pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Daratumumab (Darzalex) +VMP for Multiple Myeloma

August 29, 2019

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TABLE OF CONTENTS

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List of Abbreviations

AEs	Adverse Events
CI	Confidence Interval
CGP	Clinical Guidance Panel
CyBorD	Bortezomib, cyclophosphamide, dexamethasone
DOR	Duration of Response
MM	Multiple Myeloma
NDMM	Newly Diagnosed Multiple Myeloma
NMA	Network Meta-analysis
ORR	Overall response rate
OS	Overall survival
pCODR	pan-Canadian Oncology Drug Review
PFS	Progression Free Survival
VMP	Bortezomib, melphalan and prednisone

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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 daratumumab (Darzalex) + bortezomib, melphalan and prednisone (DVMP) for multiple myeloma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding daratumumab + VMP for multiple myeloma conducted by the 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 daratumumab + VMP for multiple myeloma, a summary of submitted Provincial Advisory Group Input on daratumumab + VMP for multiple myeloma, and a summary of submitted Registered Clinician Input on daratumumab + VMP for multiple myeloma and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

On November 27, 2018, Health Canada approved the following indication: daratumumab in combination with bortezomib, melphalan and prednisone, for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. Daratumumab is also approved:

- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy, and
- for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or who are refractory to both a PI and an IMiD.

The reimbursement request is for daratumumab in combination with bortezomib, melphalan and prednisone, for the treatment of patients with newly diagnosed multiple myeloma who are not suitable for autologous stem cell transplant.

Of note, the submitter stated that based on the provincial protocol or patient-specific factors, the use of cyclophosphamide, bortezomib, dexamethasone (CyBorD) in place of VMP should be considered, where appropriate and as determined by the clinician, within each jurisdiction. pCODR requested that the submitter provide evidence to support the use of CyBorD in place of VMP. A non-randomized study was identified by the submitter to support the clinical equivalency of CyBorD and VMP for newly diagnosed patients with MM where there is no intent for stem cell transplantation. Of note, a rapid response was conducted at CADTH to identify literature on the comparative effectiveness of CyBorD and VMP for newly diagnosed patients with MM where there is no intent for stem cell transplantation and the identical non-randomized study was identified.[1] A critical appraisal of the non-randomized study is detailed in Section 7 of the Report and the Clinical Guidance Panel's interpretation of the comparative effectiveness of CyBorD and VMP are detailed further in Section 1 of the report.

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1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One randomized, open-label, active-controlled phase 3 trial (ALCYONE trial) met the inclusion criteria.[2] ALCYONE trial was funded by Janssen Research and Development and in collaboration with academic authors, contributed to the design. The aim of this trial was to examine the effect and safety of adding daratumumab to VMP compared to VMP alone in patients with newly diagonsed multiple myeloma (NDMM). The ALCYONE trial enrolled 706 patients from 25 countries across North and South America, Europe, and the Asia-Pacific region in 162 sites. An interactive Web-response system (IWRS) was used to randomly assign patients in a 1:1 ratio to DVMP (daratumumab group) or VMP alone (control group). There were 350 patients randomized to the daratumumab group and 356 patients to the control group. Randomization was stratified according to the International Staging System (ISS) disease stage (I, II, or III, with higher stages indicating a poorer prognosis, stages are determined on the basis of albumin and ß2-microglobulin levels), geographic region (Europe vs. other), and age (<75 years vs. ≥75 years). Treatment assignments were not blinded.[2]

The primary efficacy endpoint of ALCYONE was progression-free survival defined in accordance with the International Myeloma Working Group criteria.[2]

Key secondary outcomes included overall response rate, complete response rate, minimal residual disease, time to response, duration of response and overall survival. Additional endpoints included patient-reported outcomes assessed using the European Organization for Research and Treatment of Cancer (EORTC) –QLQ-C30 questionnaire, EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L) questionnaire and health resource utilization.[2]

Efficacy Results (Refer to Table 1)

At a median follow-up of 16.5 months (clinical data cut-off June 12, 2017) the risk of disease progression or death in the DVMP group was 50% lower compared to the VMP group (hazard ratio 0.50, 95% confidence interval [CI], 0.38 to 0.65; P<0.001).[2] At median follow-up of 27.8 months (clinical data cut-off June 12, 2018), the risk of disease progression or death in the DVMP group was 57% lower compared to the VMP group (HR 0.43, 95% confidence interval [CI], 0.35 to 0.54; P<0.001).[3]

At a median follow-up of 16.5 months, there were 45 deaths reported in the DVMP group and 48 deaths reported in the VMP group.[2] The median OS was not reached in patients randomized to DVMP or VMP group at a median follow-up of 16.5 months and 27.8 months. At a median follow-up of 27,8 months, there were [redacted] deaths in the DVMP group compared to [redacted] deaths in the VMP group with a total of [redacted] deaths (HR = [redacted]).[3] (*Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this safety information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed.*)

The overall response rate reported appeared high in the DVMP group (90.9%) and 73.9% in the VMP group (odds ratio = 3.55, 95% CI: 2.30-5.49, p<0.0001). There was a statistically significant difference in very good partial response or better in favour of the DVMP group than in the VMP group (71.1% vs. 49.7%, P<0.001).[2] Similarly, for the rate of

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complete response or better, there was a statistically significant difference in favour of the DVMP group than in the VMP group (42.6% vs. 24.4%, P<0.001).[3]

Negative status for minimal residual disease (MRD) was associated with longer progression-free survival than positive status, irrespective of trial treatment. The rate of MRD negativity was 5 times higher in DVMP patients compared with VMP patients (DVMP=27.4%, VMP=7.0%; odds ratio = 5.01, 95% CI: 3.13-8.03, p<0.0001).[3]

The estimated percentage of patients who continued to have a response after 18 months was 77.2% in the DVMP group and 60.4% in the VMP group.[2]

The median duration of response was not reached (95% CI, could not be estimated) in the DVMP group and 21.1 months (95% CI, 18.4 to 24.5) in the VMP group at a median follow-up of 27.8 months.[3]

From baseline to follow-up at 3 months, there was a statistically significant mean difference reported for the EORTC QLQ-C30 GHS subscale in favour of the DVMP group compared to VMP.[3]

Grade 3 or 4 Safety Outcomes (Refer to Table 1)

The most commonly reported adverse event of grade 3 or 4 was neutropenia followed by thrombocytopenia.[2] The safety data were similar at 27.8 months for neutropenia and thrombocytopenia. Overall, adverse events were balanced in the DVMP and VMP group.

Table 1: Highlights of Key Outcomes

	Median Follow-up	
Efficacy Outcome	**16.5 months***	**27.8 months**
Progression free survival[3]	HR=0.50, 95% CI 0.38-0.65) P<0.001[2]	HR=0.43, 95% CI 0.35 - 0.54, p<0.001[3]
Overall Survival[3]	DVMP (death in 45 patients) vs. VMP (death in 48 patients)[2] Median overall survival was not reached in DVMP and VMP	DVMP (death in [redacted] patients) vs. VMP (death in [redacted] patients) HR = [redacted][3] Median overall survival was not reached in DVMP and VMP
Overall Response Rate	DVMP(90.9%, 95% CI) vs. VMP(73.9%)[2], P<0.001	odds ratio = 3.55, 95% CI: 2.30-5.49, p<0.0001) [3]
Complete Response or better	DVMP(42.6%) vs. VMP(24.4%)[2], P<0.001	odds ratio = 2.45, 95% CI 1.78-3.37, p<0.0001[3]

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	Median Follow-up	
Efficacy Outcome	**16.5 months***	**27.8 months**
Very Good Partial Response or better	71.1% vs. 49.7%, P<0.001[2]	72.9% vs. 49.7%, P<0.001[3]
Minimum Residual Disease	DVMP (22.3%) vs. VMP(6.2%) p<0.0001[2]	DVMP (27.4%) vs. VMP(7.0%) odds ratio = 5.01, 95% CI: 3.13-8.03, p<0.0001)[3]
Duration of Response	Median duration of response was not reached (95% CI, could not be estimated) in the DVMP group and 21.3 months (95% CI, 18.4 to could not be estimated) in the VMP group.[2]	DVMP (not reached, 95% CI could not be estimated) vs. VMP (21.1 months, 95% (18.5 to 24.5)[3]
Grade 3 or 4 Safety Outcomes		
Neutropenia	DVMP (39.9%) vs. VMP (38.7%)[2]	similar results
Thrombocytopenia	DVMP (34.4%) vs. VMP(37.6%)[2]	similar results

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1.2.2 Additional Evidence

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

Patient Advocacy Group Input

From a patient's perspective, symptoms of MM that are important to control include infections, followed by kidney problems, mobility, pain, fatigue, neuropathy, and shortness of breath. Patients also indicated their emotional well-being was impacted, and symptoms may fluctuate during their treatment journey. Most symptoms of myeloma have a neutral to significant impact on day-to-day activities and quality of life. Specifically, the ability to work was reported as the most affected, followed by the ability to travel, exercise, volunteer, conduct household chores, fulfill family obligations, and spend time with family and friends. Caregivers also experienced limitations in their daily life, with ability to travel being rated as the most impacted, followed by ability to volunteer, spend time with family and friends, concentrate, fulfill family obligations, work, exercise, and conduct household chores.

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Patients receiving VMP and CyBorD had differing expectations of their treatment. Patients who received VMP reported that their most important expectations of the treatment included improved quality of life and enjoying a normal life, whereas patients that received CyBorD ranked remission and disease control as their most important expectations of their treatment. Two-thirds (n=2) of patients on VMP indicated prolonged life was an expectation that was met, and half of patients (n=6) indicated CyBorD met their expectation of disease control. All patients receiving VMP (n=3) rated their quality of life as poor or fair, whereas 58% (n=7) of CyBorD treated patients rated their quality of life as good, very good, or excellent.

Overall, most patients on VMP and CyBorD thought their treatment was effective, with only one patient on CyBorD stating it was not effective in controlling MM. Negative effects reported by respondents that received VMP included loss of short-term memory, dizziness, unsteadiness, low energy level, neuropathy, and weakness. Patients that received CyBorD reported negative effects, which included constipation, lack of appetite, nausea, diarrhea, flu-like symptoms, neuropathy, weakness in muscles, unsteadiness (balance), fatigue, hair loss, and loss of taste. One patient reported a dose reduction due to these negative effects. All patients that received VMP expressed that side effects were tolerable, whereas only 50% (n=6) of patients that received CyBorD thought the side effects were tolerable or extremely tolerable. Most side effects were rated as tolerable by VMP patients, with the exception of constipation and decreased appetite that were somewhat intolerable. Many patients on CyBorD did not experience some of the side effects listed in the survey. Among patients who received CyBorD and experienced side effects, a small to moderate proportion experienced intolerable side effects. Completely or somewhat intolerable side effects included low blood counts, fatigue, pain, and decreased appetite.

In summary, patients value remission, improved quality of life, disease control, prolonged life, fewer side effects than other treatments, and enjoying a normal life. Patients expectations for daratumumab include controlling symptoms such as infections, kidney problems, mobility, pain, fatigue, neuropathy, and shortness of breath. In addition, patients value a treatment option that would improve their day to day activities such as ability to work, travel, conduct chores and fulfill family obligations.

Provincial Advisory Group (PAG) Input

PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Clarity on patient groups eligible for treatment

Economic factors:

- Drug wastage
- Additional resources needed to monitor infusion reaction
- Unknown and variable treatment duration

Registered Clinician Input

Two clinician inputs were received, representing a total of 8 clinicians. One joint submission from seven clinicians on behalf of the Myeloma Canada Research Network, and input from an individual clinician from Cancer Care Ontario (CCO), contributed to the clinician input on DVMP for transplant-ineligible patients with multiple myeloma (MM). The clinicians reported this combination provides an improvement in tolerability, safety, and effectiveness compared to current treatments. Examples of toxicities associated with

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DVMP, included infusion or allergic reactions, respiratory infections, cytopenias, and neurotoxicity. Patients with severe renal impairment would be contraindicated for DVMP due to the melphalan component. The clinicians expressed that there is evidence to suggest that CyBorD is equivalent to VMP from a response, PFS, and OS perspective, which is based on real world evidence (RWE) and a phase II trial [LYRA] in the MM patient population. Clinicians preferred the use of CyBorD in place of VMP due to improved tolerability, safety (less toxicities), and compliance (less visits required) for patients, and CyBorD also aligns with current Canadian practices.

Overall, the majority of clinicians agreed DVMP would be used in the first-line setting for the eligible patient population, with the exception of patients who express a preference for oral therapy, or have completed or are currently completing another first-line treatment prior to funding approval of DVMP in the respective province or territory of that patient. The clinicians recommended daratumumab to be used in early lines of treatment only to maximize the benefits and ensure eligibility of patients for this treatment.

Feedback on the initial recommendation from an individual clinician from Cancer Care Ontario was received; this clinician stated that red cell typing will need to be considered if daratumumab + VMP is to be implemented. CGP noted that the cost will not be incredibly significant and agreed that red cell typing is more of a logistical consideration; and that red cell typing is already being done given the approvals for daratumumab in the relapse setting.

Summary of Supplemental Questions

See section 7 for more information.

Part 1: Critical Appraisal of non-randomized study: Bortezomib-containing regimens (BCR) for the treatment of non-transplant eligible multiple myeloma

The economic model assumed that the efficacy for CyBorD was the same as the efficacy of VMP in the ALCYONE trial. A non-randomized study was identified by the submitter to support the clinical equivalency of CyBorD and VMP for newly diagnosed patients with multiple myeloma (NDMM) who are transplant ineligible.[4] Therefore, it has been critically appraised in this section. Of note, a rapid response was conducted by CADTH to identify literature on the comparative effectiveness of CyBorD and VMP for NDMM who are transplant ineligible. CADTH did not identify any studies in addition to the non-randomized study provided by the submitter.[1]

A non-randomized study conducted by Jimenez-Zepeda et al[4] evaluated the impact of different bortezomib-containing regimens including CyBorD, VMP and VD for the treatment of transplant-ineligible MM. Based on an institutional plasma cell disorder database, between January 2005 to February 2016, 122 patients were identified of which 34% (n=42) received CyBorD, 34% (n=42) were treated with VMP and 31% (n=38) were treated with VD. The results showed CyBorD had the highest ORR among patients and all bortezomib combination agents (CyBorD, VMP and VD) had similar median OS rates. In addition, media PFS was better for patients that received VMP and CyBorD (22.4 months for the CyBorD group, 17.5 months for the VMP group, and 10.1 months for the VD group, $p = 0.04$).[4]

The Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS)[5] was used to assess the quality of the non-randomized study conducted by Jimenez-Zepeda et al.[6] It is unclear what

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criteria were used to exclude 230 patients as non-transplant eligible. Thus, the risk of bias is unclear for selection of participants. Jimenez-Zepeda et al[4] acknowledged that the number of cases is small in the CyBorD, VMP and VD groups and specifically, follow-up is shorter in the CyBorD group. The risk of bias is low for intervention (exposure) measurement, blinding of outcome assessment incomplete outcome data and selective outcome reporting. Overall, the results of this non-randomized study are generally accepted.

Part 2: Critical appraisal of the network meta-analysis (NMA)

There is a lack of direct evidence comparing daratumumab combination therapy to other current funded therapies in Canada. In Canada, CyBorD is the current treatment of choice for patients with newly diagnosed multiple myeloma that are transplant ineligible. Based on the submitter's consultations with clinical experts, the efficacy of CyBorD was assumed to be equivalent to VMP for the purpose of this NMA.[7] The results from this NMA were used to inform the economic model. As a result, a critical appraisal of the NMA was conducted

The objective of the NMA was to evaluate the relative efficacy and safety of daratumumab – based regimens versus other selected regimens for the treatment of NDMM who are ineligible for transplantation based on the outcome of progression.[7]

The submitter conducted a systematic literature review to identify all eligible studies of treatments for patients with transplant-ineligible newly diagnosed MM. This systematic search was updated in June 2018 and conference abstracts were included until September 2018. The systematic literature search conducted by CADTH identified two NMAs.[8,9] The submitter stated that PFS reported by San-Miguel et al[9] is an earlier NMA that excluded data from the clinical trial MAIA (DRd vs. Rd continuous) which has since been integrated into the NMA completed by the submitter.[10]

Using a Bayesian NMA framework, both fixed effects (FE) models and random effects (RE) models estimated the OS HRs between treatments (among other outcomes not directly applicable to the economic model). The hazard ratio and 95% confidence interval for the outcome of progression free survival and odds ratio for overall response rate were extracted and synthesized in an NMA.[7]

There were 23 trials included in the analysis for PFS. DVMP was associated with a statistically significant reduction in risk of disease progression compared to VMP and non-statistically significant PFS compared to Rd-continuous.[11]

There were 22 trials included in the analysis for overall survival. DVMP was associated with a statistically significant OS compared to VMP and non-statistically significant OS compared to Rd-continuous.[11]

Conclusions

The NMA included clinical trials with variation in the number of cycles that bortezomib was administered in the VMP regimens. The NMA was conducted using a Bayesian framework. The results from the NMA demonstrated that DVMP was associated with a statistically significant reduction in risk of disease progression compared to VMP and non-statistically significant PFS compared to Rd-continuous. DVMP was associated with a statistically significant OS compared to VMP and non-statistically significant OS compared to Rd-continuous.

Heterogeneity was present across the study populations due to different inclusion and exclusion criteria. Furthermore, the submitter acknowledged that the evidence network was not fully connected. Thus, the results for PFS and OS should be interpreted with caution as

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the confidence intervals were wide. Other outcomes of interest (e.g., health related quality of life and safety) were not explored in this NMA.

Part 3: Critical Appraisal of Naïve Comparisons and Match Adjusted Indirect Comparison (MAIC)

There were several different VMP regimens observed in the clinical trials included in the NMA, which differed in the number of cycles in which bortezomib was administered once weekly versus twice weekly, cycle length, and number of cycles. Therefore, the submitter conducted a naïve and MAIC comparison to examine the non-inferiority of VMP-modified regimens compared to VMP.

Results of the MAIC are summarized below, for more detail refer to Section 7. VMP-modified regimens demonstrated non-inferiority to VMP VISTA for ORR, PFS, OS and other safety outcomes, except for peripheral neuropathy (where VMP-modified regimens seem to be better than VMP VISTA regimen). For complete response, VMP-modified regimens seem to be worse than VMP VISTA regimen.

Conclusions

The method used to extract Individual patient data (IPD) from Kaplan Meier curves presents limitations in the quality of the data reported. However, steps were taken to validate this data by enlisting a second investigator. Secondly, in the naive comparisons, measures of effect were not adjusted for baseline characteristics. Thus, MAIC comparisons were considered the best available method which adjusted for baseline variables in cases where IPD was available for only one treatment arm. A limitation of unanchored comparisons is that absolute outcomes can be predicted from the baseline characteristics. Due to the bias in this assumption and possibility of unanchored comparisons exceeding the magnitude of treatment effects, results should be interpreted with caution. The submitter recommended that until a randomized comparison is performed, an appropriate method is propensity score matching.[3]

While a systematic review of the literature was conducted to identify clinical trials for the treatments to be compared, comparisons of the baseline characteristics of the trials pre- and post-matching are unclear. Outcome measures were clearly defined. In addition, although algorithms were developed to extract IPD from Kaplan Meier curves, the availability of IPD would provide more robust data.

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Comparison with Other Literature

An additional retrospective cohort study (one abstract and one poster) was identified by CGP to provided additional context on real-world outcomes with bortezomib-containing regimens and lenalidomide plus dexamethasone for the treatment of transplant ineligible MM patients; this cohort study included transplant ineligible MM patients: 423 patients treated with cyclophosphamide, bortezomib, and prednisone (CyBorP)/CyBorD; 160 patients treated with Ld, 204 patients treated with bortezomib (velcade), melphalan, and prednisone (VMP); and 55 patients treated with bortezomib (velcade) and dexamethasone/prednisone (Vd/VP). The primary outcomes reported were: ORR, PFS, and OS for transplant ineligible patients treated with CyBorD/CyBorP, Ld, VMP (Bortezomib weekly) or VD/VP, each given as reported previously but with dose-adjustments at the discretion of the treating physician to maintain patients on therapy. A brief summary of the study design and results is provided Section 8 of the report.

1.2.3 Factors Related to Generalizability of the Evidence

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

[Table 2]: Assessment of generalizability of evidence for Daratumumab for newly diagnosed Multiple Myeloma

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td>Population</td><td>ECOG Performance Status</td><td>The majority of patients in the Daratumumab group and Control group had an ECOG performance score of 1 (52.0% and 48.6% respectively).
<table><tr><td colspan="3">ECOG score, n(%)</td></tr><tr><td></td><td>Daratumumab n=350</td><td>Control n=356</td></tr><tr><td>0</td><td>78/350 (22.3%)</td><td>99/356 (27.8%)</td></tr><tr><td>1</td><td>182/350 (52.0%)</td><td>173/358 (48.6%)</td></tr><tr><td>2</td><td>90/350 (25.7%)</td><td>84/358 (23.6%)</td></tr></table></td><td>Are the trial results generalizable to patients with an ECOG score of 2 or higher?</td><td>Patients with an ECOG of 3 are confined to a bed or chair for >50% of the time. In general, ECOG status is a prognostic factor for many treatments. In the ALCYONE trial, ECOG 1 or 2 patients had a hazard ratio that was not as good as ECOG 0 patients but not statistically different. ECOG 3 or higher patients would likely have an inferior hazard ratio but also might have a higher complication rate. However, it is likely that they would benefit from a Daratumumab based therapy. Treatment of DVMP, regardless of patient's ECOG performance status, should be left to the discretion of the physician.</td></tr>
</table>

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Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
	Patients with primary amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma and prior radiation therapy within 14 days of randomization	The ALCYONE trial excluded patients with primary amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma and prior radiation therapy within 14 days of randomization. PAG is seeking clarity that daratumumab + VMP (DVMP) would be limited to patients without primary amyloidosis or monoclonal gammopathy of clinical significance (e.g., end organ damage), or smoldering multiple myeloma. PAG is also seeking clarity on whether patients who receive urgent radiation prior to starting DVMP treatment, would be eligible.	Are the trial results generalizable to patients with primary amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma and prior radiation therapy within 14 days of randomization?	In the ALCYONE trial there were no patients with Monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma or amyloidosis. In addition patients with MGUS or smoldering myeloma are not usually offered treatment until they progress to multiple myeloma. Because the ALCYONE trial did not include these patients, there are no data to suggest they benefit. The natural history of amyloid is sufficiently different from multiple myeloma (with higher rates of cardiac, renal, Gastrointestinal involvement) and thus generalizing the results of the ALCYONE to amyloidosis would be risky. However, physicians may consider DVMP if the patient has met the criteria for multiple myeloma and presents with amyloidosis, but should proceed with caution. Would not include MGUS smoldering myeloma or amyloidosis without evidence of concomitant myeloma in the funding inclusion criteria. Involved field radiation within 14 days of treatment with DVMP would likely be safe and acceptable and these patients were likely excluded from the ALCYONE trial to make interpretation of adverse events more clean.
Intervention	Dosage	PAG noted the dose of bortezomib in the trial is different than the dose in Canadian practice (e.g., given on a once weekly schedule for all cycles) and is seeking guidance on the dose of bortezomib to be used when in combination with daratumumab and the	Is the trial dosage generalizable to patients in Canada?	Refer to Table in 1.3 Conclusions for overview of Bortezomib and steroid dose. Bortezomib has been given at different doses in different trials. We do know that intravenous or prolonged twice weekly dosing is associated with painful peripheral

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Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		generalizability of the ALCYONE trial to Canadian practice. The presubmission information describes a 6-week cycle dosing regimen. The recommended dose of Daratumumab is 16mg/kg body weight administered intravenously over weeks 1 to 6, weeks 7 to 54 and week 55 onwards until disease progression. Bortezomib 1.3mg/m^2 body surface area subcutaneous injection in cycle 1, cycle 2 to 9 Melphalan 9mg/m^2 per oral and prednisone 60mg/m^2 days 1 to 4 of each bortezomib cycle		neuropathy. In the Vista trial (that compared VMP to melphalan-prednisone), Bortezomib was given as 1.3 mg/m^2 twice weekly x 4 weeks subcutaneously for four 4-weekly cycles and then reduced to weekly for the remaining cycles. In the ALCYONE trial the Bortezomib was given subcutaneously 8 times during the first 6 week cycle and then 4 times subcutaneously during each subsequent cycle. Over 36 weeks there were 28 Bortezomib injections in the VMP arm of the ALCYONE trial and 40 in the Vista trial. The PFS was 24 months in the Vista trial for VMP and was 21.3 months for the VMP arm in the ALCYONE trial. The PFS does not look significantly inferior despite the lower dose of Bortezomib. In Canada for both VMP and CyBorD, Bortezomib is given once weekly subcutaneously in 4 week cycles for a total of 36 infusions over 36 weeks (compared to 28 in ALCYONE). Thus, Bortezomib schedule used in Canada should be as clinically effective but perhaps a bit more toxic than the ALCYONE regimen. It is not likely that these variations will result in significantly different clinical or toxicity outcomes from that seen in the trial. CGP acknowledged the MAIC conducted by the submitter which assessed the non-inferiority (in terms of efficacy and tolerability outcomes) of VMP-modified regimens given in two trials (MMY3007 & GIMEMA-QW) compared to the VMP regimen prescribed in the VISTA trial and noted the

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Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
				Methods Team critical appraisal and conclusions of the MAIC (i.e., the results should be interpreted with caution).
Comparator	VMP	The comparator of VMP in the ALCYONE trial is a funded option, it is rarely used in this patient population.	Is VMP considered a relevant comparator?	VMP itself is likely less active and less convenient than the commonly used lenalidomide and dexamethasone regimen (Rd). The progression-free survival (PFS) seen for Rd in the First trial was 25.5 months versus 18.1 months for VMP in the ALCYONE trial. The PFS for CyBorD is difficult to be certain, it has been studied most often as a pre-transplant regimen. In a real-world analysis by the Canadian myeloma working group, the PFS of CyBorD was similar to VMP but inferior to lenalidomide and dexamethasone. Daratumumab + VMP is superior to VMP and looks promising compared to CyBorD and lenalidomide (although no direct evidence). In the real-world experience by the Canadian Myeloma Working Group, CyBorD and other Bortezomib regimens including VMP had similar efficacy and superimposable Kaplan Meir PFS and overall survival curves. At the time of the recruitment of the ALCYONE trial, both Bortezomib alkyloid steroid backbone and Rd were considered standard of care. VMP is a widely used standard across Europe and Rd in Canada has only recently been available and funded. It is unlikely that a RCT comparing DVMP, Daratumumab + Rd, Rd and Daratumumab + CyBorD will occur. The MAIA data comparing Rd and Daratumumab + Rd is

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Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
				forthcoming in the next 2+ years. This submission (DVMP) gets a Daratumumab regimen in the front line setting, but will not likely be the Daratumumab regimen moving forward (once MAIA data are available). The key is to give patient population options.
Outcomes			None identified	
Setting			None identified	
Abbreviations: CyBorD = bortezomib, cyclophosphamide and dexamethasone; ECOG= Eastern Cooperative Oncology Group; MGUS = Monoclonal gammopathy of undetermined significance; PFS = progression-free survival; Rd = lenalidomide and dexamethasone; VMP = bortezomib, melphalan and prednisone				

1.2.4 Interpretation

Burden of Illness and Need

In Canada there were approximately 2,900 new myeloma cases in 2017.[12] Of these, there were 1,700 in men, and 1,200 new cases of myeloma in women. There were 1,450 deaths from myeloma in 2017 accounting for approximately 4 deaths for every 100,000 people. Interestingly, myeloma is one of the few cancers where there has been a statistical increase in the age standardized 5-year relative survival rates comparing the period of 1992 to 1994 to 2006-2008. The prevalence of myeloma is about 3.5 times the incidence. The median age for diagnosis of myeloma is age 65.

There are other options for the treatment of non-transplant eligible multiple myeloma patients. Whereas the efficacy demonstrated for DVMP in the ALCYONE trial looks superior to the PFS and OS seen with other current standard of care options, it remains to be seen through longer trial follow-up and even additional randomized clinical trials which of the "under development treatment regimens" will show the best efficacy and tolerability. The hazard ratio for Daratumumab + RD versus RD looks very promising. There is a need for more effective, funded treatment options for this patient population.

Effectiveness & Safety

The data reviewed from the ALCYONE trial supports using DVMP (i.e., Bortezomib, Melphalan and Dexamethasone) for first line treatment of non-transplant eligible myeloma patients. The PFS improvement is clinically relevant, secondary end-points are all consistent and all prognostic subgroups benefitted. The toxicity profile was acceptable with an increased frequency of infusion reactions and a small increase in infections and pneumonia. Quality of life (QoL) was measured in this trial with two different scoring utilities-the EORTC QLQ-C30 and the EQ 5D-5C utilities. Apart from the first time point where Daratumumab + VMP had a significantly improved QoL from both utilities, there was no significant difference in the QoL measurements at any time-point over the 24 months that measurements were taken. Thus, the improved efficacy of the Daratumumab + VMP regimen seems to outweigh the added burden of the Daratumumab intravenous infusions and related adverse-events (described above).

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Although the drugs and doses are not identical when comparing CyBorD and VMP, the clinical efficacy looks similar and one might expect to see comparable levels of enhancement when combining CyBorD with Daratumumab although at present there are no data to show this.

The Manufacturer conducted a network meta-analysis to compare the results of multiple randomized clinical trials, looking at first line therapy for non-transplant eligible multiple myeloma. This was further evaluated by pCODR. Although the results showed that some Rd regimens had comparable efficacy to Daratumumab + VMP, the other regimens evaluated had inferior PFS and OS. However most of the regimens that were evaluated were not relevant to practise in Canada (not used). In addition, the credible intervals were wide; making it necessary to interpret any conclusions with caution.

The doses of drugs used in the ALCYONE trial are slightly different (shown in the table below Section 2 Background Clinical Information) than is used in the BMP (VMP) regimen used commonly in Canada although there may be regional variations. In fact, given that the BMP used in Canadian clinical practice is administered every 4 weeks rather than 6, there is a higher dose of Bortezomib administered over a 36-week period. There is also a higher dose of Prednisone, although both more closely approximate the doses used in the CyBorD regimen. It is not likely that these variations will result in significantly different clinical or toxicity outcomes from that seen in the trial.

Upfront Daratumumab may result in different levels of activity for Daratumumab combinations used in second or third line. Strategies to limit multiple lines of treatment with Daratumumab combinations without additional data to support the efficacy should be considered.

There are no data to support Daratumumab + VMP as a pre-transplant regimen. Trials to show added efficacy would be required.

There will be several options for patients who relapse from DVMP. Many of these patients will still be on Daratumumab. If they have a long response (greater than the median) this would suggest that they are sensitive to Bortezomib and a combination with a proteasome inhibitor could be considered such as carfilzomib, lenalidomide and dexamethasone or even CyBorD. If their remission is on the short side, then a lenalidomide or pomalidomide-based regimen might be best (without a proteasome inhibitor). In either case, if they progress while still on Daratumumab, likely further treatments with Daratumumab would not be that effective.

For non-transplant eligible patients who have just completed first line therapy with a non-Daratumumab regimen (VMP, CyBorD or LD), it would likely make sense to reserve Daratumumab-based therapy until second line as per the Pollux or Castor trials as their evidence of enhanced clinical efficacy for these patients. There is no data to support providing the Daratumumab as an adjuvant post treatment for these patients.

1.3 Conclusions

The Clinical Guidance Panel concluded there is a net clinical benefit of DVMP (daratumumab, bortezomib, melphalan and dexamethasone) for first line treatment of non-transplant eligible myeloma patients. The data that support using daratumumab + VMP for first line treatment of non-transplant eligible myeloma patients come from the randomized clinical trial described above (ALCYONE). This was a well-conducted sufficiently powered trial with no significant identified methodological weaknesses. This trial clearly shows a 50% risk of progression or death in newly diagnosed non-transplant eligible patients compared to the standard of care control group according to the trial publication, and more even favourable results with the longer follow-up data. Key secondary end-points consistently support the primary end-point strengthening the conclusion of significant clinical benefit with the addition of daratumumab to VMP. The toxicity

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profile of the Daratumumab arm was similar to the control arm, with exception of 25% infusion reactions including 5% grade 3-4 infusion reactions and an increase in infections and pneumonia. These added toxicities did not affect quality of life as there were no significant differences in quality of life between DVMP and VMP at multiple time-points. Interestingly, DVMP had a statistically superior quality of life at the first (3-month) time-point (for the EORTC QLQ-C30 GHS subscale and the EQ-5D-5L VAS).

These results are also consistent with another randomized clinical trial that show convincing enhanced clinical effects with Daratumumab combined with Lenalidomide and Dexamethasone (D-RD).[8]

Special consideration:
Dosing of Bortezomib:
The dosing of bortezomib in the ALCYONE trial was twice weekly during the first cycle for four of the six weeks in the cycle. In subsequent cycles, bortezomib is administered only once weekly x 4 of the 6 weeks. The bortezomib is given subcutaneously. However, toxicities including hematologic and neurologic from bortezomib are reduced with subcutaneous and once weekly administration without sacrificing efficacy.[13] As a result, once weekly subcutaneous bortezomib has become standard of care for many regimens.

Second line Daratumumab mono-therapy and combinations:
Combinations of daratumumab with bortezomib or lenalidomide (and dexamethasone) have shown enhanced activity over the double combination without daratumumab for recurrent multiple myeloma.[14,15] Daratumumab as employed in these combinations has been approved by Health Canada and recently been funded in many Canadian provinces. These studies did not include patients who had received daratumumab as first line therapy. Relapsing patients may not be expected to respond as well to a second line Daratumumab combination if administered directly after progression on a front line daratumumab-containing regimen. As the clinical literature evolves, it may be possible to define clinical scenarios where retreatment with a daratumumab-containing regimen may be successful. This may need to be evaluated on a case by case basis.

Extrapolation of ALCYONE results to other alkylator combinations- daratumumab + CyBorD:
In Canada, CyBorD is used by many hematologists for the first line treatment of transplant eligible and also higher risk non-transplant eligible patients. These two regimens (CyBorD and VMP) contain the same ingredients-steroids, bortezomib and an akylating agent. There are some differences in dosing between the two regimens. In CyBorD, bortezomib is given as 1.3 mg/m^2 subcutaneously weekly. In Daratumumab + VMP, bortezomib is given subcutaneously twice weekly x 4 weeks in the first 6 week cycle then once weekly x 4 in remaining cycles. Thus, over a 36 week period, there are 36 doses of bortezomib administered for CyBorD and 28 doses administered in VMP. Regarding the steroids, in CyBorD patients receive 40 mg x 4 weekly for cycle one and then 40 mg once weekly for up to 9 cycles. Thus in 36 weeks they will receive 1440 mg of dexamethasone. This is equivalent to 9600 mg of prednisone. In VMP, patients will receive 60 mg/m^2 or about 100 mg on average per patient daily for 4 days with each cycle. This is administered every 6 weeks. Thus in 36 weeks patients receiving DVMP will receive about 2400 mg of prednisone. There is thus a significant difference (25% less steroid is delivered in VMP) in the amount of steroid in these two regimens with CyBorD patients receiving 4 x the amount of steroid as VMP patients. It is difficult to compare the different alkylator agents in these two regimens.

We conclude that in the absence of a randomized clinical trial that compares Daratumumab + CyBorD to CyBorD, it is likely that a similar enhancement in efficacy will be seen by adding Daratumumab to CyBorD given that:

- they are very similar regimens with similar clinical efficacy and toxicity

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- Daratumumab has enhanced all regimens that it has been added to (e.g., Pollux, Castor and MAIA trials)
- there is no reason to expect enhanced toxicity as the two components have non overlapping toxicity profiles.

Doses of Bortezomib and steroid in CyBorD and VMP over a 36 week period

Regimen	Bortezomib	Steroid (converted to Prednisone equivalents)
CyBorD	36-1.3 mg/m^2 doses	9600 mg
VMP (in trial)	28-1.3 mg/m^2 doses	2400 mg
BMP (Canada)*	36-1.3 mg/m^2 doses	3600 mg

*BMP in Canada may differ depending on province, centre and physician (e.g. 1.5mg/m^2 dose of bortezomib is used in Alberta)

The best data available to compare these two regiments is from the Tom Baker cancer centre in Calgary.[6] This group retrospectively reported on their experience treated non-transplant eligible myeloma patients with VMP, CyBorD or BD. The CyBorD treated patients were mildly older (76 versus 73), had more patients with stage 3 disease (42% versus 31%) and with high-risk genetics (16.6% versus 14.2%). The treatment regimen was based on physician choice. The VMP bortezomib dosing was higher than in the ALCYONE trial and patients received twice weekly bortezomib intravenously for 4 -6 week cycles. The overall response rate was 95% for CyBorD and 80.9% for VMP. The CR rates were 19% for both regimens. The OS was the same for both regimens but there was a trend to improved PFS for CyBorD. CyBorD was tolerated better with peripheral neuropathy being the major toxicity in the VMP regimen. 33% of VMP patients discontinued treatment versus 2% in the CyBorD arm. We would not expect neuropathy to be a problem with daratumumab + VMP as the bortezomib is given subcutaneously and twice weekly for only the first cycle.

In a real world experience that analyzed 842 patients from 11 centres the two regimens had superimposable PFS and OS curves.[16] In this analysis, the PFS curves for lenalidomide and dexamethasone-treated patients were statistically superior to both bortezomib-containing regimens. Overall survival was not statistically different.

Non-transplant eligible patients:

The majority of patients in Canada that undergo transplant are treated with CyBorD induction therapy. These patients receive 4-9 cycles and undergo ASCT when they have maximized their response. At present Daratumumab is not used upfront for these patients. However, if Daratumumab-VMP is funded for non-transplant eligible patients there may be interest from physicians and patients to extend Daratumumab containing regimens for the transplant patients. However, at present, there are no data that indicates the outcomes from ASCT are enhanced by an upfront induction regimen that contains Daratumumab.

Leveraging National Database to Inform Future Direction of Multiple Myeloma Treatment:

The CGP would like to highlight the importance of a national database - Canadian Multiple Myeloma Database, and encourage continued research to help evaluate the impact of new myeloma treatments and inform the optimal future direction of multiple myeloma treatment.

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2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

Multiple myeloma is a neoplasm of malignant plasma cells. These cells usually reside in the bone marrow and for this reason the disease is based in bones. Plasma cells secrete immunoglobulin proteins and multiple myeloma is characterized by detection of a serum clonal immunoglobulin protein (paraprotein) or increased levels of one of the subunits of these paraproteins – serum immunoglobulin free light chains. Myeloma is diagnosed when a bone marrow shows greater than 10% clonal plasma cells. The disease requires treatment when the proliferation of these plasma cells causes "end-organ" damage-either boney lytic lesions, anemia, hypercalcemia or renal dysfunction secondary to the deposition of the myeloma paraprotein in the kidney. More recently these criteria have been modified to include three other indications for treatment: high levels of the serum free light chains (ratio >100), detection of two or more lesions in the bone or bone marrow on magnetic resonance imaging, or a bone marrow showing 60% or greater clonal plasma cells.[17] Multiple myeloma is non curable and the overall the current prognosis of multiple myeloma is approximately 6 years,[18] but patients who can undergo autologous stem cell transplantation (ASCT) have an expected median survival of 8 years.[19] Elderly patients greater than age 75 have an expected median survival of 5 years.

In Canada there were approximately 2,900 new myeloma cases in 2017.[12] Of these, there were 1,700 in men, and 1,200 new cases of myeloma in women. There were 1,450 deaths from myeloma in 2017 accounting for approximately 4 deaths for every 100,000 people. Interestingly, myeloma is one of the few cancers where there has been a statistical increase in the age standardized 5-year relative survival rates comparing the period of 1992 to 1994 to 2006-2008. The prevalence of myeloma is about 3.5 times the incidence. The median age for diagnosis of myeloma is age 65.

Staging of myeloma can separate patients into different prognostic groups. The International Myeloma working group (IMWG) staging is based on the values of serum albumin and beta 2 microglobulin (B2M). Stage 1 includes patients whose values of these two tests are both normal. Stage 3 includes patients whose B2M is greater than 5.5 mg/L and stage 2 includes patients who do not fit into either of these. The recent "revised IMWG staging criteria" includes the results of cytogenetics or LDH and defines t(4:14), t(14;16), or deletion of 17p as high-risk genetics changes. The median overall survival of IWMG stage 1 is 62 months, stage 2 is 44 months and stage 3 is 29 months.[20] Using the revised IMWG criteria, stage 1 disease has a median survival that was not reached, 83 months for stage 2, and 43 months for stage 3.[21]

2.2 Accepted Clinical Practice

Treatment is initiated once a diagnosis of symptomatic multiple myeloma is made. Treatment is dependent on whether a patient is eligible for ASCT and the risk profile of the patient as defined by the revised IMWG criteria. Patients generally under age 70 and without significant co-morbidities may be candidates for ASCT. These patients will undergo 3-4 cycles of induction therapy prior to stem cell harvest and then undergo high dose therapy and stem cell transplantation. Tandem transplants may be offered to high-risk patients with revised IMWG stage 3 (for review see Cejalvo & de la Rubia, 2015[22]). Post ASCT, patients will benefit from maintenance therapy with lenalidomide with increased PFS and OS as shown in a recent meta-analysis.[23] They will also benefit from two years of bisphosphonate therapy particularly if they have documented lytic bone disease.[24] The monoclonal antibody denosumab may have superior activity to zoledronic

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acid.[25] Induction regimens can include bortezomib –containing regimens, lenalidomide and low dose dexamethasone regimens, carfilzomib-lenalidomide regimens or other multi-drug combinations. Whereas in the US, bortezomib, lenalidomide and dexamethasone has become the current standard of care, in Canada the regimens used most often are CyBorD[26] or VMP. In a randomized trial that evaluated the role of ASCT, the PFS was 50 months for patients treated with VRd (bortezomib, lenalidomide and dexamethasone) followed by ASCT versus 36 months for those treated with VRd without transplantation. However, OS was similar in the two groups.[27] The 4 year OS was 81 % and 82%. In other trials, patients with low-risk myeloma had a 4 year OS of 86% compared to 68% for those with high-risk cytogenetics ($p<0.001$).[28] The type of induction therapy was not a prognostic factor.

Patients who are not eligible for ASCT may be treated with any of the regimens described above for the transplant group. Historically these patients were treated with melphalan and prednisone (MP). The addition of thalidomide to melphalan and prednisone (MPT) was superior to melphalan and prednisone (MP) based upon the results of several randomized trials. A meta-analysis showed superior response rates, PFS and OS.[29] The type of induction therapy was not a prognostic factor. VMP (Bortezomib, Melphalan and prednisone) also has superior OS to MP.[30,31] Lenalidomide and dexamethasone (Rd) was compared to the melphalan-containing regimen MPT (melphalan, prednisone and thalidomide). In this trial, PFS was superior for continuous Rd versus MPT or Rd stopped after 18 months.[32] Lenalidomide and dexamethasone is a regimen that has the advantages of being given entirely orally and is usually well tolerated in the elderly but may be difficult in patients with renal compromise. VRd was studied in the transplant ineligible groups and has shown both a statistically significant PFS and an OS benefit over Rd based on the SWOG S0777 trial.[18] However toxicities were greater with VRd and more than twice as many patients (23% versus 10%) discontinued therapy due to side effects.

CyBorD has been studied in transplant eligible patients.[33] 63 patients were treated in a phase 2 trial. The ORR was 89% with 62% achieving a very good partial response (VGPR). Although 81% underwent subsequent ASCT, the median PFS was 40 months and the 5-year PFS and OS were 42% and 70%. In a non clinical trial setting,[26] 109 newly diagnosed patients with multiple myeloma were treated with the CyBorD combination in preparation of ASCT. The ORR was 98% including a 79% VGPR post ASCT. It was well tolerated with no severe peripheral neuropathy and minimal hematologic toxicity. It was considered convenient and cost effective. Similar regimens with the same drugs have been compared to 4 drug regiments including both bortezomib and lenalidomide and in the EVOLUTION trial, there were no improvements in outcome to the 4 drug regimens.[34] A non-randomized comparison of Rd, CyBorD, VMP and VD/VP showed improved PFS with Rd and a trend towards improved OS with Rd. The PFS and OS curves for CyBorD and VMP were very similar.[4]

These data are further discussed below:

Alternate options for treatment of newly diagnosed multiple myeloma:

There are five **other** chemotherapy combinations that are currently used or are being evaluated for the treatment of non-transplant eligible previously untreated multiple myeloma:

Standard of care:

- lenalidomide and dexamethasone
- VMP
- CyBorD

Under exploration:

- lenalidomide, velcade and dexamethasone
- daratumumab, lenalidomide and dexamethasone

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As of yet, there are no trials that inform which of these combinations-daratumumab or non-daratumumab combinations-has the best clinical efficacy and safety profile for this patient population. Like Daratumumab, bortezomib, melphalan and prednisone, the two other combinations under exploration seem to be superior to the current standard of care options (VMP, RD) to which they were compared. There is no comparative data using CyBorD as the control treatment.

a. Lenalidomide and Dexamethasone

First line non-transplant eligible patients with multiple myeloma are often treated with lenalidomide and dexamethasone (LD). This is based on results from the FIRST trial (Frontline Investigation of Revlimid and Dexamethasone versus Standard of care Melphalan, Prednisone and Thalidomide).[32] In this trial, 1623 patients were randomized to LD in 28-day cycles for 18 months or continuously until disease progression or to melphalan, prednisone and thalidomide.

Patients were eligible for the trial if they had previously untreated, symptomatic and measurable myeloma and were older than age 65 or under age 65 but ineligible for ASCT. Patients were excluded if they had an ECOG of greater than 2, renal failure requiring dialysis, a neutrophil of count of less than 1000 and a platelet count of less than 50,000, liver function tests greater than 3 x normal and peripheral neuropathy. They needed to be willing to undergo anti thrombotic therapy.

The characteristics of the patients at baseline were well balanced. The median age was 73, 40% had ISS stage 3, 21% had ECOG 2 and 17-20% had high-risk cytogenetics.

LD was associated with an 80-85% Grade 3 or 4 adverse event rate and the most common were hematologic and infections. As compared to MPT continuous LD was associated with fewer hematologic and neurologic adverse events and a moderate increase in infections and fewer second primary hematologic cancers.

The overall response rates were 75%, 73% and 62% for LD continuous, LD 18 and MPT respectively ($p< 0.001$). The CRs were 15%, 14% and 9% respectively. The median PFS for continuous LD was 25.5 months, 20.7 months for LD-18 and 21.2 months for MPT ($p<0.001$). OS was not significantly different (59%, 56% and 51% at 4 years) and both LD arms were superior to the MPT control.

b. CyBorD

The CyBorD regimen was developed as a collaboration between Princess Margaret Hospital in Toronto and the Mayo Clinic in Scottsdale Arizona. Initially the regimen included cyclophosphamide 300 mg.m2 weekly by mouth in a 4 week cycle, bortezomib, 1.3 mg/m2 IV twice weekly on week 1 and 2 and dexamethasone by mouth daily x 4 for weeks 1, 2 and 3. A sequential trial was performed on 60 patients where the first 30 received this dose but the second 30 received only once weekly IV bortezomib and reduced dexamethasone to weekly in cycles 3 onwards.[35] The primary endpoint of the study was OR after 4 cycles. Toxicity was also documented.

The results of this trial are shown in the table below:

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Table 1. Overall response

ITT	Cohort 1 (n = 33)	Cohort 2 (n = 30)	All (n = 63)
ORR	88%	93%	90%
CR/nCR	39%	43%	41%
VGPR or better	61%	60%	60%
After 4 cycles	(n = 28)	(n = 27)	(n = 55)
ORR	96%	93%	95%
CR/nCR	46%	48%	47%
VGPR or better	71%	63%	67%
Toxicity			
Any ≥ Gr 3 AE	48%	37%	
Gr ≥ 3 Thrombocytopenia	21%	0%	
Gr ≥ 3 Neutropenia	12%	7%	
Gr ≥ 3 Anemia	9%	0%	
Gr ≥ 3 PN	6%	0%	
Any Gr PN	64%	57%	
Bortezomib doses reduced	21%	13%	
Dex dose reduced	30%	20%	

ITT indicates intention to treat; ORR, overall response; CR, complete response; nCR, near complete response; VGPR, very good partial response; GR, grade; AE, adverse event; and PN, peripheral neuropathy.

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The authors concluded that the high response rate was maintained and the toxicity was reduced with the low dose regimen. More recently bortezomib has been administered subcutaneously to reduce neurologic toxicities.

CyborD has been used as initial therapy for transplant eligible patients with newly diagnosed multiple myeloma because of the deep and rapid response.[33] In one trial in this patient population, the ORR was 89% with 62% achieving a very good partial response or CR.

c. VRd

The SWOG S0777 trial evaluated the addition of bortezomib to Lenalidomide and Dexamethasone (VRd) versus Rd alone for the treatment of previously untreated non-transplant eligible multiple myeloma patients.[18]

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In this trial, 525 patients in 139 participating institutions were enrolled. Patients had measurable disease with an ECOG of 3 or less, CRAB symptoms, and hemoglobin of >9, PMN of >1 $x10^{25}$ and platelets of >80,000. The RVD regimen was given as 8 - 21 days cycles with Lenalidomide 25 mg daily x 14 days, plus oral dexamethasone at 20 mg daily on days 1, 2, 4, 5, 8, 9, 11 and 12. Bortezomib was administered as 1.3 mg/m2 IV on days 1, 4, 8 and 11. The Rd regimen was given in 28 days cycles with Lenalidomide at 25 mg orally x 21 days plus dexamethasone 40 mg on days 1, 8, 15, and 22. The primary endpoint was PFS. Patients were allowed delayed ASCT.

The median follow-up was 55 months and the two groups were balanced with the exception of more women and older age in the Rd group. Overall 43% were over age 65, 33% had IMWG stage 3 and 69% of patients underwent ASCT. FISH was performed on 316 patients and 33% were deemed high-risk by either t(4:14), t(14;16) or chromosome 17 deletion.

Adverse events of grade 3 or higher occurred in 82% of the VRd group and 75% of the Rd. A total of 23% and 10% patients respectively discontinued induction treatment because of adverse events. There was a significantly increased grade 3 or greater incidence of neurologic events and gastrointestinal adverse events with the VRd regimen. The authors postulated that the incidence of grade 3 or higher neurologic s/e's would have been reduced. The cumulative overall incidence of secondary primary cancers was 4.0%. This is less than the 6.9% cumulative risk in a recent meta-analysis of Lenalidomide containing regimens including those with Melphalan (which may contribute to the relatively higher risk that was found in the meta-analysis).[36]

The median PFS was 43 months in VRD versus 30 months in Rd with a p value of 0.0018 and HR of 0.712. The median OS was significantly improved with an OS of 75 months in VRd versus 64 months in Rd (p=0.025 and HR 0.709). The overall response rate was 82 % in VRd versus 72 % in Rd.

d. Daratumumab-RD

Patients over age 65 who were transplant ineligible were randomized 1:1 to Rd or Rd+ Daratumumab (MAIA study).[8] Stratification included; ISS stage I, II, III, geography (NA versus rest of world) and age >75. All patients received 28-day cycles of R 25 mg orally for 21/28 days and Dexamethasone 40mg orally on Days 1, 8, 15 and 22. In the D-Rd arm, Daratumumab was given at 16 mg/kg IV weekly for cycles 1-2 then Q2m was for cycles 3-6 then monthly. Treatment was continued in both arms until progression or toxicity. The primary endpoint was PFS. Key secondary endpoints included ORR, MRD and safety.

737 patients were randomized from 14 countries. Key baseline parameters were balanced between the two arms. The median age was 73 (45-90), 44% of patients were ≥ age 75, two thirds of patients had ECOG 1 or greater, 29% were IMWG stage 3 and 14 % were high-risk on FISH.

There were higher rates (5% or more difference) of grade 3/ 4 pneumonia, neutropenia (50% versus 35%), and leukopenia in the D-Rd arm.

After a median follow-up of 28 months, the hazard ratio for PFS was a very promising 0.55, (P<0.0001). The median PFS was 31.9 months for the Rd arm and not reached for the D-Rd arm. The CR for D-Rd was 47.6% versus 24.7 for Rd. The improved PFS was seen in all pre-specified subgroups but less of an effect was seen in the high-risk cytogenetics subgroup.

The data discussed above and supporting these regimens is summarized in this table:

Table showing patient populations and PFS of relevant non-transplant eligible trials for newly diagnosed MM.

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Trial	Regimen	Median age (years)	Stage III (%)	High-risk genetics (%)	Median PFS (months)	OS (%)	Ref
FIRST	Rd continuous	73	40	17	26	59 (4-year)	[32]
	MPT	73	40	19	21	51 (4-year)	
SWOG-0777	VRd	43%>65	33		43		[18]
	Rd				30		
MAIA	DRd	73	29	14	Not reached		[8]
	Rd				31.9		
ALCYONE	DVMP	71	41	17	Not reached		ASH 2018
	VMP	71	36	15	18.1		
CYBOR-D		ND*	ND	38	40 (*91% ASCT)		[26]

* Not described

2.3 Evidence-Based Considerations for a Funding Population

We suggest the following modifications to the criteria used in the ALCYONE trial:

- As first line therapy for patients not eligible for ASCT due to comorbid illnesses or advanced age
- Have a Hb of greater than 75, pmn >1, plat >70. Patients with more severe cytopenias may be treated with caution.
- LFTs less than 2.5 x normal and bilirubin < 1.5x normal
- Creatinine Clearance of > 40 ml/min. Patients with lower creatinine clearances may be treated with caution.
- ECOG of 0-4 (at discretion of physician)
- Non curable cancers within 3 years of treatment. Patients with other cancers felt to be cured may be treated.
- Allowing treatment in the presence of neuropathy with caution would be acceptable.

Patients with MGUS, smoldering myeloma or amyloidosis without evidence of myeloma were excluded; patients with amyloid and evidence of myeloma may be treated with caution. Refer to Table 2: Assessment of generalizability of evidence for Daratumumab + VMP in multiple myeloma, and Sections 1.2.3 Interpretations and 1.3 Conclusions for evidence-based considerations for a funding population.

2.4 Other Patient Populations in Whom the Drug May Be Used

Refer to 1.2 Conclusions of the Clinical Guidance Report.

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3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Myeloma Canada (MC), provided input on DVMP), and daratumumab (Darzalex) in combination with cyclophosphamide, bortezomib (Velcade), and dexamethasone (DCyBorD), as first line treatment for newly diagnosed adult patients with MM who are not eligible for an autologous stem cell transplant. Please note that pCODR requested clarification from the submitter on the reimbursement request, and the submitter confirmed that the reimbursement request was for DVMP, but not D-CyBorD.

Two online surveys, one for patients and one for caregivers, were conducted from September 12th, 2018 to January 17th, 2019. These surveys were directed to Canadians through MC support groups, as well as to Americans and Europeans through the International Myeloma Foundation, Myeloma United Kingdom and Myeloma Patients Europe groups, respectively. The objective of the surveys was to collect data from MM patients and/or their caregivers who have experience with DVMP, or D-CyBorD, however, there were few patients worldwide with experience on either of these two regimens. There were no patients who had direct experience with the drug under review included in this patient advocacy group input summary. Since the current standard of care for this indication is treatment with CyBorD or VMP in Canada and the United States (US), the focus of this patient advocacy group input summary is to illustrate the patient and caregiver experience with these two important comparative treatments to the drug under review. A total of 16 patients responded to the survey. Four Canadian patient respondents had experience with VMP as their first line of treatment, but only 3 completed the survey, and for some questions, only 2 provided a response. Twelve patient respondents had experience with CyBorD as their first line of treatment, and for many questions, only 10 provided a response. A total of 12 caregivers responded to the survey; 2 respondents reported experience caring for a patient on VMP and 10 respondents reported experience caring for a patient on CyBorD as first line treatment with no prior stem cell transplant.

MC referred to previous patient advocacy submissions they had made for pCODR 10084 carfilzomib (Kyprolis) and pCODR 10088 ixazomib (Ninlaro) in 2016 and 2017, respectively, to inform the Disease Experience, Experiences with Currently Available Treatments, and Improved Outcomes sections of this summary, as they do not believe the results have changed. MC acknowledged there have been advances in treatments for MM, however, it continues to be a serious disease impacting both patients and caregivers. In addition, MC stated the side effects of treatment are still inconvenient and new treatments give patients, and their caregivers, reasons to be hopeful. These previous submissions included information obtained from two online surveys, one for patients and one for caregivers, conducted from August 15th, 2016, to August 31st, 2016. Both surveys were designed to understand the impact of MM on the lives of patients and caregivers and the effect of treatments on their myeloma, as well as experiences with carfilzomib. A total of 344 patients and 123 caregivers responded to these surveys. The ixazomib submission included information from two additional surveys conducted to collect information specific to the patient and caregiver experience with ixazomib from May 24th, 2016 to June 10th, 2016, and November 15th, 2016 to December 2nd, 2016, respectively. A total of 35 patients and 4 caregivers responded. Responses to specific questions on carfilzomib and ixazomib were not included in this report. Table 3.1 summarizes all the surveys and how they were used in the current patient advocacy summary, as well as respondent demographic information.

Table 3.1: Summary of data sources used for the patient advocacy group summary

	pCODR 10084 Carfilzomib		pCODR 10088 Ixazomib		pCODR 10148 Daratumumab + VMP (current submission)	
	Patients	Caregivers	Patients	Caregivers	Patients	Caregivers
Date of data collection	August 15th - 31st, 2016	August 15th - 31st, 2016	May 24th - June 10th, 2016	Nov. 15th - Dec. 2nd, 2016	Sept. 12th, 2018 - Jan. 17th, 2019	Sept. 12th, 2018 - Jan. 17th, 2019

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	pCODR 10084 Carfilzomib		pCODR 10088 Ixazomib		pCODR 10148 Daratumumab + VMP (current submission)	
	Patients	Caregivers	Patients	Caregivers	Patients	Caregivers
Number of respondents	344	123	35	4	16*	12
Geographic location of respondents						
Canada	238	82	9	1	4	10
USA	104	40	26	3	0	2
Australia	0	1	0	0	0	0
Isreal	2	0	0	0	0	0
Specific sections	Section 3.1.1: Experiences Patients have with Multiple Myeloma; 3.1.3: Impact of Multiple Myeloma and Current Therapy on Caregivers				**3.1.2: Patients' Experiences with Current Therapy for Multiple Myeloma; 3.1.3: Impact of Multiple Myeloma and Current Therapy on Caregivers	
*A total of 4 patient respondents had experience with VMP and 12 with CyBorD. Only 3 patient respondents on VMP completed the survey. **Note: Only information on VMP and CyBorD were presented in the current therapies section (i.e., excluded specific information on ixazomib and carfilzomib) as these were the relevant comparators in the patient population under review (first-line setting).						

From a patient's perspective, symptoms of MM that are important to control include infections, followed by kidney problems, mobility, pain, fatigue, neuropathy, and shortness of breath. Patients also indicated their emotional well-being was impacted, and symptoms may fluctuate during their treatment journey. Most symptoms of myeloma have a neutral to significant impact on day-to-day activities and quality of life. Specifically, the ability to work was reported as the most affected, followed by the ability to travel, exercise, volunteer, conduct household chores, fulfill family obligations, and spend time with family and friends. Caregivers also experienced limitations in their daily life, with ability to travel being rated as the most impacted, followed by ability to volunteer, spend time with family and friends, concentrate, fulfill family obligations, work, exercise, and conduct household chores.

Patients receiving VMP and CyBorD had differing expectations of their treatment. Patients who received VMP reported that their most important expectations of the treatment included improved quality of life and enjoying a normal life, whereas patients that received CyBorD ranked remission and disease control as their most important expectations of their treatment. Two-thirds (n=2) of patients on VMP indicated prolonged life was an expectation that was met, and half of patients (n=6) indicated CyBorD met their expectation of disease control. All patients receiving VMP (n=3) rated their quality of life as poor or fair, whereas 58% (n=7) of CyBorD treated patients rated their quality of life as good, very good, or excellent.

Overall, most patients on VMP and CyBorD thought their treatment was effective, with only one patient on CyBorD stating it was not effective in controlling MM. Negative effects reported by respondents that received VMP included loss of short-term memory, dizziness, unsteadiness, low energy level, neuropathy, and weakness. Patients that received CyBorD reported negative effects, which included constipation, lack of appetite, nausea, diarrhea, flu-like symptoms, neuropathy, weakness in muscles, unsteadiness (balance), fatigue, hair loss, and loss of taste. One patient reported a dose reduction due to these negative effects. All patients that received VMP expressed that side effects were tolerable, whereas only 50% (n=6) of patients that received CyBorD thought the side effects were tolerable or extremely tolerable. Most side effects were rated as tolerable by VMP patients, with the exception of constipation and decreased appetite that were somewhat intolerable. Many patients on CyBorD did not experience some of the side effects listed in the

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survey. Among patients who received CyBorD and experienced side effects, a small to moderate proportion experienced intolerable side effects. Completely or somewhat intolerable side effects included low blood counts, fatigue, pain, and decreased appetite.

In summary, patients value remission, improved quality of life, disease control, prolonged life, fewer side effects than other treatments, and enjoying a normal life. Patients expectations for daratumumab include controlling symptoms such as infections, kidney problems, mobility, pain, fatigue, neuropathy, and shortness of breath. In addition, patients value a treatment option that would improve their day to day activities such as ability to work, travel, conduct chores and fulfill family obligations.

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 Myeloma Canada.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Multiple Myeloma

As per the input submitted by MC, this section is taken from the previous patient input summaries included in the pCODR 10084 carfilzomib (Kyrpolis) and pCODR ixazomib (Ninlaro) submissions for MM.

When Myeloma Canada asked patient respondents to rate on a scale of 1 to 5 (where 1 is not important and 5 is very important), how important it is to control various symptoms of myeloma, patient respondents indicated that infections were the most important, followed by kidney problems, mobility, pain, fatigue, neuropathy and shortness of breath. Based on the responses below, all symptoms were important to very important.

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

Myeloma Canada also asked respondents to rate on a scale of 1 to 5 (where 1 is not at all and 5 is significant impact), how much symptoms associated with myeloma impact or limit

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day-to-day activity and quality of life. Patient respondents indicated their ability to work was the 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, the majority of patients expressed symptoms associated with myeloma had a neutral or higher impact.

Ability to:	1 - Not at all	2	3	4	5 - Significant impact	N/A	Total
Work	10.23% 31	14.19% 43	16.83% 51	14.19% 43	29.70% 90	14.85% 45	303
Exercise	8.61% 26	19.21% 58	24.17% 73	24.83% 75	21.85% 66	1.32% 4	302
Travel	13.25% 40	16.23% 49	27.15% 82	17.88% 54	24.17% 73	1.32% 4	302
Volunteer	16.33% 49	18.00% 54	23.33% 70	18.33% 55	19.00% 57	5.00% 15	300
Concentrate	12.67% 38	24.33% 73	23.00% 69	21.00% 63	17.33% 52	1.67% 5	300
Conduct household chores	14.62% 44	22.26% 67	29.24% 88	20.60% 62	12.62% 38	0.66% 2	301
Fulfill family obligations	18.94% 57	25.58% 77	27.91% 84	13.62% 41	11.96% 36	1.99% 6	301
Spend time with family and friends	22.85% 69	25.17% 76	24.83% 75	14.57% 44	11.92% 36	0.66% 2	302

The following quotes provided by Myeloma Canada help illustrate the effect and impact of myeloma 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."*

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3.1.2 Patients' Experiences with Current Therapy for Multiple Myeloma

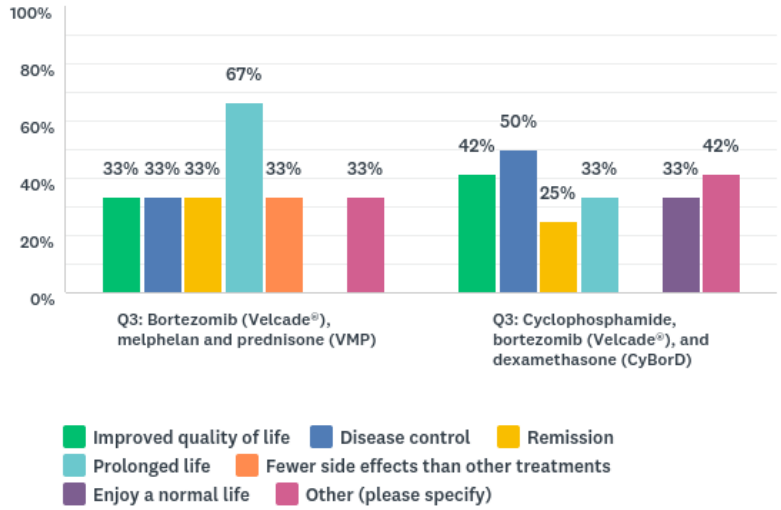
The current standard of care for adult patients with MM who are not amenable to an autologous stem cell transplant (ASCT), include VMP and CyBorD. Of the 4 patients treated with VMP, 3 were on the treatment for 7-12 months, and 1 did not respond. Results found that enjoying a normal life and improved quality of life were the most important expectations among 2 respondents treated with VMP who answered this question.

Of the respondents that received CyBorD, 8 patients were on the treatment for 1-6 months, and 4 patients were on the treatment for 7-12 months. Based on the results from 12 respondents, remission was the most important expectation with 50% (n=6) ranking it as number 1, followed by disease control with 17% (n=2) ranking it as number 1.

Expectations fulfilled by VMP and CyBorD are illustrated in Figure 3.1. Of the patients that received VMP, 2 (67%) indicated prolonged life was an expectation that was met although it was ranked among the least important for all 3 patients on this treatment. Only 1 (33%) patient attested to the following expectations being met: improved quality of life, disease control, remission, and fewer side effects than other treatments. No patients treated with VMP reported enjoying a normal life as an expectation fulfilled by this treatment.

Based on the top ranked expectations for treatment with CyBorD, 6 (50%) of patients indicated disease control was an expectation that was satisfied, however only 3 (25%) of patients indicated remission was fulfilled. Prolonged life was also among the expectations ranked as highly important, and 4 (33%) patients indicated this expectation was fulfilled. Although enjoying a normal life and improved quality of life were not ranked as the most important expectations, 5 (42%) patients reported improved quality of life and 4 (33%) patients reported enjoying a normal life were expectations that were fulfilled by CyBorD. No patients reported fewer side effects of CyBorD compared to other treatments as an expectation that was fulfilled.

Figure 3.1: Expectations fulfilled by VMP (n=3) and CyBorD (n=12)



The effectiveness of rating VMP and CyBorD in MM was evaluated and is illustrated in Figure 3.2. All patients (n=3) rated VMP as effective, very effective, or extremely effective, whereas 50% (n = 6) rated CyBorD as the same. Only 1 (8%) patient on CyBorD rated the treatment as not effective in controlling MM.

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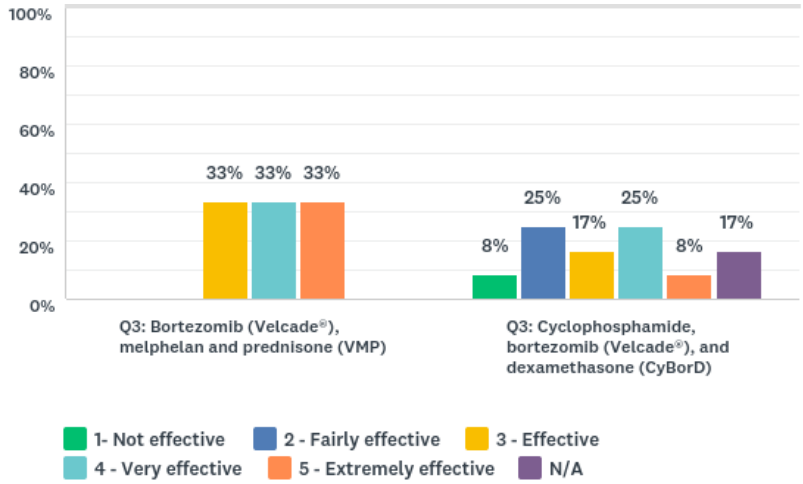
Figure 3.2: Effectiveness rating of VMP (n=3) and CyBorD (n=12) in controlling myeloma



Participants were asked about negative effects associated with the treatment regimens, and 67% in both VMP (n = 2) and CyBorD (n = 8) answered yes. Negative effects reported from patients that received VMP included loss of short-term memory, dizziness, unsteadiness, low energy level, neuropathy, and weakness. Patients that reported negative effects included constipation, lack of appetite, nausea, diarrhea, flu-like symptoms, neuropathy, weakness in muscles, unsteadiness (balance), fatigue, hair loss, and loss of taste. One patient reported a dose reduction due to these negative effects. One patient stated *"Knocked out my immune system (my neutrophil count was zero) - got 3 injections of Neupogen to stimulate my bone marrow."* Another commented, *"It didn't stop the development of lesions on my spine."* Patients that received CyBorD also reported negative cognitive effects such as brain fog, anxiety, and worrying.

All 3 patients on VMP found it to be overall tolerable. While most side effects were tolerable for patients that received VMP, constipation and decreasing appetite were reported as somewhat intolerable by 1 patient (33%) per symptom.

Of the 12 patients on CyBorD, 25% (n=3) rated it as extremely tolerable, 25% (n=3) rated it as tolerable, 25% (n=3) rated it as somewhat intolerable, and 17% (n=2) rated it as completely intolerable. Many patients did not experience side effects (N/A) with CyBorD, but of those that did, some patients had intolerable experiences. Specifically, low blood counts were rated as completely (n=2; 17%) or somewhat (n=2; 17%) intolerable; fatigue was as completely (n=2; 17%) or somewhat (n=1; 8%) intolerable; pain was rated as completely (n=2; 17%) or somewhat (n=1; 8%) intolerable; and decreased appetite was rated as completely (n=1; 8%) or somewhat (n=2;17%) intolerable. All other completely or somewhat intolerable side effects were reported 2 patients or less per symptom, which included infections (n=2), diarrhea (n=1), nausea/vomiting (n=2), constipation (n=2), dyspnea (n=1), and fever (n=1). Infusion reactions and headaches were reported to be tolerable CyBorD side effects.

Quality of life, as illustrated in Figure 3.3, was rated as poor (n=1; 33%) or fair (n=2; 67%) by patients who received VMP, whereas 17% (n=2) of patients who received CyBorD rated quality of life as poor or fair. The majority of CyBorD patients rated quality of life as good (n=4; 33%), and some even rated it as very good (n=1; 8%) or excellent (n=2; 17%). When patients were asked if their treatment met their expectations, 2 patients treated with VMP said yes, while 1 stated treatment was still in progress, and only 1 patient treated with

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CyBorD said yes. A number of patients treated with CyBorD commented it was too early to tell, and other reasons for their expectations response, included:

"I had 1/2 the expected reduction in light chains"

"The tumor hasn't shrunk IgM came down, but going up again, so no further ahead except feeling awfl"

"My free light chain kappa numbers were 265, 121, 134, 90, 112 . Fluctuated"

"Stopped disease progression, but didn't get me near remission"

"No, Did not lower serum free light chains to remission levels."

"Feel really good without chemo."

"didn't know what to expect"

Patients were also asked if their treatment improved their health and well-being. Only 1 patient treated with VMP responded yes, while the other 2 indicated it was too soon to tell. One patient had stated, *"I would like to know what percent reduction in my side effects I might eventually expect after my program ends."* Of the CyBorD respondents, 3 responded yes, 5 responded no, and 4 responded that it was too soon to tell. CyBorD patients also provided the following input:

"Overall I think I've had less broken bones than I would have had if I didn't do the treatment."

"Move better. Weight returning"

"My myeloma is same as before, but I felt terrible, no quality of life"

"Only kept it getting worse"

"Knocked out my immune system."

Of the respondents who received VMP, when asked if their treatment improved their long-term health outlook, 2 responded yes and 1 responded it was too soon to tell. One patient mentioned, *"I was treated with 9 cycles of the above, however, I have been without any treatment for the following 3 years, although that may just about be coming to an end."* When patients who receive CyBorD were asked if their treatment improved their long-term health outlook, 2 responded yes, 4 responded no, 5 responded it was too soon to tell, and 1 did not provide a response. Additionally, patients receiving CyBorD commented:

"I don't think it's lengthen my life"

"I was expecting 8 cycles of this and done. It's been 2 1/2 years and 6 drug regimens"

"I was taken off Cyclophosphamide after about 6 weeks and kept on Velcade and Dexamethasone only because the combination of the three knocked out my immune system."

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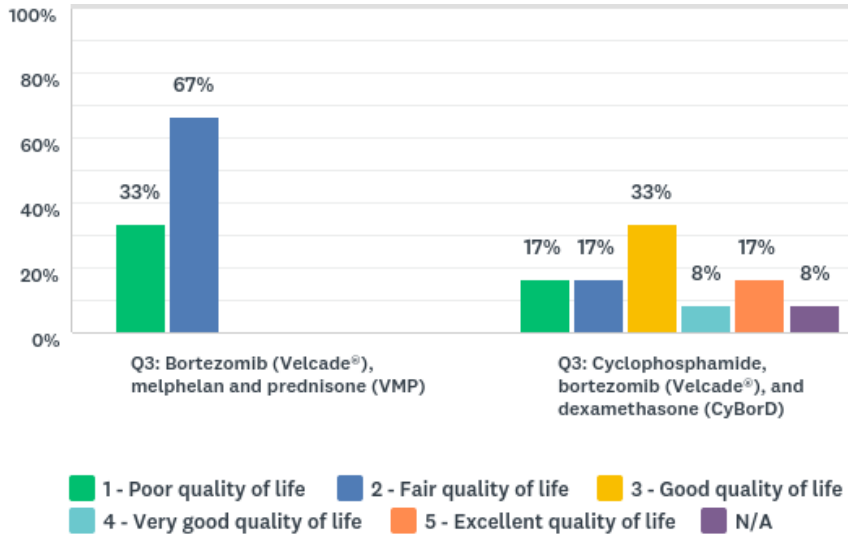
Figure 3.3: Quality of Life Rating by Patients on VMP (n=3) or CyBorD (n=12)



3.1.3 Impact of Multiple Myeloma and Current Therapy on Caregivers

As per the input submitted by MC, part of this section is taken from the previous patient input summaries included in the pCODR 10084 carfilzomib (Kyrpolis) and pCODR ixazomib (Ninlaro) submissions for MM.

From the caregiver survey conducted in 2016, which was initially reported in the pCODR 10084 carfilzomib submission, when caregiver respondents were asked to rate on a scale of 1 to 5, where a rating of 1 "not at all" and 5 is "significant impact", how much caring for someone with myeloma 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, to concentrate, fulfill family obligations, to work, exercise, and to conduct household chores. The total number of caregiver respondents for this answer ranged from 115 to 120.

To following quotes illustrate how much a caregiver's life can be affected along with the patient:

"My concentration is great because I keep a notebook on all my husband's 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!"

With respect to the MC survey conducted on caregivers from September 12th, 2018 to January 17th, 2019, 2 caregivers of patients that received VMP and 10 caregivers of patients that received CyBorD responded to the survey. The 2 caregivers of VMP patients and 8 caregivers of CyBorD patients reported challenges while helping patients manage side effects of their treatment, illustrated in Figures 3.4 and 3.5. One caregiver of a patient treated with VMP reported their ability to travel and to concentrate was highly affected. Caregivers of VMP patients also reported their ability to work, volunteer,

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conduct household chores, and ability to spend time with family were affected. All caregivers (n=2) reported some effect on their ability to concentrate, and no caregivers reported an effect on their ability to exercise when caring for a patient with VMP. Caregivers of CyBorD-treated patients reported their abilities to work (n=4; 40%), spend time with family (n=4; 40%), concentrate (n=4; 40%), travel (n=3; 30%), exercise (n=3; 30%), volunteer (n=3; 30%), and conduct household chores (n=2; 20%) were highly affected. Only one caregiver (10%) reported no effect on abilities to work, travel, exercise, volunteer, and conduct household chores, and two caregivers (20%) reported no effect on ability to concentrate when caring for a patient with CyBorD. All caregivers of patients with CyBorD reported some effect on their ability to spend time with family.

Figure 3.4. Effect of managing side effect on caregiver (VMP)

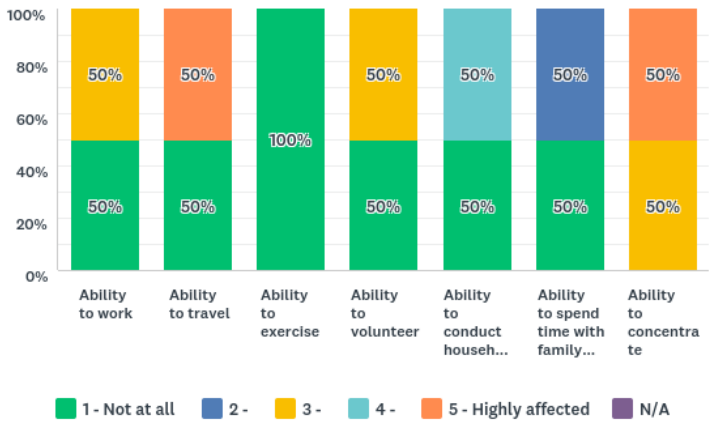
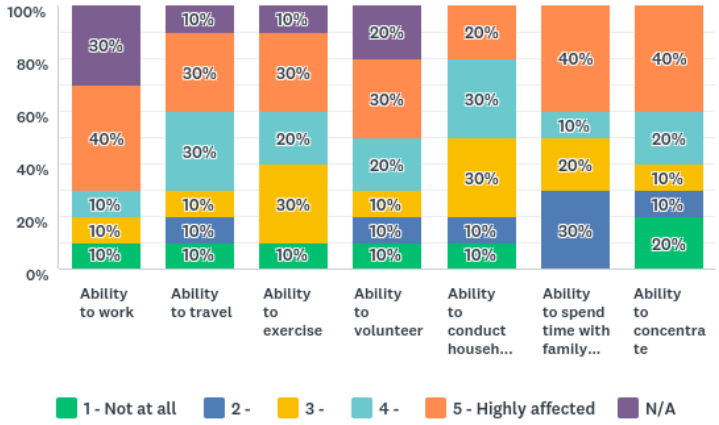


Figure 3.5. Effect of managing side effects on caregiver (CyBorD)



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3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Daratumumab in combination with Bortezomib (Velcade®), Melphelan, and Prednisone , and Daratumumab (Darzalex®) in combination with Cyclophosphamide, Bortezomib (Velcade®), and Dexamethasone (CyBorD)

There were no patients that had direct experience with DVMP or D-CyBorD included in the Myeloma Canada submission.

3.3 Additional Information

None.

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4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

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

Clinical factors:

- Clarity on patient groups eligible for treatment

Economic factors:

- Drug wastage
- Additional resources needed to monitor infusion reaction
- Unknown and variable treatment duration

Please see below for more details.

4.1 Currently Funded Treatments

Bortezomib/melphalan/prednisone (VMP), cyclophosphamide/bortezomib/dexamethasone (CyBorD), and lenalidomide/dexamethasone (Rd) are funded in all the provinces for patients with newly diagnosed multiple myeloma who are not suitable for autologous stem cell transplant.

PAG noted that CyBorD is the current treatment of choice for patients with newly diagnosed multiple myeloma that are transplant ineligible. Although the comparator of VMP in the ALCYONE trial is a funded option, it is rarely used in this patient population. Therefore, PAG is seeking information on the use of daratumumab in combination with other bortezomib-based regimens (e.g., CyBorD or BMD).

4.2 Eligible Patient Population

The ALCYONE trial excluded patients with primary amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma and prior radiation therapy within 14 days of randomization. PAG is seeking clarity that daratumumab + VMP (DVMP) would be limited to patients without primary amyloidosis or monoclonal gammopathy of clinical significance (e.g., end organ damage), or smoldering multiple myeloma. PAG is also seeking clarity on whether patients who receive urgent radiation prior to starting DVMP treatment, would be eligible.

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 VMP or other bortezomib-regimens for newly diagnosed multiple myeloma not eligible for transplant (e.g., CyBorD);
- Patients who recently completely VMP and who have not yet experienced progression.

If switching to DVMP or adding daratumumab to VMP is appropriate in these patients, PAG is seeking guidance on the dosing schedule administered and when in treatment

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daratumumab addition can be considered.

4.3 Implementation Factors

The weekly dosing schedule in the first cycle, the every three weeks in cycle 2 to 9, and the every four weeks thereafter until progression is difficult for many patients, especially those who would have to travel far to and from cancer centres with the resources to administer and monitor daratumumab infusions. The recommended dosing/schedule for newly diagnosed multiple myeloma differs from relapsed or refractory myeloma, PAG noted this may lead to potential dosing errors. PAG noted that processes would need to be in place, prior to implementation of daratumumab, to minimize dosing errors and patient confusion.

PAG is also seeking guidance on the use of a 90 minute daratumumab infusion beginning with the third dose, as this has been adopted in practice in the USA to reduce chair time. PAG noted the dose of bortezomib in the trial is different than the dose in Canadian practice (e.g., given on a once weekly schedule for all cycles) and is seeking guidance on the dose of bortezomib to be used when in combination with daratumumab and the generalizability of the ALCYONE trial to Canadian practice.

As treatment is continued until progression, the unknown duration of treatment is a barrier to implementation for planning resources to deliver and fund the drug.

Additional resources will be required for pre-medication, drug preparation, administration time and monitoring for multiple severe adverse effects including infusion reactions. PAG identified that one to one nurse to patient may be required given the high rate of infusion reactions and the frequency of infusion rate adjustments. As daratumumab interferes with cross-matching for blood transfusions, patients would also need to have RBC phenotyping prior to starting daratumumab. PAG noted that the significantly increased chair time compared to current treatment is a barrier to implementation, given the additional resources needed as well as slower infusion time to reduce the risk of infusion reactions with daratumumab.

PAG noted there in the ALCYONE trial, there was a higher incidence of infections with DVMP. PAG is seeking guidance on the use of G-CSF with DVMP to minimize potential infections and neutropenia.

PAG has concerns for incremental costs due to drug wastage, specifically in centers where vial sharing would be difficult. Although there are two vial sizes available, dosage is based on weight and there will be some drug wastage as any unused portion would be discarded. PAG is seeking guidance on the use of dose rounding (e.g., round within 10% of calculated dose to nearest vial size) as this would minimize drug wastage.
The high cost of daratumumab, as an add-on therapy, is a barrier to implementation.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the optional sequencing of all available therapies for multiple myeloma. For patients who receive DVMP in the first-line setting and then progress,

- What would be the best treatment after progression following DVMP?
- Sequencing of subsequent second- and third-line therapies such as carfilzomib-based regimens (e.g., KRD), Rd, pomalidomide, re-treatment with bortezomib-based regimens.
- Clarity on whether patients would be ineligible for re-treatment with

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daratumumab-based regimens in subsequent lines of therapy.

PAG noted that daratumumab was recently reviewed for the treatment of patients with multiple myeloma who have received at least one prior therapy. PAG is seeking guidance on the optimal use of daratumumab and preference to use daratumumab in the first-line setting or reserve daratumumab for downstream treatment.

For patients who receive the nine cycles of daratumumab in combination with a bortezomib-based regimen followed by daratumumab single-agent, PAG is seeking guidance on the appropriateness of adding a bortezomib-based regimen at relapse to daratumumab.

4.5 Companion Diagnostic Testing

None.

4.6 Additional Information

None.

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5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician inputs were received, representing a total of 8 clinicians. One joint submission from seven clinicians on behalf of the Myeloma Canada Research Network, and input from an individual clinician from Cancer Care Ontario (CCO), contributed to the clinician input on daratumumab in combination with bortezomib, melphalan, and prednisone (DVMP) for transplant-ineligible patients with multiple myeloma (MM). The clinicians reported this combination provides an improvement in tolerability, safety, and effectiveness compared to current treatments. Examples of toxicities associated with DVMP, included infusion or allergic reactions, respiratory infections, cytopenias, and neurotoxicity. Patients with severe renal impairment would be contraindicated for DVMP due to the melphalan component. The clinicians expressed that there is evidence to suggest that cyclophosphamide, bortezomib and dexamethasone (CyBorD) is equivalent to bortezomib, melphalan, and prednisone (VMP) from a response, progression-free survival (PFS), and overall survival (OS) perspective, which is based on real world evidence (RWE) and a phase II trial [LYRA] in the MM patient population. Clinicians preferred the use of CyBorD in place of VMP due to improved tolerability, safety (less toxicities), and compliance (less visits required) for patients, and CyBorD also aligns with current Canadian practices.

Overall, the majority of clinicians agreed DVMP would be used in the first-line setting for the eligible patient population, with the exception of patients who express a preference for oral therapy, or have completed or are currently completing another first-line treatment prior to funding approval of DVMP in the respective province or territory of that patient. The clinicians recommended daratumumab to be used in early lines of treatment only to maximize the benefits and ensure eligibility of patients for this treatment.

Please see below for details from the clinician input(s).

5.1 Current Treatment(s) for this Type of Cancer

The clinicians stated that there are various treatment options available for patients with MM who are ineligible for an autologous stem cell transplant (ASCT) including lenalidomide and dexamethasone (Rd), CyBorD, and VMP. Recent Canadian data suggest that CyBorD and VMP are equivalent efficacy, however, CyBorD has a better toxicity profile. Two clinicians indicated the most appropriate comparator was CyBorD, and one clinician indicated it was CyBorD or VMP. Although there is no head-to-head trial comparing Rd and CyBorD, real world evidence may also suggest equivalency between CyBorD and Rd for overall survival (OS) and slight superiority of Rd for PFS. Two clinicians indicated a preference for first-line treatment with Rd, followed by CyBorD or VMP for first-line treatment. One clinician indicated they would use Rd or VMP for first-line treatment. In Saskatchewan and British Columbia, it was noted funding is only available for Rd or CyBorD. The clinicians reported the choice of first-line treatment would take into consideration tolerability, PFS outcomes, and patient comorbidities. For example, bortezomib-based therapies such as CyBorD or VMP would be used for patients with poor renal function, high-risk cytogenetics, and significant bone marrow suppression. One clinician indicated that in most centres in Ontario, access to cytogenetic results may not be available fast enough before requiring therapy initiation, which may impact treatment choice (e.g., using bortezomib-based therapy for high-risk cytogenetics).

5.2 Eligible Patient Population

There was consensus among the clinicians that the patient population in the request aligns with current needs. One clinician indicated the patient population is not one of an unmet

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need. The trial criteria were deemed applicable to clinical practice, and should be strictly applied given the toxicities associated with VMP (e.g., patients should be fit enough). Although the clinical trial excluded patients with cytopenias, renal impairment, prior cancers, and plasma cell leukemia, the clinicians indicated patients in clinical practice should be eligible for this treatment at the physician's discretion.

There was concern on the uptake of this regimen given CyBorD is more commonly used across the provinces, and VMP is more complicated to administer and is more toxic. The clinicians suggested future work on a per-province basis could evaluate if CyBorD or Rd with daratumumab could be used in place of DVMP.

5.3 Relevance to Clinical Practice

Six clinicians reported having experience with the drug combination under review. One clinician indicated that DVMP would likely replace front line bortezomib-based regimens for the treatment of all patients transplant ineligible. It was also discussed that patients may prefer Rd since it is administered orally, which would offset use of first-line DVMP, but Rd may be offered after relapse as well. However, using it in 3rd or 4th line could seriously reduce the effectiveness of the drug, and thus, was recommended to be used in earlier lines of treatment. Patients who are high-risk, elderly, have renal failure, or are contraindicated to lenalidomide-based therapies are thought to particularly benefit DVMP. One clinician reported the addition of daratumumab to bortezomib-based regimens (i.e. VMP in first line, and bortezomib with dexamethasone in second line and beyond) for MM is well supported by phase 3 and phase 2 data, respectively, and delivers an approximate two-fold increase in PFS. Two clinicians also reiterated the benefits of DVMP in terms of improvements in PFS.

Concerns about the potential for infusion or allergic reactions was expressed with the first infusion of daratumumab, however, it was stated these reactions are rare in Canada as measures to minimize toxicities have been in place. There were also concerns about respiratory infections for patients given daratumumab, however this is an issue Canadian clinicians are aware of to deal with proactively. Increased rates of cytopenias were also cited as a side effect to be aware of. The ability to make dose and schedule adjustments would be required for safety/toxicity reasons, specifically the potential for neurotoxicity, associated with bortezomib. One clinician also expressed the administration of VMP is more complicated, and thus patients should be able to understand the regimen and take the oral treatment as prescribed.

It was noted that there are no absolute contraindications for the addition of daratumumab to VMP. Thus, a patient eligible for VMP would be eligible to receive DVMP.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

All clinicians would use DVMP in first-line treatment for newly diagnosed MM adult patients who are not eligible for ASCT. One clinician reported preference for D-CyBorD followed by second line Rd, or if Rd had been given upfront, it would make sense to confirm availability of daratumumab for addition to second-line proteasome inhibitor-based therapy (e.g., D-Vd, D-CyBorD/DVMP). For patients that prefer drugs that is administered in all oral regimen, Rd would be a first-line treatment option, since DVMP requires patients to come in twice a week for IV administration. Thus, for these patients, second-line DVMP would be considered.

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5.5 Companion Diagnostic Testing

No companion diagnostic testing was identified. The clinicians commented that red blood cell phenotyping should be conducted pre-treatment to avoid any delays in blood transfusions, which many patients with MM will require. Additionally, the DIRA absorption test to determine complete responses accurately is not funded; however, it does not impact treatment decisions.

5.6 Additional Information

No additional information provided.

5.7 Implementation Questions

5.7.1 In regards to question 3.4 above, please consider the optimal sequencing following treatment with DVMP, specifically: re-treatment with daratumumab-based regimens, carfilzomib-based regimens, lenalidomide-dexamethasone, pomalidomide, and/or re-treatment with bortezomib-based regimens. In addition, please also consider the preferred regimen for initial treatment of transplant ineligible patients, and how DVMP compares to other currently available regimens.

The clinicians indicated there are not many treatment options available, however, the majority agreed 2nd line treatment would be Rd. Third line treatment options, depending on the patient, would include pomalidomide and dexamethasone; pomalidomide, bortezomib, and dexamethasone (PVD); carfilzomib, lenalidomide, and dexamethasone (KRd); and ixazomib, lenalidomide, and dexamethasone (IRd). However, it was noted KRd use in elderly patients can be problematic after relapse on a bortezomib-based therapy due to cardiotoxicity and frequency of visits required (patient burden), and there would also be hesitancy to use 2nd line D-Rd (if approved) in elderly patients due to comorbidities.

The clinician group indicated re-treatment with daratumumab-based regimens is not recommended after relapse on first line. If patients stopped first-line daratumumab prior to progression, and there is a compelling case to re-treat for reasons such as tolerability and sensitivity, it could be considered. One clinician indicated re-treatment with a bortezomib-based regimen in the 3rd line setting.

Emerging evidence on D-Rd in front line will likely prove to be the optimal front-line regimen instead of DVMP or D-CyBorD for transplant-ineligible patients in regard to PFS and tolerability in the future.

5.7.2 In clinical practice, would you want to extend the use of daratumumab to other first-line regimens that are standardly used (e.g., weekly bortezomib regimens such as CyBorD, Rd)? If so, are you aware of any evidence of daratumumab use with other regimens?

A preference to use D-CyBorD in place of DVMP was expressed, as using cyclophosphamide instead of melphalan, and bortezomib once weekly rather than twice weekly, produces less toxicities (e.g., peripheral neuropathy, myelosuppression, cytopenia), is less leukemogenic, and is easier to dose in patients with poor bone marrow reserve and/or with renal compromise. Although grade 3-4 rates of neuropathy with twice weekly VMP are low,

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grade 2 neuropathy can drastically impair quality of life, may be painful, and often necessitates holding bortezomib. There is RWE of transplant-ineligible newly diagnosed MM patients that showed weekly CyBorD produces similar PFS and OS as VMP, despite patients on CyBorD having higher International Staging System and renal insufficiency. There is phase II evidence [LYRA] to support D-CyBorD, which is deemed reasonable to support the use of this combination on the grounds of maximizing tolerability, patient compliance (convenient schedule), and safety. The available research does not indicate any significant toxicity associated with D-CyBorD. Additionally, it aligns with current practices in Canada.

There is emerging data from a phase III trial, the MAIA trial, on D-Rd, which supports better PFS and tolerability. Five clinicians expressed interest to use D-Rd in the first-line when the data from this trial is available. Reasons for this preference included that D-Rd is easy to prescribe, well tolerated, and patients have better results (i.e. PFS) based on preliminary data compared to DVMP. One clinician additionally noted daratumumab has been combined with other MM regimens in phase I-II studies including lenolidomide, bortezomib, and dexamethasone (RVd); bortezomib, thalidomide, dexamethasone (VTd); and pomalidomide and dexamethasone (in relapsed disease). Additionally, DRd; Vd; and Kd in phase III studies with relapsed patients. There were no toxicity concerns from the results of all these studies on daratumumab combinations, and the phase III studies were reported to have better response rate, minimal residual disease, and PFS associated with the daratumumab combinations.

5.7.3 In clinical practice, if daratumumab was available, would your preference be to use daratumumab in the first-line setting or reserve daratumumab for downstream treatment for relapsed/refractory myeloma?

There was consensus among the clinicians that daratumumab would be used in first-line, and at most, in second-line, as the benefits of daratumumab were stated to be maximized in earlier lines of treatment and patients may not be able to receive a second-line treatment. One clinician commented there would be modest use of DVMP in first line, despite the inconvenience of infusions. There would still be a population of patients who require or prefer an oral regimen as first-line, or have a contraindication to bortezomib. Therefore, these patients would be considered for use of daratumumab as a later line of treatment.

5.7.4 How do you foresee the use of daratumumab in patients who are currently on lenalidomide-dexamethasone in the 1st-line setting and not eligible for transplant?

All clinicians would use daratumumab in patients currently on Rd, and would generally prescribe as second line. There was variation in responses on what daratumumab-based therapy would be used in second line. Some options included daratumumab, bortezomib, and dexamethasone (D-Vd), D-CyBorD, DVMP, or D-Rd (if approved) for this group of patients.

5.7.5 Is bortezomib maintenance starting with cycle 10 in combination with daratumumab recommended in this patient setting?

Clinicians indicated there is evidence from two phase III studies with extended duration of bortezomib within a VMP regimen, and bortezomib within a VMP and thalidomide regimen, which showed a statistically significant better PFS. A meta-analysis also demonstrated an advantage of continuous bortezomib rather than fixed-duration in patients with MM. Additionally, high-risk patients were stated to potentially benefit from continuing bortezomib,

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as well as ensuring that when patients progressed and became refractory, it could be considered refractory due to both agents. Thus, re-treatment using one or the other agent could be discounted. Of the three clinicians that did not recommend bortezomib maintenance, reasons included insufficient data to support bortezomib maintenance, and that daratumumab is considered the "maintenance" agent and is better tolerated, and thus would discontinue bortezomib as per the trial. One clinician did not know if bortezomib maintenance could be recommended in this patient setting.

5.7.6 For patients demonstrating biochemical relapse without overt CRAB criteria progression on single-agent daratumumab (i.e. after the completion of 9 cycles of DVMP), would there be interest to add bortezomib back to daratumumab or switch to an alternate agent?

Clinicians that were in agreement to add bortezomib commented that it would depend on whether the patient had a reasonable response to previous bortezomib, and if there was evidence of any bortezomib-related toxicity or refractoriness during the prior 9 cycles. Furthermore, adding bortezomib in this setting would likely delay CRAB progression and use daratumumab to maximum efficacy. One clinician in favour of adding bortezomib suggested using the national Myeloma Canada Research Network database to determine the efficacy of this approach and to determine whether or not it is extending the benefit of daratumumab. Three clinicians indicated they would switch to alternate agents, as data to support the use of bortezomib beyond 9 cycles as per the trial is insufficient. An alternate treatment that was suggested was a proteasome inhibitor-based regimen as patients would not necessarily be resistant to this class based on how the DVMP regimen is used.

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6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the safety and effect of Daratumumab in combination with bortezomib, melphalan, and prednisone (DVMP) compared to bortezomib in combination with melphalan and prednisone, (VMP) for the treatment of patients with newly diagnosed multiple myeloma (MM) who are not suitable for autologous stem cell transplant. The selection criteria table is presented in Section 6.2.1.

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 and section 8.

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 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 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention ‡	Appropriate Comparators*	Outcomes
Published or unpublished RCTs, conference abstracts, posters	Patients with newly diagnosed MM who are not suitable for autologous stem cell transplant	In a 6-week cycle dosing regimen, recommended dose of Daratumumab is 16mg/kg body weight administered intravenously over weeks 1 to 6, weeks 7 to 54 and week 55 onwards until disease progression. Bortezomib 1.3mg/m^2 BSA subcutaneous injection in cycle 1, cycle 2 to 9	Bortezomib in combination with melphalan and prednisone (VMP) Bortezomib, cyclophosphamide and dexamethasone (CyBorD) Lenalidomide and dexamethasone	▪ **Progression Free Survival (PFS)** ▪ Overall Response Rate (ORR) ▪ Very Good Partial Response (VGPR) or better rate ▪ Complete Response (CR) or better (i.e. complete and stringent complete responses) ▪ Negative Minimal Residual Disease (MRD) ▪ **Overall Survival (OS)**

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Clinical Trial Design	Patient Population	Intervention ‡	Appropriate Comparators*	Outcomes
		Melphalan 9mg/m2 per oral and prednisone 60mg/ m2 days 1 to 4 of each bortezomib cycle		▪ Safety and tolerability ▪ patient reported quality of life ▪ time required for daratumumab infusion ▪ Secondary malignancies
RCT: Randomized Control Trial; MM: Multiple Myeloma; BSA: body surface area				
‡Dosages listed are according to the trial and may be adjusted				

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

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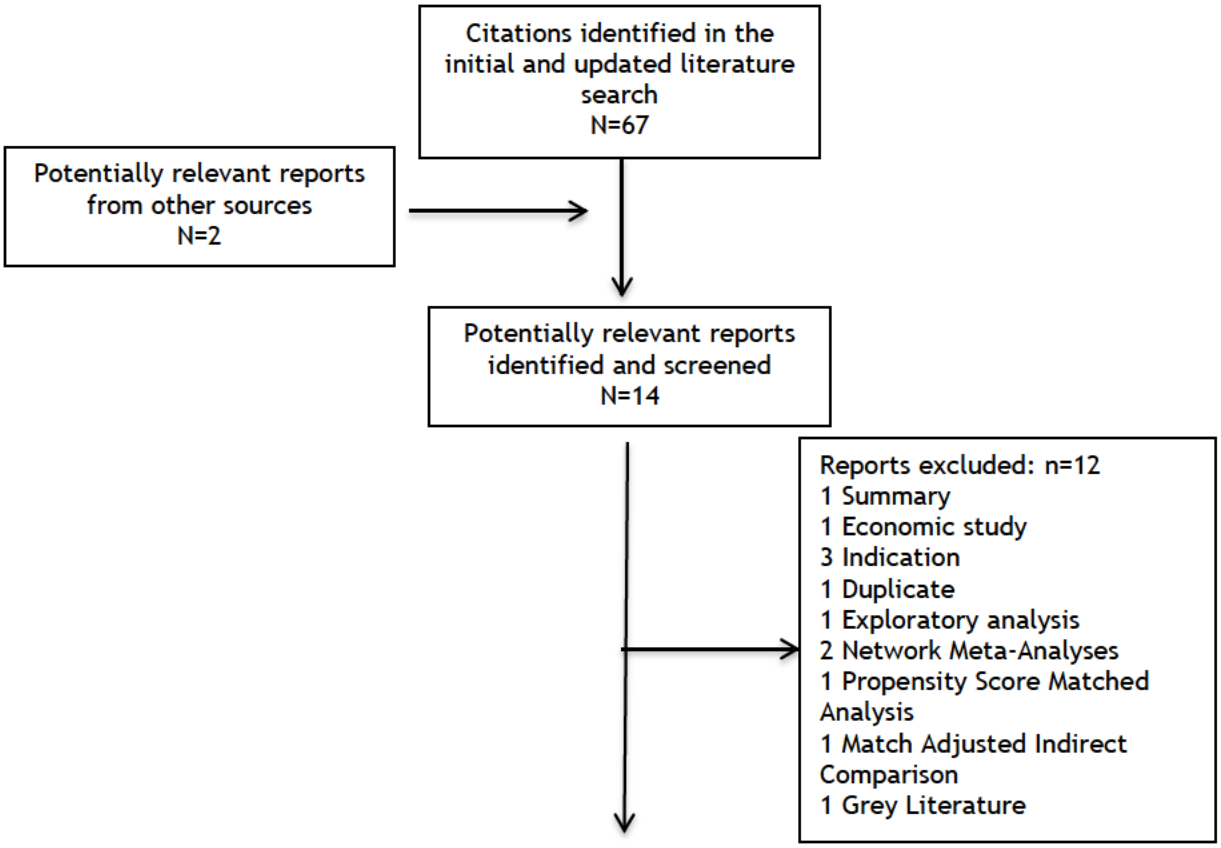
6.3 Results

6.3.1 Literature Search Results

Among the 67 potentially relevant reports identified by the search, 5 reports presenting data from ALCYONE trial were identified. The ALCYONE trial (NCT02195479) data are reported. There were 5 articles excluded and the reasons are outlined in Figure 1.

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



2 reports met the inclusion criteria:
Mateos 2018[2]
Gries 2018[37]
Clincaltrial.gov NCT02195479
Clincaltrial.gov NCT03217812

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6.3.2 Summary of Included Studies

One clinical trial (ALCYONE trial) was included in this systematic review. The key characteristics of this trial are summarized in table 4.

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
ALCYONE trial (NCT02195479) Phase III multicenter 1:1 randomized, open-label, active-controlled trial N=706 (Enrolment between February 9, 2015 to July 14, 2016) 162 sites in 25 countries across North and South America, Europe, and the Asia-Pacific region Clinical cut-off date: June 12, 2017 (second interim) Funded by Janssen Research and Development and designed it in collaboration with the academic authors	<u>Key Inclusion Criteria:</u> • patients were eligible for enrollment if they had newly diagnosed, documented MM who were NOT eligible for stem cell transplantation owing to coexisting conditions or an age of 65 years or older • hemoglobin level of 7.5 g or more per deciliter, • an absolute neutrophil count of 1.0×109 or more per liter, • aspartate aminotransferase and alanine aminotransferase levels of 2.5 or fewer times the upper limit of the normal range, • a total bilirubin level of 1.5 or fewer times the upper limit of the normal range, • a creatinine clearance of 40 ml or more per minute, • a corrected serum calcium level of 14 mg or less per deciliter (≤3.5 mmol per liter), • a platelet count of 70×109 or more per liter (if <50% of bone marrow nucleated	<u>Intervention</u> In a 6-week cycle dosing regimen, recommended dose of Daratumumab is 16mg/kg body weight administered intravenously over weeks 1 to 6, weeks 7 to 54 and week 55 onwards until disease progression. Bortezomib 1.3mg/m2 BSA subcutaneous injection in cycle 1, cycle 2 to 9 Melphalan 9mg/m2 per oral and prednisone 60mg/ m2 days 1 to 4 of each bortezomib cycle <u>Comparators</u> Bortezomib in combination with melphalan and	<u>Primary:</u> ▪Progression Free Survival (PFS) <u>Secondary:</u> ▪ Overall Response Rate (ORR) ▪ Very Good Partial Response (VGPR) or better rate ▪ Complete Response (CR) or better (i.e. complete and stringent complete responses) ▪ Negative Minimal Residual Disease (MRD) ▪ Overall Survival (OS) ▪ Safety and tolerability ▪ Quality of life

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Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	cells were plasma cells; otherwise, platelet count of >50×109 per liter), and • an Eastern Cooperative Oncology Group performance status of 0 to 2 (on a 5-point scale, with higher numbers indicating greater disability). <u>Key Exclusion Criteria:</u> • patients with primary amyloidosis, monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, Waldenström's macroglobulinemia (or other conditions in which IgM paraprotein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions), previous systemic therapy or stem-cell transplantation, cancer within 3 years before randomization (exceptions were squamous cell and basal-cell carcinomas of the skin, carcinoma in situ of the cervix, and any cancer	prednisone (VMP)	

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Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	that was considered to be cured with minimal risk of recurrence within 3 years), peripheral neuropathy, or grade 2 or higher neuropathic pain (as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE],version 4).		

Table 5: Select characteristics of included studies of Daratumumab in combination with Bortezomib, melphalan and prednisone (DVMP) in patients with newly diagnosed multiple myeloma (NDMM)

Study	ALCYONE trial
Treatment vs. Comparator	DVMP vs VMP
Primary outcome	PFS
Required sample size	A sample size of 350 patients per group (under the assumption of an annual dropout rate of 5%) was estimated to provide 85% power to detect a 27.6% lower risk of progression free survival or death in the DVMP group than in the VMP group, with the use of a log-rank test with a two-sided alpha level of 0.05[2]
Sample size	350 vs. 356
Randomization method	Stratified according to ISS disease, stages are determined on the basis of albumin and 2-microglobulin levels, geographic region (Europe vs. other), and age (<75 years vs. 75 years)
Allocation concealment	Study investigators were unaware what the next treatment allocation would be as an interactive web-based randomization system was used[38]
Blinding	Treatment assignments were not blinded[2]
ITT Analysis	Yes
Final analysis	The final overall survival analysis will occur after 330 deaths[3]
Ethics Approval	Yes

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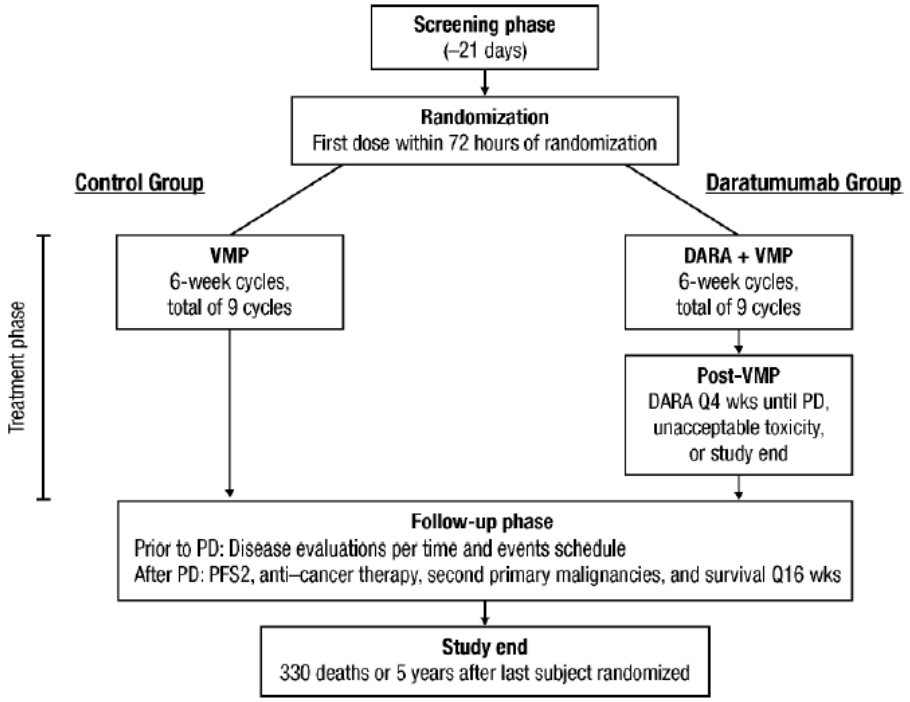
DVMP: Daratumumab plus bortezomib, melphalan and prednisone combination, VMP: Bortezomib, melphalan and prednisone combination; PFS: progression-free survival, ISS: International Staging System

a) Trials

One randomized, open-label, active-controlled phase 3 trial (ALCYONE trial) met the inclusion criteria. ALCYONE trial was funded by Janssen Research and Development and in collaboration with academic authors, contributed to the design. The aim of this trial was to examine the effect and safety of adding daratumumab to VMP (DVMP) compared to VMP alone in patients with newly diagonsed MM. The ALCYONE trial enrolled 706 patients from 25 countries across North and South America, Europe, and the Asia–Pacific region in 162 sites. An interactive Web-response system (IWRS) was used to randomly assign patients in a 1:1 ratio to DVMP or VMP alone.[2] The IWRS was used to assign a unique treatment code, which dictated the treatment assignment and matching study treatment for the subject.[39] Randomization was stratified according to the International Staging System (ISS) disease stage (I, II, or III, with higher stages indicating a poorer prognosis, stages are determined on the basis of albumin and β2-microglobulin levels), geographic region (Europe vs. other), and age (<75 years vs. ≥75 years). Treatment assignments were not blinded.[2] Figure 1 illustrates the study design.

Figure 1. Study design[2]



Source: From Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma, Mateos et al., 378:518-28. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Abbreviations: VMP, bortezomib, melphalan, and prednisone; DARA, daratumumab; Q4 wks, every 4 weeks; PD, progressive disease; PFS2, progression-free survival on the next line of therapy; Q16 wks, every 16 weeks.

The Independent Data Monitoring Committee (IDMC) reviewed data for both preplanned interim analyses and continued to monitor safety data at regular 6-month intervals during the study.[3] There were two planned interim analyses. The first interim analysis assessed only safety after 100 patients had received at least two treatment cycles (12 weeks) or had discontinued treatment. According to the submitter in the interim analysis, in order to reach statistical significance, a minimum of 216 progression-free survival events, representing 60% of planned events, would need to be accumulated which was observed at a median follow-up of 16.5 months.[10] The second interim analysis assessed cumulative safety and efficacy when approximately 231 events of disease progression or death had occurred (i.e., 64% of the planned 360 events for the final analysis; an alpha of 0.0103 was spent) at a median follow-up of 16.5 months.[3] The final overall survival analysis will occur after 330 deaths.[3]

A third analysis was conducted following the second interim analysis to provide one year of additional follow-up with a median follow-up of 27.8 months.[3]

The primary efficacy endpoint of ALCYONE was progression-free survival defined as the duration from the date of randomization to either progressive disease or death, whichever came first. Disease progression was defined in accordance with the International Myeloma Working Group criteria.[2]

If PFS is deemed statistically significant, the following secondary outcomes including overall response rate, very good partial response or better rate, complete response or better rate, minimum residual disease negativity rate and overall survival will be sequentially tested adopting a hierarchical testing approach.[40]

The key secondary outcomes are defined below:

Overall response rate was defined as the proportion of patients who achieved partial response or better, according to the International Myeloma Working Group criteria, during or after the study treatment.[2]

Complete response rate was defined as the percentage of patients achieving complete response, as defined by a negative immunofixation of serum and urine, the disappearance of any soft-tissue plasmacytomas, and <5% plasma cells in the bone marrow. For those patients with a negative or low serum protein electrophoresis (≤0.2 g/L) and suspected daratumumab interference on immunofixation, a reflex assay with anti-idiotype antibody was used to confirm daratumumab interference and rule out a false-positive immunofixation. Patients who had confirmed daratumumab interference but met all other clinical criteria for stringent complete response or complete response were considered to have achieved stringent complete response or complete response.[2]

Minimal residual disease (MRD) was assessed by the Adaptive clonoSEQ® Assay (version 2.0; Adaptive Biotechnologies, Seattle, WA, USA). Based on time points specified in the protocol, aspirate samples were examined. MRD–negativity rate was defined as the proportion of patients who were negative for MRD at any time point after randomization. For analysis purposes, patients in the intention to-treat population without MRD assessment were considered as having positive MRD.[2]

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Time to response was defined as the time between randomization and the first efficacy evaluation in which the patient had met all criteria for partial response or better. For patients without a response, data were censored either at the date of progressive disease or, in the absence of progressive disease, at the last disease evaluation before the start of subsequent antimyeloma treatment.[2]

Duration of response was calculated from the date of initial documentation of a response (partial response or better) to the date of the first documented evidence of progressive disease. This was defined according to the International Myeloma Working Group criteria. For patients who had not progressed, data were censored at the last disease evaluation before the start of any subsequent antimyeloma therapy.[2]

Overall survival was defined as the time from randomization to the date of the patient's death. If the patient remained alive or their status was unknown, then the patient's data were censored at the date the patient was last known to be alive.[2]

Additional endpoints included patient-reported outcomes assessed using the European Organization for Research and Treatment of Cancer (EORTC) –QLQ-C30 questionnaire, EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L) questionnaire and health resource utilization.[2]

a) ***Populations***

ALCYONE randomized 350 patients to the DVMP group and 356 patients to the VMP group.[2] The baseline characteristics were well balanced in the DVMP and VMP groups with a median age of 71 years in both the DVMP and VMP groups. The patient demographics and baseline disease characteristics in the intention-to-treat population are presented in Table 6.[2]

Table 6: Patient demographics and baseline disease characteristics in the intention-to-treat population[2]

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Characteristic	Daratumumab Group (N = 350)	Control Group (N = 356)
Age		
Median (range) – yr	71.0 (40–93)	71.0 (50–91)
Distribution – no. (%)		
<65 yr	36 (10.3)	24 (6.7)
65-74 yr	210 (60.0)	225 (63.2)
≥75 yr	104 (29.7)	107 (30.1)
Race – no. (%)		
White	297 (84.9)	304 (85.4)
Black	3 (0.9)	3 (0.8)
Asian	47 (13.4)	45 (12.6)
Other or unreported	3 (0.9)	4 (1.1)
ECOG performance status – no. (%)†		
0	78 (22.3)	99 (27.8)
1	182 (52.0)	173 (48.6)
2	90 (25.7)	84 (23.6)
Type of measurable disease – no. (%)		
IgG	143 (40.9)	140 (39.3)
IgA	49 (14.0)	53 (14.9)
Other‡	6 (1.7)	3 (0.8)
Detected in serum and urine	91 (26.0)	105 (29.5)
Detected in urine only	43 (12.3)	37 (10.4)
Detected in serum free light chains only	18 (5.1)	18 (5.1)
ISS disease staging – no. (%)§		
I	69 (19.7)	67 (18.8)
II	139 (39.7)	160 (44.9)
III	142 (40.6)	129 (36.2)
Cytogenetic profile – no. (%)¶		
Standard-risk cytogenetic abnormality	261/314 (83.1)	257/302 (85.1)
High-risk cytogenetic abnormality#	53/314 (16.9)	45/302 (14.9)
Median time since initial diagnosis of multiple myeloma (range) – mo	0.76 (0.1–11.4)	0.82 (0.1–25.3)**

Source: From Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma, Mateos et al., 378:518-28. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

* The intention-to-treat population was defined as all patients who underwent randomization.
† Eastern Cooperative Oncology Group (ECOG) performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability.
‡ Includes IgD, IgM, IgE, and biclonal.
§ The International Staging System (ISS) disease stage is derived on the basis of the combination of serum ß2-microglobulin and albumin levels. Higher stages indicate more severe disease. 17
¶ Cytogenetic risk based on fluorescence in situ hybridization or karyotype testing. Cytogenetic data assessed by next-generation sequencing for the total intention-to-treat population were not available at the data cutoff date, and analysis is ongoing.
# Subject may have had at least one high-risk abnormality [del17p, t(4;14), or t(14;16)].
** At the time of initial diagnosis, the subject with median time since initial myeloma diagnosis of 25.3 months did meet IMWG diagnostic criteria for multiple myeloma with hemoglobin <10

g/dL and bone marrow plasma cells ≥10%. A decision was made by the physician not to initiate treatment at the time of diagnosis. The patient's disease was stable and actively monitored until treatment was begun at a later date.

b) Interventions

Treatment assignments were not blinded.[2] Patients received up to nine (42-day) cycles.[2] Bortezomib was administered subcutaneously (1.3 mg per square meter of body-surface area, twice weekly on weeks 1, 2, 4, and 5 of cycle 1 and once weekly on weeks 1, 2, 4, and 5 of cycles 2 through 9). Oral melphalan (9 mg per square meter) and oral prednisone (60 mg per square meter) were provided to patients once daily on days 1 through 4 of each cycle. In the DVMP group, intravenous daratumumab at a dose of 16 mg per kilogram of body weight was administered and the route of dexamethasone was either oral or intravenous (to manage infusion reactions) at a dose of 20 mg once weekly in cycle 1, every 3 weeks in cycles 2 through 9, and every 4 weeks until there was disease progression or side effects. Dexamethasone at a dose of 20 mg was substituted for prednisone on day 1 of each cycle.[2]

c) Patient Disposition

Table 7: *Patient Disposition*

Category	DVMP Group, n	VMP Group, n
Randomized	**350**	**356**
Received treatment	**346**	**354**
Discontinued	**Cycles 1-9: 67 Cycles 10+: 33**	**117**
Withdrawals due to progressive disease	**Cycles 1-9: 23 Cycles 10+: 30**	**47**
Withdrawals due to adverse events	**Cycles 1-9: 17 Cycles 10+: 0**	**33**
Withdrawals due to death	**Cycles 1-9: 11 Cycles 10+: 2**	**8**
Withdrawals due to other reasons	**Cycles 1-9: 16 Cycles 10+: 1**	**29**

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d) Limitations/Sources of Bias

Since treatment assignment was not blinded, this introduces potential bias as participants may have been aware of which treatment was received. According to clinician input, patients who are ≥70 years of age are considered transplant-ineligible in Canada, whereas the ALCYONE trial considered patients who were ≥65 years old to be transplant-ineligible.[2]

Overall, the ALCYONE trial used VMP as a treatment comparator whereas CyBorD is the current treatment of choice in Canada for patients with NDMM that are transplant ineligible. In addition, the relevant comparator of Rd-continuous was not included in the ALCYONE trial.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Progression Free Survival (PFS)

At a median follow-up of 16.5 months (clinical data cut-off: June 12, 2017), the risk of disease progression or death in the DVMP group was 50% lower compared to the VMP group (hazard ratio [HR]= 0.50, 95% confidence interval [CI] 0.38 - 0.65; P<0.001).[2]

Table 8. Kaplan–Meier estimate of the 12-month, 18-month, 24-month and 30-month rate of progression free survival in the ITT analysis[3]

PFS Measure	DARZALEX® Group (DVMP) (N = 350)		Control Group (VMP) (N = 356)
Number of events, no (%)	134 (38.3)		223 (62.6)
Median, months (95% CI)	NE (32.2-NE)		19.1 (17.9-20.4)
HR (95% CI)[a]		0.43 (0.35-0.54)	
p-value[b]		<0.0001	
18-month PFS rate, % (95% CI)	73.2 (68.1-77.6)		55.0 (49.4-60.3)
24-month PFS rate, % (95% CI)	63.0 (57.5-67.9)		36.2 (30.9-41.6)
30-month PFS rate, % (95% CI)	59.9 (54.2-65.1)		27.9 (22.5-33.5)
36-month PFS rate, % (95% CI)	56.4 (49.6-62.5)		NE (NE, NE)

CI = confidence interval; DVMP = daratumumab-bortezomib-melphalan-prednisone; NE = not evaluable; PFS = progression-free survival; VMP = bortezomib-melphalan-prednisone

[a] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS (I, II, or III), region (Europe vs Other) and age (<75 years vs ≥75 years) as randomised. A hazard ratio <1 indicates an advantage for DVMP.

[b] p-value is based on the log-rank test stratified with ISS (I, II, or III), region (Europe vs Other) and age (<75 years vs ≥75 years) as randomised.

After 231 events of disease progression (64% of the planned 360 events for the final analysis), an interim analysis of median progression free survival (PFS) was performed. The results of the analysis passed the prespecified stopping boundary. NE denotes could not be estimated.[2]

At median follow-up of 27.8 months (clinical data cutoff June 12, 2018), the risk of disease progression or death in the DVMP group was 57% lower compared to the VMP group (HR 0.43, 95% CI 0.35-0.54; P<0.001).[41] Figure 3 displays the Kaplan–Meier estimate in the intent-to-treat analysis set, median follow-up 27.8 months of PFS.[3]

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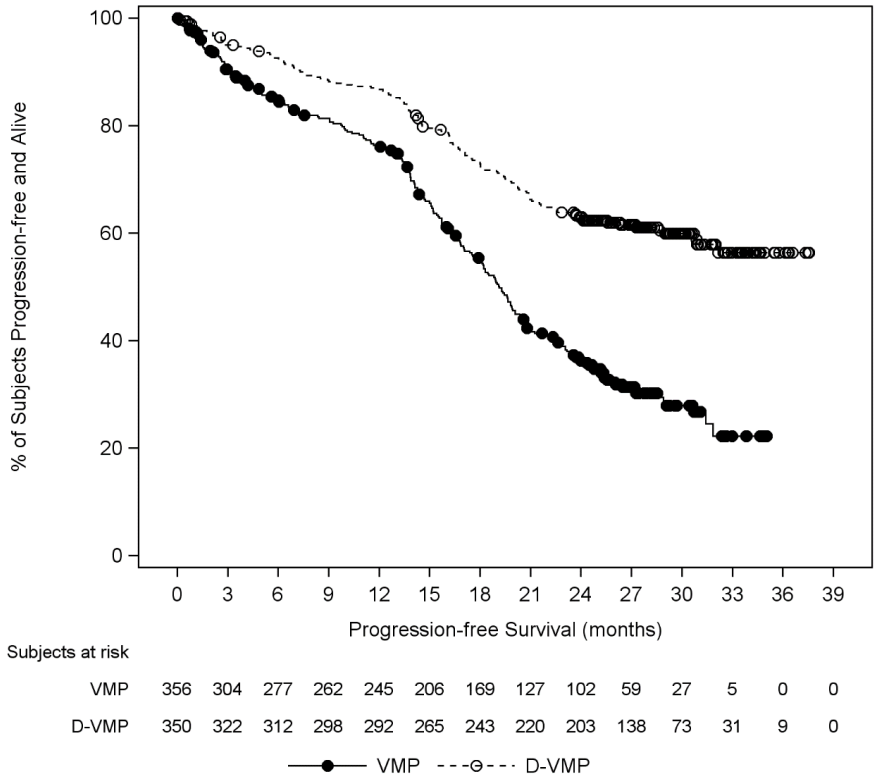
Figure 3. Kaplan–Meier Plot in the intent-to-treat analysis set, median follow-up 27.8 months of progression free survival[3]



Subgroup analyses of PFS were conducted on the following prespecified groups: patients 75 years of age or older and those with a poor prognosis (ISS disease stage III renal impairment, or high-risk cytogenetic profile). Among patients with a high-risk cytogenetic profile and standard-risk cytogenetic profile, there was a 32% and 61% lower risk of disease progression respectively in favour of patients randomized to the DVMP group compared to VMP group at a median follow-up of 27.8 months. However, the results should be interpreted with caution due to small number of patients with a high-risk cytogenetic profile.[3] See figure 4 for full details.

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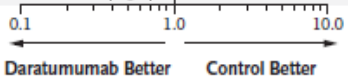
Figure 4. Prespecified Subgroup Analysis of Progression Free Survival[2]

Subgroup	Daratumumab Group	Control Group	Daratumumab Group	Control Group	Hazard Ratio (95% CI)
	no. of progression events or deaths/total no.		*median progression-free survival (mo)*		
Sex					
Male	50/160	68/167	NE	18.1	0.60 (0.42–0.87)
Female	38/190	75/189	NE	17.9	0.41 (0.28–0.61)
Age					
<75 yr	60/246	101/249	NE	17.9	0.49 (0.36–0.68)
≥75 yr	28/104	42/107	NE	20.4	0.53 (0.32–0.85)
Race					
White	79/297	121/304	NE	18.1	0.56 (0.42–0.74)
Other	9/53	22/52	NE	16.8	0.26 (0.12–0.57)
Geographic region					
Europe	80/289	121/295	NE	18.1	0.57 (0.43–0.76)
Other	8/61	22/61	NE	17.5	0.22 (0.10–0.50)
Baseline creatinine clearance					
≤60 ml/min	32/150	63/145	NE	16.9	0.36 (0.24–0.56)
>60 ml/min	56/200	80/211	NE	18.3	0.63 (0.45–0.88)
Baseline hepatic function					
Normal	73/301	115/303	NE	19.1	0.53 (0.40–0.71)
Impaired	15/46	28/52	NE	13.5	0.42 (0.22–0.80)
ISS disease stage					
I	12/69	18/67	NE	19.4	0.50 (0.24–1.05)
II	35/139	70/160	NE	17.5	0.49 (0.32–0.73)
III	41/142	55/129	NE	16.8	0.53 (0.35–0.79)
Type of multiple myeloma					
IgG	51/207	93/218	NE	17.4	0.45 (0.32–0.64)
Non-IgG	26/82	29/83	NE	NE	0.81 (0.48–1.37)
Cytogenetic profile at trial entry					
High risk	24/53	19/45	18.0	18.1	0.78 (0.43–1.43)
Standard risk	54/261	108/257	NE	17.4	0.39 (0.28–0.55)
ECOG performance status					
0	14/78	35/99	NE	19.4	0.40 (0.21–0.74)
1 or 2	74/272	108/257	NE	17.6	0.52 (0.39–0.70)



Source: From Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma, Mateos et al., 378:518-28. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Overall Response Rate (ORR)

The overall response rate (ORR) reported appeared high in the DVMP group (90.9%) and 73.9% in the VMP group (odds ratio = 3.55, 95% CI: 2.30-5.49, p<0.0001). There was a statistically significant difference in very good partial response or better in favour of the DVMP group than in the VMP group (72.9% vs. 49.7%, P<0.001). Similarly, for the rate of complete response or better, there was a statistically significant difference in favour of the DVMP group than in the VMP group at a median follow-up of 27.8 months (45.1% vs. 25.3%, P<0.001).[3]

Minimum Residual Disease (MRD)

Negative status for MRD was associated with longer progression-free survival than positive status, irrespective of trial treatment. In patients with persistent MRD, progression-free survival was reported as longer in the DVMP group than in the VMP group.[2] The odds of MRD negativity was 5 times higher in DVMP patients compared with VMP patients (DVMP=27.4%, VMP=7.0%; odds ratio = 5.01, 95% CI: 3.13-8.03, p<0.0001).[3]

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Duration of Response

The estimated percentage of patients who continued to have a response after 18 months was 77.2% in the DVMP group and 60.4% in the VMP group.[3]

The median duration of response was not reached (95% CI, could not be estimated) in the DVMP group and 21.1 months (95% CI, 18.4 to 24.5) in the VMP group at a median follow-up of 27.8 months.[3]

Table 9. Results for duration of response for patients treated with DVMP compared with VMP at median follow-up 27.8 months[3]

Duration of Response Measure	DARZALEX© Group (DVMP) (N = 350)	Control Group (VMP) (N = 356)
Responders (partial response or better) in the response-evaluable set	318	263
Number of events, no (%)	97 (30.5)	141 (53.6)
Median, months (95% CI)	NE (NE-NE)	21.1 (18.5-24.5)

CI = confidence interval; DVMP = daratumumab-bortezomib-melphalan-prednisone; NE = not estimable; PR = partial response; VMP = bortezomib-melphalan-prednisone

Overall Survival(OS)

At a median follow-up of 16.5 months, death was reported in 45 patients in the DVMP group and 48 patients in the VMP group.[2] The median OS was not reached in patients randomized to DVMP or VMP group at a median follow-up of 16.5 months and median follow-up of 27.8 months. There were [redacted] deaths in the DVMP group compared to [redacted] deaths in the VMP group with a total of [redacted] deaths. (*Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this safety information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed.*) There was a [redacted] reduction in risk of death among patients that received DVMP compared to VMP at a median follow-up of 27.8 months (HR = [redacted]).[3] (*Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this safety information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed.*)

Figure 5. Kaplan–Meier Plot in the intent-to-treat analysis set, median follow-up 27.8 months of overall survival[3]

(*Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this safety information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed.*)

Quality of Life

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EQRTC QLQ-C30) was administered on patients using an electronic site tablet device at baseline (cycle 1, day 1), month 3, month 6, month 9, and month 12 during treatment then every 6 months until disease progression. Patients were

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asked to recollect on the past week based on the following scales: physical, role, emotional, cognitive, and social functioning, global health status (GHS), pain, fatigue, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. Scores ranged from 0 to 100 with higher scores representing better HRQoL (GHS), better functioning, and more/worse symptomology.
There was moderately higher compliance of EQRTC QLQ-C30 observed in patients receiving DVMP compared to VMP during treatment.[3]

From baseline to follow-up at 3 months, Gries et al[42] reported there was a statistically significant mean difference reported for the EORTC QLQ-C30 GHS subscale in favour of DVMP of 7.6 (95% CI: 5.3 -9.8) compared to VMP 4.1 (95% CI: 1.8- 6.5) for VMP (p=0.0265); there was no statistically significant mean difference observed between baseline and 6, 9 and 12 months.

Similarly, there was a meaningful improvement from baseline in physical functioning, pain, and fatigue symptom scales achieved.

Regarding the EQ-5D-5L VAS, there was statistically significant differences in the mean change from baseline to follow-up at 3 months in patients that received DVMP 6.8 [95% CI: 4.9- 8.7] and patients that received VMP: 3.7 [95% CI: 1.7- 5.7]; p=0.0151).[3]

Safety Outcomes

Overall, adverse events were balanced in the DVMP and VMP group.[2] The most common grade 3-4 adverse events were neutropenia (39.9% and 38.7%), thrombocytopenia (34.4% and 37.6%), and anemia (15.9% and 19.8%).[2] Table 10 shows the most common adverse events during treatment in the safety population.

Table 10: Most common adverse events during treatment in the safety population*[2]

Event	DVMP Group (n=346)				VMP Group (n=354)	
	Any Grade		Grade 3 or 4		Any Grade`	Grade 3 or 4
	Cycles 1-9	All Cycles	Cycles 1-9	All Cycles	All Cycles	All Cycles
Common hematologic adverse events - no. (%)						
Neutropenia	172 (49.7)	172 (49.7)	138 (39.9)	138 (39.9)	186 (52.5)	186 (38.7)
Thrombocytopenia	169 (48.8)	169 (48.8)	119 (34.4)	119 (34.4)	190 (53.7)	133 (37.6)
Anemia	94 (27.2)	97 (28.0)	53 (15.3)	55 (15.9)	133 (37.6)	70 (19.8)
Common nonhematologic						

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Event	DVMP Group (n=346)				VMP Group (n=354)	
adverse events - no. (%)						
Peripheral sensory neuropathy	97 (28.0)	98 (28.3)	5 (1.4)	5 (1.4)	121 (34.2)	14 (4.0)
Upper respiratory tract infection	84 (24.3)	91 (26.3)	6 (1.7)	7 (2.0)	49 (13.8)	5 (1.4)
Diarrhea	81 (23.4)	82 (23.7)	9 (2.6)	9 (2.6)	87 (24.6)	11 (3.1)
Pyrexia	80 (23.1)	80 (23.1)	2 (0.6)	2 (0.6)	74 (20.9)	2 (0.6)
Nausea	70 (20.2)	72 (20.8)	3 (0.9)	3 (0.9)	76 (21.5)	4 (1.1)
Pneumonia	50 (14.5)	53 (15.3)	38 (11.0)	39 (11.3)	17 (4.8)	14 (4.0)
Secondary primary malignancy -no. (%)†	NA	8 (2.3)	NA	NA	9 (2.5)	NA

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* The safety population included all patients who received at least one dose of trial treatment. Adverse events of any grade that were reported in at least 20% of patients in either treatment group and grade 3 or 4 adverse events that were reported in at least 10% of patients in either treatment group for all treatment cycles are listed. NA denotes not applicable.
† The presence of a second primary malignancy was prespecified in the statistical analysis plan as an adverse event of clinical interest.

Data cut-off: June 12, 2017

Table 11. Most Common (At Least 5%) Grade 3 or 4 Treatment-Emergent Adverse Events by MedRA System Organ Class, Preferred Term and Maximum Toxicity Grade; Safety Analysis Set

	VMP			D-VMP		
	Total n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)	Grade 3 n (%)	Grade 4 n (%)
Analysis set: safety	354			346		
Total number of subjects with toxicity grade 3 or 4 TEAE	273 (77.1%)	184 (52.0%)	89 (25.1%)	268 (77.5%)	187 (54.0%)	81 (23.4%)
MedDRA system organ class / preferred term						
Blood and lymphatic system disorders	219 (61.9%)	145 (41.0%)	74 (20.9%)	209 (60.4%)	149 (43.1%)	60 (17.3%)
Neutropenia	137 (38.7%)	104 (29.4%)	33 (9.3%)	138 (39.9%)	106 (30.6%)	32 (9.2%)
Thrombocytopenia	133 (37.6%)	82 (23.2%)	51 (14.4%)	119 (34.4%)	84 (24.3%)	35 (10.1%)
Anaemia	70 (19.8%)	67 (18.9%)	3 (0.8%)	55 (15.9%)	53 (15.3%)	2 (0.6%)
Leukopenia	30 (8.5%)	23 (6.5%)	7 (2.0%)	28 (8.1%)	22 (6.4%)	6 (1.7%)
Lymphopenia	22 (6.2%)	13 (3.7%)	9 (2.5%)	26 (7.5%)	18 (5.2%)	8 (2.3%)
Infections and infestations	52 (14.7%)	46 (13.0%)	6 (1.7%)	80 (23.1%)	73 (21.1%)	7 (2.0%)
Pneumonia	14 (4.0%)	13 (3.7%)	1 (0.3%)	39 (11.3%)	38 (11.0%)	1 (0.3%)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: TEAE = treatment-emergent adverse event.
Note: Adverse events are reported using MedDRA version 20.0.
Note: Percentages in the total column and toxicity grade columns are calculated with the number of subjects treated in each group as denominator.
[TSFAE03AA.RTF] [/SAS/3699/54767414MMY3007/FILES/RE/IA2/PROGRAMS/TSFAE03AA.SAS] 28AUG2017, 04:34

Source: European Medicines Agency[43]

Five percent of patients withdrew from the DVMP arm due to AEs compared to 9% in the VMP. In terms of study discontinuation due to infections, there were three patients (1%) in the DVMP arm compared to five patients (1%) in the VMP arm and one patient withdrew in each group due to pneumonia. For infusion related reactions, five patients (1%) withdrew from the DVMP group.

6.4 Ongoing Trials

The following NCT03217812 study is ongoing, information in the table below was retrieved from Clincialtrial.gov.[44]

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Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study NCT03217812 A Phase 3, Multicenter, Randomized, Controlled, Open-label Study of VELCADE (Bortezomib) Melphalan-Prednisone (VMP) Compared to Daratumumab in Combination With VMP (DVMP), in Subjects With Previously Untreated Multiple Myeloma Who Are Ineligible for High-Dose Therapy (Asia Pacific Region) Estimated enrollment: 210 Actual study start date: Nov 23, 2017 Estimated Primary Completion date: Oct 30, 2020 Estimated Study Completion Date: Sept 30, 2023	<u>Key Inclusion Criteria:</u> • Documented multiple myeloma satisfying the calcium elevation, renal insufficiency, anemia, and bone abnormalities (CRAB) diagnostic criteria, monoclonal plasma cells in the bone marrow greater than or equal to (>=) 10 percent (%) or presence of a biopsy proven plasmacytomas, and measurable secretory disease, as assessed by the central laboratory, and defined in protocol • Newly diagnosed and not considered candidate for high-dose chemotherapy with stem cell transplantation (SCT) due to: being age >= 65 years, or in participants less than (<) 65 years: presence of important comorbid conditions likely to have a negative impact on tolerability of high dose chemotherapy with stem cell transplantation • Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 • Meet the clinical laboratory criteria as specified in the protocol • A woman of childbearing potential must have a negative serum or urine pregnancy tests at screening within 14 days prior to randomization <u>Key Exclusion Criteria:</u>	Treatment A: VMP Alone Velcade (bortezomib) 1.3 milligram per square meter (mg/m^2) as subcutaneous (SC) injection, twice weekly at Weeks 1, 2, 4 and 5 in Cycle 1 followed by once weekly at Weeks 1, 2, 4 and 5 in Cycles 2 to 9, melphalan 9 mg/m^2 (if serum creatine is greater than [>]2 milligram per deciliter [mg/dL] at baseline, participants must be administrated 4.5 mg/m^2 of melphalan, instead of 9 mg/m^2) orally, once daily (on Days 1 to 4) and prednisone 60 mg/m^2, orally, once daily on Days 1 to 4 of each cycle up to Cycle 9. Treatment B: DVMP Velcade 1.3 mg/m^2 as SC injection, twice weekly at Weeks 1, 2, 4 and 5 in Cycle 1 followed by once weekly at Weeks 1, 2, 4 and 5 in Cycles 2 to 9, melphalan 9 mg/m^2 (if serum creatine is >2 mg/dL at baseline, participants must be administrated 4.5 mg/m^2 of melphalan, instead of 9 mg/m^2), orally, once daily (on Days 1-4) and prednisone 60 mg/m^2, orally, once daily, on Days 1 to 4 of each cycle up to Cycle 9. In addition, participants will also receive	<u>Primary:</u> •Very Good Partial Response (VGPR) or Better Rate at 6 Month After Last Participant First Dose •Very Good Partial Response (VGPR) or Better Rate at 3 Years After Last Participant First Dose <u>Secondary:</u> • Progression-Free Survival • Time to Next Treatment • Overall Response Rate • Complete Response Rate • Stringent Complete Response Rate • Time to Response • Overall Survival • Duration of Response • Time to VGPR or Better Response • Duration of VGPR or Better Response • EuroQoL 5-Dimension 5-

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Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	▪ Primary amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma ▪ Waldenstrom's disease, or other conditions in which Immunoglobulin M (IgM) M-protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions ▪ Prior or current systemic therapy or SCT for multiple myeloma, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 milligram per day (mg/day) for 4 days) of corticosteroids before treatment ▪ Peripheral neuropathy or neuropathic pain Grade 2 or higher, as defined by the national cancer institute common terminology criteria for adverse events (NCI-CTCAE), Version 4.03 ▪ History of malignancy (other than multiple myeloma) within 3 years before the date of randomization (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years) ▪ Radiation therapy within 14 days of randomization	daratumumab 16 milligram per kilogram (mg/kg) as intravenous (IV) infusion, once weekly, for 6 weeks in Cycle 1 and then every 3 weeks, in Cycles 2 to 9 and thereafter, once every 4 weeks until documented progression, unacceptable toxicity, or the end of study. Participants will receive pre-infusion medications before each daratumumab infusion	Level Health Status • European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Health Status • Number of Participants With Antibodies to Daratumumab • Number of Participants With Adverse Events as a Measure of Safety and Tolerability • Clinical Efficacy of DVMP in High Risk Molecular Subgroups

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Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	• Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Participants with resolved infection (that is, participants who are HBsAg negative but positive for antibodies to hepatitis B core antigen [Anti-HBc] and/or antibodies to hepatitis B surface antigen [Anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) deoxyribonucleic acid (DNA) levels. Those who are PCR positive will be excluded. EXCEPTION: Participants with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR		

Source: Clincialtrial.gov NCT03217812[44]

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7 SUPPLEMENTAL QUESTIONS

Part 1: Critical Appraisal of non-randomized study: Bortezomib-containing regimens (BCR) for the treatment of non-transplant eligible multiple myeloma

The economic model assumed that the efficacy of CyBorD was the same as efficacy of VMP in the ALCYONE trial. A non-randomized study was identified by the submitter to support the clinical equivalency of CyBorD and VMP for newly diagnosed patients with multiple myeloma (NDMM) where there is no intent for stem cell transplantation. Therefore, this non-randomized trial has been critically appraised in this report. Of note, a rapid response was conducted by CADTH to identify literature on the comparative effectiveness of CyBorD and VMP for NDMM where there is no intent for stem cell transplantation and the identical non-randomized study was identified.

A non-randomized study conducted by Jimenez-Zepeda et al[6] evaluated the impact of different bortezomib-containing regimens including CyBorD, VMP and VD for the treatment of transplant-ineligible MM. Based on an institutional plasma cell disorder database, between January 2005 to February 2016, 122 patients were identified of which 34% (n=42) received CyBorD, 34% (n=42) were treated with VMP and 31% (n=38) were treated with VD. All patients in the VMP and VD groups were treated with intravenous bortezomib, whereas 13 patients (31%) of the CyBorD group were treated with the subcutaneous route. The results showed CyBorD had the highest ORR among patients and all bortezomib combination agents (CyBorD, VMP and VD) had similar median OS rates. In addition, long PFS was noted in favour of patients that received VMP and CyBorD (22.4 months for the CyBorD group, 17.5 months for the VMP group, and 10.1 months for the VD group, p = 0.04).

The Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) was used to assess the quality of the non-randomized study conducted by Jimenez-Zepeda et al.[6] The following domains: selection of participants, confounding variables, intervention (exposure) measurement, blinding of outcome assessment, incomplete outcome data and selective outcome reporting were assessed for risk of bias.

Although 610 patients between January 2005 to February 2016 were identified from the institutional plasma cell disorder database, it is unclear what criteria was used to exclude 230 patients as non-transplant eligible. Thus, the risk of bias is unclear for selection of participants.

Jimenez-Zepeda reported that the clinical characteristics were approximately similar across patients that received CyBorD, VMP and VD, however, it was noted that the proportion of Stage 1 cases was fewer in the VD cohort.

The risk of bias is low for intervention (exposure) measurement, blinding of outcome assessment incomplete outcome data and selective outcome reporting. Overall, the results of this non-randomized study are generally accepted.

Part 2: Critical appraisal of the network meta-analysis (NMA)

Background

There is a lack of direct evidence comparing daratumumab combination therapy to other current funded therapies in Canada. In Canada, Bortezomib, cyclophosphamide and dexamethasone (CyBorD) is the current treatment of choice for patients with newly diagnosed multiple myeloma that are transplant ineligible. Based on the submitter's consultations with clinical experts, the efficacy of CyBorD was assumed to be equivalent to VMP for the purpose of this NMA.[7] The results from this NMA were used to inform the economic model. As a result, a critical appraisal of the NMA was conducted.

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Objectives of NMA

The objective of the NMA was to evaluate the relative efficacy and safety of daratumumab – based regimens versus other selected regimens for the treatment of NDMM who are ineligible for transplantation based on the outcome of progression free survival (PFS) and overall survival (OS).

Methods

Search and study selection

The submitter conducted a systematic literature review to identify all eligible studies of treatments for patients with transplant-ineligible newly diagnosed MM. This systematic search was updated in June 2018 and conference abstracts were included until September 2018.[7] The inclusion and exclusion criteria of the NMA are presented in Table 1.

Table 1: Inclusion and exclusion criteria for NMA[38]

Clinical effectiveness	Inclusion Criteria	Exclusion Criteria
Publication type	published peer-reviewed reports, conference abstracts from 2012	observational studies, single arm trials, pharmacokinetic or pharmacodynamic studies, editorials and reviews
Population	Patients with multiple myeloma who are ineligible for ASCT	Indications other than ASCT-ineligible MM
Intervention	bortezomib, prednisone, lenalidomide, dexamethasone, thalidomide, cyclophosphamide, bendamustin, interferon, vincristine, Daratumumab, Melphalan, doxorubicin, carfilzomib, cisplatin, elotuzumab, etoposide, ixazomib, panobinostat, pomalidomide, vorinostat or a combination treatment with at least one of these drugs	• Not front-line treatment • Non-pharmacologic treatments, such as surgery or radiotherapy alone
Outcomes	Response: ORR, CR, sCR, PR, VGPR, and MRD • Survival and disease progression: OS, SD, PD, and PFS • Treatment discontinuation • All adverse events grade ≥3	health-related quality of life, economic evaluation outcomes, other clinical outcomes, etc. in the absence of the outcomes of interest
Language restrictions	English language	

A systematic search of EMBASE, PubMed, Cochrane, The American Society of Haematology (ASH), American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) was conducted. In addition to the aforementioned databases, existing meta-

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analyses/reviews and clincialtrials.gov were also searched.[45] While the systematic literature search was conducted in May to June 2017, an update was performed in June 2018.[45] The systematic literature search conducted by CADTH identified one NMA[9] and the submitter provided one additional NMA.[46] The submitter stated that PFS reported by San-Miguel et al[9] is an earlier NMA that excluded data from the clinical trial MAIA (DRd vs. Rd continuous) which has since been integrated into the NMA completed by the submitter.[10]

NMA methodology

Using a Bayesian NMA framework, both fixed effects (FE) models and random effects (RE) models estimated the OS HRs between treatments (among other outcomes not directly applicable to the economic model).[45] The NMA incorporated results from the one-year update of ALCYONE (Dimopoulos et al., 2018), as well as the most recent data from the FIRST trial (Facon et al., 2018).[7]

NMA Results

Included Studies

A NMA was performed using 23 RCTs and 22 RCTs for PFS and OS respectively.[11] Please see Figure 1 and Figure 2 for PFS and OS network diagrams respectively.[45]

Figure 1. NMA network diagram for PFS[45]

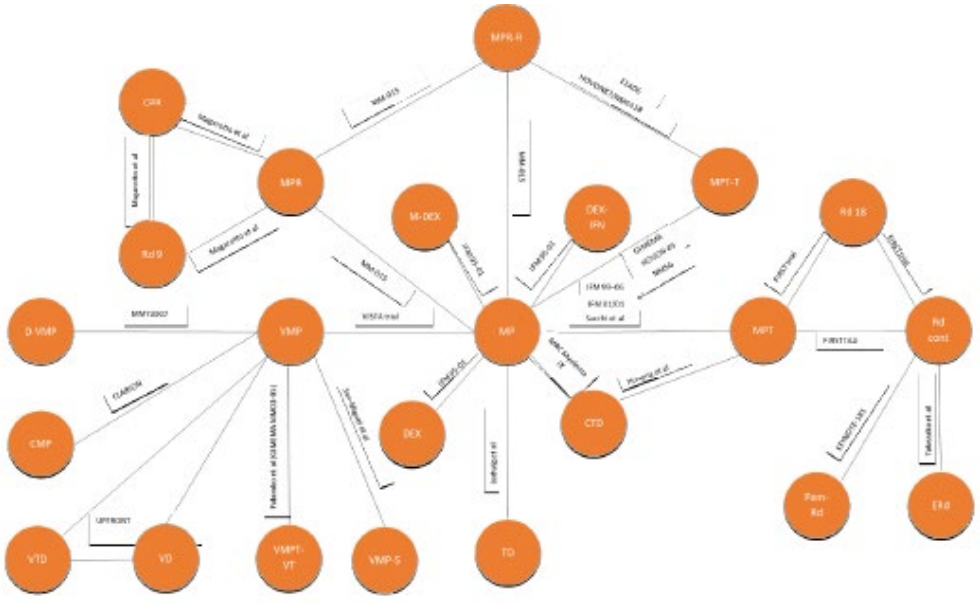

Figure 2. NMA network diagram for OS[45]

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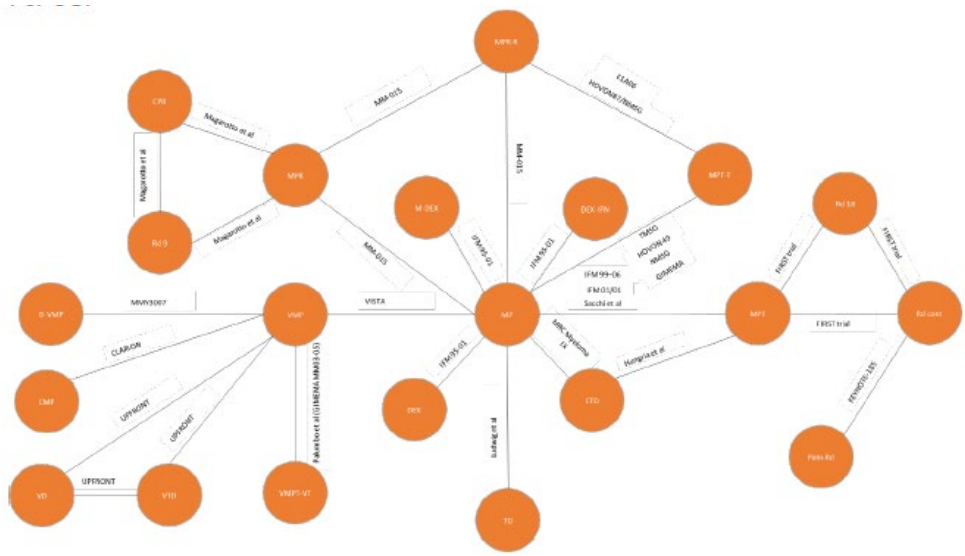
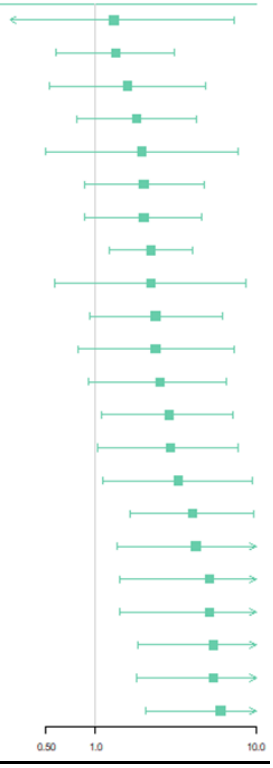


Progression-free Survival (PFS)

There were 23 trials included in the analysis for PFS.[11] DVMP was associated with a statistically significant reduction in risk of disease progression compared to VMP and non statistically significant PFS compared to Rd-continuous.[45] Table 3 presents the results of the NMA for PFS.

Table 3. Results of NMA for PFS[45]

Reference = D-VMP	PFS HR	CrI LL	CrI UL
ERd	1.32	0.24	7.34
VMPT-VT	1.35	0.58	3.14
Rd continuous	1.61	0.53	4.91
VTD	1.82	0.77	4.31
PemRd	1.96	0.50	7.79
VD	2.02	0.86	4.76
CMP	2.02	0.87	4.66
VMP	2.23	1.23	4.04
VMP-S	2.24	0.57	8.65
MPT	2.39	0.93	6.23
Rd18	2.39	0.79	7.39
MPR-R	2.54	0.92	6.63
MPT-T	2.89	1.1	7.27
CTD	2.96	1.04	7.81
M-DEX	3.31	1.13	9.61
MP	4.05	1.66	9.78
MPR	4.25	1.38	12.40
Rd 9	5.19	1.44	17.74
CPR	5.19	1.44	17.65
DEX-IFN	5.46	1.87	15.86
TD	5.46	1.83	16.10
DEX	6.04	2.07	17.55



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Overall Survival (OS)

There were 22 trials included in the analysis for overall survival. [11] DVMP was associated with a statistically significant OS compared to VMP and non-statistically significant OS compared to Rd-continuous. Both the FE model and the RE model were fitted to the data. The FE model had the best fit suggested by a lower DIC, yet a RE model was chosen due to the observed heterogeneity in the network.[45]

Table 4 presents the results of the NMA for OS.

Table 4. Results of NMA for OS[45]

(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until June 30, 2020 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier).

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.[47] Details of the critical appraisal are presented below.

Table 4: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis adapted from Jansen et al[47]

ISPOR Questions	Details and Comments‡
1. Is the population relevant?	**Yes.** The study populations of all the included trials in the NMA matched in review indication, which was to evaluate the efficacy and safety of daratumumab in combination with bortezomib, melphalan, and prednisone in the treatment of adult patients with multiple myeloma not eligible for transplant
2. Are any critical interventions missing?	**Yes.** The NMA does not include CyBorD.
3. Are any relevant outcomes missing?	**Yes.** Other outcomes of interest (e.g., health related quality of life and safety) were not explored.
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 review was provided which described in detail the systematic literature review process used in the NMA. The information sources, search strategy and study selection criteria were clearly described.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**No.** There were no closed loops in the NMA.
7. Is it apparent that poor quality studies were included thereby leading to bias?	**Yes.** The Cochrane risk of bias tool and the Jadad questionnaire evaluated the quality.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	**No.** There was no selective reporting of outcomes.

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ISPOR Questions	Details and Comments‡
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.** There was heterogeneity across the study populations in the included trials in the NMA
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?	Heterogeneity was explored by the submitter. For PFS and OS analysis of treatment comparisons, I^2-tests were conducted. Based on the I^2-test results, a RE model was preferred[45]
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	**Yes.** The Bayesian NMA framework preserves randomization within trials and minimize bias due to lack of randomization across trials.[45]
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 possible.** There was no closed loop for the relevant comparisons.
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?	**Yes.** 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.**
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	**Yes.**
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**No.**
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 is presented in Figure 1 and Figure 2.
19. Are the individual study results reported?	**Yes.** The submitter provided the direct comparisons for PFS and OS across all of the trials included in the NMA.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	**Yes.** The submitter has provided the direct comparisons of PFS and OS for all of the trials included in the NMA.
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?	**No.**

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ISPOR Questions	Details and Comments‡
23. Is the impact of important patient characteristics on treatment effects reported?	**No.**
24. Are the conclusions fair and balanced?	**Yes.** The overall conclusions of the NMA are fair and the relevant comparators identified by members of CGP and PAG included VMP and Rd-continuous. The NMA does not include CyBorD.
25. Were there any potential conflicts of interest?	**Unclear.**
26. If yes, were steps taken to address these?	**Unclear.**

Conclusions

The NMA included clinical trials with variation in the number of cycles that bortezomib was administered in the VMP regimens.[7] The NMA was conducted using a Bayesian framework.[45] The results from the NMA demonstrated that DVMP was associated with a statistically significant reduction in risk of disease progression compared to VMP and non-statistically significant PFS compared to Rd-continuous.[45] DVMP was associated with a statistically significant OS compared to VMP and non-statistically significant OS compared to Rd-continuous.[45]

Heterogeneity was present across the study populations due to different inclusion and exclusion criteria. Furthermore, the submitter acknowledged that the evidence network was not fully connected. Thus, the results for PFS and OS should be interpreted with caution as the confidence intervals were wide. Other outcomes of interest (e.g., health related quality of life and safety) were not explored in this NMA.

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Part 3: Critical Appraisal of Naïve Comparisons and Match Adjusted Indirect Comparison (MAIC)

Background

For patients with newly diagnosed multiple myeloma (NDMM) who are transplant ineligible, bortezomib in combination with melphalan and prednisone (VMP) has been indicated as treatment for this group of patients. Specifically, VMP regimens may be classified as VMP where bortezomib is administered twice weekly in early cycles and VMP-modified regimens where bortezomib is prescribed once weekly in early cycles.[48] There were several different VMP regimens observed in the clinical trials included in the NMA, which differed in the number of cycles in which bortezomib was administered once weekly versus twice weekly, cycle length, and number of cycles, therefore, the submitter conducted a naïve and MAIC comparison to examine the non-inferiority of VMP-modified regimens compared to VMP.

Objectives

The objective was to examine the non-inferiority of VMP-modified regimens compared to VMP for outcomes related to efficacy and tolerability.

Methods

The submitter conducted a systematic literature review in PubMed across all non-inferiority margins in oncology clinical trials. An average of the retrieved margins was used to interpret the results for each endpoint. Both naïve and MAICs were performed. The systematic literature search conducted by CADTH identified one MAIC which compared DVMP and Rd-continuous.[49]

Naïve comparison

Individual patient data (IPD) from VISTA and MMY3007 studies and reported summary baseline characteristics and outcomes from GIMEMA MM-03-05 (after amendment) and PETHEMA were extracted and used in the analysis of the following outcomes: complete response and overall response rate, progression-free survival, overall survival, time to progression, time to response and safety. Odds ratios (OS) and rate difference (RD) were calculated for binary outcomes like response and adverse events with two-sided 95% CIs to compare VMP regimens. Table 1 outlines the VMP regimens prescribed in different trials

Table 1. Criteria of VMP regimens[48]

Trial	Treatment arms	Bortezomib	Melphalan	Prednisone
ALCYONE (MMY3007)	VMP-modified	Twice weekly during cycles 1, then once weekly during cycle 2 to 9	9 mg/m^2 on days 1 to 4, during each of nine 6-week cycles	60 mg/m^2 on days 1 to 4, during each of nine 6-
GIMEMA	VMP-modified (9 once weekly	Bortezomib therapy was modified to		

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Trial	Treatment arms	Bortezomib	Melphalan	Prednisone
	cycles, VMP-GIMEMA-QW)	once weekly during cycles 1 to 9 (all 5-week cycles)		
VISTA TRIAL	VMP			
PETHEMA	VMP-modified	Twice weekly during cycle 1 (6-week cycle) and once weekly during cycles 2-6 (5-week cycles).	9 mg/m^2 on days 1 to 4, for one 6-week cycle and five 5-week cycles	60 mg/m^2 on days 1 to 4, for one 6-week cycle and five 5-week cycles

Matching adjusted indirect comparison (MAIC)

As the naïve comparisons included treatment effects that were not adjusted for baseline characteristics, MAIC comparisons were conducted in which patients in the VMP VISTA treatment arm were matched according to characteristics of those in the pooled VMP-modified treatment arms. An "unanchored" indirect comparison was conducted as no pairwise comparison was available. A MAIC weight was assigned for each patient in the VMP VISTA trial based on observed characteristics. These weights were used to calculate weighted outcomes. The following baseline variables were included in the analysis:

- Median age
- Male
- ISS state, categorical variable
- Median β2-microglobulin, mg/L
- Median Albumin, g/L
- Median Creatinine, µmol/L
- Creatinine clearance <30 mL/min, n (%)
- High-risk cytogenetics

Analyses

The primary analysis compared pooled VMP-modified regimens (MMY3007 & GIMEMA-QW trials) with the VMP regimen outlined in the VISTA trial. In addition, a supplemental analysis was conducted that compared pooled VMP-modified regimens across 3 trials (MMY3007, GIMEMA-QW & PETHEMA). While the comparators included in the aforementioned trials (GIMEMA-QW & PETHEMA) were outside the scope of this review, the results from the primary and supplemental analysis are reported.

MAIC results

Progression Free Survival (PFS)

For the MAIC comparison, [redacted]. (*Non-disclosable information was used in this pCODR Guidance*

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Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.)

<u>Overall Survival (OS)</u>

For the MAIC comparison, [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.*)

<u>Complete Response (CR)</u>

[redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.*)

<u>Overall Response Rate (ORR)</u>

[redacted] (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.*)

<u>Time to progression (TTP)</u>

For the MAIC comparison, [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.*)

<u>Safety outcomes</u>

The MAIC comparison for [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.*)

The MAIC comparison for [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.*)

The MAIC comparison for [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.*)

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Conclusions

The method used to extract IPD from Kaplan Meier curves presents limitations in the quality of the reported data. However, steps were taken to validate this data by enlisting a second investigator. Secondly, in the naiive comparisons, measures of effect were not adjusted for baseline characteristics. Thus, MAIC comparisons were considered the best available method which adjusted for baseline variables in cases where IPD was available for only one treatment arm. A limitation of unanchored comparisons is that absolute outcomes can be predicted from the baseline characteristics. Due to the bias in this assumption and possibility of unanchored comparisons exceeding the magnitude of treatment effects, results should be interpreted with caution. The submitter recommended that until a randomized comparison is performed, an appropriate method is propensity score matching. A citation identified in the CADTH literature search was a propensity score matched analysis[50] which found that the median PFS for DVMP was not reached vs 20.6 months for VISTA VMP. The unadjusted and adjusted HRs were statistically significant.

While a systematic review of the literature was conducted to identify clinical trials for the treatments to be compared, comparisons of the baseline characteristics of the trials pre- and post-matching are unclear. Outcome measures were clearly defined. In addition, although algorithms were developed to extract IPD from Kaplan Meier curves, the availability of IPD would provide more robust data.

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8 COMPARISON WITH OTHER LITERATURE

An additional retrospective cohort study (one abstract and one poster) was identified by CGP to provide additional context real-world outcomes with bortezomib-containing regimens and lenalidomide plus dexamethasone for the treatment of transplant ineligible MM patients. A brief summary of the study design and results is provided below. Of note,

Overview of the identified literature

1. Jimenez-Zepeda et al 2018:[4,16] An abstract and poster described a retrospective cohort study. Data were collected between 2007 and July 2018 for 423 transplant ineligible MM patients treated with: cyclophosphamide, bortezomib, and prednisone (CyBorP)/CyBorD; 160 patients treated with Ld, 204 patients treated with bortezomib (velcade), melphalan, and prednisone (VMP); and 55 patients treated with bortezomib (velcade) and dexamethasone/prednisone (Vd/VP).[4,16] Baseline characteristics are reported in Figure 5. Again, methodological details are limited due to the abstract and poster presentation only. Patients were not matched and a lower creatinine value in the Ld group compared to Vd, CyBorD and VMP was noted (p=0.001). The primary outcomes reported were: ORR, PFS, and overall survival (OS) for transplant ineligible patients treated with CyBorD/CyBorP, Ld, VMP (Bortezomib weekly) or VD/VP, each given as reported previously but with dose-adjustments at the discretion of the treating physician to maintain patients on therapy.[4,16] Very good partial response (VGPR) was also reported. Survival curves were constructed according to the Kaplan-Meier method and compared using the log rank test; a p value of <0.05 was considered significant.

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Table 8.1 Summary of Retrospective Cohort Study

Title	2008 Real-World Outcomes with Bortezomib-Containing Regimens and Lenalidomide Plus Dexamethasone for the Treatment of Transplant Ineligible MM Patients: A Multi-Institutional Report from the National Myeloma Canada Research Network (MCRN) Database[4,16]			
Author	Victor Jimenez-Zepeda et al.			
Report Date	December 2018			
Report Type	Poster Abstract			
Study Design	Retrospective Cohort			
Data Cut-Off Date	2007 – 01/07/2018			
Patient Population	Transplant ineligible MM			
Drug of Interest	CyBorD/CyBorP	Ld	VMP	Vd/VP
Patient Number	423	160	204	55
Outcomes	- ORR - PFS - OS - ≥ VGPR			
Study Notes	- Patients were not matched and a lower creatinine value in the LD group compared to VD, CyBorD and VMP was noted (p=0.001).*			
[Abbreviations]: CyBorD - Cyclophosphamide plus Bortezomib plus Dexamethasone; CyBorP – Cyclophosphamide plus Bortezomib plus Prednisone; Ld – Lenalidomide plus Dexamethasone; ORR – Overall Response Rate; OS - Overall Survival; PFS – Progression Free Survival;; Vd – Bortezomib plus Dexamethasone; VP – Bortezomib plus Prednisone; VGPR – Very Good Partial Response; VMP – Bortezomib (velcade) plus Melphalan plus Prednisone *Only reported in the posterJimenez-Zepeda et al., 2018b[4]				

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Outcomes

Outcomes for all three reports are summarized in the Table below:

Table 8.2 Summary of efficacy outcomes

Title	Drug	N	Median Follow-Up Time (months)	Outcomes				
				ORR (%)	Median PFS (months)	Median PFS2 (months)	≥VGPR (%)	Median OS (months)
Jimenez-Zepeda et al 2018[4,16]	CyBorD/ CyBorP	423	NR	NR	19.3	N/A	53	51†
	Ld	204	NR	NR	25	N/A	56	66.5†
	VMP	160	NR	NR	20.5	N/A	46	59.5†
	Vd/VP	55	NR	NR	13.7	N/A	51	29.4†
	Overall	842	NR	83	20.4	N/A	52	54.1

† p-value is >0.05

[Abbreviations]: CyBorD - Cyclophosphamide plus Bortezomib plus Dexamethasone; CyBorP – Cyclophosphamide plus Bortezomib plus Prednisone; Ld – Lenalidomide plus Dexamethasone; ORR – Overall Response Rate; OS - Overall Survival; PFS – Progression Free Survival; PFS2 – Time to Second Objective Disease Progression; Vd – Bortezomib plus Dexamethasone; VP – Bortezomib plus Prednisone; VGPR – Very Good Partial Response; VMP – Bortezomib plus Melphalan plus Prednisone

Both the poster and the abstract by Jimenez-Zepeda et al. 2018 retrospectively evaluated 842 patients.[4,16] Four-hundred and twenty-three patients were treated with CyBorD/CyBorP, 204 patients with VMP, 160 patients with Ld, and 55 patients with Vd/VP. For the entire cohort, median OS was 54.1 months, median PFS was 20.4 months, ORR was 83%, ≥VGPR was 52%. A ≥VGPR rate of 53% was observed for patients treated with CyBorD/CyBorP, 46% for VMP, 56% for L and 51% for Vd/VP (p=0.3). Median PFS for patients treated with CyBorD/CyBorP was 19.3 months, 20.5 months for VMP, 13.7 months for Vd/VP and 25 months for LDd (p=0.03). Median OS for patients treated with CyBorD/CyBorP was 51 months, 59.5 months for VMP, 29.4 months for Vd/VP, and 66.5 months for Ld (p=0.07). Figure 8.1 and Figure 8.2 are the figures as reported in Jimenez-Zepeda et al. 2018 abstract[16] and in the Jimenez-Zepeda et al. 2018 poster.[4]

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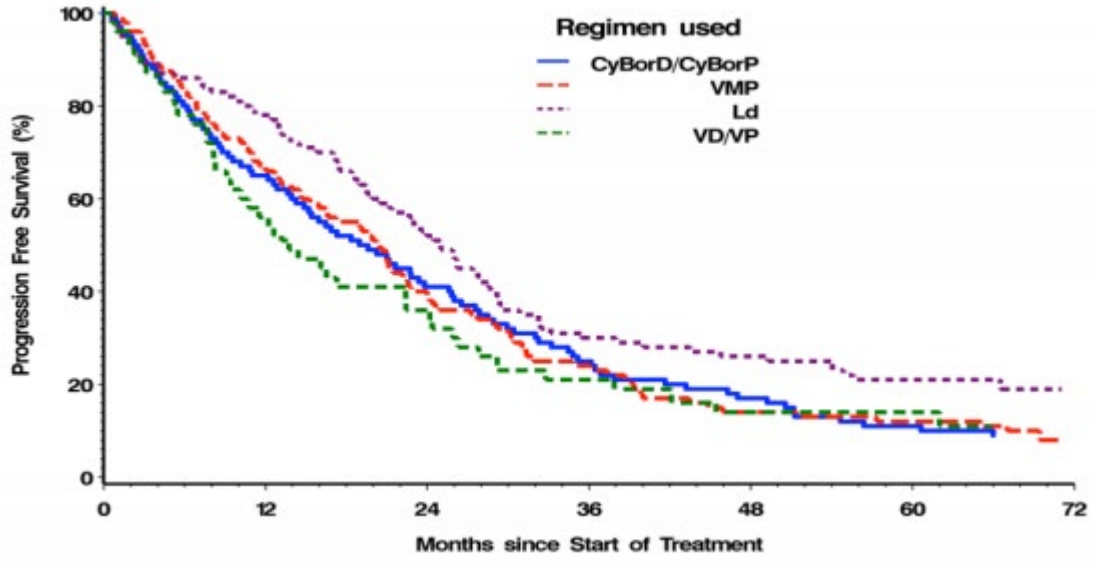
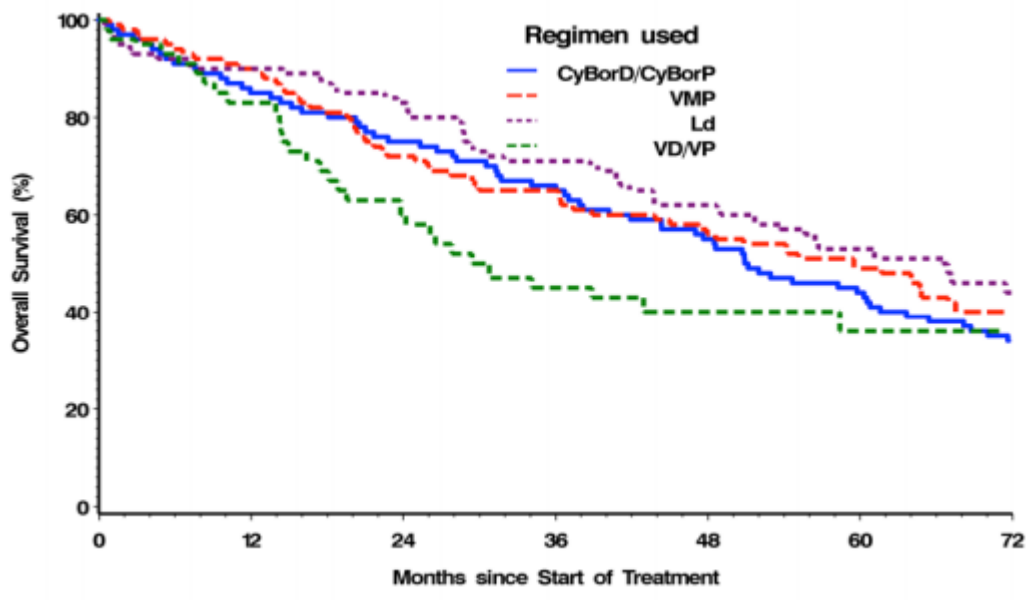
Figure 8.1 Progression-free survival according to treatment regimen. The median PFS was longer for Ld patients (25 months) compared to CyBorD/CyBorP, VMP and Vd/VP, 19.3, 20.5 and 13.7 months respectively (p=0.03)



Source: Republished with permission of the American Society of Hematology, from Real-world outcomes with bortezomib-containing regimens and lenalidomide plus dexamethasone for the treatment of transplant ineligible MM patients: a multi-institutional report from the National Myeloma Canada Research Network (MCRN) database, Jimenez-Zepeda V et al., 132 (Suppl 1), 2018; permission conveyed through Copyright Clearance Center, Inc.

Figure 8.2. Overall survival clinical outcome as reported in Jimenez-Zepeda et al. 2018 abstract [16]



Source: Republished with permission of the American Society of Hematology, from Real-world outcomes with bortezomib-containing regimens and lenalidomide plus dexamethasone for the treatment of transplant ineligible MM patients: a multi-institutional report from the National Myeloma Canada Research Network (MCRN) database, Jimenez-Zepeda V et al., 132 (Suppl 1), 2018; permission conveyed through Copyright Clearance Center, Inc.

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9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Myeloma Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on daratumumab + VMP. 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. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

This Initial Clinical Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. A Final Clinical Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Clinical Guidance Report will supersede this Initial Clinical Guidance Report.

The Myeloma Clinical Guidance Panel is comprised of four clinicians. 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.

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APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials December 2018, Embase 1974 to 2019 January 18, Ovid MEDLINE(R) ALL 1946 to January 18, 2019

#	Searches	Results
1	(daratumumab* or darzalex* or HuMax-CD38 or HuMaxCD38 or JNJ 54767414 or JNJ54767414 or 4Z63YK6E0E).ti,ab,ot,kf,kw,hw,nm.	1846
2	Bortezimib/ or (bortezomib* or Velcade* or Bomib* or Borcade* or Bortega* or Bortero* or Bortesum* or Egybort* or Exfucikanet* or Imozet* or Mibor* or Neomib* or Nyubortez* or Velkeyd* or Zegomib* or Zuricade* or Bortecad* or Chemobort* or HSDB7666 or HSDB 7666 or LDP341 or LDP 341 or MG341 or MG 341 or MLN341 or MLN 341 or BXCL101 or BXCL 101 or NSC681239 or NSC 681239 or PS341 or PS 341 or 69G8BD63PP).ti,ab,ot,kf,kw,hw,nm.	37522
3	Melphalan/ or (melphalan* or Alkeran* or Sarcolysin* or Sarkolysin* or Alphalan* or Melpha* or meddphalan* or merphalan* or L-PAM or phenylalanine mustard or peptichemio* or AT290 or AT-290 or BRN2816456 or BRN 2816456 or CB3025 or CB 3025 or CCRIS374 or CCRIS 374 or EINECS205-726-3 or EINECS 205-726-3 or Evomela* or HSDB3234 or HSDB 3234 or Levofalan* or Levofolan* or Levopholan* or melfalan* or phenylalanine nitrogen mustard or alanine nitrogen mustard or melphalon* or melphelan* or phenylalanine 2037 or NSC-C04853 or NSCC04853 or NSC8806 or NSC 8806 or NSC 241286 or NSC241286 or SK15673 or SK 15673 or Q41OR9510P).ti,ab,ot,kf,kw,hw,nm.	53693
4	(DVMP or D-VMP).ti,ab,ot,kf,kw.	17
5	((daratumumab* or darzalex* or DARA) and VMP).ti,ab,ot,kf,kw.	28
6	(1 and 2 and 3) or 4 or 5	238
7	6 use cctr	16
8	6 use medall	16
9	*daratumumab/ or (daratumumab* or darzalex* or HuMax-CD38 or HuMaxCD38 or JNJ 54767414 or JNJ54767414).ti,ab,kw,dq.	1398
10	*bortezomib/ or (bortezomib* or Velcade* or Bomib* or Borcade* or Bortega* or Bortero* or Bortesum* or Egybort* or Exfucikanet* or Imozet* or Mibor* or Neomib* or Nyubortez* or Velkeyd* or Zegomib* or Zuricade* or Bortecad* or Chemobort* or HSDB7666 or HSDB 7666 or LDP341 or LDP 341 or MG341 or MG 341 or MLN341 or MLN 341 or BXCL101 or BXCL 101 or NSC681239 or NSC 681239 or PS341 or PS 341).ti,ab,kw,dq.	25856
11	*melphalan/ or (melphalan* or Alkeran* or Sarcolysin* or Sarkolysin* or Alphalan* or Melpha* or meddphalan* or merphalan* or L-PAM or phenylalanine mustard or peptichemio* or AT290 or AT-290 or BRN2816456 or BRN 2816456 or CB3025 or CB 3025 or CCRIS374 or CCRIS 374 or EINECS205-726-3 or EINECS 205-726-3 or Evomela* or HSDB3234 or HSDB 3234 or Levofalan* or Levofolan* or Levopholan* or melfalan* or phenylalanine nitrogen mustard or alanine nitrogen mustard or melphalon* or melphelan* or phenylalanine 2037 or NSC-C04853 or NSCC04853 or NSC8806 or NSC 8806 or NSC 241286 or NSC241286 or SK15673 or SK 15673).ti,ab,kw,dq.	32822
12	(DVMP or D-VMP).ti,ab,kw,dq.	17
13	((daratumumab* or darzalex* or DARA) and VMP).ti,ab,kw,dq.	28
14	(9 and 10 and 11) or 12 or 13	94

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15	14 use oemezd	63
16	15 not conference abstract.pt.	11
17	7 or 8 or 16	43
18	remove duplicates from 17	30
19	15 and conference abstract.pt.	52
20	limit 19 to yr="2014 -Current"	45
21	18 or 20	75
22	limit 21 to english language	71

2. Literature search via PubMed

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

Search	Query	Items found
#6	Search #5 AND publisher[sb]	1
#5	Search (#1 AND #2 AND #3) OR #4	14
#4	Search DVMP[tiab] OR D-VMP[tiab] OR ((DARA[tiab] OR daratumumab*[tiab] OR Darzalex*[tiab]) AND VMP[tiab])	3
#3	Search melphalan*[tiab] OR Alkeran*[tiab] OR Sarcolysin*[tiab] OR Sarkolysin*[tiab] OR Alphalan*[tiab] OR Melpha*[tiab] OR meddphalan*[tiab] OR merphalan*[tiab] OR L-PAM[tiab] OR phenylalanine mustard[tiab] OR peptichemio*[tiab] OR AT290[tiab] OR AT-290[tiab] OR BRN2816456[tiab] OR BRN 2816456[tiab] OR CB3025[tiab] OR CB 3025[tiab] OR CCRIS374[tiab] OR CCRIS 374[tiab] OR EINECS205-726-3[tiab] OR EINECS 205-726-3[tiab] OR Evomela*[tiab] OR HSDB3234[tiab] OR HSDB 3234[tiab] OR Levofalan*[tiab] OR Levofolan*[tiab] OR Levopholan*[tiab] OR melfalan*[tiab] OR NSC-C04853[tiab] OR NSCC04853[tiab] OR NSC8806[tiab] OR NSC 241286[tiab] or NSC241286[tiab] OR NSC 8806[tiab] OR SK15673[tiab] OR SK 15673[tiab] OR Q41OR9510P[rn]	11332
#2	Search bortezomib*[tiab] OR Velcade*[tiab] OR Bomib*[tiab] OR Borcade*[tiab] OR Bortega*[tiab] OR Bortero*[tiab] OR Bortesum*[tiab] OR Egybort*[tiab] OR Exfucikanet*[tiab] OR Imozet*[tiab] OR Mibor*[tiab] OR Neomib*[tiab] OR Nyubortez*[tiab] OR Velkeyd*[tiab] OR Zegomib*[tiab] OR Zuricade*[tiab] OR Bortecad*[tiab] OR Chemobort*[tiab] OR HSDB7666[tiab] OR HSDB 7666[tiab] OR LDP341[tiab] OR LDP 341[tiab] OR MG341[tiab] OR MG 341[tiab] OR MLN341[tiab] OR MLN 341[tiab] OR NSC681239[tiab] OR NSC 681239[tiab] OR PS341[tiab] OR PS 341[tiab] OR 69G8BD63PP[rn]	8083
#1	Search daratumumab*[tiab] OR darzalex*[tiab] OR HuMax-CD38[tiab] OR HuMaxCD38[tiab] OR JNJ 54767414[tiab] OR JNJ54767414[tiab] OR 4Z63YK6E0E[rn]	372

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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: Darzalex/daratumumab, 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: Darzalex/daratumumab, 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: Darzalex/daratumumab, 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 (1946-18Jan2019) with in-process records & daily updates via Ovid; Embase (1974-18Jan2019) via Ovid; The Cochrane Central Register of Controlled Trials (Dec 2018) 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 Darzalex/daratumumab, Velcade/bortezimib and Alkeran/melphalan.

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No filters were applied to limit retrieval by publication type. 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 June 6, 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), the European Society for Medical Oncology (ESMO) and the American Society of Hematology (ASH) 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.

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