician believed that as a second-line therapy, PVd outcomes compare favourably with Kd and DVd even with the large number of lenalidomide and bortezomib-refractory patients in the PVd study. Another clinician highlighted that carfilzomib cannot be given to all patients because of cardiovascular factors; PVd would be a very good option for these patients. The inclusion and exclusion criteria specified in the trial are generally applicable in practice. A clinician highlighted that PVd is very safe in the context of renal failure. All three agents in PVd can be given in full doses and are not renally excreted. The clinician would not restrict eligibility based on the ECOG score. The clinicians did not have suggestions on specific subgroups to include or exclude from therapy.

5.3 Relevance to Clinical Practice

Two clinicians providing input noted that PVd is a convenient and low-toxicity regimen and can be administered outside major centres. The clinicians added that PVd is better tolerated than Kd, a challenging regimen to give to elderly patients due to cardiovascular concerns which, although uncommon, can be serious and are difficult to predict. Also, in the absence of an option for weekly dosing, patients and their caregivers find the ≥6 visits a month for Kd very challenging for long-term use. According to two clinicians, PVd is also less onerous than DVd, although there is no evidence directly comparing these two regimens. Patients who have issues with DVd's infusion schedule or reactions to daratumumab may therefore opt for PVd treatment.

5.4 Sequencing and Priority of Treatments with Pomalidomide (PVd)

According to a clinician, the PVd regimen allows the introduction of the most potent immunomodulatory derivative—pomalidomide—earlier in the sequence of multiple myeloma regimens than was previously possible. Also, the phase 3 evidence supporting PVd provides the most information about response and PFS using a triplet in a truly lenalidomide-refractory population, rather than trying to isolate results in smaller subsets from the other large studies.

The clinician stated that patients progressing on lenalidomide-containing first-line therapy would have two potential pathways. One would utilize DVd as the second therapy, and within this pathway two scenarios could be considered: 1) DVd second-line, Kd third-line, with pomalidomide + dexamethasone (Pd) fourth-line; 2) DVd in second line, PVd third-line — since patients would likely remain sensitive to a proteasome inhibitor after the eight fixed-duration cycles of bortezomib. The clinician noted that POM + dex alone is not a very active regimen with a median PFS of only four months, so a pomalidomide triplet combination would be preferable even in this later setting.

The clinician continued by saying that in another general pathway, PVd would be a good second-line regimen for patients with more limited geographic and/or psychosocial challenges, reluctance for long-term IV therapies and certain comorbidities. The clinician noted that a surprisingly high proportion of MM patients do not go beyond second-line therapy in the real world, so PVd would offer a potent and less onerous triplet therapy in patients felt to be limited to only two regimens. With some reservations owing to the lack of final results in high-risk cytogenetics, the clinician anticipates that the combination of a proteasome inhibitor and immunomodulatory derivative in PVd would be quite effective, possibly more so than Kd or DVd in lenalidomide-refractory patients. Another clinician clarified that lenalidomide would be

given before PVd and could not be used in subsequent following therapies. Both clinicians concluded that PVd would better serve patients as another therapeutic option rather than a replacement of existing regimens. However, another clinician felt that PVd could replace DVd and Kd in a vast majority of patients in the second line setting given the PFS and ease of administration. Conversely, the fourth clinician only saw this regimen being an option for a few patients i.e., those not eligible to receive carfilzomib and still responsive to proteasome inhibitors.

5.5 Companion Diagnostic Testing

This aspect does not apply to the current review according to the clinician inputs.

5.6 Additional Information

None.

5.7 Implementation Questions

5.7.1 In regards to question 3.4 above, please consider the optimal sequencing of treatment for relapsed/refractory multiple myeloma for patients that are eligible as well as ineligible for autologous stem cell transplant, specifically: ixazomib-based, carfilzomib-based, lenalidomide-based, daratumumab-based, and bortezomib-based regimens. In clinical practice, if pomalidomide/bortezomib/dexamethasone was available…

5.7.2 What line of therapy would you prefer to use the pomalidomide triplet therapy?

A clinician answered that they would likely use the therapy as second-line in most instances, with a few for third-line as mentioned previously. Another clinician had a different view and thought that daratumumab would be selected for second line and PVd would follow in the third line. The latter clinician also mentioned that Kd would be accessible after DVd as long as patients had experience with three prior lines of therapy and may be preferable depending on time of relapse.

5.7.3 Would you prefer to use pomalidomide over currently available novel triplet therapies?

One clinician would prefer it in general over Kd (which is not a triplet). Another clinician would likely prefer it in the second line after lenalidomide-based treatment, over DVd in most patients. On the other hand, another clinician would reserve it for third line in carfilzomib-ineligible patients. Two clinicians indicated that pomalidomide would be preferred in situations where frequent parenteral drug administration places an undue burden on the patient/caregiver.

5.7.4 When would you prefer to use pomalidomide over currently available novel triplet therapies?

One clinician would prefer it in general over Kd (which is not a triplet). Another clinician would likely prefer it in the second line after lenalidomide-based treatment, over DVd in most patients. On the other hand, another clinician would reserve it for third line in carfilzomib-ineligible patients. Two clinicians indicated that pomalidomide would be preferred in situations where frequent parenteral drug administration places an undue burden on the patient/caregiver.

5.7.5 In clinical practice, can proteasome inhibitors (i.e., bortezomib, ixazomib, or carfilzomib) be used interchangeably for patients with relapsed/refractory multiple myeloma? If yes, what is the preferred proteasome inhibitor? Please comment on the preference considering patient preference, efficacy, safety, and administration.

According to three clinicians, the proteasome inhibitors are not interchangeable, mainly due to the regimen details (IV vs SC vs oral) and different toxicities, with neuropathy being the most prominent with bortezomib and least problematic with carfilzomib. The other clinician believed that PIs are largely interchangeable despite different toxicities and administration profiles. All clinicians agreed that cardiovascular and renal toxicities are generally limited to carfilzomib, making it more challenging to administer. However, the drug also has the most potent anti-myeloma effect and has been shown to be effective in patients progressing on bortezomib (but not the reverse). One clinician further commented that the ixazomib/lenalidomide/dexamethasone regimen would not likely be an option in the target population since patients that experienced first line treatments would have included lenalidomide.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the safety and effect of pomalidomide in combination with dexamethasone and bortezomib on patient outcomes compared to appropriate comparators in patients with relapsed and or refractory multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7. Section 7 includes a critical appraisal of a network meta-analysis assessing the relative efficacy of pomalidomide in combination with dexamethasone and bortezomib versus other selected therapies in patients with relapsed and or refractory multiple myeloma.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table 6.1 below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 6.1 Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs, conference abstracts	Adult patients with relapsed and or refractory who have received at least one prior therapy (including lenalidomide) Subgroups: Lenalidomide refractory	pomalidomide 4 mg orally on days 1-14 of each 21-day cycle, dexamethasone 20 mg orally on days 1, 2, 4, 5, 8, 9, 11, 12 of each 21-day cycle (cycles 1-8), then on days 1, 2, 8, 9 of each 21-day cycle (cycle 9 onwards), bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11 of each 21-day cycle (cycles 1-8), then days 1 and 8 of each 21-day cycle (cycle 9 onwards), until disease progression.	Bortezomib and Dexamethasone OR Daratumumab in combination with bortezomib and dexamethasone OR Carfilzomib in combination with dexamethasone OR Bortezomib Cyclophosphamide and dexamethasone	-**Progression Free Survival** -Duration of Response -**Overall Survival** -Time to next treatment -Overall Response Rate -**HRQoL** -Progression free survival after next line of therapy **-Adverse Events** -Neuropathy -Neutropenia -Other blood dyscrasias -Serious adverse effects (second malignancies) -Withdrawals due to adverse effects -Deaths
HRQoL: Health-related quality of life; RCT: Randomized Control Trial				

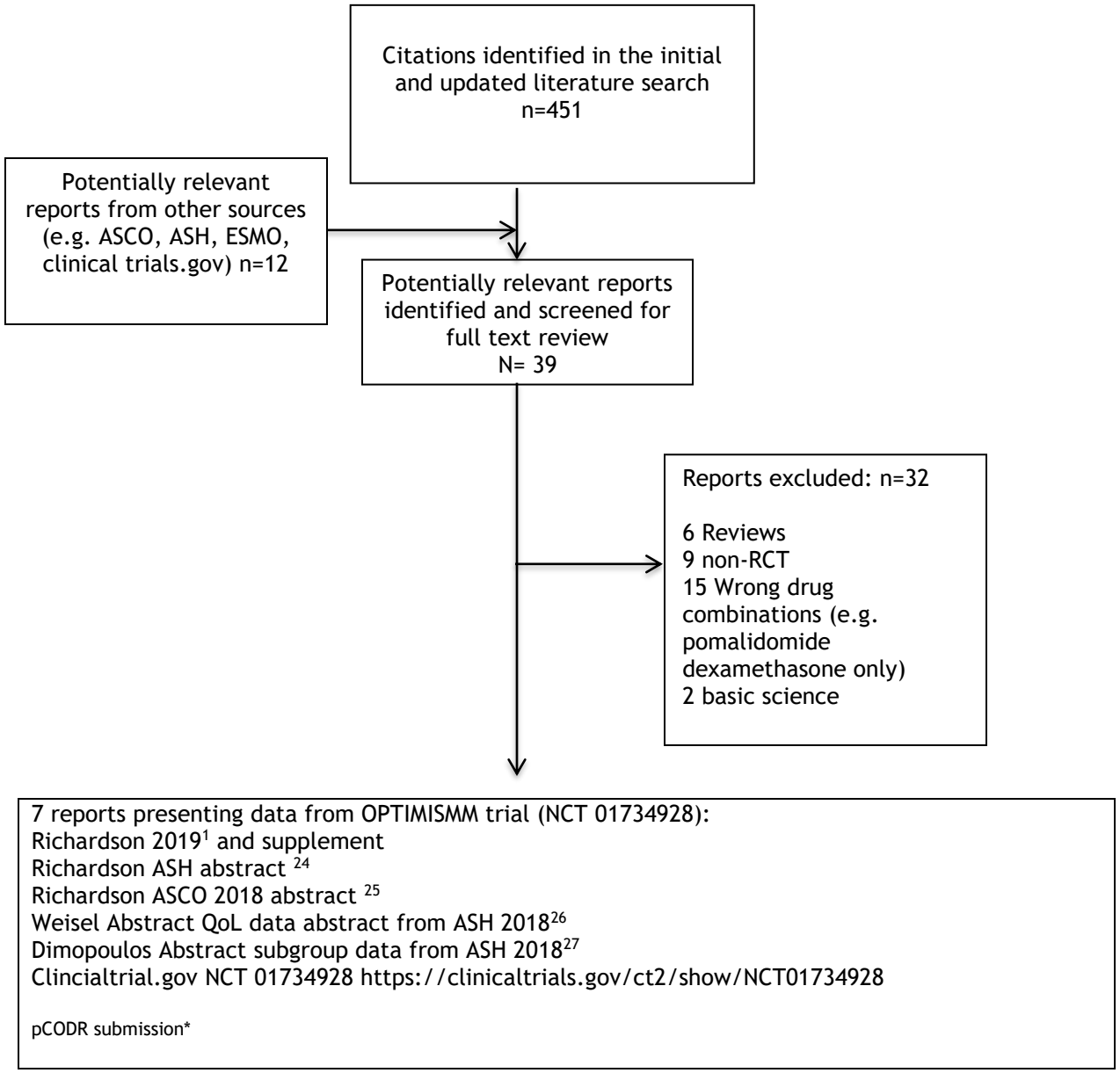
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 451 potentially relevant reports identified, one study was included in the pCODR systematic review (Figure 6.1). [1] Six citations were associated with this trial (1 publication plus supplement including the protocol and statistical analysis plan [1], 4 conference abstracts, [24-27] 1 description of trial on clinicaltrials.gov).[28] In addition, the documents provided through the pCODR submission (clinical summary report, CSR) provided an additional source of data.[3,29-31]

Figure 6.1 Sample QUOROM Flow Diagram for Inclusion and Exclusion of studies



**Note: Additional data related to the OPTIMISMM were also obtained through requests to the Submitter by pCODR.*[29]

6.3.2 Summary of Included Studies

The pCODR systematic review included one RCT, OPTIMISMM, that assessed the safety and efficacy of pomalidomide in combination with bortezomib and dexamethasone in the treatment of relapsed or refractory multiple myeloma. Characteristics of the trial are summarized in Table 6.2 and specific aspects of trial quality are summarized in Table 6.3.

Detailed Trial Characteristics

Table 6.2 Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention	Comparator	Trial Outcomes
OPTIMISMM [1](NCT01734928) Phase III International multicenter 1:1 randomized open label controlled trial N=559 (Enrolment between January 2013 and May 2017) 133 hospitals and research centres in 21 countries Data cut-off date: Oct 26, 2017 additional unplanned Sept 15, 2018 Funded by Celgene Corporation. Randomization stratified by age (≤75 vs >75), screening β2-microglobulin level (<3.5 mg/L *vs* ≥3.5 mg/L to ≤5.5 mg/L *vs* >5.5 mg/L) and number of prior lines of therapy (1 vs >1)	<u>Key Inclusion Criteria:</u> • Age >18 with multiple myeloma • measurable disease (serum (greater than or equal to 0·5 g/dL) and/or urine (greater than or equal to 200 mg/24 h) protein levels) • Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 2 • had received one to three prior regimens*, including at least 2 consecutive cycles of lenalidomide • Progressive disease during or after the last regimen (investigator assessed) • Lenalidomide refractory patients were eligible** • Bortezomib-exposed patients were eligible if they did not have progressive disease during therapy or within 60 days of the last dose regimen containing bortezomib dosed at 1·3 mg/m^2 of body surface area twice weekly. Patients who progressed on or within 60 days of a once-weekly bortezomib schedule or on a lower dose of bortezomib were included in the trial and were defined as the bortezomib-refractory patient	21 day cycle Pomalidomide 4 mg day 1-14 And Bortezomib 1.3 mg/m2/dose cycle 1-8: days 1,4,8,11 cycle 9+: days 1,8 intravenously, then subcutaneously after a protocol amendment And dexamethasone 20 mg (10 mg if >75) cycle 1-8: days 1,2,4,5,8,9,11,12 cycle 9+: days 1,2,8,9 Treatment until disease progression or intolerability	21 day cycle Bortezomib 1.3 mg/m2/dose cycle 1-8: days 1,4,8,11 cycle 9+: days 1,8 And dexamethasone 20 mg (10 mg if >75) cycle 1-8: days 1,2,4,5,8,9,11,12 cycle 9+: days 1,2,8,9 Treatment until disease progression or intolerability	<u>Primary:</u> Progression free survival (PFS) <u>Secondary:</u> Overall survival (OS) Overall response rate (partial or better) (IMWG) Duration of response Safety <u>Exploratory</u> Time to response Progression free survival after next line of therapy Quality of life EORTC QLQ-C30 EORTC QLQ-MY20 EQ 5D Efficacy analyses in subgroups (PFS, ORR, duration of response) Overall response rate per the European society for Blood and Marrow Transplantation Time to progression Pomalidomide plasma concentrations Clinical benefits (improvement in hemoglobin value,

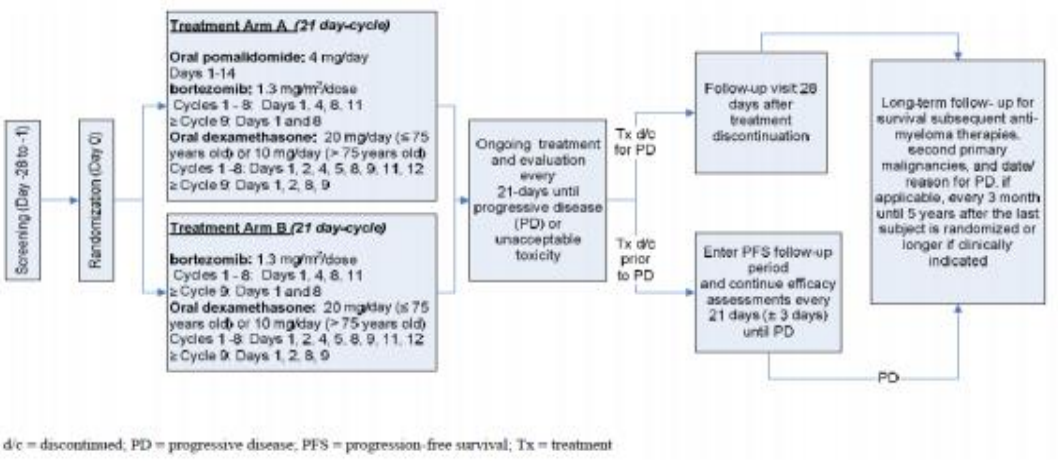
Trial Design	Inclusion Criteria	Intervention	Comparator	Trial Outcomes
	population in this trial. • Generally adequate hematologic and hepatic function <u>Key Exclusion Criteria:</u> • Progressive disease during therapy (or within 60 days) of a bortezomib-containing regimen (1.3 mg/m^2 twice weekly dosing) • Creatinine clearance <30 mL/min requiring dialysis • Grade 3 or more peripheral neuropathy or grade 2 peripheral neuropathy with pain (within 14 days) • Conditions requiring chronic steroid or immunosuppression *Induction with or without bone marrow transplantation and with or without maintenance therapy was considered to be one regimen. ** Refractoriness was defined as disease nonresponsive on therapy (failure to achieve minimal response or development of progressive disease), or progresses within 60 days of the last dose (inclusive)			improvement in renal function, improvement of ECOG PS, improvement in hypercalcemia, improvement in non-myeloma immunoglobulins) Minimal residual disease Biomarker analyses (genomic, molecular, and immune) Time to treatment failure (IMWG or European criteria) as a sensitivity analysis for PFS
Notes: EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module, MY20 = Multiple Myeloma Module, IMWG = International Myeloma Working.				

a) Trials

One ongoing, randomized, international, multi-centre, phase 3, double-blind placebo-controlled trial (OPTIMISMM) met the inclusion criteria.[1] OPTIMISMM was funded by Celgene Corporation. The aim of this trial was to examine the effect of pomalidomide bortezomib dexamethasone (PVd) combination compared with bortezomib dexamethasone (Vd) combination on efficacy and safety outcomes in patients with relapsed or refractory multiple myeloma with previous exposure to one to three prior regimens, including lenalidomide. Patients who were lenalidomide refractory were included. Refractoriness was defined as disease nonresponsive on therapy (failure to achieve minimal

response or development of progressive disease), or progresses within 60 days of the last dose (inclusive) Patients with prior bortezomib exposure were eligible if they did not have progressive disease during therapy or within 60 days of the last dose.[1] The design of the OPTIMISMM trial is depited in Figure 6.2.

Figure 6.2. Study design[2]



The trial enrolled 559 patients from 133 hospitals and research centres in 21 countries with relapsed or refractory multiple myeloma that had at least one to three prior lines of treatment (including lenalidomide).[1] Study sites included the US, Europe (including Russia, Turkey, Israel), Canada and Japan.[29] There were four Canadian centres included in the study. Patients were randomized in a 1:1 ratio to receive PVd or Vd until disease progression or intolerability.[1] Randomization occurred via a validated interactive technology system.[1] Randomization used the methods of randomly permuted blocks within strata. Randomization was stratified according to age (≤75 vs >75), screening β2-microglobulin level (<3.5 mg/L *vs* ≥3.5 mg/L to ≤5.5 mg/L *vs* >5.5 mg/L), and number of prior lines of therapy (1 vs >1).[1] Induction with or without bone marrow transplantation and with or without maintenance therapy was considered to be one regimen.[1]

The study was open label, so patients and staff at study centers were not blinded.[1] The study sponsor was blinded until study unblinding. A blinded independent review adjudication committee (IRAC) assessed both the date of disease progression and the myeloma response data[1] according to the International Myeloma Working Group (IMWG) Criteria.[32]

Study participants received treatment until disease progression or unacceptable toxicity.[1]

Outcomes

The primary outcome of OPTIMISMM was PFS.[1] This was defined as the time from randomization to disease progression or death. The primary outcome was assessed by the blinded IRAC.[1]

The hypothesis of the trial was that PVd would increase PFS and would be superior compared to Vd alone. The estimated sample size requirements for the trial was 544 patients (320 PFS events) to provide 80% power and 2-sided alpha of 0.05;[1] more detail is listed in Table 6.3.

The pre-specified key secondary end points for the OPTIMISMM trial included: OS (time from randomization until death from any cause) and overall response rate (partial response or better per IMWG).[1] These end points were included in the alpha spending function as is described in the supplement to the publication.[1] Other pre-specified secondary end points included duration of response, defined as time of first documented response to confirmed progressive disease or death from any cause for all responders, and safety outcomes, however, as described in the supplement to the full publication, these end points were not adjusted for multiplicity.[1] Pre-specified exploratory end points included: time to response as defined by time from randomization to first documented response, change in global health status, PFS after next line of therapy defined as time from randomization to second objective disease progression or death from any cause in the intent to treat population and all subgroup efficacy analyses.[1] Exploratory end points that were not included in the publication and that were described in the supplement included: overall response rate assessed by the European Bone Marrow Transplant group, time to progression, plasma pomalidomide concentrations, health benefits (improved hemoglobin, renal function, ECOG performance status, hypercalcemia, non-myeloma immunoglobulins), minimal residual disease and biomarker analysis for genomic, molecular and immune biomarkers.[1]

Subgroup analyses were pre-specified although exploratory. Pre-specified subgroups in the OPTIMISMM trial that were included in the published supplement included: gender, age group ≤ 75 vs >75, race (white vs non-white), baseline ECOG performance status (0 vs >0), baseline cytogenetic categories (high risk vs not), number of prior myeloma regimens (1 vs >1; 2 vs >2), screening ß2-microglobulin level (<3.5 mg/L *vs* ≥3.5 mg/L to ≤5.5 mg/L *vs* >5.5 mg/L), baseline albumin (<3.5 g/dL vs ≥3.5 g/dL) international staging system (I vs II vs III), baseline creatinine clearance (<45 vs ≥45 mL/min; < 60 vs ≥ 60 mL/min), refractory to lenalidomide, refractory to last therapy for MM, and prior exposure to proteasome inhibitors.[1] Subgroup analyses were not adjusted for stratification factors.[1]

Health-related quality of life (HRQoL) outcomes were exploratory. HRQoL was assessed by using the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 module (EORTC QLQ-C30) and the myeloma-specific module (EORTC QLQ-MY20) and the descriptive system of the European Quality of Life – 5 Dimensions (EQ-5D). The EORTC QLQ-MY20 is a disease-specific module for multiple myeloma. Adverse events were collected until the 28 day 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.[1] The HQoL measures were administered prior to the first day of every cycle (21 days) and at treatment discontinuation.[1]

The EORTC QLQ-C30 is a validated questionnaire for evaluation of the quality of life in cancer patients.[33]The questionnaire comprises five functional scales, three symptoms scales, 6 single item symptom scales and a global health/quality of life scale. The score ranges from 0 to 100 with a higher score

on the functional scales and global quality of life indicating better health status in contrast to a higher score on the symptom scales indicative of more complaints.[33]

A change of 10 points in physical, social, and emotional functioning, and the global health scale/QoL subscales of the EORTC QLQ-C30 has been considered to be clinically meaningful.[34] This estimate is based on an anchor-based approach with patient global ratings of change in breast and lung cancer patients over time. Patients who reported "a little change" had corresponding mean changes on the scores of 5 to 10. However, Cocks et al. performed a meta-analysis of data from 152 published studies that used anchor based approaches (with several clinical anchors) in a variety of cancers including 14 out of 152 (9%) with hematologic malignancies and 22 out of 152 (14.5% from North America). These authors found that the smallest difference reported to have clinical meaning has been reported as 4 to 10 for the global health scale /QoL subscale of the EORTC QLQ-C30.[35]

The EORTC QLQ-MY20 measures disease symptoms (pain), side effects of treatment (drowsy, thirsty, feeling ill, dry mouth, hair loss, tingling hands or feet, feeling restless or agitated, heartburn, burning or sore eyes), body image, and future perspectives.[36] There is no established minimal important difference for this scale.

In the OPTIMISMM study, there was one interim analysis for futility, which was conducted at approximately 50% PFS events, and one final analysis for PFS.[1] The sample size was amended to perform the final PFS analysis based on 320 events rather than 381 events based on phase 3 trials that showed that the PFS of the Vd arm was shorter than expected in patients who have previously received lenalidomide.[1] More detail is listed in Table 6.3 The data cut-off for final PFS analysis was October 26, 2017. Data was immature for the interim analysis that was planned for OS as there were less than 33% of the planned events. The final OS data will be the next analysis projected to occur in the third quarter of 2021.[1,2]

An OS updated analysis, which was not prespecified, was conducted with a data cut-off date of September 15, 2018; these analyses included 339 PFS events and 242 OS events.[2]

Disease Assessment

Patients were followed up for efficacy measures (electrophoresis and immunofixation of serum and urine monoclonal proteins, serum immunoglobulins, corrected serum calcium, serum free light chain assays) at baseline, the first day of each 21 day cycle, treatment discontinuation and every three weeks during the PFS follow-up phase and at the end of the PFS follow-up phase.[1] Bone marrow samples were obtained at screening and at time of complete response.[1] For patients who did not have disease progression during treatment or during the PFS follow up period, patients were followed for disease status and survival every three months for at least five years.[1]

Amendments

The study protocol was amended a total of five times. Amendments pertaining to the sample size calculation are discussed in Table 6.3.

Table 6.3 Select quality characteristics of included studies of pomalidomide-bortezomib- dexamethasone combination in patients with relapsed or refractory multiple myeloma

Study	OPTIMISMM.[1]
Treatment vs. Comparator	Pomalidomide-bortezomib- dexamethasone combination (PVd) vs bortezomib-dexamethasone combination (Vd)
Primary outcome	Progression-free survival (PFS)
Required sample size	The study was powered to detect the superiority of PVd vs Vd with respect to PFS. Details of the sample size calculation are provided in the supplement to the publication. The original sample size was for 782. This was based on 90% power and an assumption of 12 months PFS in PVd and 9 months PFS for Vd. The study was amended (protocol amendment 3) to increase the estimated PFS for PVd from 12 to 12.6 months.[29] This increased the treatment difference from 33% to 40% over Vd combination. Study power was reduced from 90% to 85% and resulted in a sample size reduction from 782 to 450 subjects. The study was amended (protocol amendment 4) to revise sample size again – power was decreased to 80%. The sample size assumed a median PFS of 12 months for PVd and 9 months for Vd. With 80% power at a 2 sided significance level of 5% this change required 381 PFS events. In order to obtain PFS events from approximately 70% of the intent to treat population for the final PFS analysis, a total of 544 subjects were required to be randomized equally (1:1 ratio) into the 2 treatments. The interim PFS analysis was to occur when 50% PFS occurred (191 events) and in interim OS was to occur when approximately 50% OS information (191 deaths) had occurred. The study was amended (protocol amendment 5) in order to conduct the PFS analysis earlier than planned. This was based upon phase 3 trials that showed that the PFS of Vd arm was expected to be shorter than the assumption of 9 months in patients with lenalidomide included in a prior line of therapy. After the amendment, assuming a hazard ratio of 0.73 for death or disease progression (PFS) 320 PFS events (approximately 57% event rate of 559) were needed (80% power and 2-sided alpha of 0.05) with 2 planned interim analyses (1 for futility at approximately 50% of the PFS events and 1 final PFS analysis.) This was based on an estimated PFS of 12 months in the PVd arm and 8.8 months in the Vd arm. For the OS analysis (key secondary end point), a total of 379 deaths would be required to detect a 33% increase in median overall survival in the PVd arm (median, 40 months) compared with the Vd arm (median, 30 months) with 75% power. The OS outcome will be tested using a step-down approach following PFS, with the assumption of 2-sided significance level of 0.05 and 1 planned interim analyses at the time of the final PFS analysis. The projected events at OS interim analysis will be approximately 50% OS information (191 events out of a total of 379 deaths). The family-wise type I error rate was controlled by a step-down approach from PFS to ORR and then to OS comparison with a 2-sided alpha level of 0.05. OS at interim analysis would be tested only if there is significance for PFS and the ORR. This is based on the Lan-Demets interpretation of the Pocock boundary.
Sample size	Total 544 randomized 1:1 PVd (n=272) vs. Vd (n=272)
Randomization method	1:1 stratified by age (≤75 vs >75), screening ß2-microglobulin level (<3·5 *vs* ≥3·5 to ≤5·5 *vs* >5·5 mg/L) and number of prior lines of therapy (1 vs >1)
Allocation concealment	Not described

Blinding	Open label, therefore no. Outcomes were assessed by blinded independent review committee. The sponsor was blinded to aggregate treatment assignments for statistical analyses and treatment-level analysis results.
ITT Analysis	Yes – ITT population was all subjects who were randomized.
Final analysis	No. As of the data cut-off (26 October 2017) the study was ongoing for additional time-to-event data. This includes overall survival. An additional unplanned interim analysis data cut-off is September 15, 2018 although this is not mature.
Early termination	No
Ethics Approval	Yes
PVd: Pomalidomide- bortezomib- dexamethasone combination; Vd: bortezomib- dexamethasone combination; PFS: progression-free survival.	

b) Population

A total of 559 patients were randomized in the OPTIMISMM trial, 281 in the PVd arm and 278 in the Vd arm.[1] Baseline characteristics were generally well balanced between the two groups, including age, ECOG PS, prior number of lines of therapy, high risk genetic mutations and baseline ISS stage III disease.[1] The median age of patients in the OPTIMISMM study was 67 years in the PVd arm and 68 years in the Vd arm and median time since diagnosis was 4.0 years in the PVd arm and 4.3 years in the Vd arm. A total of 270 out of 281 (96%) patients in the PVd arm and 256 out of 278 (92%) patients in the Vd arm had ECOG PS 0 or 1.[1]

Patients had received a median of two previous regimens prior to receiving the study drug.[1] Induction with or without bone marrow transplantation and with or without maintenance therapy was considered to be one regimen.[1]

Refractoriness was defined as disease nonresponsive on therapy (failure to achieve minimal response or development of progressive disease), or disease progression within 60 days of the last dose (inclusive).[1] Refractory meant refractory to the most recent time the medication was received.[1]

All patients had received prior lenalidomide (100%); 200/281 (71.2%) patients in the PVd arm and 191/278 (68.7%) patients in the Vd arm were lenalidomide refractory. A total of 201/281 (71.5%) patients in the PVd arm and 203 (73%) patients in the Vd arm had received prior bortezomib; of these, 24/281 (8.5%) in the PVd arm and 32/278 (11.5%) in the Vd arm were bortezomib refractory. Most patients were refractory to the last previous regimen (196/281 (69.8%) in the PVd arm and 184/278 (66.2%) in the Vd arm).[1] There were 64/281 (22.8%) and 65/278 (23.4%) patients in the PVd and Vd arms, respectively, who had received only one prior line of therapy and were identified as lenalidomide-refractory.[1]

An additional request to the manufacturer revealed that of the lenalidomide-refractory patients (200 in the PVd arm and 191 in the Vd arm) the majority (130/200 (65.0%) in the PVd arm and 133/191 (69.6%) in the Vd arm) experienced refractoriness to lenalidomide with disease progression on or within 60 days of lenalidomide combination therapy during primary treatment with lenalidomide and any other anti-myeloma agent. A smaller proportion (64/200 (32.0%) in the PVd arm and 51/191 (26.7%) in the Vd arm) experienced disease progression on or within 60 days of lenalidomide single agent therapy.

However, the manufacturer noted that the regimen, start and stop dates of each drug and starting dose of drug were collected, yet not the dose at the time of progression. Data does not distinguish between lenalidomide maintenance dose post stem cell transplant versus lenalidomide single agent as last non-discontinued drug in a regimen. Only a minority of patients (6/200 (3.0%) in the PVd arm and 7/191 (3.7%) in the Vd arm) were characterised as being refractory to lenalidomide because they were non-responders and did not progress on treatment or within 60 days of therapy. This category also included patients who failed to achieve at least a minimal response to therapy and did not have disease progression during therapy or within 60 days.[31]

A total of 161/281 (57.3%) in the PVd arm and 163/278 (58.6% in the Vd arm had received a stem cell transplant.[1]

Geographic region included the US 53/281 (18.9%) in the PVd arm and 69/278 (24.8%) in the Vd arm and other 228/281 (81.1%) in the PVd arm and 209/278 (75.2)% in the Vd arm.[1] A request to the Submitter revealed that there were a total of 13 Canadian patients from four centres included in the OPTIMISMM Study.[1] Baseline characteristics are summarized in Table 6.4.

Table 6.4 Patient characteristics in the intent to treat population.[1]

	Pomalidomide, bortezomib, and dexamethasone group (n=281)	Bortezomib and dexamethasone group (n=278)
Age (years)	67 (60–73)	68 (59–73)
≤65	123 (44%)	120 (43%)
>65	158 (56%)	158 (57%)
≤75	235 (84%)	231 (83%)
>75	46 (16%)	47 (17%)
Sex		
Male	155 (55%)	147 (53%)
Female	126 (45%)	131 (47%)
ECOG performance status		
0	149 (53%)	137 (49%)
1	121 (43%)	119 (43%)
2	11 (4%)	22 (8%)
ISS disease stage		
I	149 (53%)	138 (50%)
II	85 (30%)	90 (32%)
III	47 (17%)	50 (18%)
Cytogenetic profile by FISH		
Standard risk	137 (49%)	132 (47%)
High risk	61 (22%)	49 (18%)
Time since diagnosis (years)	4·0 (2·6–6·5)	4·3 (2·5–6·4)
Previous lines of treatment	2 (1–2)	2 (1–2)
Lines of treatment		
1	111 (40%)	115 (41%)
2	117 (42%)	104 (37%)
≥3*	53 (19%)	59 (21%)
Previous stem-cell transplant	161 (57%)	163 (59%)
Creatinine clearance (mL/min)		
<60	91 (32%)	76 (27%)
≥60	190 (68%)	202 (73%)
Previous immunomodulatory treatment	281 (100%)	278 (100%)
Lenalidomide	281 (100%)	278 (100%)
Previous alkylating agent	237 (84%)	232 (83%)
Previous proteasome inhibitor	212 (75%)	213 (77%)
Bortezomib	201 (72%)	203 (73%)
Carfilzomib	8 (3%)	11 (4%)
Ixazomib	9 (3%)	5 (2%)
Refractory disease to immunomodulatory drug	202 (72%)	193 (69%)
Lenalidomide	200 (71%)	191 (69%)
Lenalidomide in the last previous antimyeloma regimen before study entry	178 (63%)	167 (60%)
Refractory disease to proteasome inhibitor	37 (13%)	37 (13%)
Bortezomib	24 (9%)	32 (12%)
Refractory disease to last previous regimen	196 (70%)	184 (66%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. ISS=International Staging System. FISH=fluorescence in-situ hybridisation. *One patient assigned bortezomib and dexamethasone received more than three previous lines of treatment.

Table 1: **Baseline characteristics**

"Reprinted from The Lancet The Lancet Oncology, Vol.20 number 6, Richardson PG, Oriol A, Beksac M et al., Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma

previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial, Pages No.781-794, Copyright (2019), with permission from Elsevier."

c) Interventions

Of the 559 patients in the OPTIMISMM trial, 278 patients and 270 patients received the allocated intervention in the PVd and Vd arms, respectively. The study drugs were administered in 21 day cycles.[1]

Study drug was administered until disease progression or intolerability.[1]

Pomalidomide 4 mg orally was given on days 1-14.[1]

In both groups, bortezomib 1.3 mg/m^2 of body surface area was administered subcutaneously or intravenously on days 1,4,8,11 of cycle 1-8 and days 1 and 9 of cycle 9 and beyond.[1] After a total of 15 patients in the PVd arm and 19 in the Vd arm who received bortezomib intravenously, bortezomib administration was changed to subcutaneous after a protocol amendment.[1]

In both arms, dexamethasone 20 mg orally was given if age 75 or less and 10 mg orally if over age 75 on days 1,2,4,5,8,9,11 and 12 of cycles 1-8 and days 1 and 8 of cycle 9 and beyond.[1]

All patients who received pomalidomide and those with a history of deep vein thrombosis or pulmonary embolism received prophylaxis with low-dose aspirin, low molecular weight heparin or other antithrombotic or anticoagulant. Antiviral prophylaxis was considered for both arms.[1]

Dose delays/ Interruptions and Modifications

Dose interruptions and reductions were permitted.[1] Bisphosphonates, hematopoietic growth factors, platelet or red cell infusions and radiation therapy were permitted.[1] Dose modifications and interruptions for pomalidomide were based on toxicities (neutropenia, thrombocytopenia, rash, constipation, venous thromboembolic event, or other grade three or more pomalidomide-related adverse events.[1] Dose modifications for bortezomib and dexamethasone were left to the discretion of the treating physician, and were consistent with the product monographs.[1]

If the treatment was interrupted and the next cycle was delayed beyond 21 days after Day 1 of the prior cycle, then Day 1 of the next cycle was defined as the first day that treatment was resumed.

For Treatment Arm A (PVd):

- If pomalidomide dosing was withheld, then bortezomib dosing could be continued at the discretion of the treating physician.
- If pomalidomide was permanently discontinued, then the subject was permanently discontinued from all study treatments.
- If bortezomib dosing was withheld or permanently discontinued, then pomalidomide and dexamethasone could be continued at the discretion of the treating physician.
- If bortezomib and dexamethasone dosing was withheld or permanently discontinued, then pomalidomide could be continued at the discretion of the treating physician.
- If both pomalidomide and bortezomib dosing were withheld, then dexamethasone must have also been withheld.

- If dexamethasone dosing was withheld or permanently discontinued, then pomalidomide and bortezomib could be continued.

For Treatment Arm B (Vd):

- If bortezomib dosing was withheld, then dexamethasone dosing must also have been withheld.
- If bortezomib was permanently discontinued, then the subject was permanently discontinued from all study treatments.
- If dexamethasone was withheld or permanently discontinued, then bortezomib could be continued.[1]

Details of treatment exposure and dosing information are in Table 6.5.

Table 6.5 Treatment exposure and dosing information in the safety population (all patients who received at least one dose of study drug) as described in the OPTIMISMM Trial Supplement.[1]

Supplementary Table 3. Treatment exposure and dosing information in the safety population

Data are median (IQR).

BORT= bortezomib. DEX= dexamethasone. POM=pomalidomide. PVd=pomalidomide, bortezomib, and low-dose dexamethasone. Vd=bortezomib and dexamethasone.

* Cumulative dose was defined as the sum of all doses taken across the treatment period. Units: mg/m^2 for BORT.

† Dose exposure was defined as the total number of days on drug during the treatment period.

‡ Average daily dose was defined as the ratio of cumulative dose to dose exposure. Units: mg/m^2/day for BORT.

§ Relative dose intensity was defined as the ratio of dose intensity to planned dose intensity.

	PVd (n = 278)			Vd (n = 270)	
	POM	BORT	DEX	BORT	DEX
Treatment duration, median, months	8·7 (4·4–15·4)	7·6 (3·8–13·1)	7·8 (4·1–14·0)	4·9 (2·1–9·0)	4·9 (2·1–8·5)
Median no. of cycles	12 (6–21)	10 (5–18)	11 (6–20)	7 (3–12)	7 (3–12)
Median cumulative dose, mg*	521·0 (294·0–994·0)	37·2 (20·8–54·1)	1088·0 (620·0–1600·0)	29·5 (15·6–46·8)	714·0 (400·0–1280·0)
Median dose exposure, days†	154 (82–293)	33 (18–49)	70 (41–104)	24 (12–38)	48 (24–76)
Median average daily dose, mg/day‡	4·0 (3·2–4·0)	1·3 (1·1–1·3)	17·8 (11·4–20·0)	1·3 (1·1–1·3)	20·0 (13·3–20·0)
Median relative dose intensity§	0·85 (0·70–0·90)	0·80 (0·70–0·90)	0·80 (0·60–1·00)	0·90 (0·80–1·00)	0·90 (0·70–1·00)

"Reprinted from The Lancet The Lancet Oncology, Vol.20 number 6, Richardson PG, Oriol A, Beksac M et al., Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial, Pages No.781-794, Copyright (2019), with permission from Elsevier."

Concomitant Treatments and Medications[2]

- Herpes Zoster (HZ) prophylaxis for all subjects receiving bortezomib (oral acyclovir or equivalent therapy per institutional guidelines).
- Thromboembolism prophylaxis was required during the study treatment for subjects in the PVd arm. Other subjects in the Vd arm could receive antithrombotic therapy at the discretion of the treating physician.
- Bisphosphonates during the study treatment phase for subjects with myeloma-associated bone disease at the discretion of the Investigator.
- Hematopoietic growth factors (the use of myeloid growth factors was encouraged when the absolute neutrophil count (ANC) was < 1000/µL),

platelet or red blood cell (RBC) transfusions at the discretion of the Investigator.
- Radiation therapy to a pathological fracture site or to treat bone pain.

d) Patient Disposition

Enrolment for the OPTIMISMM was between January 2013 and May 2017 and data cut off was October 26, 2017. There was another interim analysis data cut-off for overall survival for September 15, 2018, although this was not prespecified. There were 712 patients screened and 153 did not meet study eligibility criteria. There was no description of the reasons for study ineligibility. A total of 559 patients were randomized, 281 allocated to PVd and 278 allocated to Vd. Three patients in the PVd arm and eight patients in the Vd arm did not receive the study intervention.[1]

Patients were followed for a median of 15.9 months (IQR 9.9 to 21.7) [1]; this ranged from 0 to 57 months.[29] As of the data cut-off date, October 26,2017, 93 patients (33.1%) in the PVd arm and 45 patients (16.2%) in the Vd arm were continuing treatment.[1] As of the data cut-off date of September 15, 2018, patients were followed for a median follow up of 26.2 months. [2]

As seen in Table 6.6, treatment discontinuations were lower in patients who received PVd 185/281 (65.8%) compared to those who received Vd 225/278 (80.9%).[1] Study discontinuations were similar in each arm, although there were 10 withdrawal of consent in the PVd arm and 17 withdrawal of consent in the Vd arm.[1]

In the safety population there were 86 deaths in each arm. Twenty-seven (9.7%) in the PVd arm and 12 (4.4%) in the Vd arm died during treatment period or within 28 days after receiving the last dose of study treatment. Discontinuation rates were (65.8%) in the PVd arm and (80.9%) in the Vd arm, with disease progression being the most common reason for discontinuation in both treatment arms.[1]

There were 35/281 (12.5%) patients in the PVd arm and 28/278 (10.1%) patients in the Vd arm, for a total of 63 (11.3%) patients in the intent to treat population that had a protocol violation. The violations in order of frequency: SAE submitted later than the required timeline, pomalidomide counselling not performed, biomarker sampling without consent, patient did not meet key safety criteria for taking drug on cycle 1 day 1, incorrect treatment assignment, stratification or randomization error, did not meet prior regimens number criteria, met medical history exclusion criteria, missing baseline skeletal survey, antithrombotic prophylaxis not given without medical reason, and washout period for prior treatment of procedure not met.[2] Generally the protocol violations appeared balanced between the groups.

Subsequent anti-cancer therapies

A total of 163/278 (58.6%) patients in the Vd arm received subsequent anti-myeloma therapies, and 109/163 (66.9%) of these received pomalidomide. In the PVd arm, 21/281 (7.5%) received subsequent pomalidomide.[1] After corticosteroids and pomalidomide, the most frequent antineoplastic agents received in the PVd and Vd arms, respectively, were: cyclophosphamide (11.0% and 15.1%), daratumumab (14.2% and 10.8%) carfilzomib (10.3% and 14.0%), and bortezomib (9.3% and 13.3%) lenalidomide (6.0% vs. 11.9%). Ixazomib, elotuzumab, panobinostat, thalidomide, melphalan, bendamustine were used in less than 5% of

patients; there were several other therapies used in smaller proportions of patients (doxorubicin, autologous stem cell transplant, pembrolizumab, etoposide, cisplatin, radiotherapy and antimetabolites).[2] With the exception of subsequent pomalidomide, the types and percentages of subsequent anti-myeloma therapies were similar between treatment arms.

Table 6.6 Patient Disposition at the time of primary data analysis[2]

	POM+BTZ+ LD-DEX N=281	BTZ+LD-DEX N=278	All subjects N=559
Randomized, Not Treated, n (%)	**3 (1.1)**	**8 (2.9)**	**11 (2.0)**
Subjects Treated, n (%)			
Ongoing	93 (33.1)	45 (16.2)	138 (24.7)
Discontinued	185 (65.8)	225 (80.9)	410 (73.3)
Primary Reason for Treatment Discontinuation, n (%)			
Progressive Disease	110 (39.1)	131 (47.1)	241 (43.1)
Adverse Event	30 (10.7)	49 (17.6)	79 (14.1)
Withdrawal of Consent	21 (7.5)	21 (7.6)	42 (7.5)
Death	18 (6.4)	9 (3.2)	27 (4.8)
Other	6 (2.1)	12 (4.3)	18 (3.2)
Lost to Follow-up	0	2 (0.7)	2 (0.4)
Pregnancy	0	1 (0.4)	1 (0.2)
Subjects who Entered Progression-free Follow-up Phase, n (%)			
Ongoing	5 (1.8)	4 (1.4)	9 (1.6)
Discontinued	19 (6.8)	30 (10.8)	49 (8.8)
Primary Reason for PFS Follow-up Phase Discontinuation, n (%)			
Progressive Disease	14 (5.0)	23 (8.3)	37 (6.6)
Other	1 (0.4)	5 (1.8)	6 (1.1)
Withdrawal of Consent	2 (0.7)	2 (0.7)	4 (0.7)
Death	2 (0.7)	0	2 (0.4)
Subjects Discontinued from Study, n (%)	**102 (36.3)**	**110 (39.6)**	**212 (37.9)**
Primary Reason for Discontinuation from Study, n (%)			
Death	87 (31.0)	89 (32.0)	176 (31.5)
Withdrawal of Consent	10 (3.6)	17 (6.1)	27 (4.8)
Lost to Follow-up	3 (1.1)	4 (1.4)	7 (1.3)
Other	2 (0.7)	0	2 (0.4)

e) Limitations/Sources of Bias

- The trial was open-label and therefore, investigators and patients were not blinded to treatment assignment. Therefore, the trial may be at risk for biases related to blinding that can affect the internal validity. These can include bias in terms of patient selection for eligibility or performance bias because of knowledge of assigned treatment. Given that pomalidomide is administered

orally, blinding and placebo control could have been possible. Patients in the PVd arm may have been more likely to adhere to experimental therapy and investigators may have been more likely to discontinue treatment in the Vd arm given the open-label nature of the trial. This may have biased the results in favour of PVd.

- The trial did not provide any statement on methods used to ensure allocation concealment, which, if not actually concealed would introduce selection bias.
- In open-label trials there is a possibility that assessment of subjective measures such as HRQoL may be biased. This may also apply to the assessment of subjective adverse events. It is possible that an outcome of disease progression may be biased in such a trial if the investigator was not blinded. In the OPTIMISMM trial, a central independent review of the primary outcome and tumour response was performed by blinded experts. This blinded IRAC served to decrease bias.
- Pre-specified secondary endpoints were tested sequentially (PFS, then ORR then OS); the interim OS data did not meet the pre-specified superiority boundary. The OS data was not mature at the time of the interim analysis for the OS data (at PFS maturity). The other secondary end points (duration of response and safety) as well as some exploratory end points were presented at the time of final PFS analysis, but without multiplicity adjustment. Therefore, the p-values reported were noted for descriptive purposes only. The lack of adjustment for multiplicity control limits the interpretation of these end points.
- Pre-specified subgroup analyses were reported in the trial. However, the subgroups (including, for example, patients who were lenalidomide refractory and different age groups) were not adjusted for multiplicity, adequately powered, nor included in the statistical hierarchy. The interpretation of results for subgroup analyses is therefore limited. Additionally, the interpretation of any differences in end points in subgroups is limited because of the small number of patients in the subgroups.
- Similarly, HRQoL end points were exploratory, not adequately powered, not included in the statistical hierarchy and not adjusted for multiplicity. Therefore, any interpretation of HRQoL end points is limited.
- In addition to concerns around allocation concealment which may impact subjective end points such as HRQoL, as well as greater number of treatment discontinuations in the Vd arm, the interpretation of any HRQoL outcomes in the OPTIMISMM trial was impaired by the lower completion rates of questions in the Vd arm than in the PVd arm at each cycle. Thus, the lower compliance to HRQoL questionnaires in the control group could bias results in favour of pomalidomide.
- Time to next line of therapy (time to subsequent anti-myeloma therapy) is not listed as a pre-specified end point in the trial protocol, however, results are reported. The interpretation of this end point is therefore limited.
- The sponsor Celgene Corporation 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. An external statistician who was unblinded generated reports for the external independent data monitoring committee. The sponsor also funded the medical writing of the OPTIMISMM publication.[1] There were two employees of Celgene Corporation included in authorship of the OPTIMISMM publication.[1] The extent to which the use of independent investigators and data analysts may have influenced the results and reporting of the trials is unknown.

6.3.3 Detailed Outcome Data and Summary of Outcomes

Key outcomes reported at the primary analysis (October 26, 2017) are shown in Table 6.7. Key secondary endpoints were tested in a sequential approach (ORR and OS).[1] OS data was not mature as of the data cut-off of October 26, 2017. Other secondary endpoints were not included in the alpha spending function and analyzed without multiplicity adjustment; therefore all of the *P*-values reported are for descriptive purposes only and the interpretation of these results is limited.[1] Similarly, outcomes reported in the September 15, 2018 unplanned interim analysis for OS are included in Table 6.7. OS data are not mature as of the data cut-off of September 15, 2018.

Table 6.7: Efficacy and harms outcomes reported at the primary analysis for the OPTIMISMM trial comparing pomalidomide bortezomib dexamethasone combination vs. bortezomib dexamethasone combination in patients with relapsed or refractory multiple.[1]

Efficacy outcomes[1]					
Analysis date	**Study arms**	**OS, median (months)**	**PFS, median (months)**	**ORR**	HRQoL
PFS final analysis (October 26, 2017)	PVd n=281 Vd n=278	Not reached 31.24 (95% CI: 27.01, NE) [29] HR=0.98 95%CI: 0.73-1.32 *P*=0.894 * Pre-specified stopping boundary of p = 0.031 was not crossed, therefore not significant Data not mature – only 176 events (31.5%).	11.20 (95%CI: 9.66 – 13.73) 7.10 (95%CI: 5.88 – 8.48) HR=0.61 95%CI: 0.49-0.77 *P* <0.0001	231/281 (82.2%) 139/278 (50.0%) OR=5.02 95%CI: 3.35-7.52 *P* <0.001	No difference in EORTC-QLQ-C30 GHS/QoL domain in either arm over time, No difference in EORTC-QLQ-C30 GHS/QoL domain in either arm between groups at any time point.
September 15, 2018	PVd n=281 Vd n=278	40.54 (95% CI: 29.83, NE) 30.46 months (95% CI: 24.61, 35.94) HR=0.91, 95%CI: 0.70, 1.18, *P*=0.476[2] Data not mature, only 242 events (43.3%)[2] Not prespecified interim analysis.	10.9 (95% CI: 9.5, 13.6) 6.9 (95% CI: 5.6, 8.2 HR=0.62, 95%CI: 0.50, 0.76 *P*<0.001	Not available	Not available

	Harms Outcomes, n (%)[1]	
	PVd n= 278	**Vd n= 270**
Treatment related Deaths	27 (9.7)	12 (4.4)
Overall Grade 3/4 TRAE's	251 (90.3)[2]	190 (70.4)[2]
Neutropenia	116 (41.7)	23 (8.5)
Thrombocytopenia	76 (27.3)	79 (29.3)
Anemia	39 (14.0)	38 (14.1)
Peripheral neuropathy	23 (8.3)	12 (4.4)
Constipation	7 (2.5)	1 (<1)
Fatigue	23 (8.3)	10 (3.7)
Diarrhea	20 (7.2)	9 (3.3)
Pneumonia	32 (11.5)	17 (6.3)
Hypokalemia	17 (6.1)	11 (4.1)
Hyperglycemia	25 (9.0)	14 (5.2)
Syncope	14 (5.0)	6 (2.2)
SAEs	159 (57.2)	114 (42.2)
WDAEs	31 (11.2)	50 (18.5)

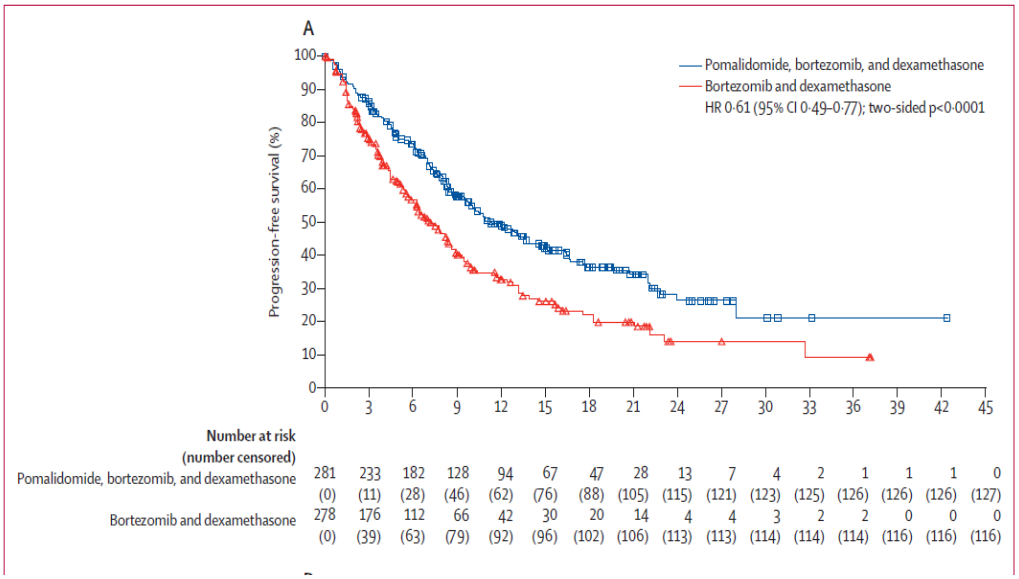
AE = adverse events; **CI** = confidence interval; **HR** = hazard ratio; **OR** = odds ratio; **ORR** = overall response rate; **OS** = overall survival; **PFS** = progression free survival; **SAE** = serious adverse event; **TRAE = treatment related adverse events; WDAE** = withdrawal due to adverse event
*HR/OR <1 favours PVd

Efficacy Outcomes

Progression-free Survival – Primary Outcome of OPTIMISMM.

The OPTIMISMM trial met its primary outcome at the final PFS analysis which showed improved PFS with PVd versus Vd.[1] PFS was defined as the duration from the randomization to the date of confirmed progression of disease or death. A blinded IRAC assessed both the date of disease progression and the myeloma response data[1] according to the IMWG Criteria and the censoring rule according to FDA guidelines.[2,32] Patients were followed for a median of 15.9 months (IQR 9.9-21.7). As of the date of the October 26, 2017 data cut-off, there were a total of 316 PFS events (154/281 in the PVd arm and 162/278 in the Vd arm).[1] The median PFS was 11.20 months (95% CI: 9.66 – 13.73) in the PVd arm and 7.10 months (95% CI: 5.88-8.48) in the Vd arm (HR=0.61, 95%CI: 0.49-0.77, two sided *P*<0.0001).[1] In the PVd arm, the estimated 6 and 12-month event-free survival rates were 73.38% and 49.47%, respectively; in the Vd arm, the estimated 6 and 12-month event-free survival rates were 56.64% and 32.45%, respectively.[29]

Figure 6.3 Progression free survival analysis of OPTIMISMM trial by treatment arm at the October 26, 2017 data cut[1]



Reprinted from The Lancet The Lancet Oncology, Vol.20 number 6, Richardson PG, Oriol A, Beksac M et al., Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial, Pages No.781-794, Copyright (2019), with permission from Elsevier.

As of September 15, 2018, PFS was assessed by investigator based on IMWG criteria using a censoring rule according to EMA guideline. At the Sep 15, 2018 data cut-off, a total of 339 PFS events had occurred. The median PFS was 10.9 months (95% CI: 9.5, 13.6) in the PVd arm and 6.9 months (95% CI: 5.6, 8.2) in the Vd arm HR=0.62, 95%CI: 0.50, 0.76, two sided *P*<0.001). [31]

Generally, PFS results were consistent across subgroups as of the October 26, 2017 data cut-off.[1] The PFS advantage was maintained in all patient subgroups: age groups, baseline ECOG performance status, baseline cytogenetic categories, number of prior myeloma regimens, international

staging system (I vs II vs III), baseline creatinine clearance, refractory to lenalidomide, refractory to last therapy for MM, prior exposure to proteasome inhibitors.[1] Although subgroup analyses of results were pre-specified, these end points were exploratory in nature and therefore interpretation of the findings is limited. Figure 6.4 presents descriptive statistics and HR (95%CI) estimates for PFS in protocol defined subgroups for the OPTIMISMM trial.[1]

For patients with multiple myeloma that was refractory to lenalidomide, there were 120/200 events, with a median PFS of 9.53 months (95% CI 8·05,11.30) in the PVd arm and 118/191 events with a median PFS of 5.59 months (95% CI 4.44,7.00) in the Vd arm HR 0.65 (95% CI 0.50,0.84); *P*=0·0008.[1] Patients with one prior line of therapy experienced 45/111 events with a median PFS of 20.73 months (95% CI 15.11,27.99) in the PVd arm and 52/115 events with a median PFS of 11.63 months (95% CI 7.52,15.74) in the Vd arm; HR 0.54 (95% CI 0.36,0·82); *P*=0·0027.[1] Patients with prior exposure to proteasome inhibitors had 118/212 events and a median PFS of 10.91 months (95% CI 8.41,13.73) in the PVd arm and 132/213 events with a median PFS of 6.31 months (95% CI 5.19, 8.31) in the Vd arm; HR 0.57 (95% CI 0.44, 0·73); *P*<0.001).[1] Patients with high-risk cytogenetics (by fluorescence in situ hybridization and defined as at least on high-risk abnormality of del(17p), t(4;14), or t(14;16)) had 37/61 events and a median PFS of 8.44 months (95% CI 4.86,13.73) in the PVd arm and 34/49 events with a median PFS of 5.32 months (95% CI 2.27,8.31) in the Vd arm; HR 0.56 (95% CI 0.35, 0.90); *P*=0·015).[1]

A request for additional information from the manufacturer revealed that for patients with multiple myeloma that were refractory to the last previous treatment as of the October 26, 2017 data cut-off, there were 110/196 events, with a median PFS of 10.18 months (95% CI 8.28,13.14) in the PVd arm and 112/184 events with a median PFS of 5.88 months (95% CI 4.44, 7.52) in the Vd arm HR 0·60 (95% CI 0.46, 0.78); *P*=0·0001. Conversely, for those who were not refractory to the last previous treatment there were 44/85 events, with a median PFS of 16.36 months (95% CI 10.74, 22.08) in the PVd arm and 50/94 events with a median PFS of 9.23 months (95% CI 7.36, 13.14) in the Vd arm HR 0·61 (95% CI 0·41, 0.93); *P*=0.0184.[31]

As described in the supplement to the OPTIMISMM trial, for patients who had received only one prior line of therapy and were refractory to lenalidomide there were 25/64 events and a median PFS of 17·84 months (95% CI 12.02–not estimable) in the PVd arm *vs* 31/65 events and a median PFS of 9·49 months (95% CI 6·34–16·20) in the Vd arm HR 0·55 (95% CI 0·33–0·94); *P*=0·0276 although this subgroup was not pre-specified.[1]

Figure 6.4 pre-specified subgroup analysis for progression free survival for the OPTIMISMM trial[1]

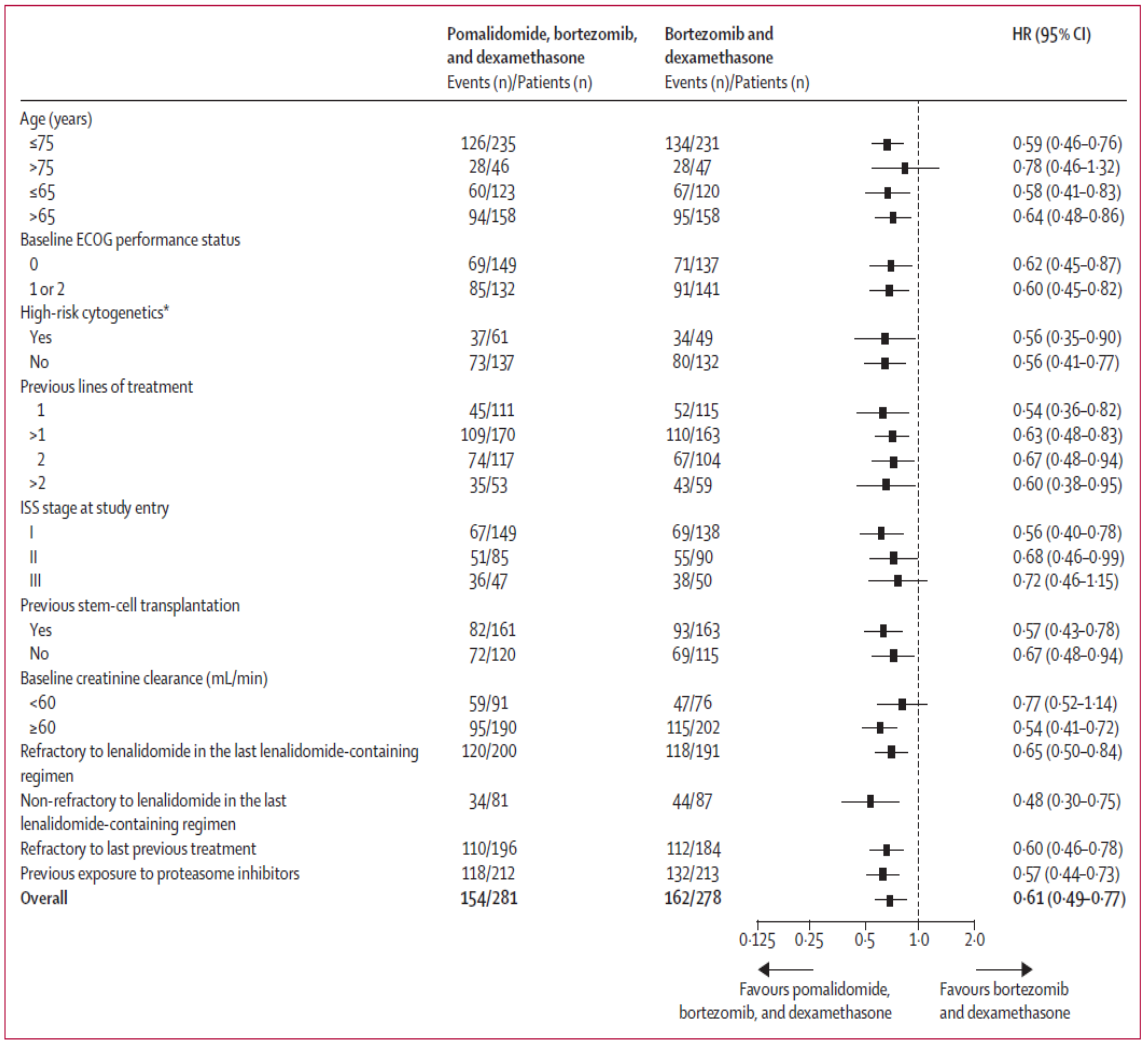


Figure 3: **Prespecified subgroup analyses for progression-free survival**
HR=hazard ratio. ECOG=Eastern Cooperative Oncology Group. ISS=International Staging System. *Defined as at least one high-risk abnormality—del(17p), t(4;14), or t(14;16).

Reprinted from The Lancet The Lancet Oncology, Vol.20 number 6, Richardson PG, Oriol A, Beksac M et al., Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial, Pages No.781-794, Copyright (2019), with permission from Elsevier.

Duration of Response

Duration of response was a secondary end point, although this end point was analysed without control for Type 1 error.[1] Duration of response was defined as the time of first documented response to confirmed progressive disease or death from any cause for all responders (partial or better).[1] The median duration of response was 13.7 months (95% CI 10.9, 18.1) in the PVd arm and 10.9 months (95% CI: 8.1, 14.8) in the Vd arm.[1]

Overall Survival

The OS analysis is immature therefore interpretation of this data is limited. There were similar OS events in both study arms as of the interim analysis data cut-off, October 26, 2017.[1] Overall survival (OS) was defined as the time from date of randomization to the date of death from any cause.[1] As of the data cut-off October 26, 2017, (median follow up 15.9 months) there were a total 87/281 (31%) deaths in the PVd arm and 89/278 deaths (32%) in the control arm. This was an overall event rate of 176/559 (31.5%).[1] OS did not cross the pre-specified early stopping boundary for the interim analysis.[1] The OS difference between treatment arms resulted in a HR of 0.98 (95% CI: 0.73, 1.32) *P* = 0.89.[1] Median OS from Kaplan-Meier estimates had not been reached in the PVd arm and was 31.2 months for the Vd arm (95%CI: 27, not estimable).[2] Estimated 24 month event free survival rates were 59.5% for the PVd arm and 60.91% for the Vd arm. The estimated 36 month event free survival rates were 50.5% for the PVd arm and 39.7% for the Vd arm.[2] The final OS analysis will occur when 379 OS events have occurred.[1]

As of an updated analysis on September 15, 2018, a total of 242 OS events (43.3%) had occurred. There were 116/281 deaths with a median OS duration of 40.54 months (95% CI: 29.83, not evaluable) in the PVd arm and 126/278 deaths with a median OS of 30.46 months (95% CI: 24.61, 35.94) in the Vd arm HR=0.91, 95%CI: 0.70, 1.18, two sided *P*=0.476). [2] This data is still not mature. The interim analysis was not pre-specified.[30]

Time to subsequent anti-myeloma therapy

Time to subsequent anti-myeloma therapy was an exploratory end point that was not pre-specified in the OPTIMISMM trial protocol.[1] Time to subsequent anti-myeloma therapy was defined as the duration in months from the date of randomization to the date of subsequent anti-myeloma therapy. The median time to subsequent anti-myeloma therapy was 22.24 months (95% CI 17.18,29.50) in the PVd arm and 8.51 months (95% CI: 7.26 – 10.02) in the Vd arm (HR=0.42, 95%CI: 0.33-0.54, *P*<0.001).[1]

Overall Response Rate

Overall response rate was a secondary end point that was included in the alpha spending function as is described in the supplement to the publication.[1] Overall response rate was defined as the proportion of patients who achieved partial or better response (a best response of stringent complete response, complete response, very good partial response or partial response) according to IMWG criteria.[32] The ORR was 231/281 (82.2%) and 139/278 (50%) in the PVd and Vd arms, respectively; odds ratio 5.02 (95% CI 3.35-7.52; P<0.001.).[1] Table 6.8 presents further details of response and response by subgroups.

Table 6.8 Treatment response rates in the ITT population of the OPTIMISMM trial.[2]

	POM+BTZ+ LD-DEX N=281	BTZ+LD-DEX N=278	All Subjects N=559
Overall Response Category, (n %)			
sCR	9 (3.2)	2 (0.7)	11 (2.0)
CR	35 (12.5)	9 (3.2)	44 (7.9)
VGPR	104 (37.0)	40 (14.4)	144 (25.8)
PR	83 (29.5)	88 (31.7)	171 (30.6)
SD	32 (11.4)	106 (38.1)	138 (24.7)
PD	11 (3.9)	16 (5.8)	27 (4.8)
NE / Not Done [a]	7 (2.5)	17 (6.1)	24 (4.3)
Dichotomized Response, n (%)			
sCR or CR or VGPR or PR	231 (82.2)	139 (50.0)	370 (66.2)
SD or PD or NE [a]	50 (17.8)	139 (50.0)	189 (33.8)
Odds Ratio (POM+BTZ+LD-DEX vs BTZ+LD-DEX) [b] [Two-sided 95% CI]	5.02 [3.35, 7.52]		
p-value [c]	<0.001		

BTZ = bortezomib; CI = confidence interval; CR = complete response; IMWG = International Myeloma Working Group; IRAC = Independent Response Adjudication Committee; ITT = intent=to treat; LD-DEX = low-dose dexamethasone; NE = not evaluable; PD = progressive disease; POM = pomalidomide; PR = partial response; sCR = stringent complete response; SD = stable disease; VGPR = very good partial response.

[a] Including subjects who did not have any response assessment data, or whose only assessment was response not evaluable.

[b] Odds ratio is for POM+BTZ+LD-DEX:BTZ+LD-DEX.

[c] P-value is based on a Cochran-Mantel-Haenszel test, stratified by age (≤ 75 versus > 75), prior number of antimyeloma regimens (1 versus > 1), and beta-2 microglobulin at screening (< 3.5 mg/L versus ≥ 3.5 mg/L, ≤ 5.5 mg/L versus > 5.5 mg/L).

Quality of Life- Change in global health status

The HRQoL end points were added as study end points to the OPTIMISMM trial at protocol amendment 1.[1] The HRQoL end points were exploratory,[1] and therefore the interpretation of this data is limited. The study measures were administered prior to the first day of every cycle (21 days) and at treatment discontinuation.[1] The primary HRQoL end points was the global health status domain of the EORTC QLQ-C30, secondary domains of interested included physical functioning, pain, fatigue domains of EORTC QLQ-C30, disease symptoms and treatment domains of EORTC QLQ-MY20 and EQ-5D-3L utility. Other HRQoL end points included the remaining domains of the EORTC QLQ-C30 and EORTC QLQ-MY20.[1]

The HRQoL evaluable population were those who had completed the EORTC QLQ-C30 questionnaire at baseline and at least one post-baseline assessment. The change in scores from baseline was determined for each treatment arm at each visit.[1] A mixed model repeated measures analysis was used to estimate overall least square means for change from baseline across all visits and least squared means for change from baseline at day 1 of cycle 5,9,19 and 25 within each treatment group, and the difference between treatment groups.[37] Time for first clinically meaningful deterioration was assessed. A clinically meaningful change, defined as ≥10-point deterioration from baseline, was used for EORTC QLQ-C30 and EORTC QLQ-MY20.[37] This corresponds with a minimally important difference of 10

which has been described in the literature for the physical, social, and emotional functioning subscales and the global health status quality of life domains.[34]

Compliance based on the number of subjects expected to complete the questionnaire at each visit was greater than 80% for both groups for most visits.[37]. However, the number of available patients providing data for the quality of life (QoL) measure (QLQ-C30) gradually declined with the number of responders declining to less than 50% at cycle 14. Response rates continued to decline thereafter with data available from 33 patients in the PVd group and 10 patients in the Vd group at cycle 26.

The population with HRQoL end points included 240/281 (85.4%) in the PVd arm and 209/278 (75.2%) in the Vd arm.[37] Baseline scores for the global health status/QoL domain of the EORTC QLQ-C30 were 61.0 (SD 23.2) in the PVd arm and 63.5 (SD 21.3) in the Vd arm.[1] A request to the manufacturer revealed that missing data in the HRQoL end points were handled according to the published scoring manual for each measure.

Generally, in both arms the global health status/QoL domain of the EORTC QLQ-C30 did not change over time, in either group, with no statistical or clinical differences over time in either group from baseline to the end of available data (cycle 26 on the graph).[37] There were no statistical or clinical differences between treatments arms at any cycle on the global health status/QoL domain based on observed data, or the mixed-effects model from baseline to the end of available data (cycle 26 on the graph).[37] This is shown graphically in Figure 6.5 and 6.6.

Mixed-model repeated measure (MMRM) analyses showed statistically significant worsening in Least square (LS) means QLQ-C30 global QoL domain score in patients in the PVd group compared to the Vd group at Day 1 of Cycle 5 (difference = -2.883 [95% CI: -5.345,-0.42]; P = 0.0219) and Day 1 of Cycle 9 (difference = -2.914 [95% CI: -5.498,-0.33]; P = 0.0272). However, these differences were not clinically meaningful. After imputing missing data using a pattern-mixture model, the differences between treatment groups in LS mean changes from baseline were reduced and were non-statistically significant (p>0.05) at all assessment visits (Day 1 of Cycles 5, 9, 19, and 25).

Figure 6.5 HRQoL analysis based on global health status/QoL domain change from baseline based on observed data.[37]

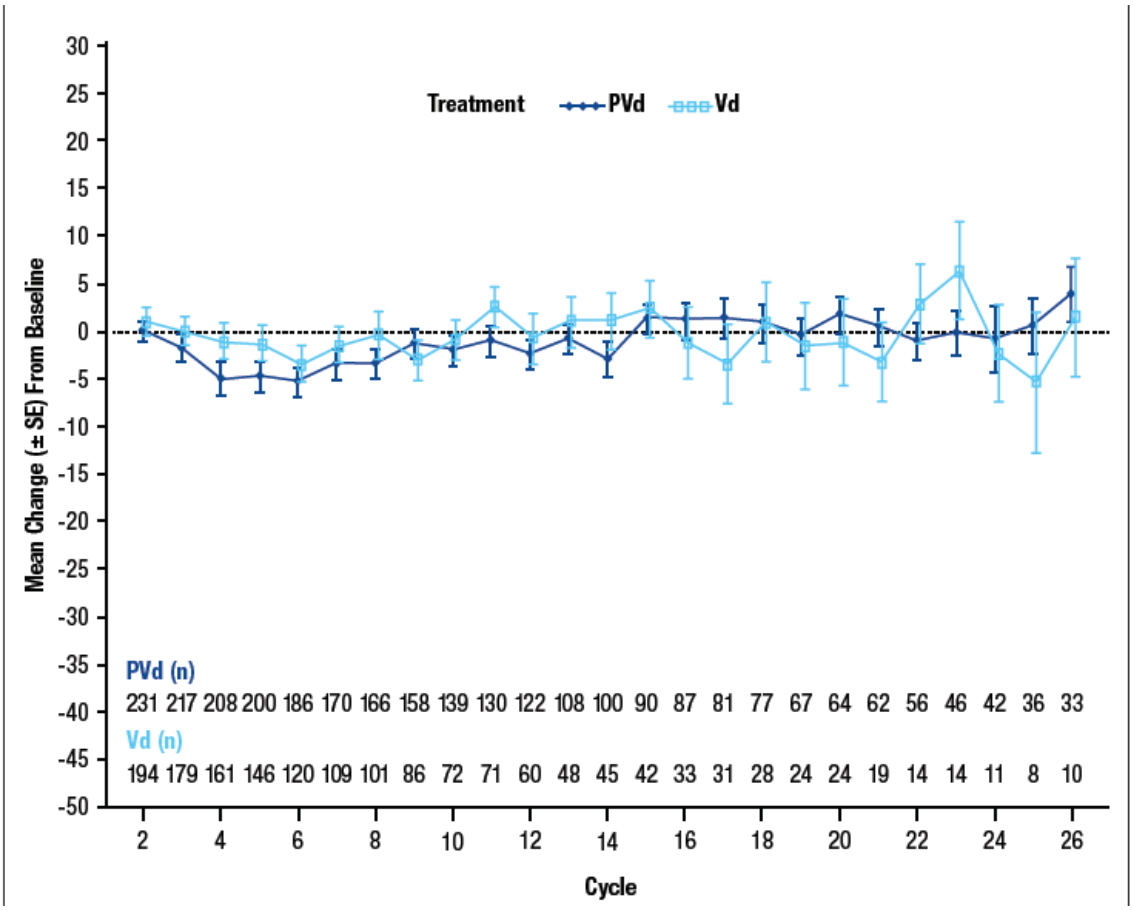
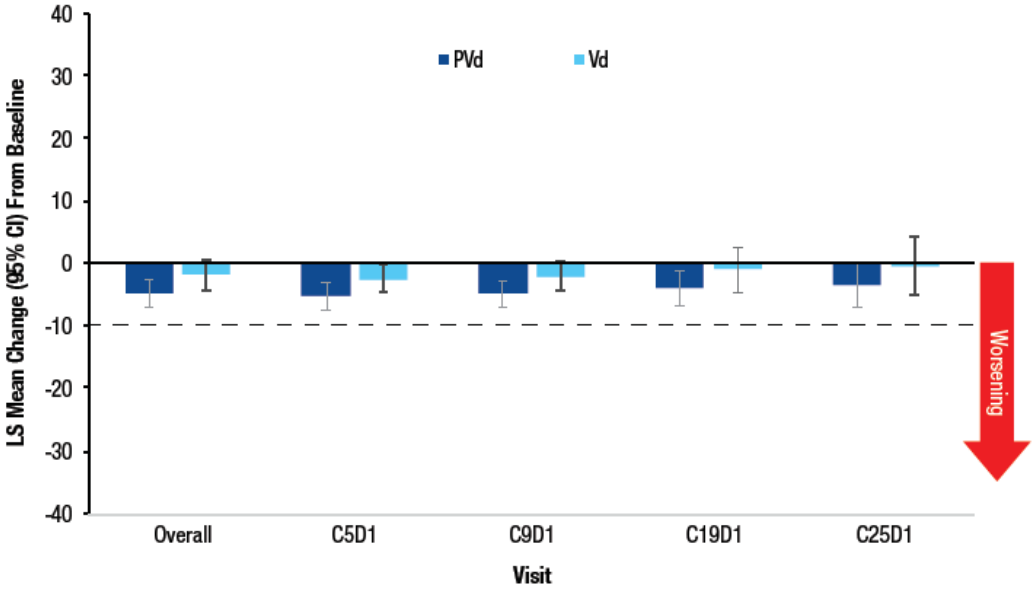


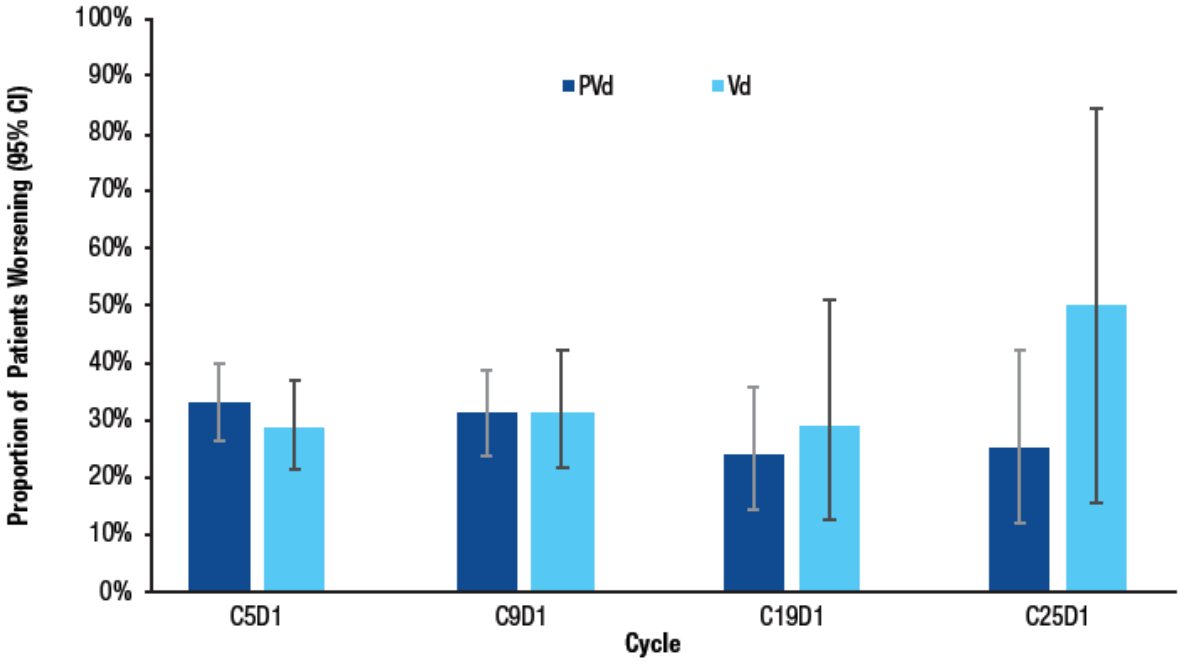
Figure 6.6 HRQoL analysis based on global health status/QoL domain change from baseline based on mixed model repeated measure analysis.[37]



	Overall	C5D1	C9D1	C19D1	C25D1
PVd (n)	231	200	158	67	36
Vd (n)	194	146	86	24	8
Difference	–2.928	–2.883	–2.914	–2.992	–3.039
95% CI	–5.686 to –0.169	–5.345 to –0.420	–5.498 to –0.33	–7.182 to 1.198	–8.563 to 2.485

There was no statistical difference in the proportion of patients in either arm who met the definition for clinically meaningful deterioration for the global health status/QoL domain of the EORTC QLQ C30.[37] This is presented graphically in Figure 6.7.

Figure 6.7 HRQoL analysis based on global health status/QoL domain proportion of subjects with clinically meaningful deterioration data.[37]



	C5D1	C9D1	C19D1	C25D1
PVd (n)	200	158	67	36
Vd (n)	146	86	24	8
Odds ratio	1.18	0.99	0.90	0.21
95% CI	0.73 to 1.89	0.55 to 1.79	0.30 to 2.70	0.03 to 1.57

Overall, the mixed-effects model suggested patients demonstrated a similar time to first clinically meaningful worsening (median time 3.0 months in the PVd arm and 3.4 months in the Vd arm; findings were not statistically significant, and were similar when deaths were censored.[37]

The results of mixed-model repeated measure analyses for the secondary domain of interest (physical functioning, pain, and fatigue domains of the QLQ-C30; disease symptoms and side effects of treatment domains of the QLQ-MY20; and health utility of EQ-5D) showed no significant and clinically meaningful differences in LS mean changes from the baseline between the treatment groups at any assessment visits (Day 1 of Cycles 5, 9, 19, and 25). Patients in both treatment groups experienced an improvement in the disease symptoms of the QLQ-MY20 across all post-baseline assessment visits.

Progression free survival after next line of therapy

PFS after next line of therapy was an exploratory end point and defined as the duration in months from the date of randomization to the date of second objective disease progression or death from any cause in the intent to treat population.[1] The median PFS after next line of therapy was 22.44 months (95% CI 18.96 – not

estimable) in the PVd arm and 16.95 months (95% CI: 14.69-21.09) in the Vd arm (HR=0.76, 95%CI: 0.59-0.99, *P*<0.041).[1]

Time to Response

Time to response was an exploratory end point in the OPTIMISMM trial and not included in the pCODR clinical review protocol. The pCODR review team decided to report this endpoint here as matter of completeness and interest to the reader. It was defined as the duration in months from the date of randomization to the date of response.[1] Response was based on IRAC review for those patients who had at least partial response during the study; this includes those with stringent complete response, complete response, very good partial response and partial response.[1] The median time to response was 0.9 months (IQR 0.8-1.4) in the PVd arm and 1.4 months (IQR 0.8-1.9) in the Vd arm.[1]

Time to progression

Time to progression was an exploratory endpoint in the OPTIMISMM trial, not included in the pCODR clinical review protocol. The pCODR review team decided to report this endpoint here as matter of completeness and interest to the reader. Time to progression was 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 136/281 (48.4%) patients in the PVd arm and 150/278 (54.%) patients in the Vd arm, respectively, had progression of multiple myeloma. The median time to progression was 13.14 months (95%CI: 10.48, 16.62 months) in the PVd arm and 7.79 months (95% CI: 6.34, 8.71) in the Vd arm (HR=0.57, 95%CI: 0.45,0.72).[29]

Overall Response Rate defined by the European Society for Blood and Marrow transplantation

The ORR as defined by the European Society for Blood and Marrow Transplantation was an exploratory end point in the OPTIMISMM trial, not included in the pCODR clinical review protocol. The pCODR review team decided to report this endpoint here as matter of completeness and interest to the reader. In the PVd arm, the proportion with complete response was 44/281 (15.7%) and those with partial response was 186/281 (66.2%).[29] In the Vd arm, the proportion with complete response was 11/278 (4.0%) and those with partial response was 128/278 (46.0%). Those with ORR (complete and partial response) were 230/281 (81.9%) in the PVd arm and 139/278 (50.0%) in the Vd arm (OR 4.93, 95% CI 3.29,7.39).[29] These results are very similar to the secondary end point ORR analysis using the IMWG criteria.

Time to treatment failure

Time to treatment failure is not included in the pCODR clinical review protocol. The pCODR review team decided to report this endpoint here as matter of completeness and interest to the reader. This was an exploratory end point that was added at Protocol Amendment 5 to the trial. The definition was the time from randomization to the earliest of: progressive disease as determined by the IRAC (without censoring), discontinuation from treatment of PFS follow up phase, start of another anti-myeloma treatment and death.[1] The median time to treatment failure was 8.54 months (95%CI: 7.36, 10.12 months) in the PVd arm and 4.67 months (95% CI: 3.84,5.49) in the Vd arm (HR=0.54, 95%CI: 0.44,0.65).[29]

Clinical benefits

Time to treatment failure is not included in the pCODR clinical review protocol. The pCODR review team decided to report this endpoint here as matter of

completeness and interest to the reader. Clinical benefits were assessed through improvements (at least one category) in hemoglobin, renal function, ECOG performance status, hypercalcemia and non-myeloma immunoglobulins. These end points were exploratory.

The median time to first improvement in hemoglobin was 4.07 weeks (min 0.6, max 56.1 weeks) in the PVd arm and 1.71 weeks (min 0.4, max 38.3 weeks) in the Vd arm.[29]

The median time to first improvement in serum creatinine was 2.71 weeks (min 0.4, max 27.0 weeks) in the PVd arm and 3.0 weeks (min 0.6, max 49.3 weeks) in the Vd arm.[29]

The median time to first improvement in ECOG performance status was 8.0 weeks (min 3.0, max 109 weeks) in the PVd arm and 6.9 weeks (min 3.0, max 32.0 weeks) in the Vd arm.[29]

Improvement in hypercalcermia was not reported in the available documents.

The median time to first improvement in non-myeloma immunoglobulins was 6.6 weeks (min 3.0, max 91 weeks) in the PVd arm and 9.1 weeks (min 3.0, max 63.0 weeks) in the Vd arm.[29]

Other exploratory end points

Data were not available for minimal residual disease, or other biomarker data.

Harms Outcomes

The OPTIMISMM trial provided data on the harm outcomes of interest. Harms data are summarized in Table 6.9. 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, 278 patients in the PVd arm and 270 in the Vd arm.

As there was a longer treatment duration with PVd than with Vd, the adverse events results are reported both as percentages and as adverse events per 100 person years. These analysis was added as a change to the original analysis plan.[1]

At least one treatment related adverse event (TRAE) occurred in 277/278 (99.6%) and 264/270 (97.8%) patients in the PVd and Vd arms, respectively. At least one TRAE related to any study drug occurred in 267/278 (96.0%) and 226/270 (83.7%) patients in the PVd and Vd arms, respectively; and there were at least 215/278 (77.3%) and 126/270 (46.7%) patients in the PVd arm and Vd arm, respectively, who experience at least on grade 3 or 4 TRAE related to any study drug. [2]

More patients in the PVd arm experienced at least one grade 3 or 4 TEAE: 251/278 (90.3%) patients in the PVd arm and 190/270 (70.4%) patients in the Vd arm. Similarly, there were more serious TEAE in the PVd arm 159/277 (57.2%) than the Vd arm 114/270 (42.2%). There were more TEAEs leading to dose reduction of any study drug in the PVd arm 200/278 (71.9%) in the Vd arm 139/279 (51.5%) and TEAEs leading to interruption of any study drug (87.8% versus 67%).[2]

In terms of TEAE of interest infections and infestations (all grade) occurred in 80.2% and 64.8% in patients in the PVd and Vd arms, respectively.[2] Grade 3 or 4 infections and infestations occurred in 86/278 (30.9%) of PVd patients, and 48/270

(17.8%) of Vd patients.[2] It was reported that those patients with infections did not have febrile neutropenia.[2] The most common hematologic adverse events was neutropenia. All-grade neutropenia occurred in 130/278 (46.7%) patients in the PVd arm and 29/270 (10.8%), patients in the Vd arm. Grade 3/4 neutropenia occurred in 41.7% and 8.5% of patients in the PVd and Vd arms, respectively. Febrile neutropenia occurred in 9 (3.2%) patients in the PVd arm, and zero in the Vd arm.[1] All-grade thrombocytopenia occurred in 102/278 (36.7%) patients in the PVd arm and 103/270 (38.1%), patients in the Vd arm. Grade 3/4 thrombocytopenia occurred in 27.3% and 29.3% of patients in the PVd and Vd arms, respectively.[2] The incidence of all grade peripheral sensory neuropathy (all grade) occurred in 133 (47.8%) patients in the PVd arm and 100 (37.1%) in the Vd arm. Pulmonary embolism (grade 3 or 4) occurred in 11/278 (4.0%) and 1/270 (0.4%) of the PVd and Vd arms, respectively.[2]

Deaths

A total of 27/278 (9.7%) and 12/270 (4.4%) patients in the PVd and Vd arms, respectively, died during treatment or within 28 days of receiving the last dose of study treatment.[1] Overall, eight deaths were reported as treatment-related. Six (2.1%) deaths were reported to be treatment related occurred in the PVd arm, owing to pneumonia (2), unknown cause (2), cardiac arrest (1) cardio-respiratory arrest (1). Two deaths in the Vd arm were reported as treatment related (1 pneumonia, 1 hepatic encephalopathy). In the PFS follow up period, it there were 59 (21.2%) deaths in the PVd arm and 74 (27.4%) in the Vd arm.[1]

During the first 60 days there were 3.6% deaths in the PVd arm and 4.8% in the Vd arm. At 100 days there were 7.2% and 8.1% deaths for the PVd and Vd arms, respectively. [2] On treatment deaths at 60 days were 2.9% and 3.7% for PVd and Vd and on treatment deaths at 100 days were 5.4% and 4.4 for PVd and Vd, respectively.[1]

Serious Adverse Events

There were 159/278 (57.2%) and 114/270 (42.2%) patients in the PVd and Vd arms, respectively who had at least one serious adverse event (SAE). The most common SAEs were pneumonia 32/278 (11.5%) in the PVd arm and 17/270 (6.3%) in the Vd arm.[1]

Adverse Events of Interest

Hematological toxicity

There was an increase in the frequency and severity of neutropenia for the PVd as compared to the Vd arm, however, thrombocytopenia was similar in the arms. All-grade neutropenia occurred in 130/278 (46.7%) patients in the PVd arm and 29/270 (10.8%), patients in the Vd arm. Grade 3/4 neutropenia occurred in 41.7% and 8.5% of patients in the PVd and Vd arms, respectively.[1] All-grade thrombocytopenia occurred in 102/278 (36.7%) patients in the PVd arm and 103/270 (38.1%) patients in the Vd arm. Grade 3/4 thrombocytopenia occurred in 27.3% and 29.3% of patients in the PVd and Vd arms, respectively.[1] Anemia, lymphopenia and leukopenia were similar in the PVd and Vd arms. Febrile neutropenia occurred in 9 (3.2%) patients in the PVd arm, and zero in the Vd arm.[1]

Neuropathy
Overall, there was an increase in the frequency and severity of peripheral neuropathy for the PVd arm compared to the Vd arm. The incidence of all grade peripheral sensory neuropathy occurred in 133 (47.8%) patients in the PVd arm and 100 (37.1%) in the Vd arm. Rates of grade 3 or higher peripheral neuropathy were 8.3% and 4.4% in the PVd and Vd arms, respectively.[1]

Second Primary Malignancy (SPM)
Second primary malignancy occurred in 9 (3.2%) and 4 (1.5%) of the PVd and Vd arms, respectively.[1] This was also reported as 2.7 and 1.2 SPM per 100 person years in the PVd and Vd arms, respectively. Invasive hematologic and solid tumour second primary malignancy occurred in 2 (0.7%) of the PVd and 1 (0.4%) of the Vd arm (also reported as 0.58 and 0.30 per 100 person years in the PVd and Vd arms, respectively).[1]

Infections
Infections and infestations (all grade) occurred in 223/278 (80.2%) and 175/270 (64.8%) patients in the PVd and Vd arms, respectively.[2] Grade 3 or 4 infections and infestations occurred in 86/278 (30.9%) of PVd patients, and 48/270 (17.8%) of Vd patients.[1] It was reported that those patients with infections did not have febrile neutropenia.[1]

Pulmonary embolism
Pulmonary embolism (grade 3 or 4) occurred in 11/278 (4.0%) and 1/270 (0.4%) of the PVd and Vd arms, respectively.[1]

Table 6.9: TRAE Grade 3 or 4 reported in ≥ 2% in either study arm[2]

System Organ Class/Preferred Term[a]	POM+BTZ+LD-DEX N=278 n (%)	BTZ+LD-DEX N=270 n (%)
Subjects with at Least 1 NCI CTCAE Grade 3 or 4 TEAE	**251 (90.3)**	**190 (70.4)**
Blood and Lymphatic System Disorders	**154 (55.4)**	**112 (41.5)**
Neutropenia	116 (41.7)	23 (8.5)
Thrombocytopenia	76 (27.3)	79 (29.3)
Anaemia	39 (14.0)	38 (14.1)
Leukopenia	15 (5.4)	5 (1.9)
Lymphopenia	12 (4.3)	8 (3.0)
Febrile neutropenia	9 (3.2)	0 (0.0)
Infections and Infestations	**86 (30.9)**	**48 (17.8)**
Pneumonia	32 (11.5)	17 (6.3)
Influenza	7 (2.5)	4 (1.5)
Sepsis	6 (2.2)	1 (0.4)
Metabolism and Nutrition Disorders	**71 (25.5)**	**49 (18.1)**
Hyperglycaemia	25 (9.0)	14 (5.2)
Hypokalaemia	17 (6.1)	11 (4.1)
Hypophosphataemia	11 (4.0)	5 (1.9)
Hyponatremia	7 (2.5)	8 (3.0)
Hyperkalaemia	7 (2.5)	2 (0.7)
Hyperuricaemia	2 (0.7)	7 (2.6)
Nervous System Disorders	**57 (20.5)**	**32 (11.9)**
Peripheral sensory neuropathy	23 (8.3)	12 (4.4)
Syncope	14 (5.0)	6 (2.2)
General Disorders and Administration Site Conditions	**50 (18.0)**	**31 (11.5)**
Fatigue	23 (8.3)	10 (3.7)
Asthenia	8 (2.9)	8 (3.0)
Pyrexia	6 (2.2)	2 (0.7)
General physical health deterioration	3 (1.1)	7 (2.6)
Gastrointestinal Disorders	**36 (12.9)**	**19 (7.0)**
Diarrhoea	20 (7.2)	9 (3.3)
Constipation	7 (2.5)	1 (0.4)
Respiratory, Thoracic and Mediastinal Disorders	**24 (8.6)**	**13 (4.8)**
Pulmonary embolism	11 (4.0)	1 (0.4)
Dyspnoea	8 (2.9)	3 (1.1)
Cardiac Disorders	**22 (7.9)**	**12 (4.4)**
Atrial fibrillation	9 (3.2)	2 (0.7)
Cardiac failure	3 (1.1)	2 (0.7)
Renal and Urinary Disorders	**19 (6.8)**	**6 (2.2)**
Acute kidney injury	9 (3.2)	4 (1.5)
Vascular disorders	**17 (6.1)**	**8 (3.0)**
Hypertension	8 (2.9)	4 (1.5)
Skin and Subcutaneous Tissue Disorders	**9 (3.2)**	**0 (0.0)**
Rash	6 (2.2)	0 (0.0)

Table 6.10: Summary of Key Harms Outcomes in the OPTIMISMM trial[2]

Serious Adverse Events (SAE) occurring in ≥1% of Patients.[2]		
Treatment Arm	**PVd n=278**	**Vd n=270**
At least one SAE, n (%)[1]	159 (57.2)	114 (42.2)
Pneumonia	32 (11.5)	17 (6.3)
Influenza	8 (2.9)	4 (1.5)
Lower respiratory tract infection	8 (2.9)	2 (0.7)
Respiratory tract infection	6 (2.2)	0 (0)
Septic shock	6 (2.2)	0 (0)
Sepsis	5 (1.8)	1 (0.4)
Clostridium difficile colitis	4 (1.4)	0 (0)
Bronchitis	3 (1.1)	2 (0.7)
Infection	3 (1.1)	1 (0.4)
Lung infection	3 (1.1)	1 (0.4)
Upper respiratory tract infection	2 (0.7)	3 (1.1)
Atrial fibrillation	7 (2.5)	2 (0.7)
Cardiac failure	3 (1.1)	2 (0.7)
Pyrexia	11 (4.0)	5 (1.9)
General physical health deterioration	5 (1.8)	9 (3.3)
Non-cardiac chest pain	3 (1.1)	2 (0.7)
Death	3 (1.1)	0 (0)
Syncope	6 (2.2)	5 (1.9)
Pulmonary embolism	8 (2.9)	1 (0.4)
Dyspnea	4 (1.4)	1 (0.4)
Pleural effusion	2 (0.7)	3 (1.1)
Diarrhea	5 (1.8)	6 (2.2)
Acute kidney injury	8 (2.9)	6 (2.2)
Anemia	3 (1.1)	5 (1.9)
Febrile neutropenia	5 (1.8)	0 (0)
Thrombocytopenia	1 (0.4)	3 (1.1)
Hyperviscosity syndrome	0 (0)	3 (1.1)
Basal cell carcinoma	4 (1.4)	1 (0.4)
Hyperglycemia	3 (1.1)	1 (0.4)
Back pain	3 (1.1)	1 (0.4)
Deep vein thrombosis	4 (1.4)	4 (1.5)
Hypotension	3 (1.1)	1 (0.4)
Femur fracture	1 (0.4)	3 (1.1)

Treatment delay or interruption due to adverse events

More patients in the PVd arm required treatment discontinuing, delays, or interruptions due to adverse events (Table 6.11).

Table 6.11: Treatment discontinuation, delay, or interruption due to adverse events in the OPTIMISMM trial.[2]

Subjects with at Least 1 TEAE Leading to Discontinuation of Any Study Drug	**80 (28.8)**	**51 (18.9)**
TEAE Leading to Discontinuation of POM	31 (11.2)	N/A
TEAE Leading to Discontinuation of BTZ	67 (24.1)	50 (18.5)
TEAE Leading to Discontinuation of DEX	47 (16.9)	51 (18.9)
Subjects with at Least 1 TEAE leading to Dose Reduction of POM, BTZ or DEX	**200 (71.9)**	**139 (51.5)**
TEAE Leading to Dose Reduction of POM	113 (40.6)	N/A
TEAE Leading to Dose Reduction of BTZ	145 (52.2)	112 (41.5)
TEAE Leading to Dose Reduction of DEX	118 (42.4)	78 (28.9)
Subjects with at Least 1 TEAE Leading to Dose Interruption of Any Drug	**244 (87.8)**	**181 (67.0)**
TEAE Leading to Interruption of POM	223 (80.2)	N/A
TEAE Leading to Interruption of BTZ	223 (80.2)	175 (64.8)
TEAE Leading to Interruption of DEX	209 (75.2)	160 (59.3)

Withdrawal due to adverse events

In total, 31/278 (11.2%) and 50/270 (18.5%) patients in the PVd and Vd arms, respectively, had an AE leading to discontinuation of the lead study treatment.[1] The most common AEs leading to discontinuation of any study drug in either arm included peripheral sensory neuropathy, peripheral sensorimotor neuropathy, fatigue and pulmonary embolism.[1]

6.4 Ongoing Trials

No pertinent randomized controlled trials that compared PVd to another therapy in relapsed or refractory were located.

7 SUPPLEMENTAL QUESTIONS

7.1 Critical appraisal of the network meta-analysis

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of brigatinib:

- Critical appraisal of the network meta-analysis comparing the efficacy and safety of pomalidomide in combination with bortezomib and dexamethasone (PVd) compared to other therapy options in adult patients with relapsed or refractory multiple myeloma (RRMM).

7.1.1 Background

The population of interest for pomalidomide in combination with bortezomib and low dose of dexamethasone (PVd) are patients with RRMM who are lenalidomide exposed. Patients who are refractory to lenalidomide was a subgroup also evaluated in the network meta-analysis (NMA). The objective of the NMA was to evaluate the relative efficacy and safety of PVd in comparison to other treatment options among adult patients with RRMM.

7.1.2 Methods

Search and study selection

The Submitter conducted an NMA based on a previous systematic literature review performed by Celgene Global in the following databases: MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials. The systematic literature review was conducted on May 9, 2018 and posters and abstracts submitted to ASH 2018 were systematically searched on December 14, 2018. Table 7.1 outlines the inclusion and exclusion criteria for the systematic literature review.

Table 7.1: Inclusion and exclusion criteria for systematic review

Clinical effectiveness	Inclusion Criteria
Study design	Randomized controlled trials
Population	Adult (human) patients (≥18 years) with diagnosed rrMM, including the following sub-groups if interest: • Age (≤75 yrs vs >75 yrs; ≤65 yrs vs >65 yrs) • ECOG PS (0; >0) • High-risk cytogenetics (yes vs no) • Prior lines of therapy (1; >1; 2; >2) • ISS stage at study entry (I; II; III) • Prior stem-cell transplant (yes vs no) • Refractory (or non-refractory) to lenalidomide in last lenalidomide-containing regimen (yes vs no) • Refractory to last prior therapy (yes vs no) • Prior exposure to PIs (yes vs no) Specific focus on studies conducted in the above patients in North America and Europe Studies of at least 40 patients
Intervention	• Bendamustine in combination with bortezomib and dexamethasone • Bortezomib monotherapy

	• Bortezomib in combination with dexamethasone • Bortezomib in combination with pegylated, liposomal doxorubicin PVd in RRMM - NMA 8 • Bortezomib in combination with cyclophosphamide and dexamethasone (following first relapse after IMiD--based induction • Carfilzomib in combination with lenalidomide and dexamethasone • Carfilzomib in combination with dexamethasone • Daratumumab monotherapy • Daratumumab in combination with lenalidomide and dexamethasone • Daratumumab in combination with bortezomib and dexamethasone • Elotuzumab in combination with lenalidomide and dexamethasone • Ixazomib in combination with lenalidomide and dexamethasone • Lenalidomide in combination with dexamethasone • Panobinostat in combination with bortezomib and dexamethasone • Pomalidomide in combination with dexamethasone (Pd) • Pomalidomide in combination with dexamethasone and cyclophosphamide • Pomalidomide in combination with dexamethasone and daratumumab • Pomalidomide in combination with bortezomib and dexamethasone (PVd)
Comparators	• Bendamustine in combination with bortezomib and dexamethasone • Bortezomib monotherapy • Bortezomib in combination with dexamethasone • Bortezomib in combination with pegylated, liposomal doxorubicin • Bortezomib in combination with cyclophosphamide and dexamethasone (following first relapse after IMiD--based induction • Carfilzomib in combination with lenalidomide and dexamethasone • Carfilzomib in combination with dexamethasone • Daratumumab monotherapy • Daratumumab in combination with lenalidomide and dexamethasone • Daratumumab in combination with bortezomib and dexamethasone • Elotuzumab in combination with lenalidomide and dexamethasone • Ixazomib in combination with lenalidomide and dexamethasone • Lenalidomide in combination with dexamethasone • Panobinostat in combination with bortezomib and dexamethasone • Pomalidomide in combination with dexamethasone (Pd) • Pomalidomide in combination with dexamethasone and cyclophosphamide • Pomalidomide in combination with dexamethasone and daratumumab • Pomalidomide in combination with bortezomib and dexamethasone (PVd)
Outcomes	Efficacy • Progression free survival (PFS) • Time to progression (TTP) • Overall survival (OS) • Overall response rate (ORR) by modified IMWG criteria [complete response (CR); very good partial response (VGPR); partial • Stable disease • Progressive disease • Time to response • Time to treatment failure • Time to next treatment • Progression free survival on next-line therapy (PFS2) Safety • Adverse Events • Abnormal laboratory test • Dose limiting toxicities events
Language restrictions	English studies only
Time	From January 1, 2004

NMA methodology

The Submitter stated that a thorough assessment of heterogeneity was performed in terms of comparability of study design characteristics.[38] There was significant heterogeneity present on ISS stage at baseline, the number of prior therapies and PFS definition across studies. The methods team noted there were variation in prior lenalidomide exposure across the included trials in the evidence network. The Submitter outlined that the CASTOR trial presented a significant difference in the Vd arm design which has a fixed schedule, with a maximum medication time of 24 weeks when compared to other included trials: Kropff 2017, ENDEAVOR, PANORAMA-1 and MM-007 which relied on continuous treatment over the trial duration. The Submitter stated that because there were significant differences in the study populations, a risk of bias assessment was not performed for the studies included in the review.[38]

The Submitter performed a Bayesian model for the NMA. The outcomes investigated were overall survival, progression-free survival, objective response rate, and severe adverse events. Thus, the likelihood-link function was specified as log-normal. Both fixed and random-effect models were coded. The median hazard ratio (HR) and 95% credible interval for each treatment versus other treatments included in the network were generated. Although fixed and random-effect models were fitted to the data, there was a lack of studies comparing the same set of treatment and a random-effect model did not converge. Thus, a fixed-effect model was used as the base-case model.[39]

For each outcome, the surface under the cumulative ranking (SUCRA) was calculated for each treatment. A SUCRA value of 1 was deemed to be the best treatment whereas a treatment certain to be the worst had a value of 0.

Match Adjusted Indirect Comparison (MAIC) methodology

A MAIC was performed for PFS and OS outcomes from the Vd arm of the CASTOR trial and from OPTIMISMM trials using time-dependent split Cox model. Two Cox models were fitted for each outcome: between 0 to 24 weeks and from 24 weeks to onward. The Submitter stated that based on the assumption of adequate matching, the HR between CASTOR and OPTIMISMM trials from 0 to 24 weeks is expected to be close to 1 and captures residual between study heterogeneity. The Cox HR obtained from 24 weeks to onward captured both residual between-study heterogeneity and the fixed- vs. flexible-Vd schedule between the CASTOR and OPTIMISMM-007 trial.[39]

7.1.3 Results

Based on the systematic literature review conducted, 5,106 abstracts were retrieved. There were 104 citations selected as potentially relevant for the NMA of which 23 trials were identified.[39] Reasons for studies excluded during screening were provided in the PRISMA flow diagram. The following five therapies were included in the NMA: bortezomib dexamethasone (Vd), Carfilzomib dexamethasone (Kd), Bortezomib cyclophosphamide dexamethasone (Vcd), Daratumumab, bortezomib and dexamethasone (Dvd) and panobinostat, bortezomib and dexamethasone (PanVd). Although PANVd was included in the NMA, it was not identified as relevant comparator for this pCODR review as it is currently not publicly funded in the target population. Table 7.2 outlines the baseline characteristics for the included trials in the evidence networks.

Table 7.2. Baseline characteristics for the included trials in the evidence networks.[40]

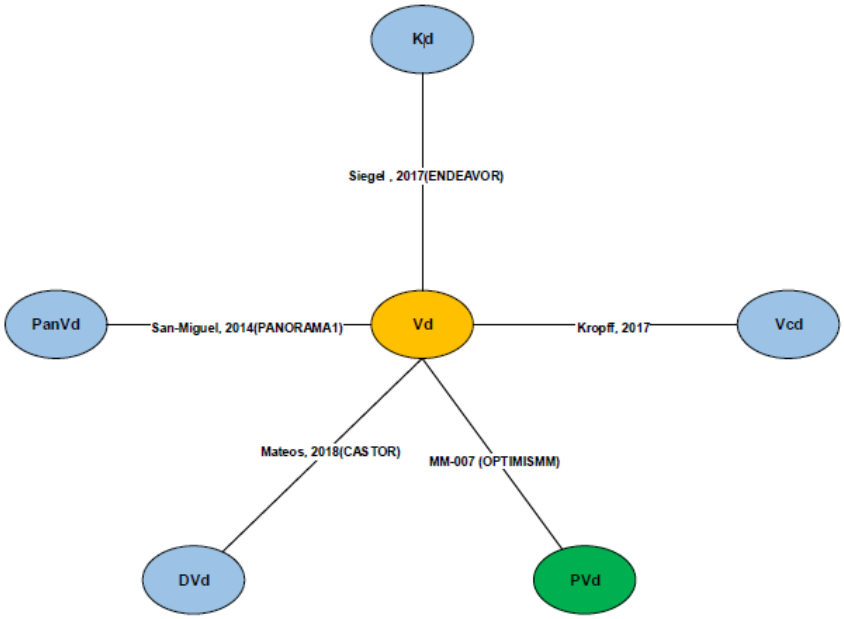
	Dimopoulos, 2016 ENDEAVOR[5]	Moreau, 2017 ENDEAVOR (2nd line)[41]	Kropff 2017[4]	San-Miguel, 2014 PANORAMA1[42]	Richardson, 2016 PANORAMA1 (IMiD - exposed)[6]	Palumbo, 2016 CASTOR[43]	MM-007 OPTIMISMM[7]
Age							
Mean (SD)	NR	NR	70 (8.9)	NR	NR	NR	66 (10.1)
Median (Range)	65 (30-89)	65 (36-89)	NR	63 IQR: (56-68)	62 (28-82)	64 (20-88)	68 (27-89)
Males, %	50%	NR	55%	53%	53%	NR	54%
International Staging System, %							
Stage I	44%	48%	18%	40%	42%	20%	31%
Stage II	0%	28%	25%	26%	24%	39%	37%
Stage III	0%	24%	28%	21%	20%	22%	30%
Stage II-III	56%	0%	0%	0%	0%	0%	0%
Missing/unknown	0%	0%	29%	13%	14%	19%	3%
Prior treatment, %							
Prior chemotherapy (advanced disease)	NR	NR	NR	NR	NR	NR	NR
Prior immunomodulatory therapy	NR	NR	NR	NR	NR	NR	NR
Prior stem cell transplant	NR	NR	0%	57%	NR	NR	NR
Prior proteasome inhibitor	NR	NR	NR	NR	NR	NR	NR
Prior Immunomodulatory/Proteosome Inhibitor Therapy	NR	NR	NR	NR	NR	NR	NR
Prior lenalidomide	38%	21%	0%	20%	32%	NR	100%
Prior thalidomide	49%	NR	0%	51%	81%	NR	100%
Prior bortezomib	54%	42%	15%	43%	40%	NR	72%
Prior bortezomib + lenalidomide	NR	NR	NR	NR	16%	NR	NR
Lines of prior therapy, %							
0	0%	NR	3%	0%	NR	0%	0%
1	50%	NR	57%	51%	NR	47%	40%
2	33%	NR	29%	30%	NR	29%	40%
3	0%	NR	10%	18%	NR	14%	20%
2 or 3	0%	NR	0%	0%	NR	0%	0%
Other	17%	NR	1%	0%	NR	10%	0%
Refractory to lenalidomide, %	25%	NR	NR	NR	NR	21%	70%
ECOG Performance status, %							
0	49%	52%	NR	44%	45%	NR	51%
1	45%	42%	NR	49%	0%	NR	43%
2	7%	6%	NR	6%	0%	NR	6%
≥ 1	0%	0%	NR	0%	55%	NR	0%
Missing/Unknown	0%	0%	NR	1%	0%	NR	0%

NMA Results

Progression Free Survival (PFS)

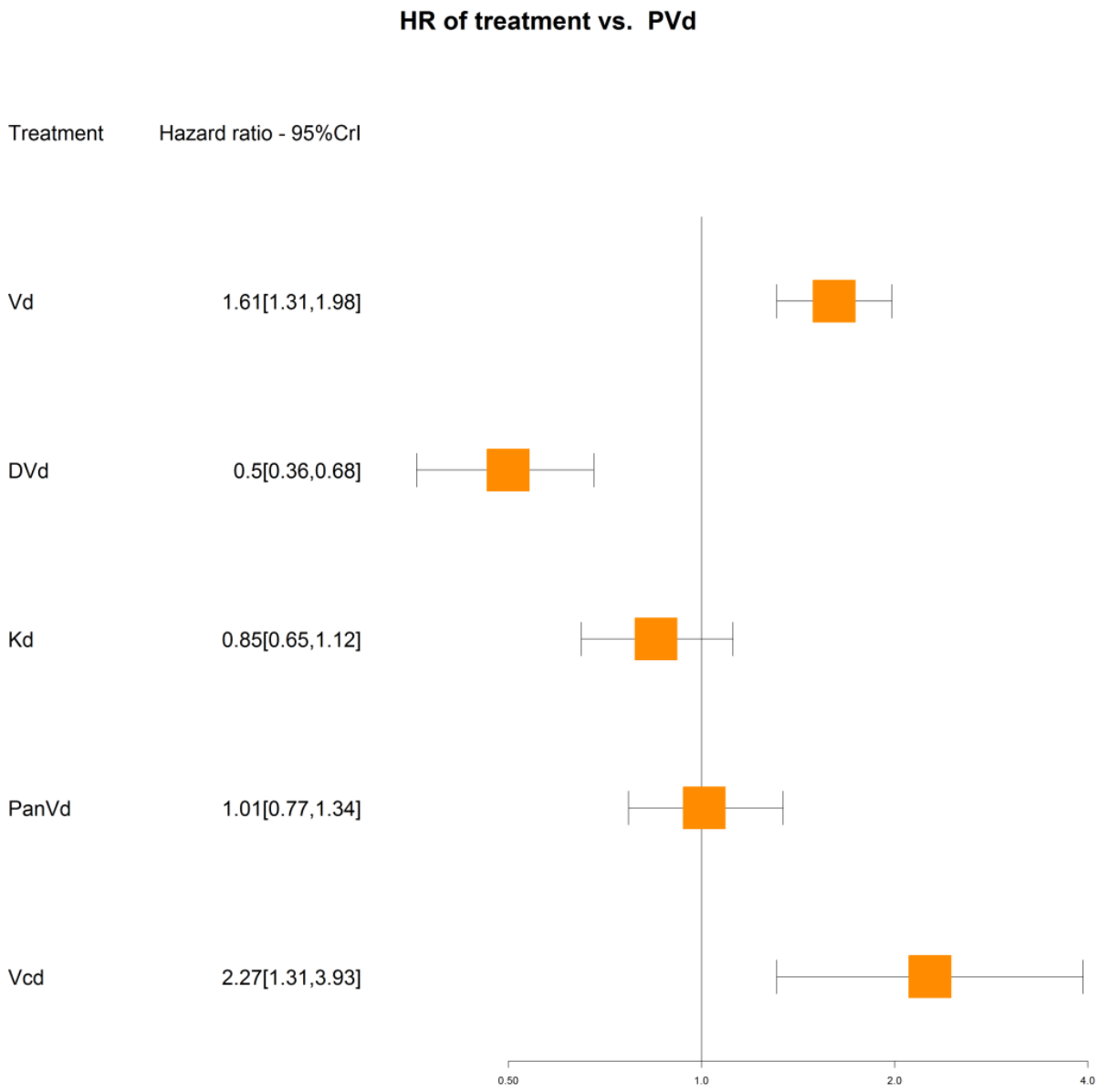
There were five studies included in the network of evidence for PFS-ITT population. Figure 7.1 presents the network of evidence.

Figure 7.1. Network of evidence for PFS-ITT population[39]



PVd was associated with a statistically significant longer PFS than Vd and Vcd whereas DVd was associated with a statistically significant longer PFS than PVd. Kd showed a non-statistically significant longer PFS than PVd in the ITT population. Figure 7.2 outlines the HR for PFS-ITT population when the comparator is PVd.

Figure 7.2. HR for PFS-ITT population.[39]

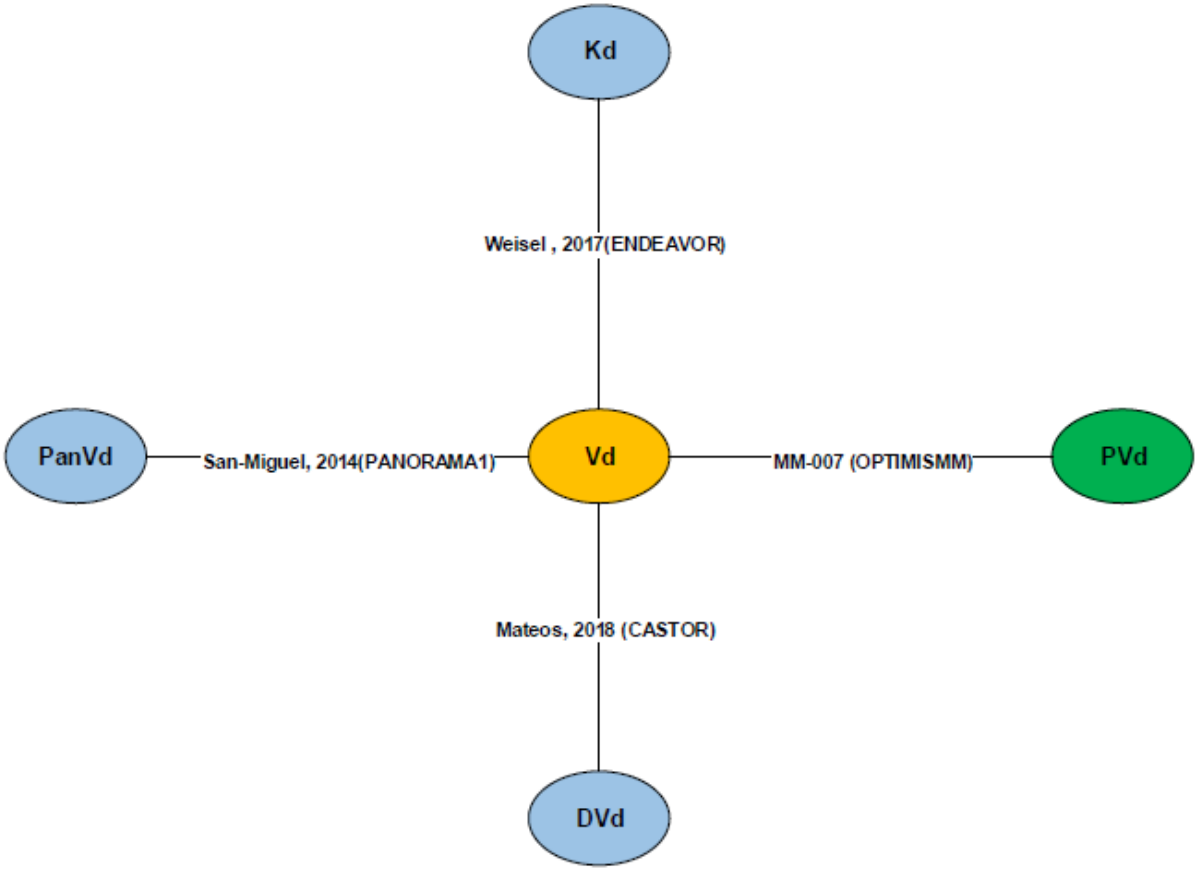


Note: An HR<1 indicates comparator is associated with longer PFS when compared to reference. An HR>1 indicates the reference is associated with longer PFS vs. the comparator.

Based on the SUCRA value provided for PFS-ITT, treatment with Dvd was considered to be the best followed by treatment with Kd, PVd, Vd and Vcd.

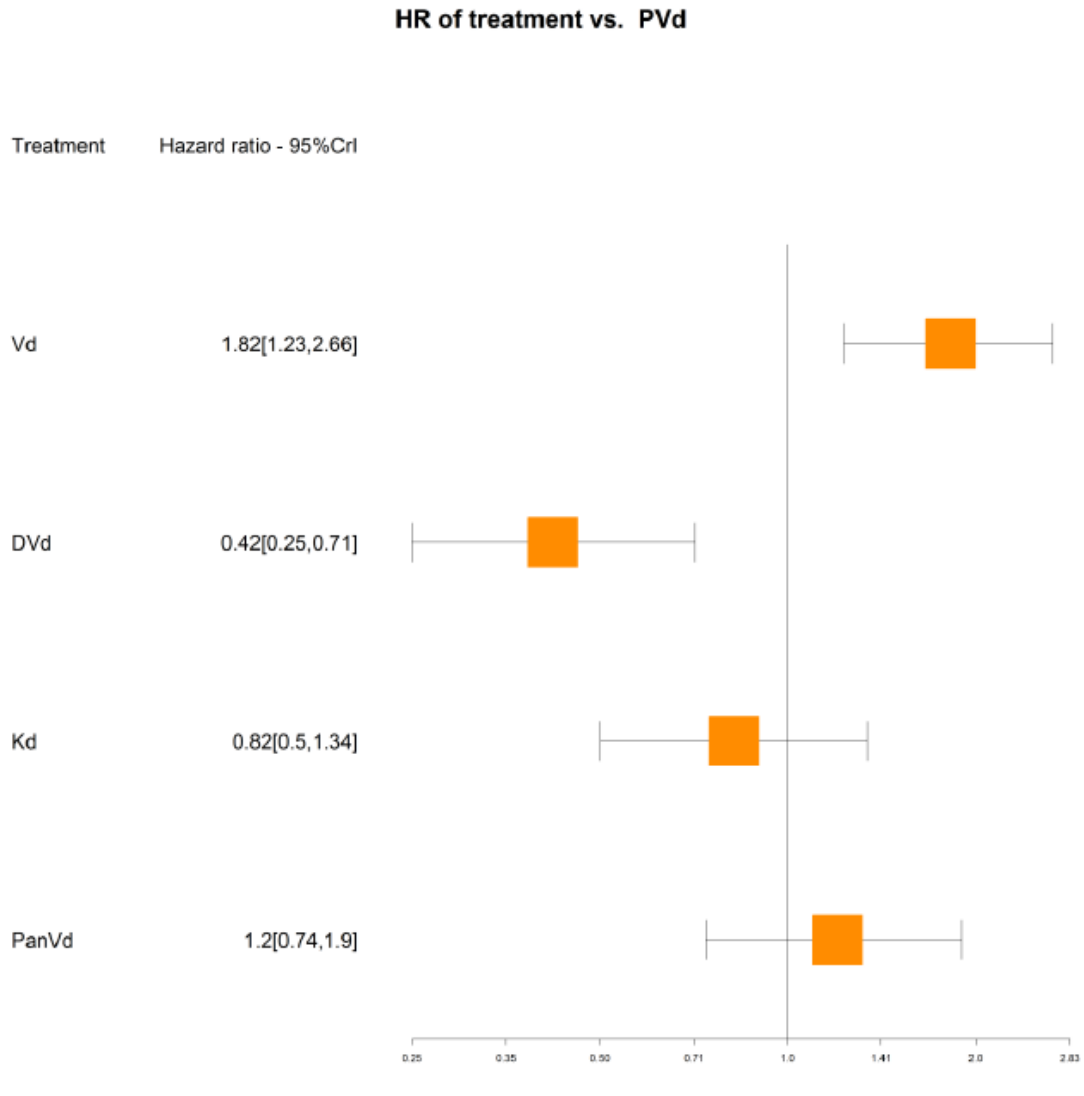
Four studies reported data for second line only population. Figure 7.3 displays the network of evidence.

Figure 7.3. Network of evidence for PFS-Lenalidomide-exposed population[39]



PVd was associated with a statistically significant longer PFS than Vd whereas DVd was associated with a statistically significant longer PFS than PVd. Kd showed a non-statistically significant longer PFS than PVd in the second line only population. Figure 7.4 displays the PFS-second line only population NMA results when the comparator is PVd.

Figure 7.4. HR vs. treatment for PFS-Lenalidomide-exposed population.[39]

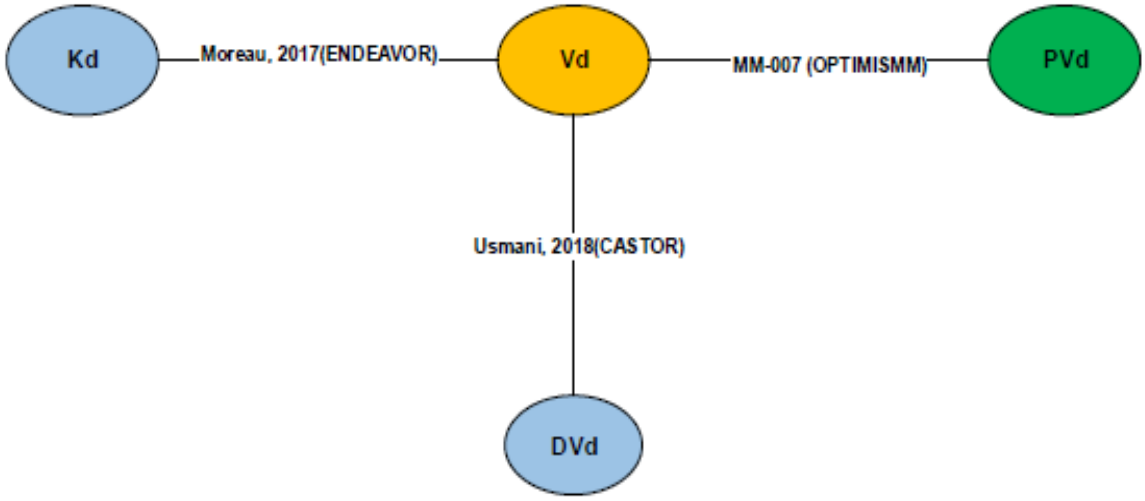


Note: A HR<1 indicates that the comparator is associated with a longer PFS than PVd. A HR>1 indicates that PVd is associated with a longer PFS than the comparator. Statistical significance is achieved when the 95% CrI excludes 1.

Based on the SURCRA values provided for PFS-second line only population, treatment with Dvd was considered the best followed treatments with Kd, PVd and Vd.

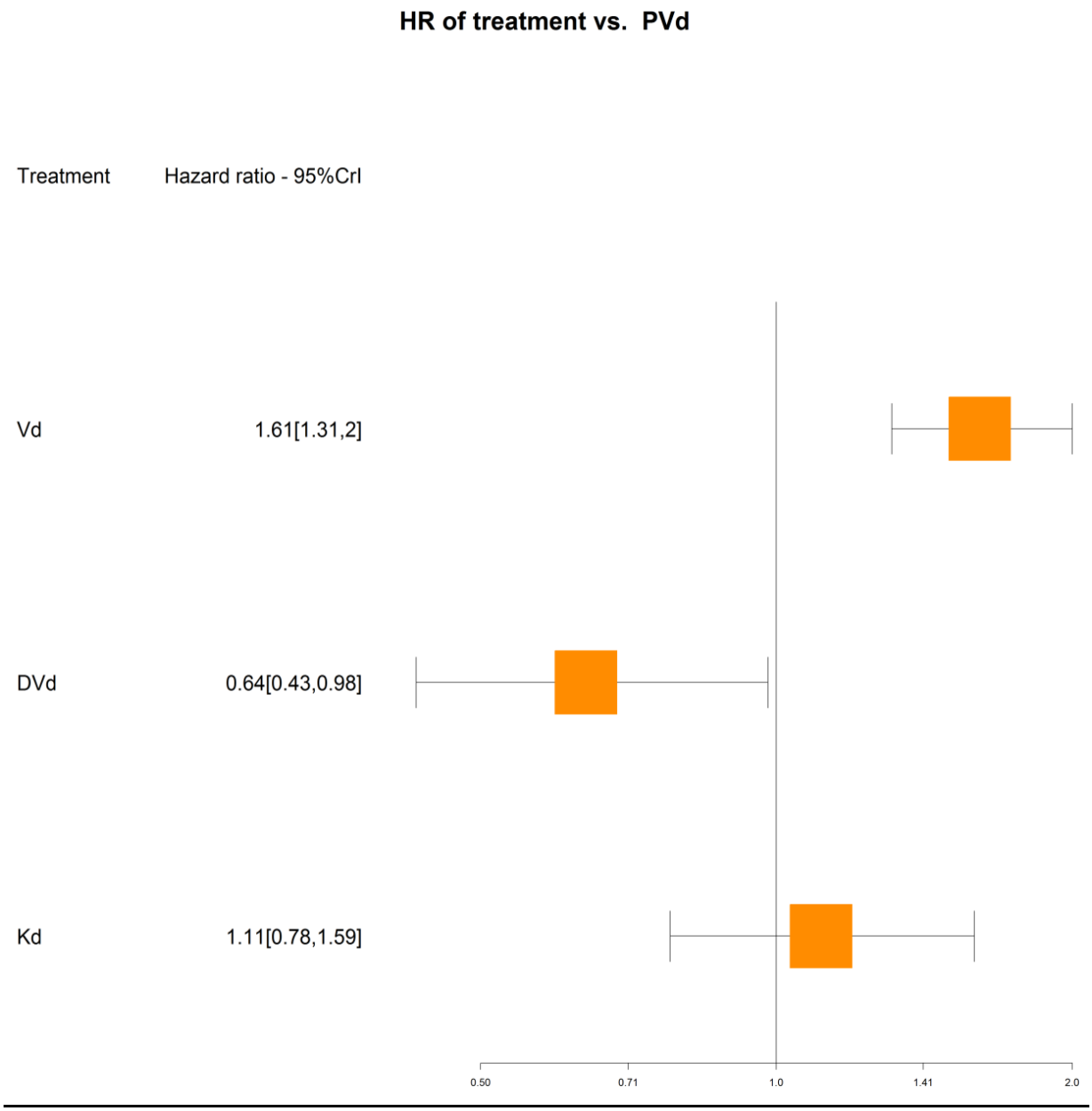
Three studies reported data for lenalidomide-exposed population. Figure 7.5 displays the network of evidence when the comparator is PVd in the lenalidomide-exposed population.

Figure 7.5. Network of evidence for PFS-Lenalidomide-exposed population[39]



PVd is associated with a statistically significant longer PFS than Vd whereas DVd is associated with a statistically significant longer PFS than PVd in the lenalidomide exposed population. Kd showed a non-statistically significant difference in PFS compared to PVd. Figure 7.6 displays the PFS NMA results when the comparator is PVd in the lenalidomide-exposed population.

Figure 7.6. HR vs. treatment for PFS-Lenalidomide-exposed population.[39]



Note: An HR<1 indicates comparator is associated with longer PFS when compared to reference. An HR>1 indicates the reference is associated with longer PFS vs. the comparator.

Based on the SURCRA values provided for PFS- lenalidomide exposed population, treatment with DVd was considered the best followed by treatment with PVd, Kd and Vd.

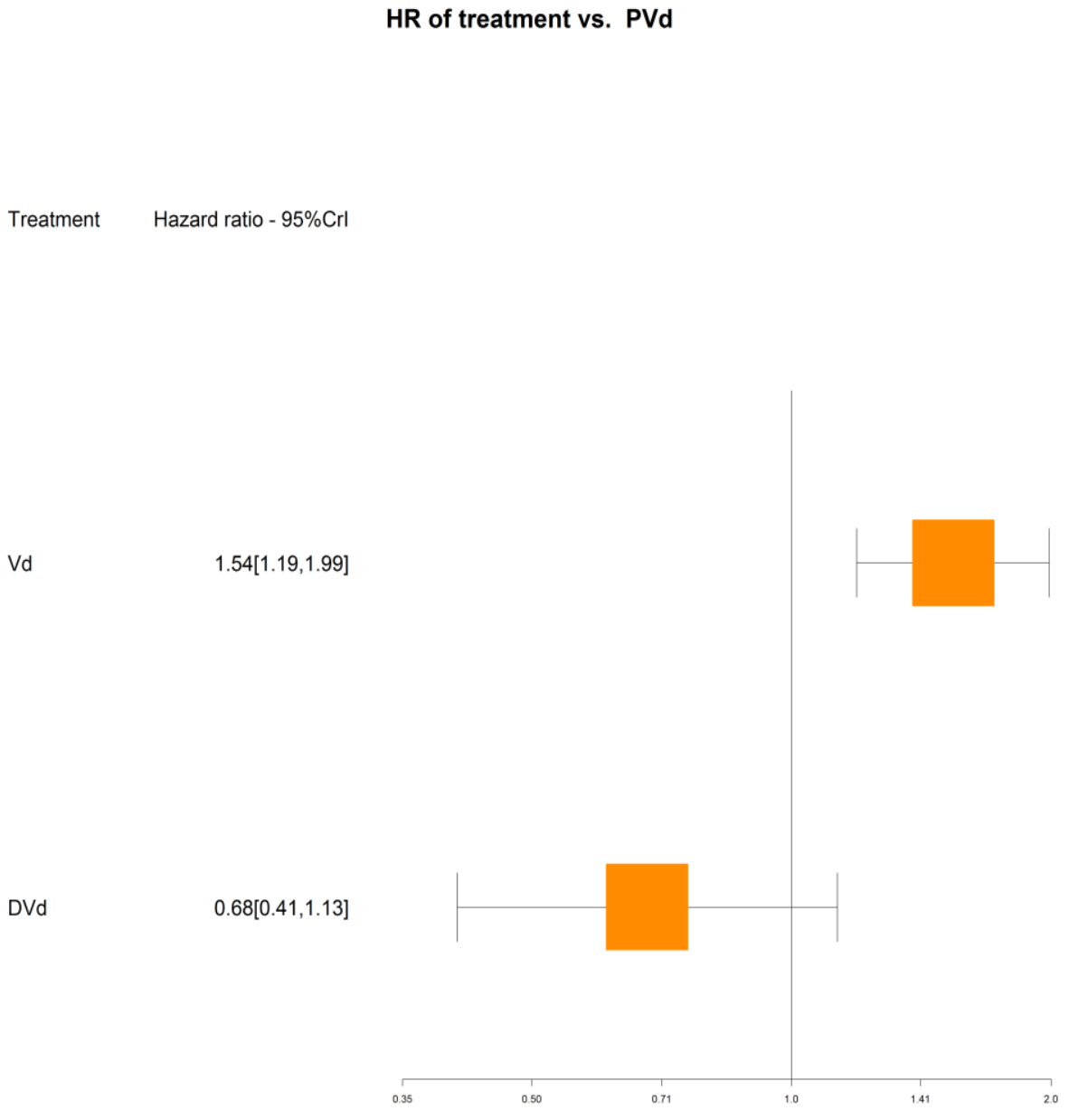
Two studies reported data for lenalidomide-refractory population. Figure 7.7 displays the network of evidence when the comparator is PVd in the lenalidomide-refractory population.

Figure 7.7. Network of evidence for PFS – Lenalidomide-refractory population.[39]

Note: in gold, reference treatment for the NMA, in green PVd, treatment of interest

PVd is associated with a statistically significant longer PFS than Vd whereas DVd showed a non-statistically significant longer PFS than PVd in the lenalidomide refractory population. Figure 7.8 displays the PFS NMA results when the comparator is PVd in the lenalidomide-refractory population.

Figure 7.8. PFS NMA results when the comparator is PVd in the lenalidomide-refractory population.[39]

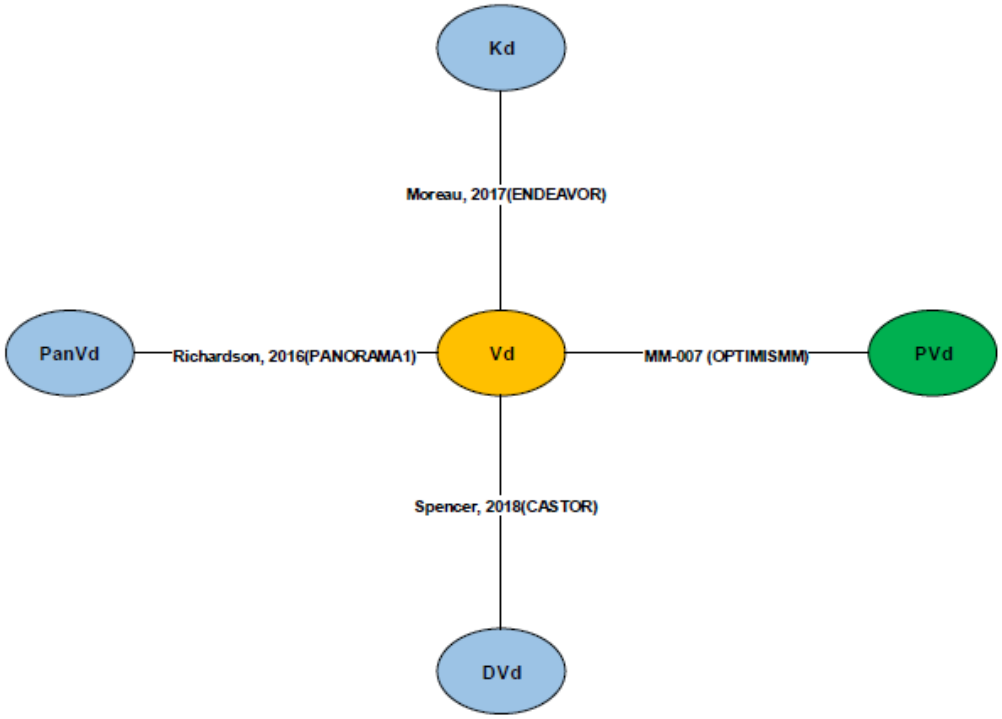


Note: An HR<1 indicates comparator is associated with longer PFS when compared to reference. An HR>1 indicates the reference is associated with longer PFS vs. the comparator.

Based on the SURCRA values provided for PFS-lenalidomide-refractory population, treatment with DVd was considered the best followed by treatment with PVd and Vd.

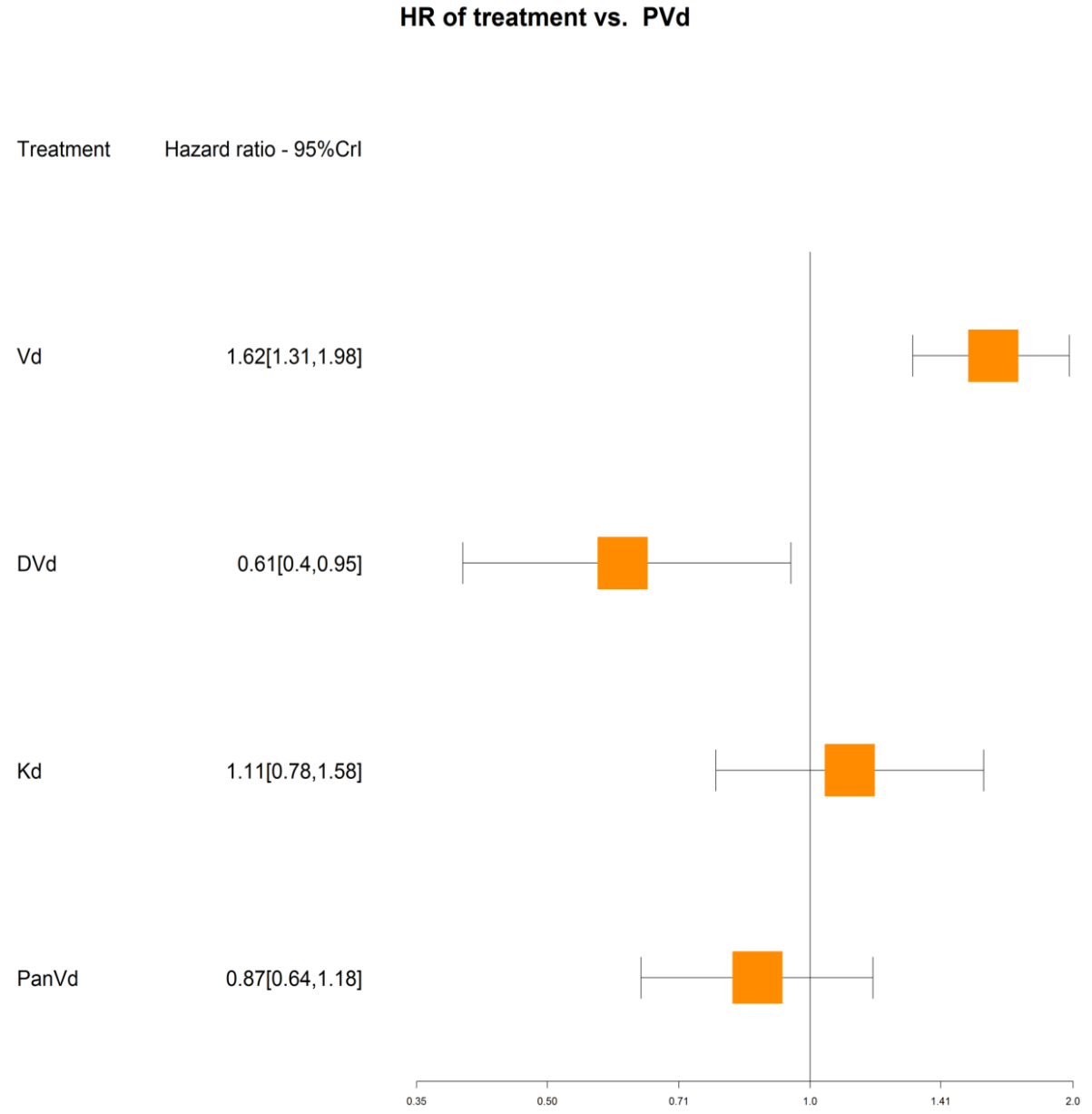
There were four studies included in the network of evidence for PFS-IMiD exposed population. Figure 7.9 presents the network of evidence for PFS-IMiD exposed population.

Figure 7.9. Network of evidence for PFS-IMiD exposed population.[39]



PVd is associated with a statistically significant longer PFS than Vd whereas DVd showed statistically significant longer PFS than PVd in the IMiD exposed population. PVd showed a non-statistically significant difference in PFS than Kd. Figure 7.10 displays the PFS NMA results when the comparator is PVd in the IMiD exposed population.

Figure 7.10. PFS NMA results when the comparator is PVd in the IMiD exposed population.[39]



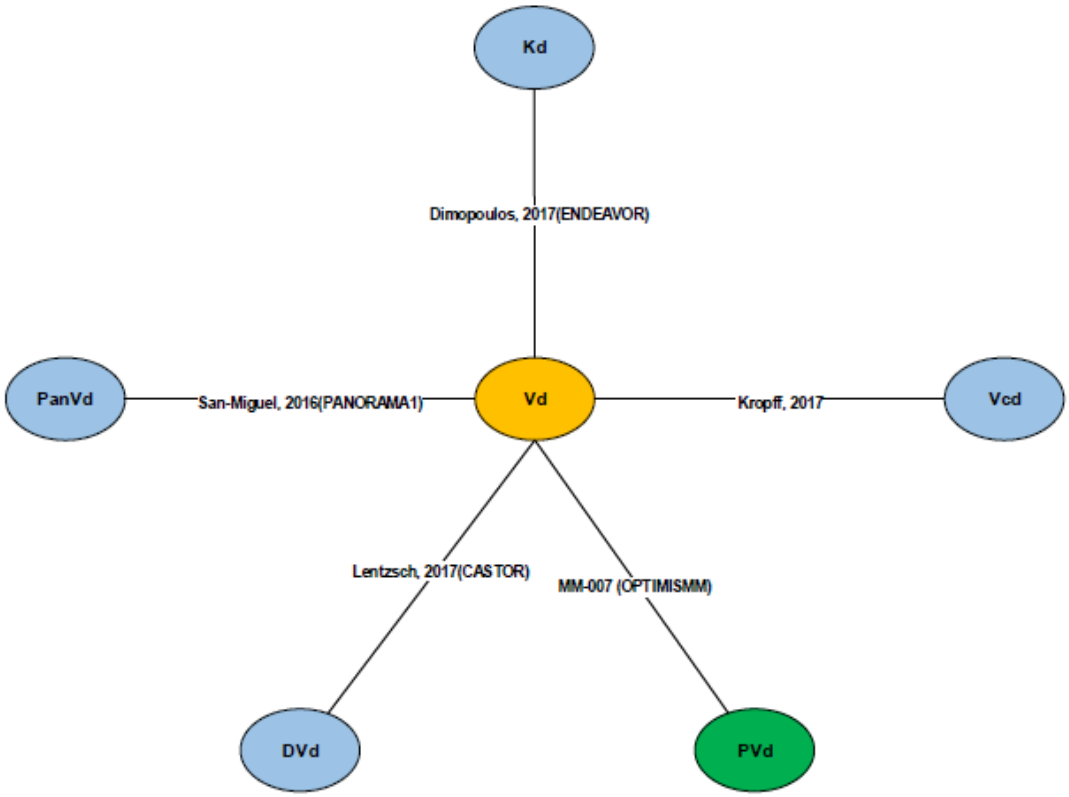
Note: A HR<1 indicates that the comparator is associated with a longer PFS than PVd. A HR>1 indicates that PVd is associated with a longer PFS than the comparator. Statistical significance is achieved when the 95% CrI excludes 1. P (best) corresponds to the Bayesian probability for the comparator to be associated with a longer PFS than PVd.

Based on the SUCRA value provided for PFS-IMiD exposed population, treatment with DVd was considered the best followed by treatment with PVd, Kd and Vd.

Overall Survival (OS)

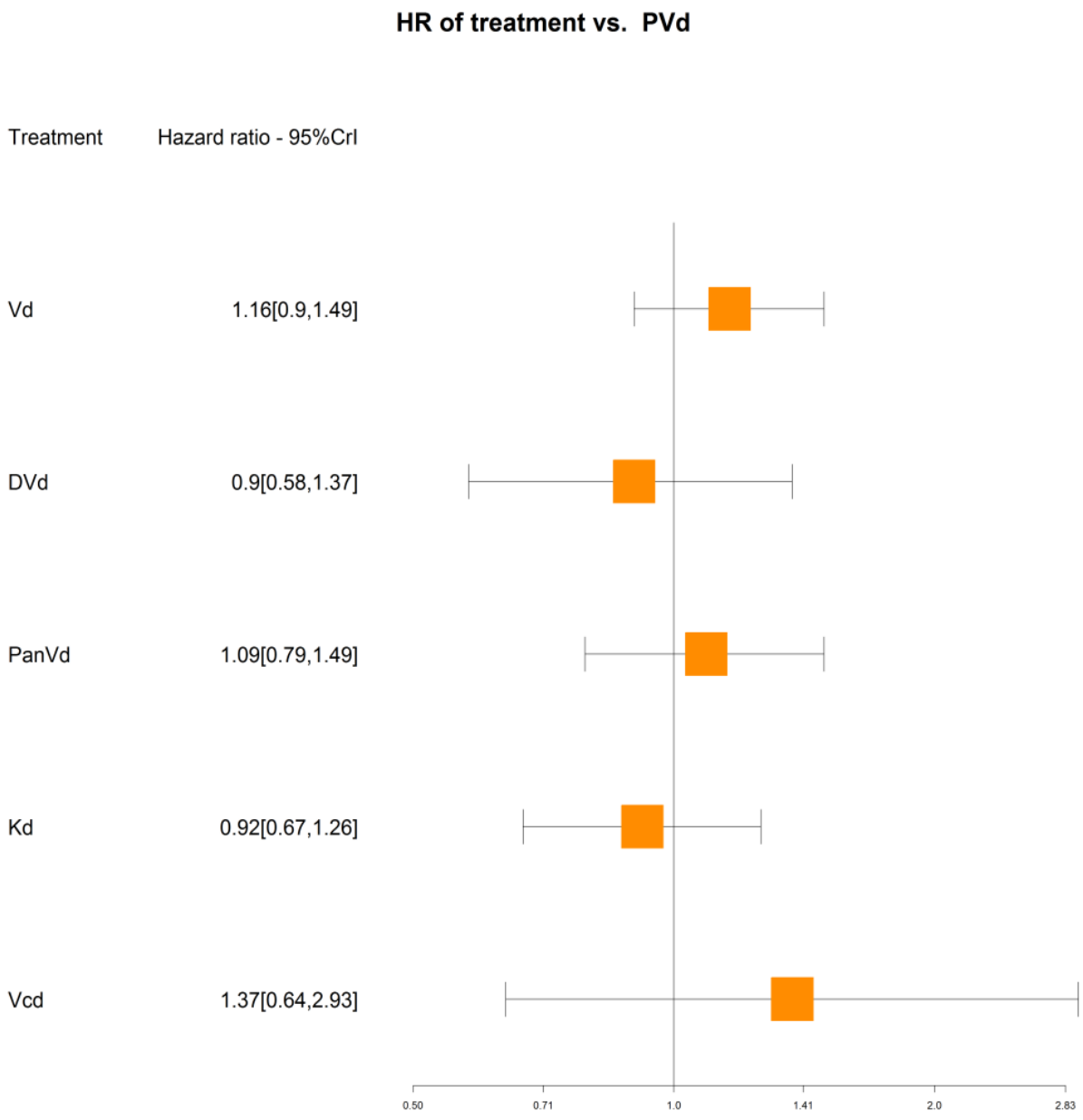
There were five studies included in the network of evidence for OS-ITT population. Figure 7.11 presents the network of evidence for OS-ITT population.

Figure 7.11. Network of evidence for OS-ITT population.[39]



PVd showed a non-statistically significant longer OS time than Vd and Vcd in the ITT population. DVd and Kd showed a non-statistically significant longer OS time than PVd in the ITT population. Figure 7.12 displays the OS NMA results when the comparator is PVd in the ITT population

Figure 7.12. HR of treatment vs. PVd for OS-ITT population.[39]



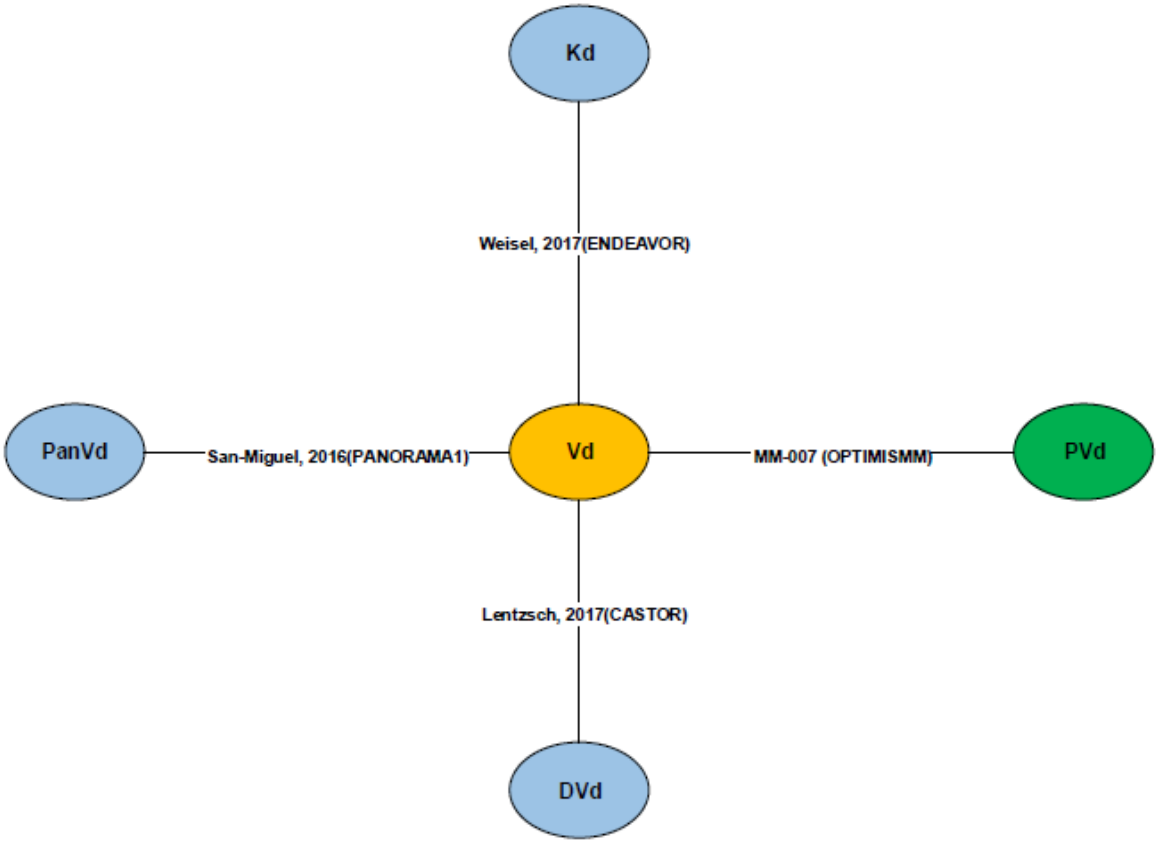
Note: An HR<1 indicates comparator is associated with longer PFS when compared to reference. An HR>1 indicates the reference is associated with longer PFS vs. the comparator.

Based on the SUCRA value provided for OS-ITT population, treatment with Kd was considered the best followed by treatment with DVd, PVd, Vd and Vcd.

The submitter stated that there was no network of evidence for OS for the lenalidomide refractory population as only data from the OPTIMISMM trial were available. Therefore, a NMA for this population for OS was not feasible. An assumption was made in the economic model that in absence of a NMA in the lenalidomide refractory population, the OS hazard ratios were equivalent to those for ITT population.[44]

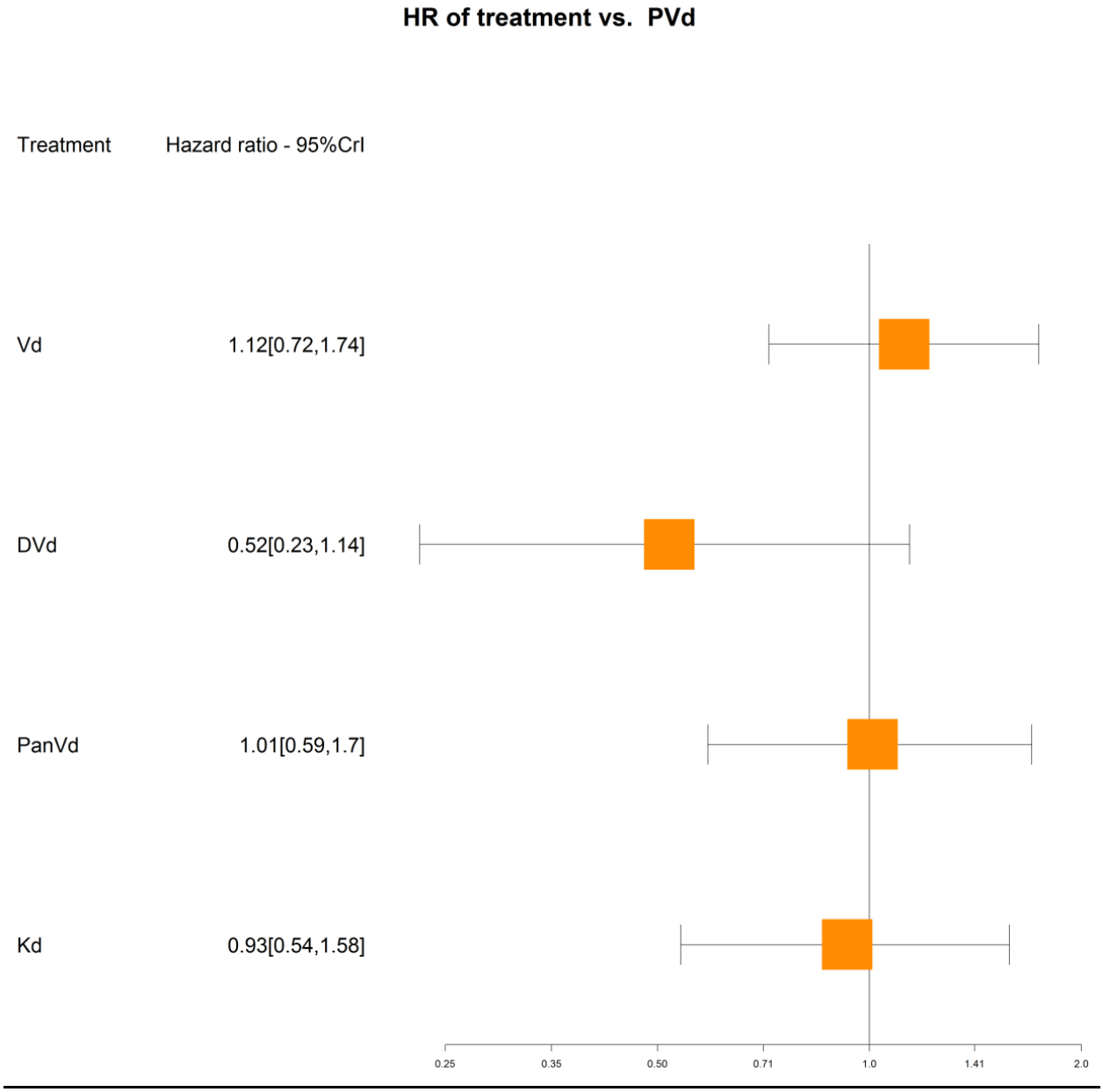
There were four studies included in the network of evidence for OS- second line only population. Figure 7.13 presents the network of evidence for OS-second line only population.

Figure 7.13 Network of evidence for OS-second line only population.[39]



DVd and Kd showed a non-statistically significant longer OS time than PVd in the second line only population. PVd showed a non-statistically significant longer OS time than Vd in the second line only population. Figure 7.14 displays the OS NMA results when the comparator is PVd in the second line only population.

Figure 7.14. OS NMA results when the comparator is PVd in the ITT population.[39]



Note: A HR<1 indicates that the comparator is associated with a longer OS time than PVd. A HR>1 indicates that PVd is associated with a longer OS time than the comparator. Statistical significance is achieved when the 95% CrI excludes 1.

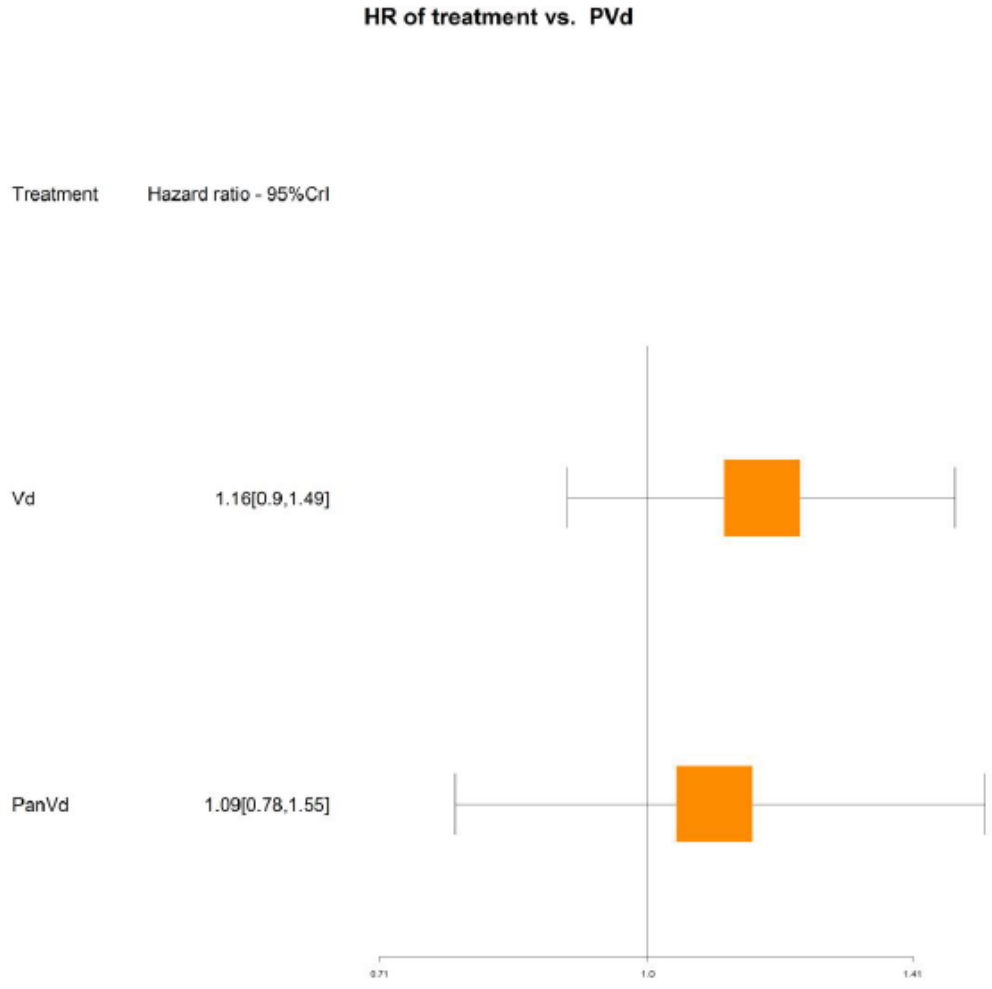
Based on the SUCRA value provided for OS-second line only population, treatment with DVd was considered the best followed by treatment with Kd, PVd and Vd.

There were two studies included in the network of evidence for OS-IMiD exposed population. Figure 7.15 presents the network of evidence for OS-IMiD exposed population. Figure 7.15 outlines the network of evidence for OS NMA results when the comparator is PVd in the IMiD exposed population

Figure 7.15 OS NMA results when the comparator is PVd in the IMiD exposed population[39]

PVd was associated with a non-statistically significant longer OS time than Vd. Figure 7.16 outlines the HR when the comparator is PVd in the IMiD-exposed population.

Figure 7.16 HR when the comparator is PVd in the IMiD-exposed population.[39]



Note: A HR<1 indicates that the comparator is associated with a longer OS time than PVd. A HR>1 indicates that PVd is associated with a longer OS time than the comparator. Statistical significance is achieved when the 95% CrI excludes 1.

Based on the SURCRA values provide for OS- IMiD-exposed population, treatment with PVd was considered the best followed by treatment with Vd.

7.1.4 Critical Appraisal of the ITC

The quality of the NMA provided by the Submitter was assessed according to the recommendations made by the ISPOR Task Force on Indirect Treatment Comparisons.[45] Details of the critical appraisal are presented below.

Table 7.3: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis adapted from Jansen et al[45]

ISPOR Questions	Details and Comments‡
1. Is the population relevant?	Yes
2. Are any critical interventions missing?	No. Kd, PanVd, PVd and DVd were included. PanVd was not identified as as relevant comparator by pCODR Clinical Guidance Panel and the Provician Advisory Group (PAG). This pCODR review does not report on the results of PanVd.
3. Are any relevant outcomes missing?	Yes. The following outcomes were not assessed: Safety and HRQoL.
4. Is the context (e.g., settings and circumstances) applicable to your population?	Yes.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	Yes. A systematic literature search used to conduct the NMA was reported. The information sources, search strategy and study selection were clearly described.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	Yes.
7. Is it apparent that poor quality studies were included thereby leading to bias?	Unclear. A risk of bias assessment was not performed for the studies included in the review.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	No. There was no selective reporting of outcomes.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	Yes. The Submitter stated that a thorough assessment of heterogeneity was performed in terms of comparability of study design characteristics (e.g. follow-up length, definition of endpoints), baseline demographic and clinical characteristics, and treatment regimens across trials.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	Yes. The Submitter did acknowledge that there was heterogeneity present on ISS stage at baseline, the number of prior therapies and PFS definition across studies. The Submitter outlined that the CASTOR trial presented a significant difference in the Vd arm design which has a fixed schedule, with a maximum medication time of 24 weeks when compared to other included trials: Kropff 2017, ENDEAVOR, PANORAMA-1 and MM-007 which relied on continuous treatment over the trial duration. The methods team noted there were variation in prior lenalidomide exposure across the included trials in the evidence network.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	Yes. The Submitter stated that for the ITT population NMA, randomization was maintained across all studies that were included in the network of evidence. For the subgroups analysed (e.g. LEN exposure), an assumption was required to be made that the baseline characteristics were balanced between the arms of the subgroups assessed. Given the limited

ISPOR Questions	Details and Comments‡
	data reported for the subgroups of interest, it was not possible to ensure this was maintained within the subgroups of the published studies; this would require the publications to report the respective baseline characteristics for the subgroups of interest, which were unavailable.[38]
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	Not applicable. There was no closed loop.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Not applicable.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	Unclear. There is an imbalance in the distribution of treatment effect modifiers across different types of comparisons in the network of trials. It is unclear if the researchers attempted to minimize the bias with the analysis.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	Yes. The Submitter stated that due to the lack of studies comparing the same set of treatments, the random-effects model did not converge. Thus, a fixed-effects model was used as the base case model.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Not applicable.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	Sub-group analyses were performed for lenalidomide exposed, second line only, IMiD exposed population.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes. The NMA evidence network is presented for each subgroup.
19. Are the individual study results reported?	Yes. The Submitter provided the base case for PFS, OS and ORR.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	Not applicable. There was no closed loop.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes. Measures of uncertainty were reported for each hazard ratio.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Yes. For each outcome, the surface under the cumulative ranking (SUCRA) was calculated for each treatment. A SUCRA value of 1 was deemed to be the best treatment whereas a treatment certain to be the worst had a value of 0.
23. Is the impact of important patient characteristics on treatment effects reported?	No.
24. Are the conclusions fair and balanced?	Yes. Reasonably interpreted the results considering the limitations of the analysis.

ISPOR Questions	Details and Comments‡
25. Were there any potential conflicts of interest?	Potentially. The submitted systematic literature review and NMA were completed by an external consultancy group hired by the Submitter.
26. If yes, were steps taken to address these?	Unclear.

7.1.5 Conclusions

Progression Free Survival

PVd was associated with a statistically significantly longer PFS than Vd and Vcd whereas DVd was associated with a statistically significant longer PFS than PVd. Kd showed a non-statistically significant longer PFS than PVd in the ITT population. In the second line only population, PVd was associated with a statistically significant longer PFS than Vd whereas DVd was associated with a statistically significant longer PFS than PVd. Kd showed a non-statistically significant longer PFS than PVd in the second line only population. In the lenalidomide exposed population, PVd is associated with a statistically significant longer PFS than Vd whereas DVd is associated with a statistically significant longer PFS than PVd. Kd showed a non-statistically significant difference in PFS compared to PVd in the lenalidomide exposed population. Among the lenalidomide refractory population, PVd is associated with a statistically significant longer PFS than Vd whereas DVd showed a non-statistically significant longer PFS than PVd. Vd is associated with a statistically significant longer PFS than Vd whereas DVd showed a statistically significant longer PFS than PVd in the IMiD exposed population. Kd showed a non-statistically significant difference in PFS than PVd in the IMiD exposed population.[39]

Overall Survival

PVd showed a non-statistically significant longer OS time than Vd and Vcd in the ITT population. DVd and Kd showed a non-statistically significant longer OS time than PVd in the ITT population. The Submitter stated that there was no network of evidence for OS for the lenalidomide refractory population as only data from the OPTIMISMM trial were available. Therefore, a NMA for this population for OS was not feasible. DVd and Kd showed a non-statistically significant longer OS time than PVd in the second line only population. PVd showed a non-statistically significant longer OS time than Vd in the second line only population. PVd was associated with a non-statistically significant longer OS time than Vd in the IMiD exposed population.[39]

Limitations

Due to concerns of a lack of risk of bias assessment performed, there may be poor quality studies included in the NMA. The validity of the NMA is based on three assumptions (i.e., similarity, homogeneity, and consistency) which were assessed in this review. There was significant heterogeneity present on ISS stage at baseline, the number of prior therapies and PFS definition across studies. In addition, the proportion of patients with prior exposure to lenalidomide varied across the included trials in the evidence network. The OPTIMISM MM-007 trial included 100% of patients with prior lenalidomide exposure in comparison to the other trials which included a very small proportion. Thus, the homogeneity assumption was violated. The Submitter outlined that the CASTOR trial presented a significant difference in the Vd arm

design which has a fixed schedule, with a maximum medication time of 24 weeks when compared to other included trials: Kropff 2017, ENDEAVOR, PANORAMA-1 and MM-007 which relied on continuous treatment over the trial duration. Thus, the similarity assumption was violated. Due to a lack of a closed loop in the evidence network, the consistency between direct and indirect comparisons could not be assessed. In addition, health related quality of life was not explored in the NMA. Finally, the submitted systematic literature review and NMA were completed by an external consultancy groups hired by the Submitter. As a result, the information provided in the reports should be viewed considering this potential conflict of interest and lack of peer-review. Based on the aforementioned limitations, the comparative efficacy estimates may be biased. Thus, the certainty in the results reported for PFS and OS is limited and should be interpreted with caution.

8 COMPARISON WITH OTHER LITERATURE

The pCODR Clinical Guidance Panel and the pCODR Method Team did not identify other relevant literature proving supporting information for this review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lymphoma/ Myeloma Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available pomalidomide (Pomalyst) in combination with bortezomib and dexamethasone for multiple myeloma (MM). 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.

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 Lymphoma/ Myeloma Clinical Guidance Panel is comprised of three clinical oncologists. 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 AND DETAILED

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials February 2019, Embase 1974 to 2019 March 25, Ovid MEDLINE(R) ALL 1946 to March 25, 2019

#	Searches	Results
1	(Pomalidomide* or Pomalyst* or Actimid* or CC4047 or CC-4047 or Imnovid* or IMID3 or IMID 3 or D2UX06XLB5).ti,ab,ot,kf,kw,hw,rn.	3616
2	exp Multiple Myeloma/	108820
3	(myelom* or kahler disease or morbus kahler).ti,ab,kw,kf.	152582
4	(plasma* adj3 (Cancer* or neoplas* or oncolog* or tumor* or tumour* or malignan* or leukemia* or leukaemia*)).ti,ab,kw,kf.	30852
5	or/2-4	195314
6	1 and 5	2799
7	6 use medall	473
8	6 use cctr	176
9	*pomalidomide/	770
10	(Pomalidomide* or Pomalyst* or Actimid* or CC4047 or CC-4047 or Imnovid* or IMID3 or IMID 3).ti,ab,kw,dq.	2507
11	9 or 10	2534
12	Multiple Myeloma/ or plasma cell leukemia/	109537

13	(myelom* or kahler disease or morbus kahler).ti,ab,kw,dq.	152034
14	(plasma* adj3 (Cancer* or neoplas* or oncolog* or tumor* or tumour* or malignan* or leukemia* or leukaemia*)).ti,ab,kw,dq.	30875
15	or/12-14	195355
16	11 and 15	2058
17	16 use oemezd	1442
18	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	1122470
19	Randomized Controlled Trial/	1016089
20	exp Randomized Controlled Trials as Topic/	288560
21	"Randomized Controlled Trial (topic)"/	156334
22	Controlled Clinical Trial/	551835
23	exp Controlled Clinical Trials as Topic/	300146
24	"Controlled Clinical Trial (topic)"/	9908
25	Randomization/	179566
26	Random Allocation/	196421
27	Double-Blind Method/	403936
28	Double Blind Procedure/	158196
29	Double-Blind Studies/	266034
30	Single-Blind Method/	77529
31	Single Blind Procedure/	34033
32	Single-Blind Studies/	79472

33	Placebos/	331204
34	Placebo/	330399
35	Control Groups/	111259
36	Control Group/	111166
37	(random* or sham or placebo*).ti,ab,hw,kf,kw.	4078568
38	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	789080
39	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	3073
40	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	2692736
41	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	95511
42	allocated.ti,ab,hw.	175290
43	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	114620
44	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	25141
45	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	958
46	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	11337
47	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	18232
48	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.	131816
49	or/18-48	5827268
50	7 and 49	50
51	17 and 49	431

52	51 not (conference review or conference abstract).pt.	148
53	8 or 50 or 52	374
54	remove duplicates from 53	304
55	51 and (conference review or conference abstract).pt.	283
56	limit 55 to yr="2014 -Current"	221
57	54 or 56	525
58	limit 57 to english language	496

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

Search	Query	Items found
#7	Search #5 AND #6	19
#6	Search publisher[sb]	532899
#5	Search #1 AND #4	459
#4	Search #2 OR #3	133155
#3	Search plasma[tiab] AND (Cancer*[tiab] OR neoplasm* [tiab] OR tumor[tiab] OR tumors[tiab] OR tumorous[tiab] OR tumour*[tiab] OR oncolog*[tiab] OR leukemia*[tiab] OR leukaemia*[tiab])	77276
#2	Search Myelom*[tiab] OR Kahler disease[tiab] OR morbus kahler[tiab]	60515
#1	Search pomalidomide[Supplementary Concept] OR Pomalidomide*[tiab] OR Pomalyst*[tiab] OR Actimid*[tiab] OR CC4047[tiab] OR CC-4047[tiab] OR Imnovid*[tiab] OR D2UX06XLB5 [rn]	625

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/

World Health Organization
http://apps.who.int/trialsearch/

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

Search: Pomalyst/ pomalidomide, multiple myeloma

Select international agencies including:

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

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

Search: Pomalyst/ pomalidomide, multiple myeloma

Conference abstracts:

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

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

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

Search: Pomalyst/ pomalidomide, multiple myeloma – last 5 years

Detailed Methodology

The literature search was performed by the pCODR Methods Team using the search strategy above.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (Feb 2019) 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 Pomalyst/ pomalidomide 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 August 1, 2019.

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, World Health Organization International Clinical Trials Registry and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. 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.

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. One member of the pCODR Methods Team independently made the final selection of studies to be included in the review.

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

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.

Data Analysis

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

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 questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

REFERENCES

1. Richardson P, Oriol A, Beksac M. Pomalidomide, bortezomib, and dexamethasone for early line treatment of lenalidomide-pretreated patients with multiple myeloma (OPTIMISMM): results of a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019.
2. Committee for Medicinal Products for Human Use. Assessment Report: Imnovid (pomalidomide). *(Euopean public assessment report)*. London (GB): European Medicines Agency; 2019: https://www.ema.europa.eu/documents/variation-report/imnovid-h-c-2682-ii-0031-g-epar-assessment-report-variation_en.pdf. Accessed 2019 Aug 20.
3. pan-Canadian Oncology Drug Review manufacturer submission: Pomalyst (pomalidomide capsules) in combination with bortezomib and dexamethasone. Mississauga (ON): Celgene Inc; 2019 Mar 15.
4. Kropff M, Vogel M, Bisping G, et al. Bortezomib and low-dose dexamethasone with or without continuous low-dose oral cyclophosphamide for primary refractory or relapsed multiple myeloma: a randomized phase III study. *Ann Hematol*. 2017;96(11):1857-1866.
5. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol*. 2016;17(1):27-38.
6. Richardson PG, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone in previously treated multiple myeloma: outcomes by prior treatment. *Blood*. 2016;127(6):713-721.
7. Richardson PG, Oriol A, Beksac M, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20(6):781-794.
8. Pomalyst (pomalidomide): 1 mg, 2 mg, 3 mg and 4 mg capsules [product monograph]. Mississauga (ON): Celgene Inc.; 2019 Jul 26: https://pdf.hres.ca/dpd_pm/00052416.PDF. Accessed 2019 Aug 20.
9. Velcade (bortezomib for injection): 3.5 mg/vial bortezomib, as the mannitol boronic ester [product monograph]. Toronto (ON): Janssen Inc.; 2005 Jan 25: https://pdf.hres.ca/dpd_pm/00048696.PDF. Accessed 2019 Aug 20.
10. Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. *Lancet Oncol*. 2011;12(5):431-440.
11. Rajkumar SV, Harousseau J-L, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood*. 2011;117(18):4691-4695.
12. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian cancer statistics 2016. Toronto (ON): Canadian Cancer Society; 2016: https://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2016-EN.pdf?la=en. Accessed 2019 Aug 20.
13. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15(12):e538-548.
14. Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. *Blood*. 2016;127(24):2955-2962.
15. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International staging system for multiple myeloma: a report from International Myeloma Working Group. *J Clin Oncol*. 2015;33(26):2863-2869.
16. Lonial S, Boise LH, Kaufman J. How I treat high-risk myeloma. *Blood*. 2015;126(13):1536-1543.
17. Venner CP, Connors JM, Sutherland HJ, et al. Novel agents improve survival of transplant patients with multiple myeloma including those with high-risk disease defined by early relapse (<12 months). *Leuk Lymphoma*. 2011;52(1):34-41.

18. Cavo M, Rajkumar SV, Palumbo A, et al. International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation. *Blood*. 2011;117(23):6063-6073.
19. Ludwig H, Durie BGM, McCarthy P, et al. IMWG consensus on maintenance therapy in multiple myeloma. *Blood*. 2012;119(13):3003-3015.
20. Palumbo A, Rajkumar SV, San Miguel JF, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. *J Clin Oncol*. 2014;32(6):587-600.
21. Durie BG, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet*. 2017;389(10068):519-527.
22. Palumbo A, Gay F, Cavallo F, et al. Continuous therapy versus fixed duration of therapy in patients with newly diagnosed multiple myeloma. *J Clin Oncol*. 2015;33(30):3459-3466.
23. Laubach J, Garderet L, Mahindra A, et al. Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group. *Leukemia*. 2016;30(5):1005-1017.
24. Richardson P, Oriol A, Beksac M. Pomalidomide (POM), bortezomib, and dexamethasone (PVd) vs bortezomib and low-dose dexamethasone (Vd) in lenalidomide (LEN)-exposed patients with relapsed or refractory multiple myeloma (RRMM): phase 3 OPTIMISMM trial (abstract 8001). *J Clin Oncol*. 2018;36(15 suppl):8001.
25. Richardson P, Oriol A, Beksac M. Pomalidomide (POM), bortezomib, and dexamethasone (PVd) vs bortezomib and low-dose dexamethasone (Vd) in lenalidomide (LEN)-exposed patients with relapsed or refractory multiple myeloma (RRMM): phase 3 OPTIMISMM trial (oral presentation 8001). American Society of Clinical Oncology Meeting; 2018; Chicago (IL).
26. Weisel K, Dimopoulos M, Moreau P, et al. Health-related quality of life among patients with relapsed or refractory multiple myeloma who received pomalidomide, bortezomib, and low-dose dexamethasone vs bortezomib and low-dose dexamethasone: results from the phase 3 OPTIMISMM study (poster 1960). *Blood*. 2018;132(Suppl 1):1960.
27. Dimopoulos M, Weisel K, Moreau P, et al. Pomalidomide + bortezomib + low-dose dexamethasone vs bortezomib + low-dose dexamethasone as second-line treatment in patients with lenalidomide-pretreated multiple myeloma: a subgroup analysis of the phase 3 OPTIMISMM trial (poster 3278). *Blood*. 2018;132(Suppl 1):3278.
28. Celgene. NCT01734928: Safety and efficacy of pomalidomide, bortezomib and low-dose dexamethasone in subjects with relapsed or refractory multiple myeloma (OPTIMISMM). *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2019: https://clinicaltrials.gov/ct2/show/NCT01734928. Accessed 2019 Aug 20.
29. Clinical study report: CC-4047-MM-007. A phase 3, multicenter, randomized, open-label study to compare the efficacy and safety of pomalidomide, bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone in subjects with relapsed or refractory multiple myeloma [CONFIDENTIAL internal manufacturer's report]. Mississauga (ON): Celgene Inc; 2018 May 21.
30. Celgene Inc response to pCODR checkpoint meeting questions on Pomalyst (pomalidomide capsules) in combination with bortezomib and dexamethasone for multiple myeloma [additional manufacturer's information]. Mississauga (ON): Celgene Inc; 2019 Jul 8.
31. Celgene Inc response to pCODR checkpoint meeting questions on Pomalyst (pomalidomide capsules) in combination with bortezomib and dexamethasone for multiple myeloma [additional manufacturer's information]. Mississauga (ON): Celgene Inc; 2019 Jun 4.
32. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20(9):1467-1473.
33. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-376.
34. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol*. 1998;16(1):139-144.

35. Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *Eur J Cancer*. 2012;48(11):1713-1721.
36. Cocks K, Cohen D, Wisloff F, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-MY20) in assessing the quality of life of patients with multiple myeloma. *Eur J Cancer*. 2007;43(11):1670-1678.
37. Health-related quality of life among patients with relapsed or refractory multiple myeloma who received pomalidomide, bortezomib, and low-dose dexamethasone vs bortezomib and low-dose dexamethasone: results from the phase 3 OPTIMISMM study[poster]. In: pan-Canadian Oncology Drug Review manufacturer submission: Pomalyst (pomalidomide capsules) in combination with bortezomib and dexamethasone. Mississauga (ON): Celgene Inc; 2019 Mar 15.
38. Celgene Inc response to pCODR checkpoint meeting questions on Pomalyst (pomalidomide capsules) in combination with bortezomib and dexamethasone for multiple myeloma [additional manufacturer's information]. Mississauga (ON): Celgene Inc; 2019 June 14.
39. Network Meta-analysis in patients with relpased or refractroy multiple myeloma. In: pan-Canadian Oncology Drug Review manufacturer submission: Pomalyst (pomalidomide capsules) in combination with bortezomib and dexamethasone. Mississauga (ON): Celgene Inc.; 2019.
40. Celgene Inc response to pCODR checkpoint meeting questions on Pomalyst (pomalidomide capsules) in combination with bortezomib and dexamethasone for multiple myeloma [additional manufacturer's information]. Mississauga (ON): Celgene Inc; 2019 July 16.
41. Moreau P, San Miguel J, Sonneveld P, et al. Multiple myeloma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(suppl_4):iv52-iv61.
42. San-Miguel JF, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. *Lancet Oncol*. 2014;15(11):1195-1206.
43. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;375(8):754-766.
44. Celgene Inc response to pCODR checkpoint meeting questions on Pomalyst (pomalidomide capsules) in combination with bortezomib and dexamethasone for multiple myeloma [additional manufacturer's information]. Mississauga (ON): Celgene Inc; 2019 July 12.
45. Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health*. 2014;17(2):157-173.