CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Initial Clinical Guidance Report

Lenalidomide (Revlimid) plus Bortezomib plus Dexamethasone for Multiple Myeloma

June 19, 2019

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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 lenalidomide (Revlimid) plus bortezomib and dexamethasone for multiple myeoma. 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 lenalidomide (Revlimid) plus bortezomib and dexamethasone for multiple myeoma 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 lenalidomide (Revlimid) plus bortezomib and dexamethasone for multiple myeoma, a summary of submitted Provincial Advisory Group Input on lenalidomide (Revlimid) plus bortezomib and dexamethasone for multiple myeoma, and a summary of submitted Registered Clinician Input on lenalidomide (Revlimid) plus bortezomib and dexamethasone for multiple myeoma, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the safety and efficacy of lenalidomide (Revlimid) in combination with bortezomib and dexamethasone on patient outcomes compared to appropriate comparators in patients with newly diagnosed multiple myeloma for whom stem cell transplantation is not intended. The reimbursement request is combination of lenalidomide, bortezomib, and low-dose dexamethasone, for the treatment of newly diagnosed multiple myeloma patients in whom stem cell transplantation is not intended. Lenalidomide has a Health Canada approval in combination with dexamethasone for the treatment of multiple myeloma patients who are not eligible for stem cell transplant. A regulatory approval will not be sought for the current reimbursement request.

Lenalidomide is an immunomodulatory drug analogous to thalidomide with anti-angiogenic and anti-inflammatory properties. Based on the SWOG S0777 trial, the induction regimen of lenalidomide is 25 mg orally once a day on days 1 – 14 plus bortezomib at 1-3 mg/m^2 intravenously on days 1, 4, 8, 11 plus 20 mg oral dexamethasone on days 1, 2, 4, 5, 8, 9, 11, and 12. Maintenance treatment included 25 mg oral lenalidomide once a day for 21 days plus 40 mg oral dexamethasone once a day for days 1, 8, 15, and 22 of each 28-day cycle.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Objective and Scope of pCODR Review

The objective and scope of this review is to evaluate the efficacy and safety of lenalidomide (Revlimid) in combination with bortezomib (Velcade) and low-dose dexamethasone as a first line treatment in patients with newly diagnosed multiple myeloma in whom stem cell transplantation is not intended. Appropriate comparators and outcomes of interest are summarized in Table 3 in section 6.2.1.

Highlights of Evidence in the Systematic Review

Three analyses of 1 randomized control trial (RCT) were included in this review [1-3]. SWOG S0777 was a phase III randomized, open labelled, two-arm, parallel arm study comparing lenalidomide (Revlimid) in combination with bortezomib (Velcade) and low-dose dexamethasone (VLd) with lenalidomide (Revlinib) in combination with low-dose dexamethasone (Ld). The patient population was newly diagnosed multiple myeloma patients with the presence of CRAB criteria (C=calcium, R=renal impairment, A=anemia, B=bone involvement), in whom stem cell transplantation is not intended, and 18 years of age or older. Highlights of evidence is summarized below in Table 1.

The SWOGS0777 was a multi-centre trial, including 139 centres in U.S.A. Of the 525 patients that were assessed for eligibility and enrolled, 264 were randomly assigned to receive VLd, and 261 to receive Ld. Randomization was generated using a dynamic allocation algorithm developed by Pocock and Simon and stratified based on International Staging System stage (I, II, III) and intent to transplant (yes vs no)[1].

The primary outcome for the trial was progression free survival (PFS) from time of randomisation and the secondary outcomes were overall survival, rate of overall response (partial or better), safety and to bank specimens for future translational medicine research.

The SWOG S0777 trial was sponsored by the National Cancer Institute (NCI) and led by Southwest Oncology Group (SWOG). The original data analysis that was published by Durie et al. 2017[1] was based on a data cutoff date of November 5, 2015. This analysis was done on the eligible analysable population per protocol. An abstract presented an updated analysis with a data cutoff of May 15, 2018.[2]

As this was a cooperative group study, not originally deisgned to support regulatory application for market authorization, the submitter obtained rights to the data for this study and developed the dataset and an analysis plan appropriate to support a regulatory submissions to health authorities. The submitter's analysis of the SWOG S0777 trial was submitted in a CSR [3]. The CSR analysis includes an additional 52 patients due to reassessment of ineligibility; these patients were excluded from the Durie 2017 publication. The CSR analysis assessed the intention to treat (ITT) population with IRAC review with SWOG censoring rules, EMA censoring and FDA censoring[3].

Durie et al. 2017[1]

For the eligible analysable population per protocol, at the November 5, 2015 cutoff date, the median age in the VLd group was 63 years (range of 56-70 years) and in the Ld group 61 year (range 56-71)[1]. The proportion of women in the VLd group was 37% and 47% for Ld[1].

The median progression free survival for VLd and Ld were 43 and 30 months; respectively (HR=0.712, 95%Cl: 0.560-0.906, p<0.0018)[1]. The median overall survival for VLd and Ld were 75 and 64 months; respectively (HR=0.709, 95%Cl: 0.524-0.959, p<0.0125) [1]. The median duration of response for VLd and Ld were 52 and 38 months; respectively (HR=0.695, p<0.0133)[1]. Adverse events of grade 3 or higher occurred in 82% of the VLd group, and 75% of the Ld group[1].

Durie et al. 2018[2]

In the updated analysis for the eligible analysable population per protocol, as of the May 15th, 2018 cutoff date, the median progression free survival for VLd and Ld were 41 and 29 months; respectively (HR=0.742, 95%Cl: 0.594-0.928, p<0.003)[2]. The median overall

survival for VLd was not reached and for Ld was 69 months; respectively (HR=0.709, 95%CI: 0.543-0.926, p<0.0114)[2]. The duration of response and adverse events were not reported in the conference abstract.

Clinical Summary Report[3]

For the ITT population, the median age in the VLd group was 63 years (range 35-85 years) and in the Ld group was 63 years (range 28-87 years) [3]. The proportion of women in the VLd group was 37.6% and 47.3% for Ld[3].

With outcomes assessed by IRAC with SWOG censoring, at the the November 5, 2015 cutoff date, the median progression free survival for VLd and Ld were 42.5 and 29.9 months; respectively (HR=0.76, 95%CI: 0.61-0.94, p<0.00862)[3]. The median overall survival for VLd was not reached, and for Ld was 67.2 months (HR=0.73, 95%CI: 0.55-0.97)[3].

At the December 1, 2016 cutoff date, the median progression free survival for VLd and Ld were 42.5 and 29.9 months; respectively (HR=0.76, 95%CI: 0.62-0.93, p<0.00862)[3]. The median overall survival for VLd and Ld were 89.1 and 67.2 months; respectively (HR=0.75, 95%CI: 0.58-0.97, p<0.02786)[3]. The median duration of response for VLd and Ld were 48.6 and 38.9 months; respectively (HR=0.83, 95%CI: 0.61-1.12, p<0.21905)[3]Adverse events of any cause occurred in 97.3% of the VLd group, and 97.7% of the Ld group[3].

Table 1: Highlights of Key Outcomes

Population	**Eligible Analysable Population (per protocol)**				**ITT Population**			
Report	**Durie et al. 2017**		**Durie et al. 2018**		**Clinical Study Report**			
Data Cut-Off	**November 5, 2015**		**May 15, 2018**		**November 5, 2015**		**December 1, 2016**	
Assessment	**Per Protocol**		**Per Protocol**		**IRAC**		**IRAC**	
	VLd (N= 241)	**Ld (N= 229)**	**VLd (N=235)**	**Ld (N= 225)**	**VLd (N= 263)**	**Ld (N= 260)**	**VLd (N= 235)**	**Ld (N=225)**
PFS, median (months)	43	30	41	29	42.5	29.9	42.5	29.9
HR (95%CI)	0.712 (0.560, 0.906)		0.742 (0.594, 0.928)		0.76 (0.61, 0.94)		0.76 (0.62, 0.93)	
p-value	0.0018		0.003		0.01038		0.00862	
OS, median (months)	75	64	Not Reached	69	Not Reached	67.2	89.1	67.2
HR (95%CI)	0.709 (0.524, 0.959)		0.709 (0.543, 0.926)		0.73 (0.55, 0.97)		0.75 (0.58, 0.97)	
p-value	0.0125		0.0114		NR		0.02786	
DOR, median (months)	52	38	NR	NR	NR	NR	48.6	38.9
HR (95%CI)	0.695 (no confidence interval reported)		NR		NR		0.83 (0.61, 1.12)	
p-value	0.0133		NR		NR		0.21905	
Harms Outcome, n (%)	**VLd (N= 241)**	**Ld (N= 229)**	NR	NR	**NR**	**NR**	**VLd (N= 262)**	**Ld (N=256)**
Grade ≥3	198 (82)	169 (75)	NR	NR	NR	NR	232 (88.5)	219 (85.5)
AE (any grade)	NR	NR	NR	NR	NR	NR	255 (97.3)	250 (97.7)
TRAE	NR	NR	NR	NR	NR	NR	251 (95.8)	245 (95.7)
WDAE	NR	NR	NR	NR	NR	NR	97 (37.0)	64 (25.0)

AE = adverse event, **CI** = confidence interval, **DOR** = duration of response, **HR** = hazard ratio, HRQoL = health-related quality of life, **NR** = not reported, **PFS** = progression free survival, **SD** = standard deviation, **TRAE** = treatment-related adverse event, **WDAE** = withdrawal due to adverse event
*HR < 1 favours VLd
ITT population PFS results presented for November 2015 and December 2016 are based on SWOG censoring rules

1.2.2 Additional Evidence Systematic Review

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

Patient Advocacy Group Input

One patient advocacy group, Myeloma Canada (MC), provided input on the review for lenalidomide plus bortezomib and dexamethasone for patients who have not had previous treatments and are not eligible for a stem cell transplant.

From a patient's perspective, patients value managing key symptoms, such as, infections, kidney problems, mobility, pain, fatigue, neuropathy and shortness of breath. The ability to work, followed by the ability to exercise, travel, volunteer, concentrate, conduct household chores, fulfill family obligations, and spend time with family were noted to impact or limit day-to-day activity and quality of life of patients. According to Myeloma Canada, when it comes to treating myeloma, it is important for patients: to maintain quality of life or normal life, manage/minimize side effects, control the disease, have access to effective treatments, control symptoms, achieve or maintain remission, and prolong survival, among others.

Of the patients who had experience with RVd, disease control and prolonged life were ranked as the most important treatment expectations followed by fewer side effects and a normal life. The majority of patients (83%) who used the RVd noted that the administration of the treatment combination had a negative effect. Patients noted that the side effect profile of RVd was tolerable or very tolerable. Myeloma patients have noted significant side-effects of their treatment, such as neuropathy and serious consequences of their myeloma such as mobility problems due to bone pain and fractions. Additional side effects were noted as follows: 50% found diarrhea somewhat intolerable, followed by constipation, fatigue, dyspnea, decreased appetite and headache. Of the 6 patients who responded to the survey, 50% indicated good quality of life, 33% rated fair quality or life and 17% noted excellent quality of life. Patient respondents who took RVd, 83% noted that the treatment combination met their expectations in treating myeloma, 67% of the 6 respondents noted that the treatment combination improved their health and well-being and 50% noted that the treatment combination improved their long term health outlook. One caregiver who had experience with RVd responded to the survey. The caregiver noted that there were no challenges while helping to manage the side effects of the treatment combination. The caregiver respondent also rated the activities of daily living as not being affected while managing these side effects.

Provincial Advisory Group (PAG) Input

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). 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:

- Incremental costs due to drug wastage, treatment duration, and budget impact

Registered Clinician Input

One single and one joint clinician input on behalf of the Myeloma Canada Cancer Research Network were provided, representing a total of six clinicians. The registered clinicians provided input on lenalidomide in combination with bortezomib and low-dose dexamethasone (RVd) for treatment of newly diagnosed multiple myeloma patients ineligible for stem cell transplant.

Clinicians noted that lenalidomide plus dexamethasone (Ld) and cyclophosphamide combined with dexamethasone plus bortezomib (CyBorD) were the most relevant comparators to RVd. Patients eligible for RVd include those newly diagnosed with multiple myeloma receiving treatment in the first-line and who are ineligible for stem cell transplant. While RVd would take place as first-line treatment, frail patients may still be considered for Ld or CyBorD for first-line therapy. In terms of sequencing, daratumumab based regimens were considered the most likely second-line therapy following RVd, followed by regimens containing pomalidomide or carfilzomib. All clinicians providing input agreed that data supports the efficacy of RVd in the first-line setting for patients ineligible for transplant.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

See Section 8 for further details on the comparison with other literature section.

Three records were identified comparing the efficacy of cyclophosphamide, bortezomib, and dexamethasone (CyBorD) to lenalidomide and dexamethasone (Rd also referred to as Ld). These records were provided by the submitter and identified through a search conducted by CADTH contained relevant information to the current review.

Jimenez-Zepeda et al 2017 abstract[4] reported the findings of a RCT comparing CyBorD to Ld for the treatment of Non-Transplant Eligible MM patients in Alberta. One-hundred and thirty patients were treated with CyBorD and 71 patients were treated with Ld. The primary outcomes were: overall response rate (ORR), progression free survival (PFS), time to second objective disease progression (PFS2). The study also reported on very good partial response (VGPR). These outcomes were presented before the median overall-survival had been reached. ORR and ≥VGPR rates were 84.8% and 56.8% for patients treated with CyBorD, and 82.8% and 54.2% for Ld (p=0.3). Median OS had not been reached for either group. Median PFS was 22.5 months for CyBorD and 29 months for Ld (p=0.2). Median PFS2 was 45.7 months for CyBorD and 39.2 months for Ld (p=0.8).

Jimenez-Zepeda et al 2018's abstract and poster[5,6] 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)[5,6]. 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 [5,6]. VGPR was also reported. 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).

Based on the three records identified, CyBorD and Ld have similar clinical outcomes. The assumption that the outcomes achieved with CyBorD could be used as markers for the otucomes achieved with Ld is likely valid.

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. The generalizability table considers the Durie 2017 population.

Table 2: Assessment of generalizability of evidence for VRd for the treatment of newly diagnosed multiple myeloma (MM) in whom stem cell transplantation is not intended. Evidence is taken from the Durie et al 2017 publication.[1]

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(SWOG S0777)</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="3">Population</td><td>Organ dysfunction</td><td>Patients without impaired renal function or compromised bone marrow function were excluded</td><td>Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population?</td><td>Bortezomib, lenalidomide and dexamethasone are commonly used drugs. The dosing of these medications would be adjusted to account for the organ dysfunction or bone marrow function as per standard practice.</td></tr>
<tr><td>Performance Status</td><td>The majority of patients enrolled in the SWOG 0777 trial had an ECOG PS of 0 or 1 while a small minority had PS 2 or 3.
<table>
<tr><th>Parameter</th><th>VLd (N=263)</th><th>Ld (N=260)</th></tr>
<tr><td>Performance Status, n(%)</td><td></td><td></td></tr>
<tr><td>0 – Fully active</td><td>106 (40.3)</td><td>36 (13.8)</td></tr>
<tr><td>1 – Restricted activity</td><td>210 (79.8)</td><td>207 (79.6)</td></tr>
<tr><td>2 – No work, ambulatory</td><td>23 (8.7)</td><td>17 (6.5)</td></tr>
<tr><td>3 – Limited self-care</td><td>23 (8.7)</td><td>17 (6.5)</td></tr>
</table></td><td>Is the trial result generalizable to patients with an ECOG score of 2 or higher?</td><td>Patients with multiple myeloma often have symptoms related to the disease which may improve with reduction of disease burden. If that symptoms is a fracture, or symptomatic anemia, then ECOG can drop to 3 very easily. Myeloma often responds to therapy, and as hemoglobin can rise, or pain settle from fracture, patients PS can likewise improve with treatment. The CGP therefore agreed that use of this combination therapy in patients with ECOG PS 0-3 may be appropriate.</td></tr>
<tr><td>Stem Cell Transplant Intention</td><td>Patients a mixed population of transplant intended and not intended with 69% of VRd patients and 68% of Rd patients had an intent to transplant. Of these, 46 (10%) of 471 patients are estimated to have proceeded to stem-cell harvest and planned transplant1. Although the intent to transplant was a stratification factor at randomisation and balanced between treatment groups, the exact number of patients that proceeded to transplant from each treatment group is not reported.
In the CSR for the ITT population, 182/263 (69.2%) of VRd and 179/260 (68.8%) of Rd patients had an intent to transplant at progression. Of these, 44/163 (27%) of VRd patients and 31/187 (16.6%) Rd patients proceeded to transplant after disease progression. Patients without disease progression who proceeded to transplant after VRd treatment was 37/75 (49.3%) and Rd treatment was 21 (25.6%).</td><td>Does this restriction in the trial limit the interpretation of the trial results with respect to the target population? How does induction treatment affect eligibility criteria for transplant?</td><td>In Canada, eligibility for autologous stem cell transplantation is determined at the time of diagnosis, and is generally only considered as part of first line therapy. In the SWOG S0777 study, criteria for enrollment was patients for whom transplant was not intended. This study was initially designed when transplants were considered in a subsequent line of therapy after relapse and a small patient population (10%) did proceed with this. The impact of this patient population on overall survival is unclear. However, since transplant was considered after relapse, the PFS seen in the VLd group would be unaffected by this, and the benefits of this regimen in the first line setting remain clinically relevant.</td></tr>
</table>

Intervention	Administration of intervention	Bortezomib intravenously at 1-3 mg/m2 on days 1, 4, 8 and 11 combined with 25mg oral lenalidomide once a day on day 1 – 14 and 20mg oral dexamethasone on days 1, 2, 4, 5, 8, 9, 11, 12.	If the dose and/or schedule, and administrating method is not standard, are the results of the trial relevant in the Canadian setting? The standard of care in most jurisdictions is to administer bortezomib subcutaneously and weekly to reduce neurotoxicity; dexamethasone is also usually administered at 40 mg on the same days of bortezomib treatment	The dosing of bortezomib would remain consistent with the Canadian standard using once a week administration subcutaneously.
	Line of therapy	First line of treatment for patients with newly diagnosed MM. All participants were excluded if they had previous cancer indications	Are the results of the trial generalizable to other lines of therapy?	VRd is appropriate in the first line setting. There is no evidence to support its use in the second line setting. Other multi-agent regimens containing novel agents such as daratumumab or carfilzomib are appropriate at the time of relapse.
Comparator	Standard of Care	The comparator was lenalidomide combined with dexamethasone.	Is this standard care in Canada? Appropriate comparator?	In Canada, cyclophosphamide, bortezomib and dexamethasone (CyBorD) or Ld are the most commonly used current therapies in the first line setting for transplant ineligible patients. Although there is are no data comparing VLd with CyBorD, the CGP agreed using Ld is a reasonable and appropriate comparator.
Outcomes	Quality of Life	Quality of life data was not collected in SWOG S0777.	Does this restriction in the trial limit the interpretation of the trial?	The absence of quality of life data does not limit the interpretation of trial, given the significant change if overall survival noted.
Setting	Countries participating in the Trial	SWOG S0777 was conducted in centers in U.S.A, no centers in Canada were included.	Do trial results apply to patients from Canadian centres? Are there any known differences in practice patterns between the countries participating in the trials and Canada?	See comments above with respect to timing of autologous stem cell transplant. Otherwise, the trial population is consistent with patients treated for myeloma in Canada.

1.2.4 Interpretation

Burden of Illness and Need:

In 2017, 2900 patients will be diagnosed with myeloma, and 1450 patients will die of the disease.[7] Despite significant advancement in the treatment and life expectancy of patients with myeloma, it still remains an incurable disease. As a result, there is ongoing need to improve care by delaying disease progression and improving overall survival, while minimizing toxicity and complications of therapy, in order to preserve quality of life. Combining highly effective myeloma therapies such as lenalidomide and bortezomib in These are not references **Effectiveness:**

Progression-free Survival (PFS)—Primary Outcome:[1-3]

After a median of 7 years of follow-up, the PFS as per protocol showed a statistically significant difference of 41 months vs. 29 months favoring the VLd arm of the SWOG S0777 study of VLd vs Ld (95% 0.742 CI: 0.594-0.928, p=0.003). External review was also conducted with three different censoring rules applied by different regulator bodies. All of the results consistently showed a marked improvement in PFS and confirm a clinical benefit of VLd over Ld. With a 12 month absolute improvement in PFS, this would be considered clinically relevant.

Overall Survival (OS):[1-3]

Similar to PFS, after 7 years of follow-up, there is a statistically and clinically significant improvement in overall survival. In the clinical summary report, the median OS was 89.1 months for VLd compared to 67.2 months for Ld. In the most recent update abstract from 2018, the HR is 0.74 (95% CI: 0.543-0.926, stratified two-sided p-value 0.0114). When adjusted for age, the clinical significance persisted regardless of being less than or greater than 75 yrs old.

Quality of Life (QOL) analysis:[1-3]

No quality of life data are available for the SWOG S0777 study. Based on patient advocacy input, 83% of patients treated with VLd felt their expectations for myeloma were being met, compared to 80% in the Ld group. Sixty-seven percent of patients also said VLd improved their health and wellbeing, compared to 83% in the Ld arm. For patients treated with either treatment regimen, the side effects were felt to be tolerable the majority of time.

The patient advocacy input is a subjective assessment of quality of life in a small group of patients. It is difficult to draw conclusions about the impact of either of these regimens, beyond anecdotal confirmation that the treatment can potentially improve QOL.

Safety:

Toxicity:[1-3]

Adverse Events (AE), grade 3 or higher, were more common in patients treated with VLd (82%), compared to Ld (75%). Adverse events were more commonly seen in patients treated with VLd for neuropathy (76 patients vs. 25 patients), and GI toxicity (53 patients vs. 17 patients). Other common side effects included hematologic toxicity and metabolic abnormalities which were similar between the two groups. Secondary malignancies and thrombotic events were rare and balanced between the two group. Although two deaths were reported in the VLd arm, these were not attributed to the treatment. The side effect profile of VLd is predictable and manageable. There were no unexpected side effects of the triplet regimen that were identified in this study.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit of VLd compared to Ld as first line therapy for patients with newly diagnosed myeloma not eligible for transplant. The CGP based its conclusion on one high-quality randomized controlled trial that demonstrated a clinically and statistically significant benefit in progression-free survival (PFS) and overall survival (OS) for VLd compared to Ld. The adverse event profiles were similar between the two groups and toxicities were predictable and manageable. Consequently, VLd can be considered a new standard therapy in the first line setting for transplant ineligible patients.

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

- In Canada, cyclophosphamide, bortezomib and dexamethasone (CyBorD) or Ld are the most commonly used current therapies in the first line setting for transplant ineligible patients. Although there are no data comparing VLd with CyBorD, using Ld is a reasonable and appropriate comparator.
- Ld and CyBorD have previously been shown to have similar efficacy.[4-6] Since VLd has demonstrated superiority over Ld, this can serve as an appropriate surrogate for Canadian patients. It is reasonable to believe that the magnitude of benefit would be similar if the comparator was CyBorD.
- In Canada, eligibility for autologous stem cell transplantation is determined at the time of diagnosis, and is generally only considered as part of first line therapy. In the SWOG S0777 study, criteria for enrollment was patients for whom transplant was not intended. This study was initially designed when transplants were considered in a subsequent line of therapy after relapse and a small patient population (10%) did proceed with this. The impact of this patient population on overall survival is unclear. However, since transplant was considered after relapse, the PFS seen in the VLd group would be unaffected by this, and the benefits of this regimen in the first line setting remain clinically relevant.
- This study provides insufficient evidence to support or refute the use of VLd as an induction regimen prior to stem cell transplant.
- VLd is appropriate in the first line setting. There is no evidence to support its use in the second line setting. Other multi-agent regimens containing novel agents such as daratumumab or carfilzomib are appropriate at the time of relapse.
- The sequencing of these other agents are dependent on the treatment and responses that patients had to first line therapy, as well as individual characteristics and comorbidities of patients. As a result, the sequence of other therapies remains unclear.
- If a patient progressed on full dose maintenance lenalidomide as outlined in the SWOG S0777 study, lenalidomide would not be considered for subsequent lines of therapy. However, if lenalidomide maintenance therapy was discontinued due to side effects or patient preference, rechallenging on a subsequent line of therapy may be appropriate.
- There is insufficient evidence to know the benefit of VLd in patients with primary amyloidosis. However, for patients with myeloma and complications of amyloidosis as a consequence of the disease, VLd would be an appropriate first line regimen if other inclusion criteria are met.
- The dosing of bortezomib would remain consistent with the Canadian standard using once a week administration subcutaneously.
- Cytogenetic testing is routinely done for patients with myeloma, at the time of diagnosis. However, this testing would not impact the choice of therapy in the first line setting. The use of cytogenetic testing would remain the same as current standard practice.
- If VLd is approved, there is no evidence to guide appropriate timing for adding bortezomib for patients already on Ld in the first line setting.

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.

2.2 Description of the Condition

Multiple myeloma is an incurable plasma cell neoplasm that represents 1.3-1.5% of all new cancers in Canada with an estimated 2900 new cases annually with 1,450 patients dying from myeloma[7]. The median age of diagnosis is 69 years with a 5-year overall survival estimated at 48.5%[7].

The morbidity and mortality from myeloma stem from direct and indirect effects of the malignant plasma cells and its monoclonal protein. The diagnosis of symptomatic multiple myeloma (myeloma that necessitates treatment) is made based on the International Myeloma Working Group (IMWG) recommendations [8]. Specifically, one must document clonal bone marrow plasma cells ≥ 10% and any one of the following: 1) Hypercalcemia, 2) Renal insufficiency, 3) Anemia, 4) Bone lesions or 5) Clonal bone marrow plasma cells ≥ 60%, Involved:uninvolved serum free light chain ratio ≥100 or > 1 focal lesions on MRI studies.

Without effective therapy, the illness results in a significant decrease in quality of life and is universally fatal. The management of symptomatic myeloma is reliant on effective systemic chemotherapy and supportive measures (pain control, antibiotics, kyphoplasty, radiation therapy, dialysis and psychosocial supports). The median survival of symptomatic myeloma has significantly improved over the last 20 years with concurrent improvements in Health Related Quality of Life (HRQOL) [9-12]. Improvements in outcomes, including overall survival have been predominantly attributed to improvements in chemotherapeutics [10,13].

2.3 Accepted Clinical Practice

The mainstay of myeloma treatment is anti-cancer drug therapy. Patients with good performance status, preserved organ function and limited comorbidities are potentially eligible for high dose chemotherapy and autologous hematopoietic stem cell transplantation, which improves median survival by 2-3 years in comparison to conventional dose therapy. Approximately half of patients newly diagnosed will not be eligible for this treatment due to advanced age, comorbidities and/or impaired functional status[14]. A strategy of early, effective and continuous therapy result in better outcomes of Overall Survival[15], Progression Free Survival 1 & 2[15], HRQOL [16,17] and possibly economics [18] rather than a strategy of intermittent therapies based on symptoms.

There are 4 main currently available/approved classes of chemotherapeutics in Canada include: 1) Alkylators such as melphalan, cyclophosphamide, liposomal doxorubicin, 2) Immunomodulatory agents (IMiD) such as thalidomide, lenalidomide and pomolidomide, 3) Proteosome Inhibitors (PI) such as bortezomib and carfilzomib, and 4) Monoclonal antibodies such as daratumumab.

For fit patients, an autologous stem cell transplant (ASCT) can be considered as part of the initial therapy of myeloma and substantially improves life expectancy. However, the toxicity of this treatment precludes its use in less fit patients. Choosing the appropriate patients for ASCT is at the discretion of the treating physician and approximately half of patients are transplant eligible. Prior to receiving high dose melphalan chemotherapy conditioning for the transplant, three or four cycles of systemic induction therapy is used to control the disease,

improve the health of the patient, and clear the bone marrow to allow for easier stem cell collection. In Canada, induction is usually with bortezomib, cyclophosphamide and dexamethasone. Patients receive one or sometimes two cycles of high dose chemotherapy with stem cell rescue as part of front line treatment. Following stem cell transplant, further consolidation therapy is sometimes given; an indefinite course of maintenance therapy with lenalidomide or bortezomib is often given with the intent to prolong remission duration and survival[19]. The administration of induction therapy, high dose chemotherapy with autologous stem cell transplant, and post-transplant consolidation and/or maintenance therapy is all considered as being part of first-line treatment.

Current standard frontline systemic therapy regimens in Canada for transplant-ineligible patients include combinations of bortezomib with an alkylating agent (melphalan or cyclophosphamide) and a corticosteroid; or lenalidomide and dexamethasone. This submission will review the use of bortezomib, lenalidomide and dexamethasone as a standard 3-drug frontline regimen.

Regardless of the choice and duration of initial therapy, myeloma will eventually relapse in the vast majority and further therapy will be required. There is no single clear choice of therapy in relapsed and/or refractory myeloma. The choice of agents used in this setting will depend on the outcomes with the regimens used in prior lines of therapy, the condition of the patient, the expected tolerance of adverse effects, and the availability of treatment options. Although patients are often not offered therapy with drugs that have been part of a regimen to which the disease has become refractory, there is evidence that combining such agents sometimes induces responses, particularly in the case of combining proteasome inhibitors and immunomodulatory drugs[20].

2.4 Evidence-Based Considerations for a Funding Population

The vast majority of newly diagnosed myeloma cases will need immediate therapy, and approximately half of these patients are transplant-ineligible.[14] Lenalidomide and bortezomib are currently approved by Health Canada for use in patients with transplant ineligible newly diagnosed multiple myeloma in combination with other drugs. However, the triplet therapy combining these agents in conjunction with dexamethasone has not been approved. The population studied in the key clinical trial under consideration here includes patients with newly diagnosed myeloma who are not intended to have a stem cell transplant. Historically, stem cell transplant was an option for patients at the time of relapsed disease, and consequently, patients were assessed whether a transplant was intended in the first line setting or not. Standard practice in Canada has evolved, and the current standard of practice is to determine eligibility for autologous stem cell transplantation at the time of diagnosis, and is generally only considered as part of first line therapy.

2.5 Other Patient Populations in Whom the Drug May Be Used

Many other triplet therapies have been studied and approved in the relapsed setting for myeloma. Recently approved regimens in Canada include daratumumab with either lenalidomide or bortezomib and dexamethasone, or carfilzomib, lenalidomide and dexamethasone. Bortezomib, lenalidomide and dexamethasone has not been studied extensively in the setting of relapsed disease. Consequently, the focus of this review will be limited to the front line setting for patient's ineligible for autologous stem cell transplant. There is insufficient evidence to extrapolate the results of this study to the transplant eligible population.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Myeloma Canada (MC), provided input on the review for lenalidomide plus bortezomib and dexamethasone for patients who have not had previous treatments and are not eligible for a stem cell transplant.

Myeloma Canada conducted two online surveys, one for patients and one for caregivers, which were available from September 12 to October 7, 2018. Canadian patients and caregivers received the survey from Myeloma Canada support groups and American patients and caregivers through the Internal Myeloma Foundation. Data were collected on the patient and caregiver experience with two treatment combinations: lenalidomide plus bortezomib and dexamethasone (LVd) or lenalidomide and dexamethasone (Ld) for patients who have not had previous treatments.

Eight patients had experience with the combination of LVd and twelve patients had experience with Ld. All of the patient respondents were not eligible for stem cell transplant. It is to be noted that not all patients responded to every question on the survey and were able to provide input on specific questions.

One caregiver who provided care to a patient on LVd and four caregivers who provided care for patients on Ld responded to the survey. Of the respondents, three of the patients who used the combination (lenalidomide (Revilimid) in combination with Bor-Dex) were Canadian, the other 5 were from the USA. The one caregiver respondent for the combination under review was from the USA. All 4 of the caregivers of the comparative treatment were Canadian.

In addition, of the six patients on the LVd regimen, one was on the treatment for 1 to 6 months, three patients were on the treatment for 7 to 12 months and two patients were on the treatment for 1 to 2 years. Of the ten patients who were on the Ld combination regimen, two were on the treatment for 1-6 months, one was on treatment for 7 to 12 months, three were on the treatment for 1 to 2 years and two were on the treatment for more than 4 years.

To inform the Disease Experience, Experiences with Currently Available Treatments, and Improved Outcomes sections of this summary, Myeloma Canada referred to previous patient advocacy submissions for carfilzomib and ixazomib in 2016 and 2017, respectively. For the pCODR 10084 Carfilzomib (Kyprolis) submission, Myeloma Canada conducted two online surveys between August 15, 2016 and August 31, 2016. A total of 344 responded to the patient survey (Survey 1) and a total of 123 responded to the caregiver survey (Survey 2). For the pCODR 10088 Ixazomib (Ninlaro) submission, Myeloma Canada conducted two additional surveys from May 24 to June 10, 2016 (survey directed to patients – Survey 3) and then another from November 15 to December 2, 2016 (survey directed to caregivers – Survey 4). A summary of their responses is provided in this report.

From a patient's perspective, patients value managing key symptoms, such as, infections, kidney problems, mobility, pain, fatigue, neuropathy and shortness of breath. The ability to work, followed by the ability to exercise, travel, volunteer, concentrate, conduct household chores, fulfill family obligations, and spend time with family were noted to impact or limit day-to-day activity and quality of life of patients. According to Myeloma Canada, when it comes to treating myeloma, it is important for patients: to maintain quality of life or normal life, manage/minimize side effects, control the disease, have access to effective treatments, control symptoms, achieve or maintain remission, and prolong survival, among others.

Of the patients who had experience with LVd, disease control and prolonged life were ranked as the most important treatment expectations followed by fewer side effects and a normal life. The majority of patients (83%) who used the LVd noted that the administration of the treatment combination had a negative effect. Patients noted that the side effect profile of LVd was tolerable or very tolerable. Myeloma patients have noted significant side-effects of their treatment, such as neuropathy and serious consequences of their myeloma such as mobility problems due to bone pain and fractions. Additional side effects were noted as follows: 50% found

diarrhea somewhat intolerable, followed by constipation, fatigue, dyspnea, decreased appetite and headache. Of the 6 patients who responded to the survey, 50% indicated good quality of life, 33% rated fair quality or life and 17% noted excellent quality of life. Patient respondents who took LVd, 83% noted that the treatment combination met their expectations in treating myeloma, 67% of the 6 respondents noted that the treatment combination improved their health and well-being and 50% noted that the treatment combination improved their long term health outlook. One caregiver who had experience with VLd responded to the survey. The caregiver noted that there were no challenges while helping to manage the side effects of the treatment combination. The caregiver respondent also rated the activities of daily living as not being affected while managing these side effects.

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

3.2 Condition and Current Therapy Information

As noted by Myeloma Canada, sections pertaining to the Condition and Current Therapy are taken from a previous pCODR submission for ixazomib (Ninlaro).

3.2.1 Experiences Patients have with multiple myeloma

When Myeloma Canada asked patient respondents to rate on a scale of 1-5, how important it is to control various aspects 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, Myeloma Canada expressed that all aspects were nearly always 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

When Myeloma Canada asked patient respondents to rate on a scale of 1-5, how much symptoms associated with myeloma impact or limit day-to-day activity and quality of life, patient respondents indicated that their ability to work was most affected, followed by the ability to exercise, travel, volunteer, concentrate, conduct household chores, fulfill family obligations, and

spend time with family. Based on the responses below, Myeloma Canada expressed that symptoms associated with myeloma have a higher than neutral 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

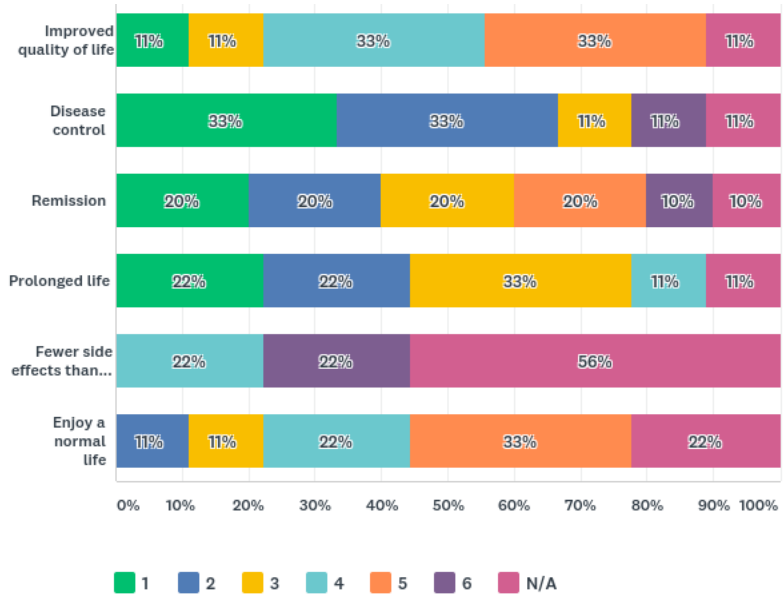
The following are quotes reported by Myeloma Canada help to illustrate the effect of myeloma on patients:

- *"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."*

3.2.2 Patients' Experiences with Current Therapy for multiple myeloma

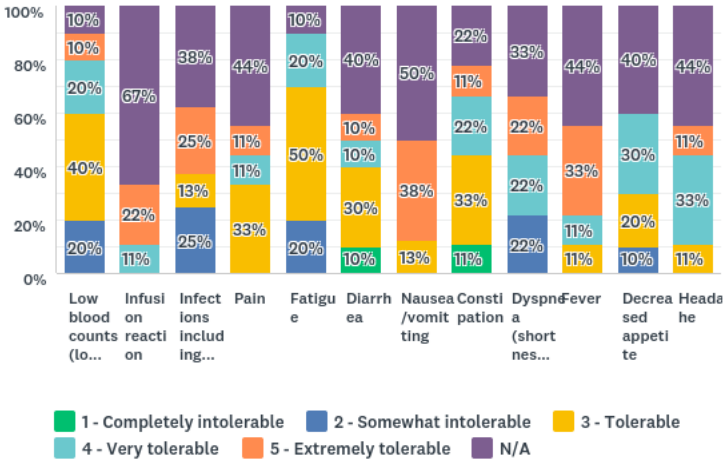
Myeloma Canada provided information for patient expectations. For the Ld group, 33% of the 10 respondents who used this treatment ranked disease control as the most important expectation followed by remission and prolonged life at 20%.

Chart 2 – Patient expectations of comparative treatment combination



Additionally, Chart 7 below illustrates that a number of the side effects were either not applicable (N/A), tolerable, very tolerable or extremely tolerable for the 10 respondents who had experience with Ld. Among these patients, 10% found diarrhea and 11% found constipation completely intolerable and 20-25% indicated that low blood counts, fatigue, dyspnea and infections were somewhat intolerable.

Chart 7 – Tolerability of each side effect experienced by comparative treatment combination



Additional verbatim open comments for the Ld combination: *less energy, steroids are very hard to live with---chronic diarrhea---lots of side effects. Put me in the hospital due to extreme water retention and water on my lungs---couldn't eat food, vomiting, diarrhea, general weakness*

As per Myeloma Canada, additional information was obtained from the patient input summary from a previous pCODR submission of 10088 Ixazomib (Ninlaro) for Multiple Myeloma. This information is noted below:

Myeloma Canada asked patient respondents in an open-ended question, "what is important to you when it comes to treating your myeloma?" A total of 261 patients provided a response. According to Myeloma Canada, the responses fell into the following categories (starting with the most important): to maintain quality of life or normal life (36%), (followed by) manage/minimize side effects (20%), control the disease (19%), access to effective treatments (15%), control symptoms (13%), achieve or maintain remission (7%), prolong survival (7%), access to a skilled medical team (6%), to be cured (5%), affordable treatments (3%), disease status (2%), maintain physical fitness (1%), minimal use of drugs (0.5%), and (lastly) to feel hopeful (0.5%).

Also, when Myeloma Canada asked patient respondents to rate the importance of access to effective treatments for myeloma on a scale of 1-5, with 1 being "not important" and 5 being "very important", a total of 97% of patients selected 5 – "very important". N = 294.

In addition, when Myeloma Canada asked patient respondents to rate the importance for the respondent and his/her physician to have choice based on each drug's known side effects on a scale of 1 -5, with 1 being "not important" and 5 being "very important", a total of 86% of patients selected 5 – "very important". N = 294.

Moreover, a total of 89% of patient respondents reported that "improvement to quality of life" was a "very important" consideration with any treatment for myeloma. N = 294.

When Myeloma Canada asked Canadian patient respondents in a multiple choice question about the financial implications of their treatment for myeloma, a total of 51% of patients selected drug costs, as well as, parking costs, followed by travel costs (33%), lost income due to work absence (32%), drug administration fees (17%), medical supply costs (16%), and accommodations costs (15%). A total of 25% of patients responded that they had no financial implications related to treatment for myeloma. N = 202. Of note, the total is greater than 100%, since respondents were able to select more than one answer; as well, only Canadian respondents were included in this question analysis.

When Myeloma Canada asked Canadian patient respondents in an open-ended question about hardships accessing treatment for myeloma. The majority of patients (74%) indicated that they had not experienced financial difficulties (patients who responded 'no', 'not that I'm aware of', 'not so far' and 'not yet' to this open ended question were combined), followed by Yes (23%),Too Soon to Tell (1%) and N/A (2%). The 'yes' responses included: denied treatment (6%), drug not covered (5%), limited to covered treatments (3%), travel to treatment (2%), cost of drugs (2%), access to physician (1%), access to available bed (1%), treatment not available (1%), and waited for treatment approval(1%). N = 155. Of note, only responses from Canadian respondents were included in this question analysis.

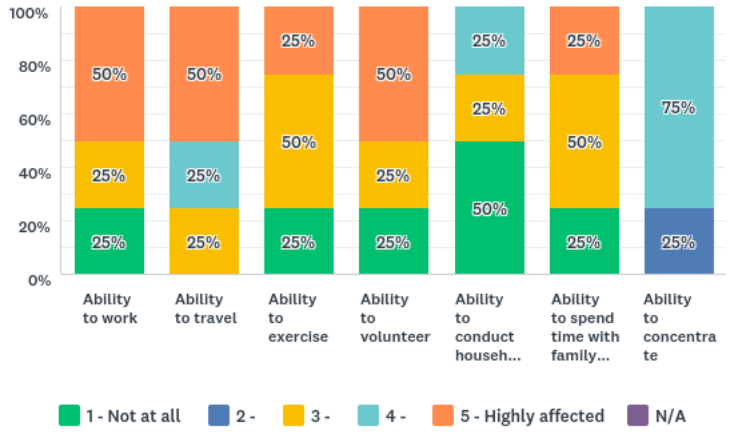
For the 10187 Carfilzomib Input, Myeloma Canada reported that the main treatments patients used at that time were as follows: dexamethasone (84%), bortezomib (77%), lenalidomide (71%), autologous stem cell transplant (60%), melphalan (57%), cyclophosphamide (44%), pomalidomide (17%), thalidomide (16%), vincristine-doxorubicin-dexamethasone (9%), and allogenic stem cell transplant (9%) (N = 295). Of note, the total percentages of responses is greater than 100%, since respondents were able to select more than one answer. Selected from a list, the side effects experienced by patients with these treatments included: fatigue (88%), neuropathy (62%), insomnia (57%), stomach issues (48%), nausea (46%), shortness of breath (43%), pain (38%), confusion (30%), 'does not apply to me as I have yet to be treated' (2%), and 'I don't know or can't remember' (0.3%). Under "other" an additional 7% of patient respondents cited stomach related issues (such as diarrhea and constipation) as a side effect, followed by skin rash (3%), cramps (2%), and emotional issues (2%).

3.2.3 Impact of Multiple Myeloma and Current Therapy on Caregivers

Four respondents who cared for someone who used the Ld treatment combination responded to the survey when asked if there were any challenges while helping to manage the side effects of the treatment combination 3 said yes and 1 said no.

Chart 9 below illustrates the effects of managing side effects on the caregiver and how the activities of daily living of the caregivers of the Ld treatment were affected by the management of the side effects. Four respondents were asked to rate the impact of caring for a patient on their daily activities on a scale of 1 – 5, with 1 being not at all, and 5 being highly affected. Of the caregivers who responded, 75% rated ability to concentrate as a 4, while 50% rated ability to work, travel and volunteer as a 5.

Chart 9 – Effect of managing side effects on caregiver



As per Myeloma Canada, additional information with respect to caregiver experience with myeloma is taken from the pCODR 10088 submission from Ixazomib (Ninlaro) for Multiple Myeloma.

Myeloma Canada asked 123 caregiver respondents in Survey 2 to rate on a scale of 1-5, with 1 = "not at all" and 5 = "significant impact", how much caring for someone with myeloma limits their day-to-day activity and quality of life. Among these respondents 115-120 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.

When Myeloma Canada asked caregiver respondents in Survey 4 in an open ended question about challenges encountered while helping to manage treatment side effects for the person they are caring for, the caregiver respondents provided the following verbatim responses:

- *"Doesn't seem to have any major side effects the dexamethasone is worse."*
- *"Tired so I give it to him at night."*
- *"My husband developed shortness of breath. Not sure if this is from Ninlaro since it developed after taking Carfilzomib and didn't go away."*

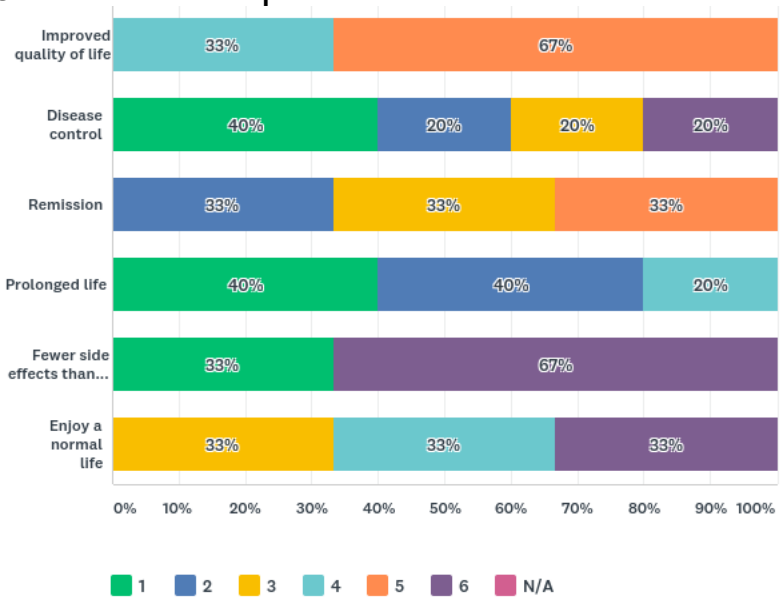
- *"Two to Three days after taking Ninlaro and Dex while taking Revlimid she crashes and is very tired for 2 days."*
- Of note, Ninlaro = ixazomib, Dex = dexamethasone, and Revlimid = lenalidomide.

3.3 Information about the Drug Being Reviewed

3.3.1 Patient Expectations for and Experiences To Date with Lenalidomide

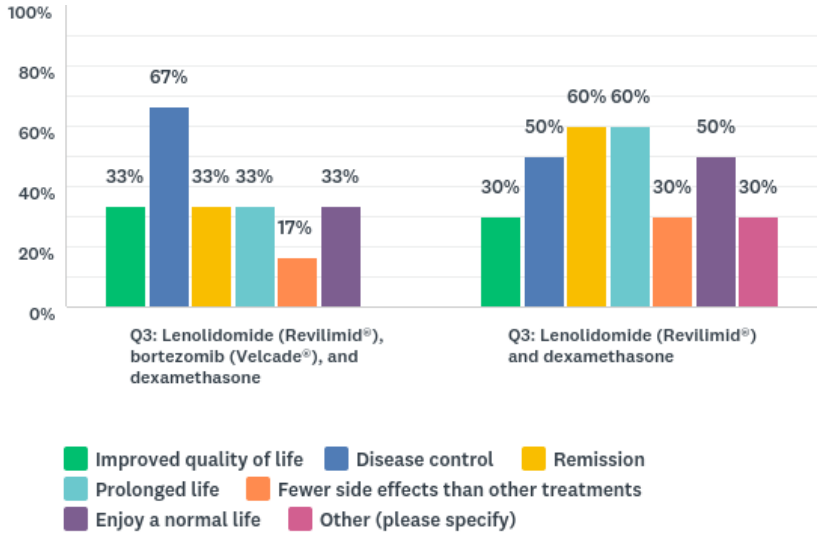
Myeloma Canada provided information on the expectations of 6 patients from treatment with RVd. These patients had not had previous treatments and were not eligible for a stem cell transplant. Chart 1 is a visual presentation of patients' responses and illustrates that 40% of respondents, of the 6 patients, who used the treatment combination under review ranked disease control and prolonged life as the most important treatment expectations followed by fewer side effects and the ability to enjoy a normal life being at 33%.

Chart 1 - Patient expectations of treatment combination under review



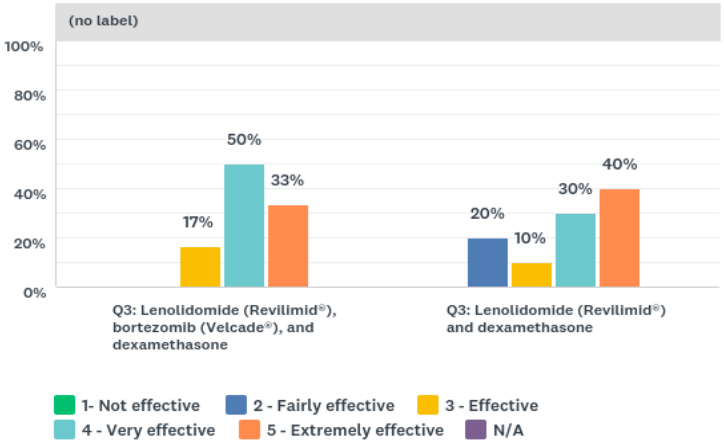
Myeloma Canada provided additional details of patients' expectations fulfilled by the type of treatment combination. Chart 3 below summarizes which treatment expectations were fulfilled by a treatment combination. Six patients received RVd and 10 patients received Ld.

Chart 3 - Expectations fulfilled by treatment combinations



Myeloma Canada collected information on the patients' effectiveness rating of treatment combinations in controlling myeloma. Of the 6 patients, 83% of respondents who used the treatment combination under review rated the effectiveness 4 or higher versus 70% of the 10 respondents for the Ld regimen.

Chart 4 - Effectiveness rating in controlling myeloma of treatment combinations



Patients who responded to the survey were asked about whether the administration of the treatment combination had a negative effect. Of the 6 patients who used the combination treatment under review, 83% replied yes, and 60% of the 10 patients who used Ld alone responded yes.

Chart 5 below illustrates the side effect tolerability of the different treatment combinations respondents had experience with. Of the 6 respondents who used the treatment combination under review, all patients (100%) of patients found the side effects to be either tolerable (50%) or very tolerable (50%). Of the 10 patients who used Ld, the majority of the respondents found the

side effects to be tolerable (30%), very tolerable (50%), extremely tolerable (10%) and 10% found the side effects to be completely intolerable.

Chart 5 – Side effect tolerability of the treatment combinations

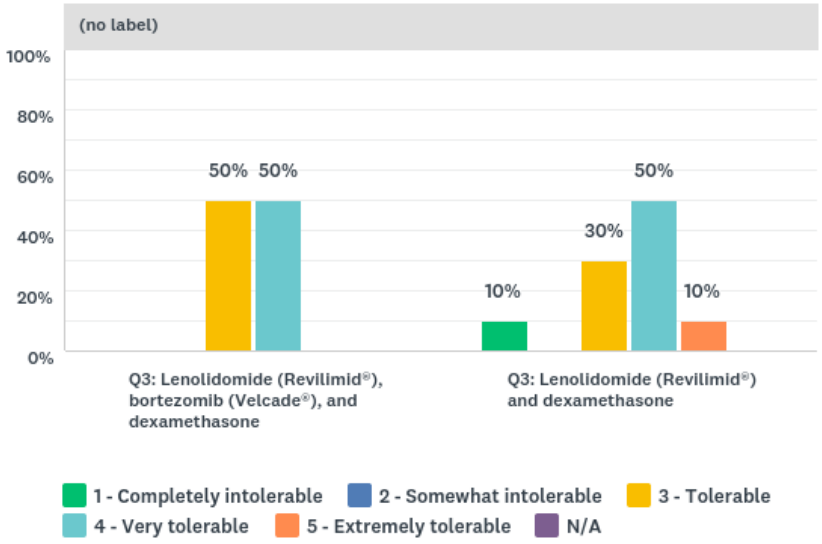
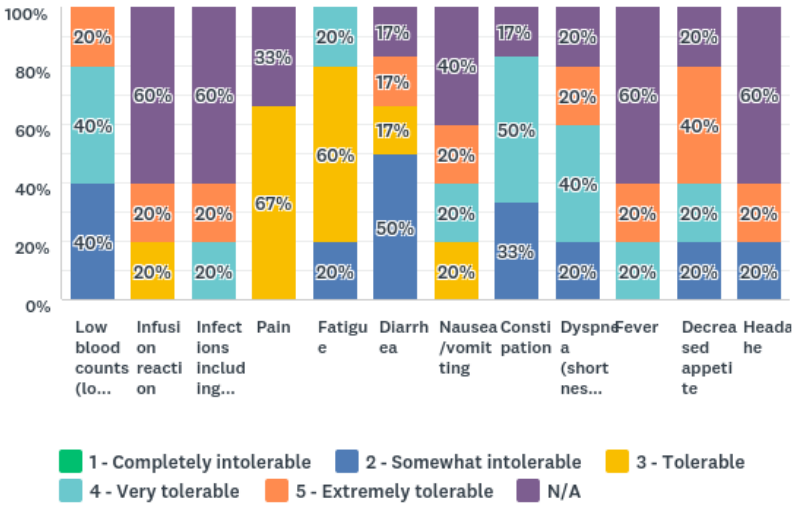


Chart 6 below illustrates that the majority of side effects for patients who used the treatment combination under review. Patients were able to rate side effects as N/A, tolerable, very tolerable or extremely tolerable. The majority of respondents (50%) found diarrhea to be somewhat intolerable, followed by constipation (33%), and 20% each for fatigue, dyspnea, decreased appetite and headache. None of the respondents found the side effects completely intolerable.

Chart 6 – Tolerability of each side effected by treatment combination under review



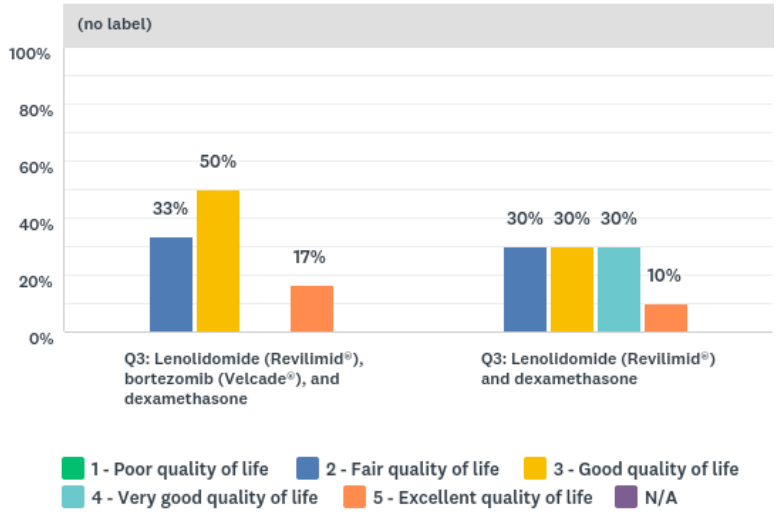
Additional verbatim open comments for the combination under review are noted below:

"once adjusted was tolerable--- chemo-brain--- Weight Gain, fatigue, weakness--- stomach issues, taste of food--- Side Effects"

One caregiver who responded to the survey and had experience with caring for a patients who was treated with the treatment combination under review, was asked if there were any challenges while helping to manage the side effects of the treatment combinations. The one caregiver said no. When asked to rate how the activities of daily living were affected while helping to manage side effects, the respondent who provided care to the patient-, rated each activity of daily living as 1 “not at all”.

Myeloma Canada collected information on the quality of life rating from the survey respondents. Chart 8 below illustrates the responses to the question that asked how patients would rate their quality of life since starting the treatment combination. Total number of respondents were 6 for the treatment combination under review and 10 for the respondents who had experience with Ld.

Chart 8 – Quality of life rating



When the respondents were asked if the treatment combination met their expectations in treating their myeloma, 83% of those who used the treatment combination under review responded yes and 80% of those who used the Ld combination responded yes. There was one open ended response among the respondents who used the treatment combination under review (VLd) – *Didn’t know what to expect*. And two comments among the respondents who used Rd alone respondents --- *It took care of the back pain and has managed the disease. Now that dosage is lower and I’m off dex, I feel better.--- It stopped working after 3-1/2 years.*

When the 6 respondents who used the treatment combination under review were asked if the treatment combination improved their health and well-being, 67% responded yes, 17% responded no and 17% selected too soon to tell. One respondent provided a comment under please explain --- *Numbers have moved to very good partial remission l*

Of the 9 patients who responded to this question and used the Rd treatment, 89% responded yes and 11% selected too soon to tell.

When the 6 respondents who used the combination under review were asked if the treatment combination improved their long-term health outlook, 50% responded yes, 17% responded no and 33% responded too soon to tell. 100% of the 8 patients who responded to this question and used the Rd combination responded yes.

3.4 Additional Information

None

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). 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:

- Incremental costs due to drug wastage, treatment duration, and budget impact

Please see below for more details.

4.1 Currently Funded Treatments

For patients with newly diagnosed multiple myeloma who are not eligible for stem cell transplantation (SCT), the standard of care is lenalidomide plus dexamethasone (Ld), cyclophosphamide/bortezomib/dexamethasone (CyBorD), bortezomib/melphalan/prednisone (VMP), and cyclophosphamide/bortezomib/prednisone (CyBorP). In most provinces, the commonly used treatments are Ld or CyBorD.

PAG noted that the SWOG S0777 trial was compared to Rd which is a relevant comparator in Canadian practice. PAG is also seeking information on comparative efficacy of lenalidomide/bortezomib/dexamethasone (VLd) to CBD.

4.2 Eligible Patient Population

PAG noted that approximately half of patients with newly diagnosed multiple myeloma are not candidates for SCT. PAG is seeking guidance on determining patients who would not be eligible for SCT and therefore, could be eligible for treatment with VLd.

PAG is seeking clarity on whether patients with newly diagnosed amyloidosis who are transplant ineligible, would be eligible for VLd in this setting. Clinicians may also want to use RVD as initial treatment in transplant eligible patients (e.g., as induction chemotherapy pre-ASCT) given the results seen for transplant ineligible patients. PAG is seeking clarity on whether patients with newly diagnosed multiple myeloma that are transplant eligible, would be eligible for RVD in this setting.

If recommended for reimbursement, PAG noted patients currently treated with Ld for newly diagnosed multiple myeloma not eligible for transplant would need to be addressed on a time-limited basis (i.e., addition of bortezomib).

There is a potential for indication creep to: other bortezomib-based regimens (i.e., addition of lenalidomide) in the first-line setting, maintenance treatment following transplant, and other lines of therapy.

4.3 Implementation Factors

The cost of lenalidomide is high and duration of therapy is indefinite since it is assumed patients will be treated until disease progression, toxicity, or patient withdrawal. 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. The budget impact may be significant but there is uncertainty in the degree of the impact. PAG also has concerns for incremental costs due to drug wastage, as wastage is frequent in clinical practice given dose modifications or progression.

In the pivotal trial, bortezomib was dosed at 1.3 mg/m^2 intravenously on days 1, 4, 8 and 11 with dexamethasone dosed at 40 mg on days 1, 8, 15, and 22. PAG noted that the standard of care in most jurisdictions is to administer bortezomib subcutaneously and weekly to reduce neurotoxicity; dexamethasone is also usually administered at 40 mg on the same days of bortezomib treatment. Some patients may not be able to tolerate the twice weekly bortezomib dose. If VLd is recommended for reimbursement, PAG is seeking guidance on the use of bortezomib and dexamethasone as per standard of care (i.e., weekly subcutaneous bortezomib and dexamethasone on the same days). PAG is also seeking guidance on whether there would be instances where patients should be given bortezomib beyond eight cycles (i.e., every two weeks as maintenance after cycle 8).

Additional pharmacy and nursing resources will be required for administration (i.e., bortezomib) and monitoring for adverse events (e.g., cytopenias).

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

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

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

4.4 Sequencing and Priority of Treatments

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

- Treatments patients would be eligible for after progression on VLd in first-line;
- Use of lenalidomide in second and subsequent lines of therapy for relapsed/refractory multiple myeloma;
- Sequencing of first and second-line therapies (e.g., carfilzomib-based,

lenalidomide-based, daratumumab-based, bortezomib-based regimens, and pomalidomide-dexamethasone) for patients that are either eligible or ineligible for autologous stem cell transplant.

PAG noted that daratumumab in combination with bortezomib, melphalan and prednisone, will be reviewed at pCODR, for the treatment of patients with newly diagnosed multiple myeloma who are not suitable for autologous stem cell transplant.

4.5 Companion Diagnostic Testing

PAG is seeking guidance on whether cytogenetic testing is routinely conducted for patients with multiple myeloma, and if yes, how are results used to guide treatment options.

4.6 Additional Information

At the time of PAG input, there was no information on pricing. PAG noted that flat pricing of the different strengths of lenalidomide tablets is a potential barrier to implementation.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One single and one joint clinician input on behalf of the Myeloma Canada Cancer Research Network were provided, representing a total of six clinicians. The registered clinicians provided input on lenalidomide in combination with bortezomib and low-dose dexamethasone (VLd) for treatment of newly diagnosed multiple myeloma patients ineligible for stem cell transplant.

Clinicians noted that lenalidomide plus dexamethasone (Ld) and cyclophosphamide combined with dexamethasone plus bortezomib (CyBorD) were the most relevant comparators to RVd. Patients eligible for RVd include those newly diagnosed with multiple myeloma receiving treatment in the first-line and who are ineligible for stem cell transplant. While RVd would take place as first-line treatment, frail patients may still be considered for Ld or CyBorD for first-line therapy. In terms of sequencing, daratumumab based regimens were considered the most likely second-line therapy following VLd, followed by regimens containing pomalidomide or carfilzomib. All clinicians providing input agreed that data supports the efficacy of RVd in the first-line setting for patients ineligible for transplant.

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

5.1 Current Treatment(s) for this Multiple Myeloma

The following treatment options were indicated as being relevant comparators for this indication: Ld, CyBorD, bortezomib plus melphalan plus prednisone (VMP), and cyclophosphamide with bortezomib and Prednisone (CyBorP). The most common treatments were agreed upon as being CyBorD and Ld.

One of the clinicians stated that CyBorD and Ld are considered equivalent in terms of efficacy based on recent Canadian data. Ld is thought to be favourable compared to CyBorD due to its ease of use and better toxicity profile. In terms of overall survival (OS), this clinician stated that recent Canadian real world data suggested an equivalency between CyBorD and Ld, but a slight superiority of Ld over CyBorD in regards to progression free survival (PFS) in an unmatched population.

5.2 Eligible Patient Population

There was agreement that eligible patients include those newly diagnosed with multiple myeloma receiving treatment in the first-line and who are ineligible for autologous stem cell transplant either due to age or presence of comorbidities. For example, ineligibility for transplant may be due to age (older than 70 years of age), or who present with neuropathy, which is contraindicated with bortezomib. These patients would not be offered the lenalidomide triplet therapy. The single clinician input stated that inclusion and exclusion criteria from the trial were considered reasonable and applicable to clinical practice. This clinician stated that CRAB criteria could be used to identify eligible patients. Unmet need in this population was identified by the joint clinician input who suggest a need for potent therapy resulting in long term disease control. For patients who are fit enough for this triplet, one of the clinicians suggested it should be considered standard of care.

Patients with high risk of cytogenic disease, where a proteasome inhibitor (PI) containing regimen appears to be important, were highlighted as a population of interest. Patients with standard risk of disease were suggested to benefit tremendously from the VLd combination. One of the clinicians stated that VLd and similar combinations, such as immunomodulators and proteasome inhibitors, show better efficacy in patients compared to combinations with only two agents, such as Ld, or even therapies containing three agents but lacking an immunomodulator or PI, such as

CyBorD. Patients who are considered frail were stated to continue being offered Ld or CyBorD. The clinician input stated that VLd is expected to be appropriate for all groups unless patients present with contraindications. It was identified that there would be no specific contraindications to this combination therapy that would not already apply to the individual agents which are available in some combinations already. There are no patient subgroups who are not expected to respond to VLd.

5.3 Relevance to Clinical Practice

The combination is well tolerated with no significant increases in toxicity compared to Ld and CyBorD. One of the clinicians highlighted data from the pivotal S0777 trial which demonstrated increased hematological toxicity with neutropenia, and non-hematological toxicity with fatigue, peripheral neuropathy, diarrhea and thromboembolism with the addition of bortezomib to lenalidomide and dexamethasone. The trial was also stated to show an increased median PFS from 30 to 43 months, and median OS from 64 to 75 months. This 11 month increase in OS was also highlighted by the second clinician input, as well as the fact that PFS curves remained separate for the duration of follow-up. Depth and duration of response were considered important considerations for both long and short term outcomes.

The lenalidomide combination therapy was stated to have proven efficacy and is already considered standard of care in the US and in Europe. VLd is different from standard Canadian treatment approaches, since it represents the first PI-immunomodulatory-steroid combination being evaluated for reimbursement in the front-line setting. Greatest benefit from the treatment is usually observed in the first-line setting and clinicians would prefer to use the best combinations as early as possible. One clinician noted that there are no studies showing negative impacts of using multi-agent and multi-class therapy early in disease. This approach also does not select for more resistant or aggressive disease at relapse. It was also identified that VLd is important to have while clinicians wait for data on the efficacy and safety of monoclonal antibodies, such as daratumumab, to become available in this setting.

5.4 Sequencing and Priority of Treatments with Lenalidomide

All clinicians agreed that VLd would be front line therapy for all eligible patients. Lenalidomide triplet therapy would be considered for all patients who would be eligible for Ld or CyBorD. However, Ld and CyBorD would still have a role in frail patients with contraindications, although this would represent a minority of patients. Having VLd as first line treatment was stated by one clinician as helping to ensure the best depth and duration of response, which would be difficult to achieve in later lines of therapy.

One clinician stated that if patients receive VLd therapy upfront, they may not be eligible for daratumumab combined with lenalidomide and dexamethasone at a later time. Carfilzomib combined with dexamethasone or pomalidomide, were indicated as other treatments potentially available for patients downstream. For patients whose treatment with VLd is stopped due to toxicity or because they are refractory to bortezomib, clinicians may refrain from using bortezomib

subsequently. One clinician stated that treatment with a PI at time of relapse will be available to patients, either as re-treatment with bortezomib or treatment with carfilzomib.

5.5 Companion Diagnostic Testing

None

5.6 Additional Information

None

5.7 Implementation Questions

5.7.1 In regards to question 3.4 above, please consider the optimal sequencing following treatment with RVD, specifically: daratumumab-based regimens, carfilzomib-based regimens, pomalidomide, and/or re-treatment with bortezomib/lenalidomide-based regimens.

5.7.2 Please also consider the preferred regimen for initial treatment of patients who are ineligible for transplant, and how RVD compares to other currently available regimens (e.g., daratumumab-based regimens).

The following sequence was suggested by one of the clinicians providing input, should the treatment currently under review be available to patients in the first line:

- Lenalidomide plus bortezomib and dexamethasone → PI-containing regimen, i.e., carfilzomib plus dexamethasone, daratumumab plus bortezomib and dexamethasone, CyBorD or VMP

The above sequence indicates PI-containing regimens as the second-line treatment option. It was noted that lenalidomide-containing regimens, such as daratumumab plus lenalidomide and dexamethasone or carfilzomib plus lenalidomide and dexamethasone, would not be provided to patients as patients would be considered refractory, unless they had stopped receiving lenalidomide due to toxicity or patient preference. Pomalidomide based regimens were also indicated as a possible second-line treatment option for patients, although this was stated to likely be reserved for later lines of therapy.

Another clinician suggested the following sequence, and indicated it being the best scenario if the treatment under review were to be used in the first line:

- Lenalidomide plus bortezomib and dexamethasone → daratumumab plus bortezomib and dexamethasone → pomalidomide based treatment, i.e., pomalidomide plus cyclophosphamide and dexamethasone → carfilzomib and dexamethasone

The following sequence was provided by another clinician, and considered the most optimal based on currently approved regimens in Canada, although it was noted that sequencing could change with more clinical data:

- Lenalidomide plus bortezomib and dexamethasone → daratumumab based regimen, i.e., daratumumab plus lenalidomide and dexamethasone → carfilzomib based triplet, i.e.,

carfilzomib plus pomalidomide and dexamethasone (CPd) or a clinical trial with a novel agent in third line

As an alternative to the above sequence, for patients who are not bortezomib refractory, the following sequence was provided:

- Lenalidomide plus bortezomib and dexamethasone → daratumumab plus bortezomib and dexamethasone → carfilzomib and dexamethasone → pomalidomide plus cyclophosphamide + dexamethasone

For patients who are bortezomib and lenalidomide refractory, the following sequence was provided:

- Lenalidomide plus bortezomib and dexamethasone → daratumumab and dexamethasone → carfilzomib and dexamethasone → pomalidomide plus cyclophosphamide and dexamethasone

In general, daratumumab based regimens were considered next choice for second-line treatment, if VLd were to be used as first line therapy. Following lines of therapy included options involving pomalidomide or carfilzomib based treatments.

The clinicians noted that daratumumab is currently not an approved first-line therapy in Canada. The ALCYONE and MAIA trials were referenced, which present data regarding front-line daratumumab plus VMP and daratumumab plus Ld, respectively; both of these regimens were stated to be alternatives to front-line VLd and superior to currently funded standards, including Ld, VMP and CyBorD. Using daratumumab in the first line would impact options available to patients in the second-line.

5.7.3 In clinical practice, is cytogenic testing routinely completed for patients with multiple myeloma? If yes, how are results used to guide treatment options (i.e., in this setting)?

All clinicians agreed that cytogenic testing is routinely conducted. Patients with high cytogenic risk (mainly del17p) generally require greater oversight and would be treated with a bortezomib based regimen. Data from Larocca A et al, ASH 2017 abstract #744 was referenced, which showed better PFS and OS for patients initially treated with bortezomib based treatment without lenalidomide compared to lenalidomide-based treatment without bortezomib. The treatment under review contains both bortezomib and lenalidomide, which may result in further benefit to patients. Maintenance with bortezomib in high risk patients may also be possible if patients are initially treated with CyBorD. One clinician stated that FISH analysis should be performed in this high risk population. However, with regimens such as lenalidomide plus bortezomib and dexamethasone, FISH analysis is of less interest. Another clinician stated that while cytogenic testing is conducted for all patients, test results do not at this time change the treatment strategy for transplant ineligible patients.

5.7.4 In clinical practice is there evidence to support the use of VLD in the first-line setting for patients who are ineligible for transplant?

All clinicians agreed that evidence supported the use of lenalidomide combined with bortezomib and dexamethasone in the first-line for patients who are ineligible for transplant. The pivotal S0777 trial was referenced, which showed an improvement in PFS and OS for patients. One of the clinicians stated wanting to use the VLd for transplant eligible patients as well.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy of Revlimid (lenalidomide capsules), bortezomib and low-dose dexamethasone (VLd) in patients with newly diagnosed multiple myeloma (MM) in whom stem cell transplantation is not intended.

Appropriate comparators and outcomes of interest are summarized in Table 3 in section 6.2.1.

No Supplemental Questions relevant to the pCODR review or the Provincial Advisory Group (PAG) were identified.

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. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A. 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 patient population is newly diagnosed patients with multiple myelomas (MM) in whom stem cell transplantation is not intended.

The definition of 'intent for/no intent for' stem cell transplantation as compared to 'eligible/ineligible' for stem cell transplantation required further clarification due to the lack of a clear operational definition within the literature.

Clarification was provided by the clinical guidance panel and the following definitions were used:

- Transplant eligible: At the time of initial diagnosis the patient requires treatment and does not have a specific contraindication to high dose chemotherapy and autologous stem cell transplantation.
- Transplant ineligible: At the time of initial diagnosis the patient requires treatment and has a specific contraindication to high dose chemotherapy and autologous stem cell transplantation (e.g. age, heart weakness, liver function inadequate for safe exposure to transplantation)
- Intent to transplant: The patient is not ineligible for autologous stem cell transplantation and may be offered autologous stem cell transplantation in the future, either as part of primary treatment or at the time of relapse
- No intent to transplant: The patient is either ineligible for autologous stem cell transplantation or, for some other reason, will never be offered autologous stem cell transplantation at any time in the future, either as part of primary treatment or at the time of relapse.

The categorization of "intent to transplant" may be fluid over the course of the patient's trajectory and has changed over time. "Intent to transplant" may mean that the transplant was not planned as part of primary treatment but that transplant might be offered in the future, perhaps as part of primary treatment but more likely as treatment for relapse.

Table 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs	Patients with multiple myelomas (MM) who are newly diagnosed in whom stem cell transplantation is not intended. Include "untreated" patients and "high risk newly diagnosed patients".	Lenalidomide in combination with bortezomib and low-dose dexamethasone (VLd). It can be followed by Lenalidomide Maintenance therapy.	Lenalidomide and dexamethasone OR Cyclophosphamide in combination with bortezombi, dexamethasone OR Daratumabab in combination with lenalidomide and bortezomib and dexamethasone†	Overall survival (All-cause mortality) Progression free survival Quality of life Response rate Grade 3 and 4 adverse events Withdrawal due to adverse effects Any adverse effects Patient preference for treatment Secondary Malignancies Time to Next Treatment
RCT: Randomized control trial; MM: Multiple myelomas				

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

† *This combination is included to encompass upcoming expected drugs for the same patient population and indication.*

6.2.2 Literature Search Results

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; the Cochrane Central Register of Controlled Trials (Jan 2019) via OVID; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Revlimid (lenalidomide) and Velcade (bortezomib) and dexamethasone and multiple myeloma.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. The search was also limited to English-language documents published between January 1, 2014 and January 17, 2019.

The search is considered up to date as of May 1, 2019.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov 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 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.

6.2.3 Study Selection

Two members of the pCODR Methods Team independently selected studies for inclusion in the review according to the predetermined protocol, all studies identified by either reviewer were included in full text review. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

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

6.2.4 Quality Assessment

Assessment of study bias was performed by two members of the pCODR Methods Team independently, differences were resolved through discussion. The SIGN-50 Checklist for randomized control trials was used. Additional limitations and sources of bias were identified by the pCODR Review Team. See table 10 for more details.

6.2.5 Data Analysis

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

6.2.6 Writing of the Review Report

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

The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.

The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.

The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

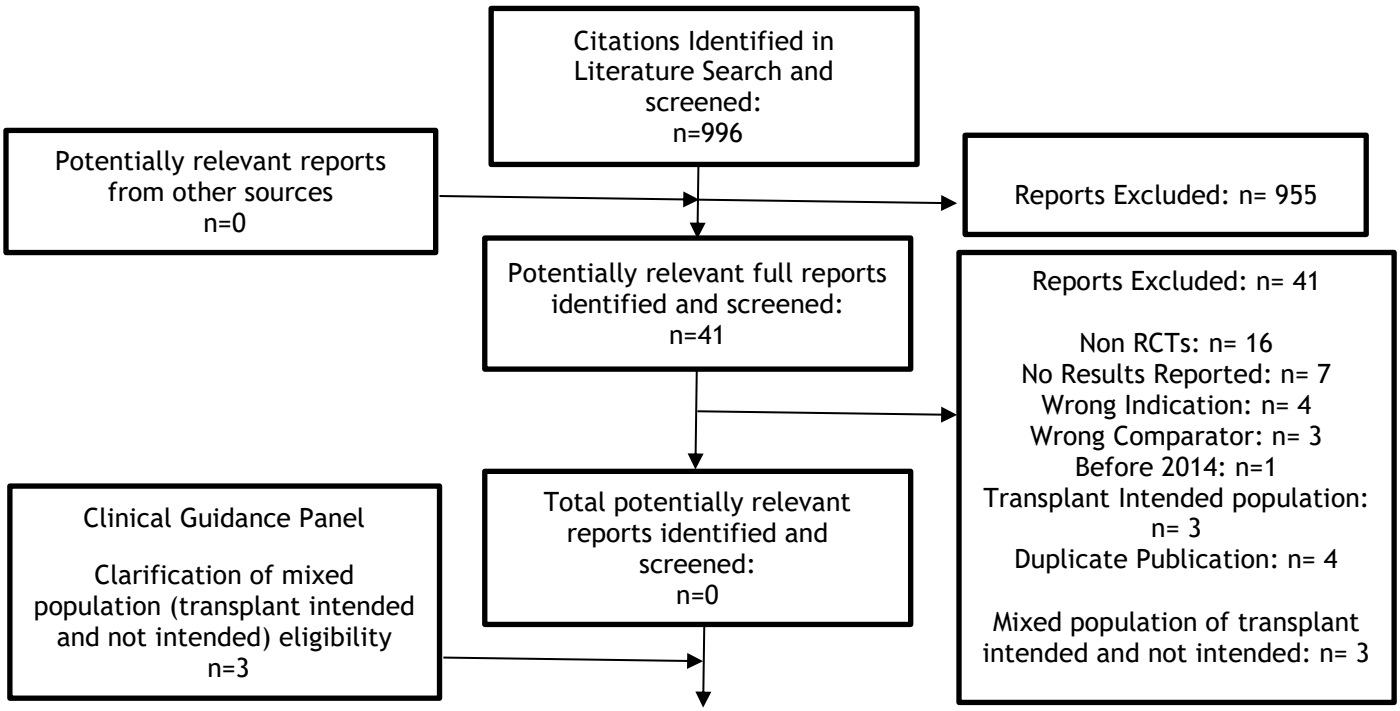
6.3 Results

6.3.1 Literature Search Results

Of the 996 reports identified in the literature search, 41 potentially relevant abstracts were identified and screened as full texts (Figure 1).

Based on the study selection criteria outlined in section 6.2.1, all 41 full texts were initially excluded (including the SWOG S0777 trial) for the following reasons: duplicate publication (n=4), not a RCT (n=16), no results reported (n=7), published before 2012 (search filter) (given the large number of literature identified, a date filter was used to include only studies published between 2014 -2019) (n=1), not in patients with multiple myeloma (n=4), wrong comparator (n=3), patient population was those intending to receive a stem cell transplant (n=3), patient population was mixed intent and no intent to transplant with no stratified outcomes presented (n=3). In further discussions with the clinical guidance panel and clarity on the definition of 'intent/no intent for transplant' as compared to 'eligible/ineligible for transplant', a decision was made to include one study (3 reports), which had a mixed intent and no intent to transplant population, previously excluded as part of the screening. Input from the CGP noted the changing nature of the definition over both a patient's treatment course and changes in practice over time. The CGP felt that intent to transplant has conceptually changed in practice. Based on this change, three reports from one RCT were included.

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



Note: Additional data related to studies SWOG S0777 were also obtained through the Submitter and summarized in a clinical summary report and Summary of Included Studies.[3]

6.3.2 Summary of Included Studies

The pCODR systematic review included one RCT, SWOG S0777[1] that assessed the safety and efficacy of Revlimid (lenalidomide) in combination with Velcade (bortezomib) and low-dose dexamethasone as a first line treatment in patients with newly diagnosed multiple myeloma. Three citations were associated with this trial (1 publication, 1 conference abstract, 1 description of trial on clinicaltrials.gov). In addition, the documents provided through the pCODR submission (clinical summary report, CSR) provided an additional source of data. Each of these reports use a different sample size of the trial patients, data cut-off date, outcome assessment and analysis approach. The reason for the different sample sizes in the different sources of data is explained further in the text. The pCODR reviewers collated data from all three data sources while highlighting relevant differences where appropriate. An overview of each of the reports is provided in Table 4.

The primary publication for this trial was published in Lancet 2017[1] by Durie et al. A second publication reported a longer-term follow-up in a conference abstract[2]. In this updated analysis n=11 patients were removed from the analysis population due to missing data, insufficient data, early/late baseline laboratory data and other reasons[2]. For data analysis, the SWOG S0777 publications by Durie et al. in 2017 and 2018 assessed eligible analysable populations per protocol with Southwest Oncology Group (SWOG), part of a National Cancer Institute (NCI) censoring rule[3]. The SWOG S0777 was a cooperative group study, not originally designed to support regulatory application for market authorization. The submitter obtained rights to the data for this study and developed a dataset and analysis appropriate to support a regulatory submissions to health authorities[3]. The submitter's analysis of the SWOG S0777 trial was submitted in a CSR[3]. The CSR analysis includes 52 more patients than the Durie publication due to reassessment of ineligibility. It assessed the intention to treat (ITT) population with an independent response adjudication committee (IRAC review) with SWOG censoring rules. An IRAC consists of hematologists with expertise and experience in the diagnosis and management of multiple myeloma that were blinded to treatment assignment to review the data and provide a retrospective, independent, verifiable, objective, and documented assessment of each randomized patient's response and date of disease progression. Along with IRAC review, the ITT population was assessed with EMA censoring as well as with FDA censoring[3].

Table 4. Summary of patient population's datasets.

	Clinical Summary Report[3]		**Primary Publication (Durie et al. 2017)[1]**		**Conference Abstract (Durie et al. 2018)[2]**	
Author	Submitter		Durie et al.		Durie et al.	
Data cutoff date	November 5, 2015 (Primary Analysis)	December 1, 2016 (Follow-up)	November 5, 2015 (Primary Analysis)		May 15, 2018 (Follow-up)	
Population	Intention to Treat		Per Protocol (eligible analysable)		Per Protocol (eligible analysable	
Treatment Arm	VLd	Ld	VLd	Ld	VLd	Ld
Enrolled	264	261	264	261	264	261
-Withdrew/invalid consent*	1	1	1	1	1	1
-Deemed ineligible	-	-	21	31	21	31
-Deemed ineligible at 2018 update[&]	-	-	-	-	7	4
Total Population Analyzed	263	260	242	230	235	226[†]
Enrolled minus Total Population Analyzed	N=2[#]		N=54		N=63	

Baseline Characteristics	See section 6.3.2.1, table 8		See section 6.3.2.1, table 7		Not Reported[&]
Outcome Assessment by IRAC	Yes		No		No
Censoring Applied	NCI – SWOG, EMA and FDA		NCI - SWOG		NCI - SWOG

Abbreviations: IRAC: Independent Response Adjudication Committee
***** deemed ineligible mainly due to missing, insufficient, or early or late baseline data (n=41)
[†] The CSR indicated the total population analyzed as 225, but correct number should be 226
[&] Missing, insufficient, early/late baseline laboratory data and other reasons (n=11)[2]
[#] The CSR does not give an account for the two patients that are missing from the analysis. It is unclear if these are the two patients who withdrew consent (n=1) and or had invalid consent (n=1).

6.3.2.1 Detailed Trial Characteristics

Table 5: Summary of trial characteristics of SWOG S0777 as reported in Durie et al. 2017[1]

Trial Design	Eligibility Criteria	Intervention	Comparator	Outcomes
SWOG S0777[1]				
Clinical trial NCT00644228 Parallel assignment, open-label, phase 3, RCT Patient enrollment: Between April 2008 and February 2012 N randomized= 525 Multicentre (139 centres in U.S.A) Randomized 1:1 ratio, stratified by: • International Staging System (I, II, or III) • Intent to transplant (yes vs no) Funded NIH, NCI, NCTN, Millennium Pharmaceuticals, Takeda Oncology Company, and Celgene Corporation	Key Inclusion Criteria: 18≥ years of age • Newly diagnosed myeloma • Presence of CRAB criteria (C=calcium, R=renal impairment, A=anaemia, B=bone involvement) Exclusion Criteria: • Patients with previous cancer prior to study registration or enrolment • Creatine clearance ≤30mL/min • Cardiac status New York Heart Association class III/IV or recent myocardial infarction • Active hepatitis B or C or HIV or uncontrolled other infection • Poorly controlled diabetes	The following VLd regimen was given as eight 21-day cycles: Bortezomib intravenously at 1-3 mg/m2 on days 1, 4, 8 and 11 combined with 25mg oral lenalidomide once a day on day 1 – 14 and 20mg oral dexamethasone on days 1, 2, 4, 5, 8, 9, 11, 12. Herpes simplex virus prophylaxis. 325mg oral aspirin once a day to reduce risk of thromboembolic complications. Upon completion of VLd regimen, patients received 25mg oral lenalidomide once a day for 21 days combined with 40mg oral dexamethasone once a day for days 1, 8, 15, 22 of each 28-day cycle. Given until patient refusal unrelated to adverse event, adverse event or side effect, disease progression or relapse,	The following Ld regimen was given as six 28-day cycles: 25mg oral lenalidomide once a day for days 1 – 21 combined with 40mg dexamethasone on days 1, 8, 15, 22. 325mg oral aspirin once a day to reduce risk of thromboembolic complications.	Primary: • Progression-free survival from time of randomisation Key Secondary: • Overall survival • Rate of overall response (partial or better) • Safety • Bank specimens for future translational medicine research

		or death or other not protocol specified reasons.		

Table 6. Select quality characteristics of SWOG S0777 for Revlimid (lenalidomide) in combination with Velcade (bortezomib) and low-dose dexamethasone in patients with newly diagnosed multiple myeloma as reported in Durie et al. 2017[1]

Study	SWOG S0777[1]
Treatment vs. Comparator	Revlimid (lenalidomide) in combination with Velcade (bortezomib) and low-dose dexamethasone
Primary outcome	PFS
Required sample size	Not Reported
Sample size	471[†]
Randomization method	1:1 stratified by dynamic allocation algorithm based on International Staging System stage (I, II, or III) and intent to transplant (yes vs no).
Allocation concealment	Yes
Blinding	No
ITT Analysis	No[††]
Final Analysis	Yes[†††]
Early Termination	No
Ethics Approval	Yes
[Abbreviations] ITT – intention to treat; PFS – progression free survival [†] - number based upon primary analysis published in Lancet 2017[1] [††] - ITT analysis provided by submitter in clinical summary report, [3] [†††] - PFS final analysis found in conference abstract[2]	

a) Trials

One randomized control trial, SWOG S0777, was included in this review and details were summarized above in Table 5. Select quality characteristics of the trial were summarized above in Table 6.

SWOG S0777 was a phase III clinical trial. The trial was a randomized, open labelled, two-arm, parallel arm study comparing bortezomib in combination with lenalidomide and low-dose dexamethasone (VLd) to lenalidomide and dexamethasone (Ld). The patient population were newly diagnosed or recurrent MM patients that were treatment naïve, and 18 years of age or older. Key patient inclusion and exclusion criteria are summarized in Table 4.

The SWOG S0777 trial was a multi-centre trial, including 139 Universities and medical centres from one country, United States of America[1]. Randomization was generated using a dynamic allocation algorithm developed by Pocock and Simon and stratified based on International Staging System stage (I, II, III) and intent to transplant (yes vs no)[1].

The primary endpoint for the trial was progression free survival (PFS) from the time of randomisation. SWOG S0777 was designed to have 87% power to detect a hazard ratio (HR) of 1.5 for VLd vs Ld with an overall study alpha of 0.05. Secondary endpoints included overall survival, rate of overall response (partial response or better), safety, and to bank specimens for future translational medicine research.

The funding for SWOG S0777 are from NIH, NCI, NCTN, Millennium Pharmaceuticals, Takeda Oncology Company, and Celgene Corporation for provision of study drug under their respective cooperative research and development agreements with the NCI[1].

b) Populations

As three different subsets of the population were included in the 3 different reports (Durie 2017, Durie 2018 and CSR), each is discussed separately and in detail below.

Durie et al. 2017

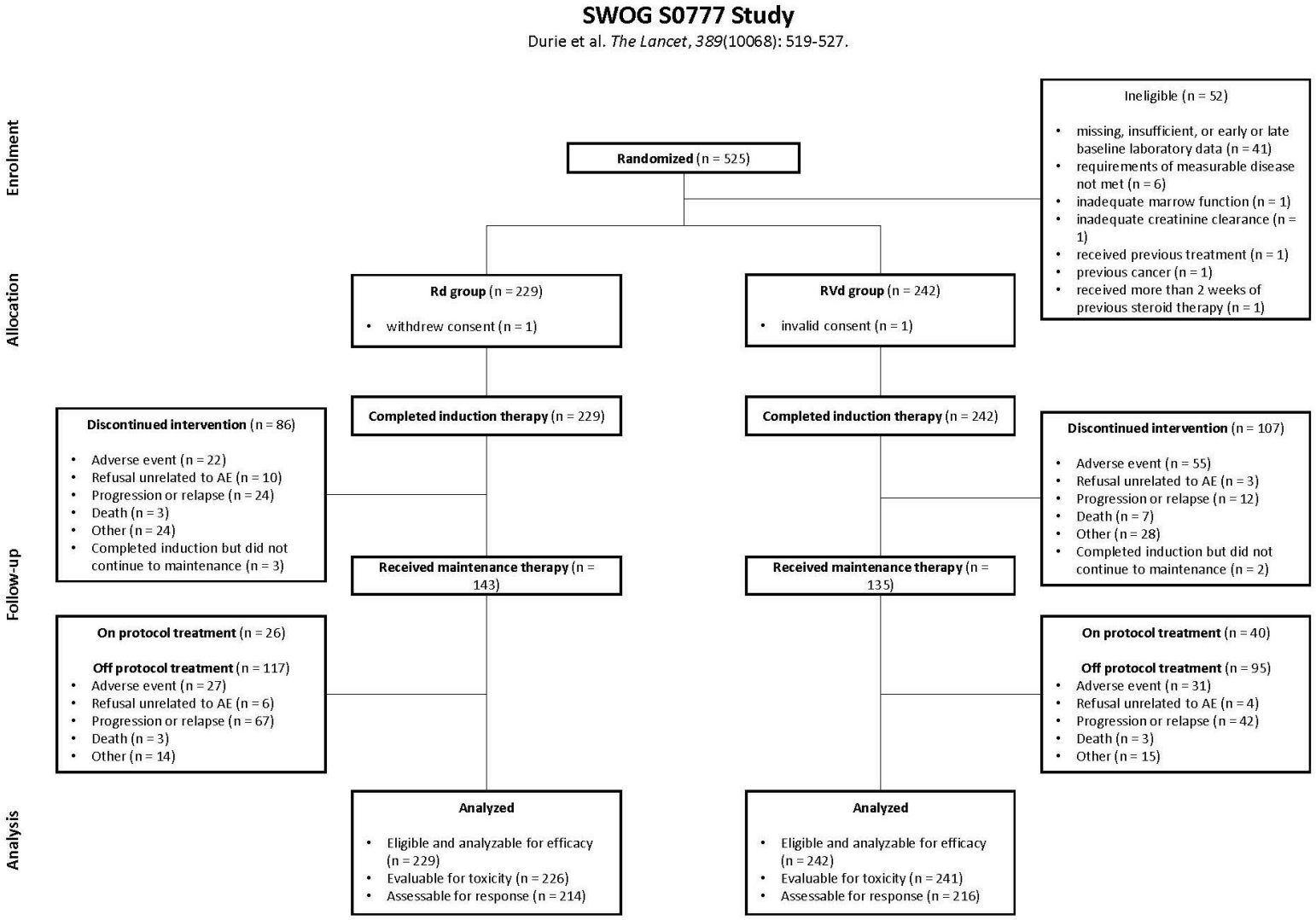
Of the 525 patients randomized, one patient from the VLd arm was removed due to invalid consent, and one patient from the Ld arm was removed due to withdrawn consent. Thus, 523 patients were included, 263 randomized to VLd, and 260 randomized to Ld[1].

During screening for eligibility, 21 patients in the VLd and 31 patients in the Ld arms were deemed ineligible mainly due to missing, insufficient, or early or late baseline data, see Figure 2 for the consort diagram from the publication[1]. Other reasons for ineligibility was due to requirements of measurable disease not met (n=6), inadequate marrow function (n=1), inadequate creatinine clearance (n=1), received previous treatment (n=1), previous cancer (n=1), or received more than 2 weeks of previous steroid therapy (n=1) [1]. Finally, 242 patients were eligible for VLd treatment and 230 were eligible for Ld treatment[1]. Population characteristics for SWOG S0777 are summarized in Table 7. The proportion of those over the age of 65 years was 38% in the VLd arm and 48% in the Ld arm. The median age in the VLd group was 63 years (range of 56-70 years) and in the Ld group 61 year (range 56-71) [1]. The proportion of women in the VLd group was 37% and 47% for Ld[1]. The majority of patients had an intent to transplant with 69% in VLd group, and 68% in Ld group[1].

Table 7. Select baseline patient characteristics for SWOG S0777 based on the eligible analysable per protocol population with a data lock of November 5, 2015 as reported in Durie et al. 2017[1].

	Total	VLd	Ld
ECOG performance status > 1	64/471 (14%)	28/242 (12%)	36/229 (16%)
Age ≥ 65 years	202/471 (43%)	93/242 (38%)	109/229 (48%)
Women	196/471 (42%)	89/242 (37%)	107/229 (47%)
Intent to transplant	324/471 (69%)	168/242 (69%)	156/229 (68%)
Serum beta 2 microglobulin concentration ≥3.5 mg/L	282/459 (61%)	141/235 (60%)	141/224 (63%)
C-reactive protein concentration ≥8 mg/L	104/444 (23%)	48/225 (21%)	56/219 (26%)
Creatine concentration ≥2 mg/dL	22/471 (5%)	11/242 (5%)	11/229 (5%)
Lactate dehydrogenase concentration ≥2 U/L	166/462 (36%)	84/236 (36%)	82/226 (36%)
Albumin concentration <3.5 g/dL	197/466 (42%)	98/239 (41%)	99/227 (44%)
Haemoglobin concentration <10 g/dL	151/471 (32%)	79/242 (33%)	72/229 (31%)
Platelet count <150 x 10^9/L	21/469 (4%)	11/241 (5%)	10/228 (4%)
International Staging System stage III	157/471 (43%)	78/242 (32%)	79/229 (34%)
Data are n/N (%). ECOG = Eastern Cooperative Oncology Group			

Figure 2. Consort diagram of SWOG S0777 trial with eligible analysable population per protocol data locked for November 5, 2015 as reported in Durie et al. 2017.[3]



Durie et al. 2018

For this updated analysis, 11 additional patients were removed from the evaluable dataset (6 patients from VLd were missing or had insufficient early/late baseline laboratory data and 5 patients from Ld had other reasons for being deemed ineligible).[2] This resulted in a total of 235 and 225 patients eligible and analyzable randomized to the VLd and Ld groups, respectively[2]. Patient characteristics within this subset of patients are not reported and it is not known how the demographic characteristics may have changed from the Durie 2017 population nor between the VLd and Ld groups.

Clinical Summary Report

In the submitter's CSR, 523 patients were included (the 2 patients excluded from the total of 525 were due to invalid/withdrawal of consent)[3], see Figure 3 below for the consort diagram for this population. 263 patients were randomized for VLd treatment and 260 were randomized for Ld treatment[3]. Baseline characteristics for this population are reported below in Table 8. The median age in the VLd group was 63 years (range 35-85 years) and in the Ld group was 63 years (range 28-87 years) [3]. The proportion of women in the VLd group was 37.6% and 47.3% for Ld[3]. The majority of patients had an intent to transplant at progression with 69.2% in VLd group, and 68.8% in Ld group[3].

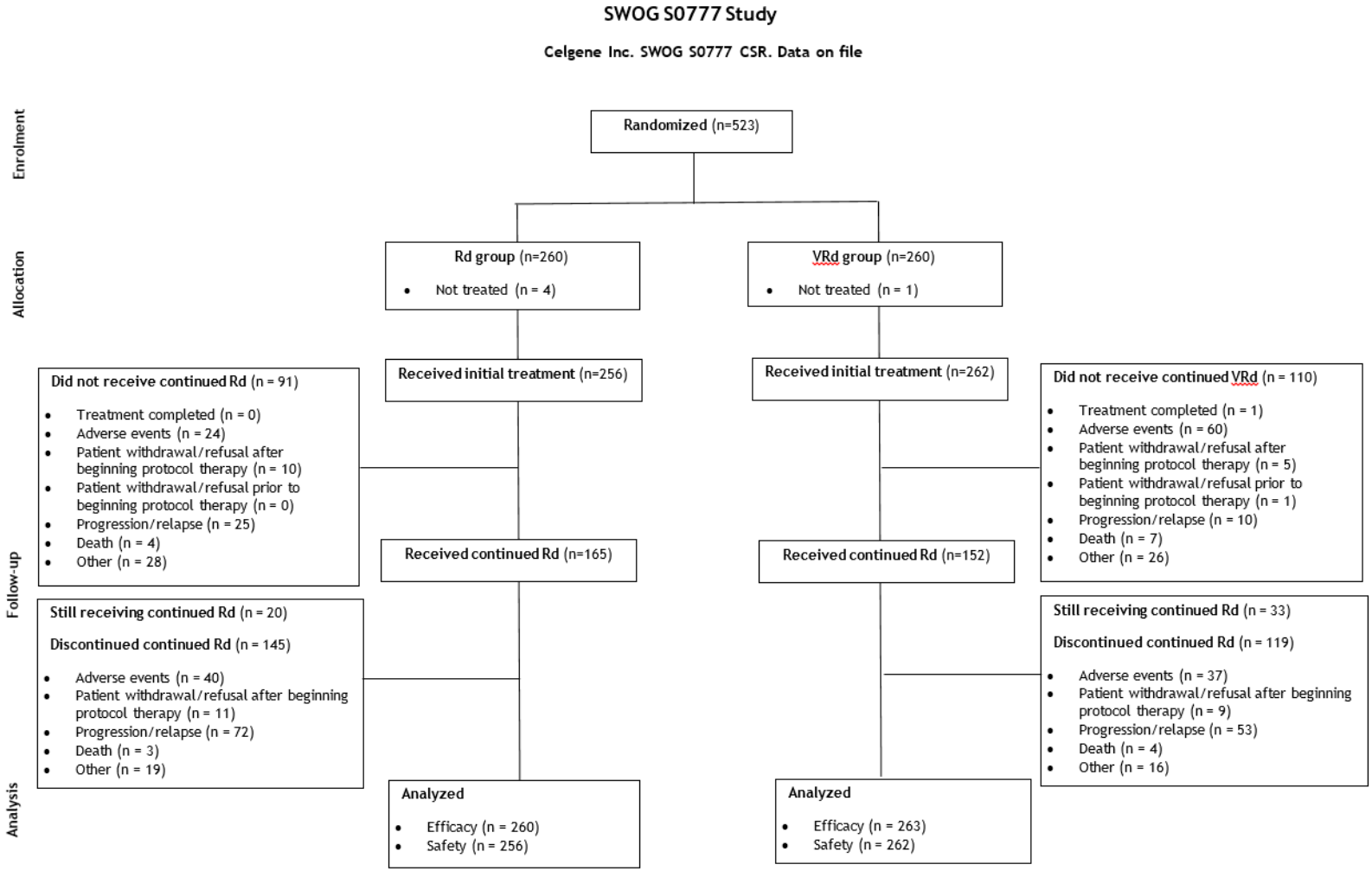
Table 8. Patient baseline clinical characteristics for SWOG S0777 based on the intention to treat population with a data lock of December 1, 2016 as reported in the clinical summary report[3].

Parameter	VLd (N = 263)	Ld (N = 260)	Total (N = 523)
Age (years)			
Median	63.0	63.0	63.0
Min, Max	35.0, 85.0	28.0, 87.0	28.0, 87.0
Age Group 1 (years), n (%)			
≤ 65	167 (63.5)	150 (57.7)	317 (60.6)
> 65	96 (36.5)	110 (42.3)	206 (39.4)
Age Group 2 (years), n (%)			
≤ 65	167 (63.5)	150 (57.7)	317 (60.6)
> 65 and ≤ 75	68 (25.9)	85 (32.7)	153 (29.3)
> 75	28 (10.6)	25 (9.6)	53 (10.1)
Sex, n (%)			
Male	164 (62.4)	137 (52.7)	301 (57.6)
Female	969 (37.6)	123 (47.3)	222 (42.4)
Race Group, n (%)			
Caucasian	210 (79.8)	207 (79.6)	417 (79.7)
Non-Caucasian	46 (17.5)	47 (18.1)	93 (17.8)
Unknown	7 (2.7)	6 (2.3)	13 (2.5)
ISS Stage, n (%)			
I	78 (29.7)	75 (28.8)	153 (29.3)
II	99 (37.6)	98 (37.7)	197 (37.7)
III	86 (32.7)	87 (33.5)	173 (33.1)
Revised ISS Stage, n (%)			
I	54 (20.5)	55 (21.2)	109 (20.8)
II	155 (58.9)	161 (61.9)	316 (60.4)
III	26 (9.9)	23 (8.8)	49 (9.4)
Missing	28 (10.6)	21 (8.1)	49 (9.4)

Parameter	VLd (N = 263)	Ld (N = 260)	Total (N = 523)
Intent to Transplant at Progression, n (%)			
No	81 (30.8)	81 (31.2)	162 (31.0)
Yes	182 (69.2)	179 (68.8)	361 (69.0)
Cytogenetic Risk, n (%)[a]			
High	30 (11.4)	36 (13.8)	66 (12.6)
Not High	210 (79.8)	207 (79.6)	417 (79.7)
Missing	23 (8.7)	17 (6.5)	40 (7.6)
Frailty Group, n (%)			
Not Frail	206 (78.3)	188 (72.3)	394 (75.3)
Frail	56 (21.3)	72 (27.7)	128 (24.5)
Missing	1 (0.4)	0 (0.0)	1 (0.2)
Frailty and Age Group, n (%)			
Age ≤ 65 years and Not Frail	142 (54.0)	120 (46.2)	262 (50.1)
Age > 65 years and/or Frail	121 (46.0)[b]	140 (53.8)	261 (49.9)[b]
Performance Status (ECOG) Category 1, n(%)			
0 – Fully active	106 (40.3)	36 (13.8)	66 (12.6)
1 – Restricted activity	210 (79.8)	207 (79.6)	417 (79.7)
2 – No work, ambulatory	23 (8.7)	17 (6.5)	40 (7.6)
3 – Limited self-care	23 (8.7)	17 (6.5)	40 (7.6)
Creatinine Clearance Group 1, n(%)			
< 60 mL/min	78 (29.7)	79 (30.4)	157 (30.0)
≥ 60 mL/min	185 (70.3)	180 (69.2)	365 (69.8)
Missing	0 (0.0)	1 (0.4)	1 (0.2)
Creatinine Clearance Group 2, n(%)			
< 50 mL/min	46 (17.5)	45 (17.3)	91 (1.4)
≥ 50 mL/min	217 (82.5)	214 (82.3)	431 (82.4)
Missing	0 (0.0)	1 (0.4)	1 (0.2)
Hemoglobin Group, n (%)			
< 10 g/dL	89 (33.8)	76 (29.2)	165 (31.5)
≥ 10 g/dL	174 (66.2)	184 (70.8)	358 (68.5)
B2 Microglobulin Group, n(%)			
≤ 5.5 mg/L	176 (66.9)	174 (66.9)	350 (66.9)
> 5.5 mg/L	85 (32.3)	84 (32.3)	169 (32.3)
Missing	2 (0.8)	2 (0.8)	4 (0.8)
Lactate Dehydrogenase Group, n(%)			
Not High (LDH ≤ 280 IU/L)	214 (81.4)	224 (86.2)	438 (83.7)
High (LDH > 280 IU/L)	44 (16.7)	32 (12.3)	76 (14.5)
Missing	5 (1.9)	4 (1.5)	9 (1.7
Albumin Group, n(%)			
≤ 35 g/L	128 (48.7)	129 (49.6)	257 (49.1)
> 35 g/L	135 (51.3)	128 (49.2)	263 (50.3)
Missing	0 (0.0)	3 (1.2)	3 (0.6)

Parameter	VLd (N = 263)	Ld (N = 260)	Total (N = 523)
[Abbreviations] VLd – Lenalidomide, bortezomib, and dexamethasone; Ld – Lenalidomide and dexamethasone [a] Cytogenetic risk assessment was not required by the protocol. [b] One subject in the RVd arm with a missing frailty is counted in the category age > 65 years and/or frail.			

Figure 3. Submitter's consort diagram with ITT population datalocked for November 5, 2015 as reported in clinical summary report[3]



c) Interventions

The protocol in the VLd regimen was given as eight 21-day cycles. Bortezomib was given at 1-3 mg/m^2 intravenously on days 1, 4, 8, 11 combined with 25 mg oral lenalidomide once a day on days 1 – 14 plus 20 mg oral dexamethasone on days 1, 2, 4, 5, 8, 9, 11, and 12. They also received herpes simplex virus prophylaxis. The protocol for the Ld regimen was given as six 28-day cycles consisting of 25 mg oral lenalidomide once a day for days 1-21 plus 40 mg oral dexamethasone on days 1, 8, 15, and 22. All patients received 325 mg oral aspirin once a day to reduce the risk of thromboembolic complications. Upon completion of induction, all patients received ongoing maintenance with 25 mg oral lenalidomide once a day for 21 days plus 40 mg oral dexamethasone once a day for days 1, 8, 15, and 22 of each 28-day cycle. With dosage adjustments as necessary using slide adjustment scale within the protocol, maintenance was continued until emergence of progressive disease, toxic effects, or patient withdrawal. For patients in whom transplant was considered in the future, stem cell collection was allowed.

PAG noted in section 4.3 that the standard of care in most jurisdictions is to administer bortezomib subcutaneously and weekly to reduce neurotoxicity; dexamethasone is also usually administered at 40 mg on the same days of bortezomib treatment. Some patients may not be able to tolerate the twice weekly bortezomib dose. This dosing regimen does not match the dosing used in SWOG 0777.

d) Patient Disposition

Patient disposition is reported separately for each analysis of the above different patient populations. A summary is provided in Table 9.

Durie et al. 2017[1]

In the SWOG publication, a per-protocol analysis was completed. Of the 242 patients eligible for VLd treatment, 137 completed induction treatment as planned1. Fifty five had adverse events or side-effects, 3 refused treatment unrelated to adverse events, 12 progressed or relapsed, 7 died and 28 other (not protocol specified) did not complete treatment as planned. With regard to dosing intensity in the VLd group, unplanned dose modification occurred in 38 of 239 patients in the induction phase. Of the 230 eligible for Ld treatment, 146 completed induction treatment as planned. Twenty two had adverse events or side-effects, 10 refused treatment unrelated to adverse events, 24 progressed or relapsed, 3 died and 24 other (not protocol specified) did not complete treatment as planned. With regard to dosing intensity in the Ld group, unplanned dose modification occurred in 27 of 223 patients in the induction phase. During maintenance therapy, unplanned dose modification occurred in 24 of 102 patient in the VLd group and 17 of 121 patients in the Ld group.

As of November 5th, 2015, there were a total of 76/242 deaths in the VLd group, and 100/229 in the Ld group. Of those, there were 2 treatment related deaths in the VLd group, and 0 in the Ld group (median follow-up time of 54 months and 56 months; respectively). At the time of the publication, 46 (10%) of 471 patients are estimated to have proceeded to stem-cell harvest and planned transplant after leaving the study. Although the intent to transplant was a stratification factor at randomisation and balanced between treatment groups, the number of patients that proceeded to transplant from each treatment group is not reported.

Durie et al. 2018[2]

In the SWOG publication for the eligible analysable population per protocol, as of May 15th, 2018, there were 102/235 deaths in the VLd group, and 125/225 in the Ld group (median follow-up time for VLd not reported and 69 months for Ld). No patient disposition data was reported.

Clinical Summary Report[3]

In the submitter's CSR, an intention to treat analysis was applied. Of the 263 patients randomized for VLd treatment and 260 randomized for Ld treatment. Lenalidomide dose reduction was reported in 21.8% of subjects in the VLd arm and 15.6% of subjects in the Ld group. Bortezomib dose reduction was reported in 44% of patients. Dexamethasone dose modification was not allowed. As of December 1st, 2016, there were 104 deaths in the VLd group, and 132 in the Ld group (median follow-up time of 60.6 months).

Table 9. Overview of patient disposition by report

	Treatment	
Durie 2017	VLd	Ld
Completed treatment as planned	137	146
Did not completed treatment as planned	28	24
Adverse events or side effects	55	22
Refused treatment unrelated to AE's	3	10
Progressed or relapse	12	24
Deaths reported from all data sources		
November 5, 2015 (Durie 2017) December 1, 2016 (CSR) May 15, 2018 (Durie 2018 Update)	76/242 104/263 105/235	100/230 132/260* 125/225

**note that fewer deaths are reported in the Durie May 15, 2018 data cutoff than the CSR Decmeber 1, 2016 data cut-off in the Ld arm. This implies that at least 7 deaths occurred within the additional 52 patients that were deemed ineligible in the Durie analysis.*

e) Limitations/Sources of Bias

The SIGN-50 quality assessment was done (see table 10) based on the eligible, analyzable per protocol population reported in the Durie et al. 2017 primary publication of SWOG S0777[1] .

The SWOG S0777 trial was of acceptable quality, based on the SIGN-50 quality checklist for randomized control trials. The study was open label, and used appropriate randomization methods with sample sizes that were targeted for sufficient statistical power of primary outcomes. Details of blinding and randomisation methods are summarized in section 6.3.2.1 under trials.

- The study was an open-label design, which may introduce bias. This means that randomization is not concealed and patients and physicians are aware of the treatment assignment.
- Patients without impaired renal function or compromised bone marrow function were excluded, potentially enriching the population of patients with better outcomes.
- Both intent to transplant at disease progression and no intent to transplant patients were included. Randomization was stratified on this variable.

- The population of the Ld group had more female patients, and a higher proportion of patients over 65.
- Quality of life data was not collected in SWOG S0777
- The funding for SWOG S0777 are from NIH, NCI, NCTN, Millennium Pharmaceuticals, Takeda Oncology Company, and Celgene Corporation for provision of study drug under their respective cooperative research and development agreements with the NCI. NCI in collaboration with the trial investigators Brian M. Durie from Southwest Oncology Group (SWOG) designed the study, collected the data, and interpreted the results which were published in the primary publication[1] and the follow up was published in a conference abstract[2].

Table 10. Sign-50 Quality Assessment

	SWOG S0777[1]
Internal Validity	
1.1 Study addresses appropriate and clearly focused question	**Yes ☒** No ☐ Can't say ☐
1.2 The assignment of subjects to treatment groups is randomized	**Yes ☒** No ☐ Can't say ☐
1.3 An adequate concealment method is used	Yes ☐ **No ☒** Can't say ☐
1.4 The design keeps subjects and investigators "blind" about treatment allocation	Yes ☐ **No ☒** Can't say ☐
1.5 Treatment and control groups are similar at the start of the trial	**Yes ☒** No ☐ Can't say ☐
1.6 The only difference between groups is the treatment under investigation	**Yes ☒** No ☐ Can't say ☐
1.7 All relevant outcomes are measured in a standard, valid and reliable way	**Yes ☒** No ☐ Can't say ☐
1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	1/264 in VLd did not have valid consent 1/261 in Ld withdrew consent
1.9 All the subjects are analyzed in the groups to which they were randomly allocated (intent to treat analysis)	**Yes ☒** No ☐ Can't say ☐ Does not apply ☐
1.10 Where the study is carried out at more than one site, results are comparable for all sites	Yes ☐ No ☐ **Can't say ☒** Does not apply ☐
Overall Assessment of the Study	
2.1 How well was the study done to minimize bias?	High quality (++) ☐ **Acceptable (+) ☒** Low quality (-) ☐ Unacceptable – reject 0 ☐
2.2 Taking into account clinical considerations, your evaluation of the methodology used and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	**Yes ☒** No ☐ Can't say ☐
2.3 Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes ☐ **No ☒** Can't say ☐

6.3.3 Detailed Outcome Data and Summary of Outcomes

Progression-free Survival

The primary endpoint was progression-free survival as evaluated with the use of a group-sequential design, with two planned interim analyses at 1/3 and 2/3 of the total number of events (defined as the time from randomisation to the date of disease progression, or death due to any cause) assessed up to 6 years[21]. A summary of progression-free survival table is summarized in table 11. Similar to above, the progression-free survival is presented by report.

Durie et al. 2017[1]

As of the November 5th, 2015 cutoff date (median follow-up of 55 months for VLd and 54 months for Ld), in the SWOG publication (analysed per protocol) the median progression-free survival for VRL and Ld were 43 and 30 months; respectively (95% 0.712 CI: 0.560-0.906, p=0.0018).

Durie et al. 2018[2]

As of May 15th, 2018 cutoff date (median follow up 84 months, 7 years), analysed per protocol, the median progression-free survival for VLd and Ld were 41 and 29 months; respectively (95% 0.742 CI: 0.594-0.928, p=0.003)[2].

Clinical Summary Report[3]

In the submitter's CSR, an intention to treat analysis was used. Two different outcome assessments and 3 different censoring rules were applied to two data-cut-offs; SWOG, EMA and FDA. SWOG censoring was the protocol-specified method and the EMA and FDA censoring rules were used for regulatory approval. The PFS was similar across all 3 censoring methods.

With outcomes assessed by IRAC with SWOG censoring, as of the November 5th, 2015 cutoff date, the median progression free survival for VLd and Ld were 42.5 and 29.9 months; respectively (95% 0.76 CI: 0.61-0.94, p=0.01038). As of the December 1st, 2016 cutoff date, the median progression free survival for VLd and Ld were 42.5 and 29.9 months; respectively (95% 0.76 CI: 0.62-0.93, p=0.00862).

Table 11. Summary of outcomes table for all publications and submission information as summarized in the clinical summary report.[4]

Durie et al: Eligible Analysable Population (per protocol)				
Data cutoff date	November 5, 2015 (Primary Analysis)		May 15, 2018 (ASH Abstract)	
Treatment arm	VLd (N = 242)	Ld (N = 229)	VLd (N = 235)	Ld (N = 225)
Median PFS (months)	43	30	41	29
2-sided 95% CI	39 to 52	25 to 39	33 to 51	24 to 37
PFS improvement (months)	13		12	
HR (95%CI) p-value	0.712 (0.560, 0.906) P= 0.0018		0.742 (0.594, 0.928) P= 0.003	
% reduction in risk of PD or death	27%		25.8%	
Clinical Study Report: ITT Population				
Assessment	**IRAC**		**Central Review**	
Data cutoff date	November 5, 2015 (Primary Analysis)	December 1, 2016	November 5, 2015	December 1, 2016

Durie et al: Eligible Analysable Population (per protocol)								
Treatment arm	VLd N = 263	Ld N = 260	VLd N = 263	Ld N = 260	VLd N = 263	Ld N = 260	VLd N = 263	Ld N = 260
Median PFS (months) (95% CI)	42.5 (34.0 to 54.8)	29.9 (25.6 to 38.2)	42.5 (34.0 to 52.5)	29.9 (25.6 to 38.2)	43.6 (37.5 to 55.2)	29.2 (23.9 to 36.6)	43.6 (37.5 to 55.2)	29.2 (23.9 to 36.6)
HR (95%CI) p-value	0.76 (0.61, 0.94) p= 0.01038		0.76 (0.62, 0.93) p= 0.00862		0.72 (0.58, 0.89) p= 0.00217		0.72 (0.59, 0.89) p= 0.00199	

Overall Survival

The number of deaths was also reported. Overall survival was assessed at followup every 6 months, until death, or to a maximum of 6 years after randomisation. The median overall survival in months is summarized in Table 12.

Durie et al. 2017[1]

In the SWOG publication for the eligible analysable population per protocol, as of November 5th, 2015, there were 76/242 deaths in the VLd group, and 100/229 in the Ld group (median follow-up time of 54 months and 56 months; respectively). The median overall survival was 75 months (65 to NR) for VLd group and 64 months (56 to NR) for Ld group. See Figure 4 for detailed Kaplan-Meier estimates.

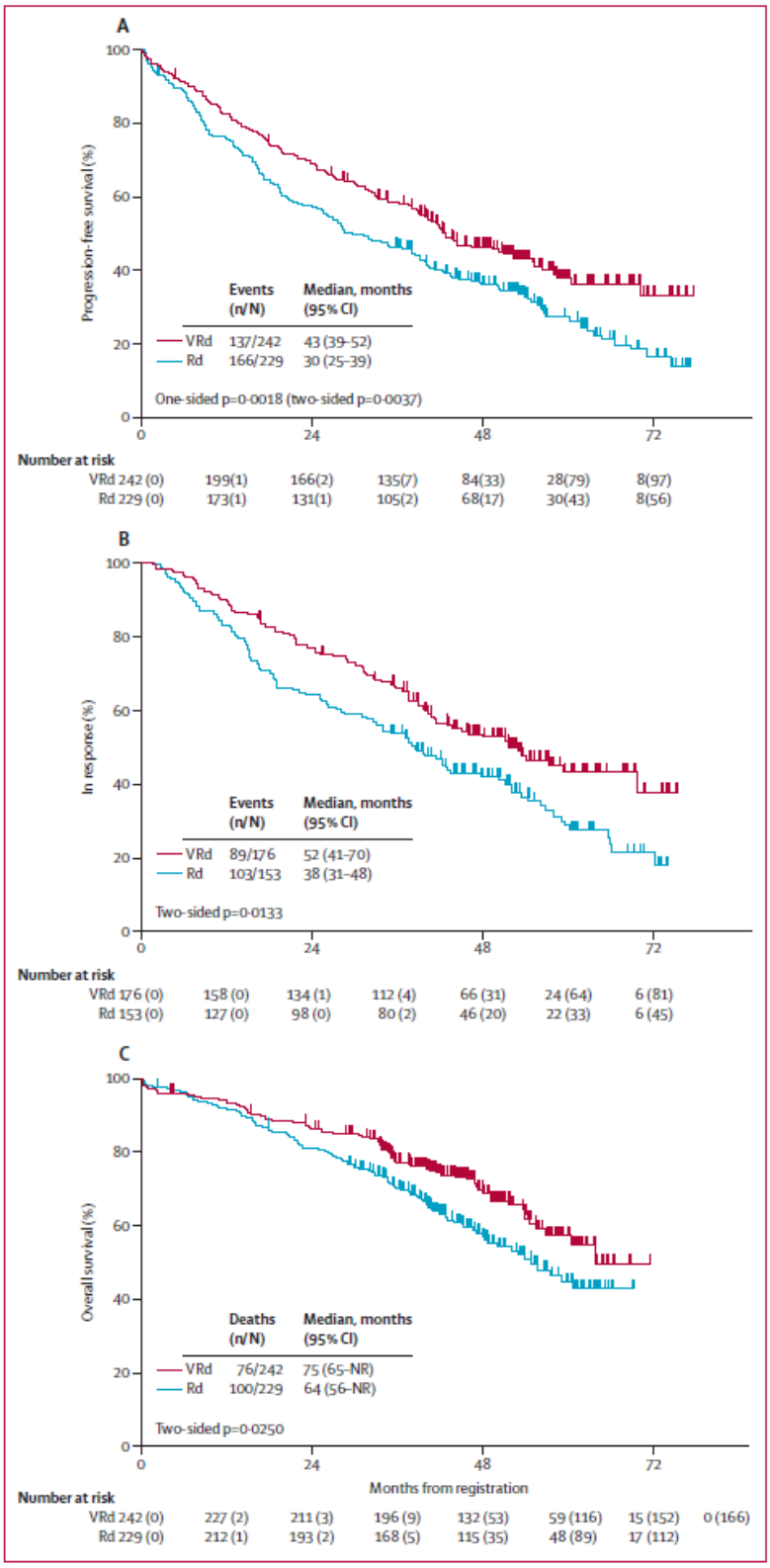
Durie et al. 2018 [2]

In the SWOG publication for the eligible analysable population per protocol, as of May 15th, 2018, there were 102/235 deaths in the VLd group, and 125/225 in the Ld group (median follow-up time was 84 months for both groups). The median overall survival was not reached by data cutoff date and not reported for VLd group, and it was 69 months for the Ld group.

Clinical Summary Report [3]

In the submitter's CSR for the intent to treat population, as of December 1st, 2016, there were 104/263 deaths in the VLd group, and 132/260 in the Ld group (median follow-up time of 60.6 months for both groups). The median overall survival in the VLd group was 89.1 months and 67.2 months for Ld group.

Figure 4. Kaplan-Meier estimates of progression free survival (A), response duration (B), and overall survival (C) by treatment group.



Source: Reprinted from The Lancet, Vol. 389, Durie BG, et al., Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial, 519-527, Copyright (2017), with permission from Elsevier.[1]

Table 12. Median overall survival in months in SWOG S0777, data are compiled from Durie et al 2017 primary publication, Durie et al 2018 conference abstract and submitter's clinical summary report.

	SWOG Publication[1]		Submitter CSR[3]		SWOG Conference[2]	
Treatment Arm	VLd	Ld	VLd	Ld	VLd	Ld
Data Cutoff Date						
November 5th, 2015	75	64	N/A	N/A	N/A	N/A
December 1st, 2016	N/A	N/A	89.1	67.2	N/A	N/A
May 15th, 2018	N/A	N/A	N/A	N/A	NR	69

Response Rate[1]

Response rate was calculated as the number of patients with documented confirmed partial response or better, which includes confirmed/unconfirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR), as best response divided by the total number of patients in each arm[21]. Response rates were compared between the two treatment arms using a stratified Cochran-Mantel-Haenszel tes. Response designations were based on the International Uniform Response Criteria for Multiple Myeloma[21].

Durie et al. 2017[1]

The number of individuals analyzed for response rate and reported in the publication is different than the population originally randomized into each treatment group (VLd N=242, Ld N=229); the reason for this is not indicated. The response rate is summarized in Table 13.

As of the November 5th, 2015 cutoff date, the overall response rate (per protocol analysis) was 176/216 (81.5%) in the VLd group, and 153/214 (71.5%) in the Ld group (median follow-up time of 54 months and 56 months; respectively) as seen in table 12. The confirmed response rate was 34/216 (15.7%) in the VLd group, and 18/214 (8.4%) in the Ld group. The VGPR response rate was 60/216 (27.8%) in the VLd group, and 50/214 (23.4%) in the Ld group. The PR rate was 82/216 (38%) in the VLd group, and 85/214 (39.7%) in the Ld group.

Table 13. Response Rate of eligible analysable population per protocol as reported in Durie et al. 2017 primary publication data locked for November 5, 2015[1].

	Patients given bortezomib with lenalidomide and dexamethasone (VRd group; n=216)*	Patients given lenalidomide and dexamethasone (Rd group; n=214)*
Confirmed response	34 (15·7%)	18 (8·4%)
Very good partial response	60 (27·8%)	50 (23·4%)
Partial response	82 (38%)	85 (39·7%)
Overall response rate (partial response or better)	176 (81·5%)	153 (71·5%)
Stable disease	34 (15·7%)	52 (24·3%)
Stable disease or better	210 (97·2%)	205 (95·8%)
Progressive disease or death	6 (2·8%)	9 (4·2%)

* The p value for differences in those with confirmed response was 0·02. The results section provides more details (unconfirmed responses are collapsed into the response category one level below).

Source: Reprinted from The Lancet, Vol. 389, Durie BG, et al., Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial, 519-527, Copyright (2017), with permission from Elsevier.[1]

Durie et al. 2018[2]

The depth of response for the eligible analysable population per protocol response was assessed incorporating new serial data and additional bone marrow results. The CR plus VGPR was 74.9% for VLd versus CR plus VGPR of 53.7% for Ld (P-value 0.006 for response differences using a stratified Cochran-Mantel- Haenszel analysis).

Clinical Summary Report[3]

In the submitter's CSR, they assessed response rate using an intention to treat analysis based on IRAC outcome assessment at post 9 weeks, post 12 weeks and post-initial treatment and reported results as of the December 1st, 2016 cutoff date in table 14. At post 9 weeks, the CR rate was 0%in both the VLd group and Ld group. The VGPR response rate was 92/263 (35.0%) in the VLd group, and 26/260 (10.0%) in the Ld group. The PR rate was 91/263 (34.6%) in the VLd group, and 106/260 (40.8%) in the Ld group. At post 12 weeks, the CR rate was 2/263 (0.8%) in the VLd group, and 0/260 (0.0%) in the Ld group. The VGPR response rate was 80/263 (30.4%) in the VLd group, and 34/260 (13.1%) in the Ld group. The PR rate was 49/263 (18.6%) in the VLd group, and 68/260 (26.2%) in the Ld group. At post-initial treatment, the CR rate was 14/263 (5.3%) in the VLd group, and 7/260 (2.7%) in the Ld group. The VGPR response rate was 139/263 (52.9%) in the VLd group, and 76/260 (29.2%) in the Ld group. The PR rate was 46/263 (17.5%) in the VLd group, and 87/260 (33.5%) in the Ld group. All the response rate had a p value of 0.00001 for differences in those with confirmed responses.

Table 14. Response Rate (ITT with IRAB) as reported in the clinical summary report[3]

Parameter	Post 9 Weeks		Post 12 Weeks		Post-Initial Treatment	
	VLd (N = 263)	Ld (N = 260)	VLd (N = 263)	Ld (N = 260)	VLd (N = 263)	Ld (N = 260)
Overall Response Rate [a]						
Complete Response (CR), n(%)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	14 (5.3)	7 (2.7)
Very Good Partial Response (VGPR), n(%)	92 (35.0)	26 (10.0)	80 (30.4)	34 (13.1)	139 (52.9)	76 (29.2)
Partial Response (PR), n(%)	91 (34.6)	106 (40.8)	49 (18.6)	68 (26.2)	46 (17.5)	87 (33.5)
Stable Disease (SD), n(%)	25 (9.5)	74 (28.5)	7 (2.7)	23 (8.8)	12 (4.6)	35 (13.5)
Progressive Disease (PD), n(%)	3 (1.1)	11 (4.2)	4 (1.5)	4 (1.5)	15 (5.7)	26 (10.0)
Response Not Evaluable (NE)[b], n(%)	52 (19.8)	43 (16.5)	121 (46.0)	131 (50.4)	37 (14.1)	29 (11.2)
p-value [c]	< 0.00001		< 0.00001		< 0.00001	
Dichotomized Response						
CR or VGPR, n(5) (2-sided 95% CI)	92 (35.0) (29.2, 40.7)	26 (10.0) (6.4, 13.6)	82 (31.2) (25.6, 36.8)	34 (13.1) (9.0, 17.2)	153 (58.2) (52.2, 64.1)	83 (31.9) (26.3, 37.6)
PR or SD or PD or NE, n(%)	171 (65.0)	234 (90.0)	181 (68.8)	226 (86.9)	110 (41.8)	177 (68.1)
p-value [d]	< 0.00001		< 0.00001		< 0.00001	
Odds Ratio (2-sided 95% CI)	4.71 (2.91, 7.63)		3.09 (1.97, 4.85)		2.96 (2.06, 4.26)	

CI = confidence interval; IRAC = Independent Response Adjudication Committee; ISS = International Staging System; ITT = intent to treat; Ld = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone.

[a] The best response of a subject.

[b] Including subjects who did not have any response assessment data, or not evaluable.

[c] Probability from Wilcoxon rank sum test with normal approximation (1 = CR, 2 = VGPR, 3 = PR, 4 = SD, 5 = PD) which excludes the category – response not evaluable (NE).

[d] Based on stratified Cochran-Mantel-Haenszel test stratified by ISS stage and intent to transplant at progression.

Duration of Response

Response duration was assessed with a stratified log-rank test.

Durie et al. 2017[1]

In the SWOG publications, as of the November 5th, 2015 cutoff date, the median duration of response in the VLd group was 52 months (95% CI: 41-70), and 38 months (95% CI: 31-48) in the Ld group (HR: 0.695; two-sided p value 0.0133).

Durie et al. 2018[2]

In the SWOG updated analysis, as of the May 15th, 2018 cutoff date, the duration of response was not reported.

Clinical Summary Report[3]

In the clinical summary report, the median duration of response was 48.6 and 38.9 monthsfor VLd and Ld respectively. The observed HR for the comparison between the two arms was 0.83 (95% Cl: 0.61 to 1.12; p=0.21905), indicating a longer duration of response in the VLd arm. From the KM estimates, 42% of patients receiving VLd indicated a response lasting at least six years compared to the 36% of patients who received Ld. This response rate is similar to the eligible analysable population per protocol response rate published in Durie et al. 2017.

Stem Cell Transplant

Patients were stratified at randomisation for their intent to transplant (yes or no). After receiving VLd or Ld, some patients went on to receive subsequent high-dose chemotherapy/allogeneic stem cell transplant or allogeneic transplant/bone marrow transplant.

Durie et al. 2017[1]

In the SWOG publications, with the eligible analysable population per protocol, 168/242 (69%) of VLd and 156/229 (68%) of Ld patients had an intent to transplant. As of the November 5th, 2015 cutoff date, 46/471 (10%) patients are estimated to have proceeded to stem-cell harvest and planned transplant, the number per arm and whether they proceeded to transplant with or without disease progression was not reported.

Durie et al. 2018[2]

An update of the number of patients that proceeded to stem-cell harvest and planned transplant as of the May 15th, 2018 cutoff date was not reported

Clinical Summary Report[3]

In the clinical summary report with the intention to treat population,182/263 (69.2%) of VLd and 179/260 (68.8%) of Ld patients had an intent to transplant at progression. As of the December 1, 2016 cutoff date, 44/163 (27%) of VLd patients and 31/187 (16.6%) Ld patients proceeded to transplant after disease progression The number of patients without disease progression who also proceeded to transplant after VLd treatment was 37/75 (49.3%) and Ld treatment was 21 (25.6%).

Adverse Events

Durie et al. 2017[1]

In the SWOG publications, as of the November 5th, 2015 cutoff date, grade 3 or higher adverse events occurred in 82% of the VLd group, and 75% of the Ld group. The most commonly reported grade 3 adverse events in the VLd group were haematological adverse events affecting the blood or bone marrow (73%), neurological (76%) and metabolic or laboratory (53%), with two deaths reported as not directly attributable to treatment. Additionally, grade 3 pain, grade 3 constitutional symptoms and grade 3 gastrointestinal events occurred in 29%, 46% and 49% of patients, respectively. The most commonly reported grade 3 adverse events in the Ld group were haematological adverse events affecting the blood or bone marrow (70%), metabolic/laboratory (51%) and constitutional symptoms (35%), with no deaths reported as an adverse event. There were 2 of 241 patients that reported secondary cancers in VLd group, and 4 of 226 patients that reported secondary cancers in Ld group. Grade 4 haematological adverse events affecting the blood or bone marrow were increased in the VLd group compared to Ld (41% and 31%, respectively). Rates of grade 3 infections were similar between groups at 29%. A summary of adverse events for this population can be found in Table 15.

Durie et al. 2018[2]

The number of secondary cancers as of the May 15th, 2018 data cutoff date was 19/235 (8%) with VLd and 16/225 (7%) with Ld. Further information on safety was not reported in this updated analysis.

Clinical Study Report[3]

Adverse events reported as of the December 1st, 2016 data cutoff in the clinical study reportthe following general statements: The most frequently reported (≥ 50% of patients) TEAEs in the VLd arm during initial treatment were fatigue, peripheral sensory neuropathy, anemia, thrombocytopenia, constipation, and hypocalcemia. Other frequently (≥ 30% of patients) reported TEAEs in the VLd arm were hyperglycemia, peripheral edema, leukopenia, diarrhea, nausea, backpain, insomnia, dyspnea, hyponatremia, decreased appetite, and dysgeusia In the Ld arm, the most frequently reported (≥ 50% of patients) TEAEs during the initial treatment were anemia, fatigue, and hyperglycemia· Other frequently (≥ 30% of patients) reported TEAEs in the Ld arm were leukopenia, thrombocytopenia, constipation, hypocalcemia, neutropenia, peripheral sensory neuropathy, and diarrhea. The most frequently reported (> 20% of patients) Grade 3 or 4 TEAEs were lymphopenia (24.0%) and peripheral sensory neuropathy (22.9%) in the VLd arm, and neutropenia (23.4%), lymphopenia (22.3%), and anemia (20.7%) in the Ld arm.

Table 15. Adverse events in SWOG S0777 as reported in Durie et al. 2017 for eligible analysable population per protocol datalocked for November 5, 2015.[1]

	Patients given lenalidomide and dexamethasone (Rd group; n=226)					Patients given bortezomib with lenalidomide and dexamethasone (VRd group; n=241)				
	1	2	3	4	5	1	2	3	4	5
Haematological										
Blood or bone marrow	25	50	70	34	0	27	49	73	41	0
Coagulation	0	0	3	0	0	0	0	5	0	0
Haemorrhage or bleeding	12	2	0	0	0	7	3	7	0	0
Infection	1	28	29	2	0	2	31	29	5	1
Lymphatics	56	18	2	0	0	66	24	5	0	0
Neurological										
Neurological	78	44	21	3	1	42	72	76	4	0
Pain	44	27	9	0	0	55	44	29	0	0
Non-haematological or non-neurological										
Cardiac arrhythmia	5	3	4	0	0	7	2	3	0	0
Cardiac general	13	11	8	0	0	15	18	18	0	0
Constitutional symptoms	60	83	35	0	0	60	89	46	1	0
Dermatology or skin	61	21	9	0	0	50	42	6	1	0
Endocrine	11	8	0	0	0	5	12	0	0	0
Gastrointestinal	84	65	17	0	0	64	85	49	3	1
Hepatobiliary or pancreas	0	0	2	0	0	0	0	2	0	0
Metabolic or laboratory	54	55	51	12	0	50	60	53	9	1
Musculoskeletal or soft tissue	25	22	13	1	0	20	28	22	1	0
Pulmonary or upper respiratory	42	25	8	1	0	55	16	15	6	0
Ocular or visual	19	8	12	0	0	37	16	6	0	0
Renal or genitourinary	2	3	8	1	0	8	3	5	0	0
Secondary cancer	0	0	3	1	0	0	0	1	1	0
Sexual or reproductive function	1	1	1	0	0	2	1	0	0	0
Vascular	0	4	16	5	0	1	8	18	4	0
Death*	0	0	0	0	0	0	0	0	0	2

We excluded events unlikely to be related to treatment. Total number of grade 3 or higher adverse events: 169 (75%) of 226 in the Rd group, 198 (82%) of 241 in the VRd group. *In neither case was the cause of death directly attributable to treatment. One patient had a cardiac arrest and the other patient died in a nursing home, cause undetermined.

Source: Reprinted from The Lancet, Vol. 389, Durie BG, et al., Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial, 519-527, Copyright (2017), with permission from Elsevier.[1]

6.4 Ongoing Trials Literature Search Results

There are 3 clinical trials investigating VLd as a first line that met the eligibility criteria of this review (Table 16).

Clinical trial NCT01530594[22] is a randomized phase III trial comparing VLd with Ld in patients with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant. It was completed in January 2013 but results have not yet been published or updated onto ClinicalTrials.gov.

Clinical Trial NCT03652064[23] is a randomized phase III trial comparing Daratumumab, Velcade (bortezomib), Lenalidomide and Dexamethasone with VLd in patients with untreated multiple myeloma and for whom hematopoietic stem cell transplant is not planned as initial therapy. The estimated study completion date is April 30, 2025. Preliminary data for this trial will be presented at the American Society of Clinical Oncology (ASCO) conference on June 3, 2019.

Clinical Trial NCT03710603[24] is a randomized phase III comparing Daratumumab, Velcade (bortezomib), Lenalidomide and Dexamethasone with VLd in patients. There is no indication whether their patient population is intending for stem cell transplant. The estimated study completion date is November 2029.

Table 16. Ongoing trials of lenalidomide in combination with bortezomib and low dose dexamethasone in patients with newly diagnosed multiple myeloma in whom stem cell transplant is not intended

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
NCT01530594[22] Randomized, open label, phase III trial Enrollment = 440 patients Randomized= NR ; Treated= NR Number of centres and number of countries NR Main Location – Saudi Arabia King Faisal Specialist Hospital & Research Center Patient Enrolment completed, dates NR Data cut-off January 2013 Final Analysis Date NR, no data reported and no publications Funding NR	<u>See below</u>	Lenalidomide and low dose dexamethasone VS Lenalidomide in combination with bortezomib and low dose dexamethasone	<u>Primary:</u> - PFS
<u>Key Inclusion Criteria:</u> 1. Patients must have newly diagnosed multiple myeloma 2. Patients must have received no prior chemotherapy for this disease. Patients must have received no prior radiotherapy to a large area of the pelvis (more than half of the pelvis). Prior steroid treatment is allowed provided treatment was not more than 2 weeks in duration. Patients must not have received any prior treatment with bortezomib or lenalidomide. 3. Patients must be ≥ 18 years of age at the time of registration. 4. Patients must have a Zubrod Performance Status (PS) of 0-3 5. Patients must have adequate marrow function as defined herein: 6. Platelet count ≥ 80 x 103/mcL, 7. ANC ≥ 1 x 103/mcL, and Hemoglobin (including patients who have been either transfused or treated with EPO) ≥ 9 g/dL. 8. Institutions must submit a local cytogenetics report and FISH analysis report			

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
9. Patients with pathologic fractures, pneumonia at diagnosis or symptomatic hyperviscosity. 10. Patients must have a calculated or measured creatinine clearance > 30 cc/min. 11. Patients must not have uncontrolled, active infection requiring intravenous antibiotics 12. Patients must not have any psychiatric illness 13. Patients must not be Hepatitis B, Hepatitis C or HIV positive 14. Patients must not have a history of cerebral vascular accident with persistent neurologic deficits. 15. Patients must be able to take aspirin 325 mg daily 16. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test 17. No prior malignancy is allowed except for adequately treated basal cell (or squamous cell) skin cancer, in situ cervical cancer or other cancer for which the patient has been disease-free for five years. 18. Patients must be offered participation in GEP molecular studies for the evaluation of genetic polymorphisms. Key Exclusion Criteria: NR			
NCT03652064[23] Enrollment = 360 patients Randomized= NR ; Treated= NR Number of centres and number of countries= NR Patient Enrolment Dates: Still Recruiting Study Completion Date: April 30, 2025 Sponsored by Janssen Research & Development, LLC	See Below	Daratumumab in combination with borteomib, lenalidomide and dexamethasone VS Lenalidomide in combination with bortezomib and low dose dexamethasone	Primary: - Percentage of participants who achieve MRD negative status Secondary: - PFS - MRD at 1 year - Durable MRD negative rate - ORR - VGPR - CR - PFS on next line therapy - OS - PR - DOR - HRQoL - Maximum observed serum concentration (Cmax) of Daratumumab - Minimum observed serum concentration (Cmin) of Daratumumab - Anit-daratumumab antibodies - Anit-rHuPH20 Antibodies
Key Inclusion Criteria: 1. 18 Years or Older 2. Diagnosis of multiple myeloma as documented per International Myeloma Working Group (IMWG) criteria Monoclonal plasma cells in the bone marrow greater than or equal to (>=)10 percentage (%) or presence of a biopsy proven plasmacytoma and documented multiple myeloma satisfying at least one of the calcium, renal, anemia, bone (CRAB) criteria or biomarkers of malignancy criteria. CRAB criteria: Hypercalcemia: serum calcium greater than (>) 0.25 millimoles per liter (mmol/L) (>1 milligram per deciliter [mg/dL]) higher than upper limit of normal (ULN) or >2.75 mmol/L (>11 mg/dL); Renal insufficiency: creatinine clearance less than (<) 40 milliliter per minute (mL/min) or serum creatinine >177 micro millimoles per liter (umol/L) (>2 mg/dL); Anemia: hemoglobin >2 g/dL below the lower limit of normal or hemoglobin <10 g/dL; Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography (PET)-CT. 3. Biomarkers of Malignancy: Clonal bone marrow plasma cell percentage >=60%; Involved: uninvolved serum free light chain (FLC) ratio >=100; >1 focal lesion on magnetic resonance imaging (MRI) studies 4. Must have measurable disease, as assessed by central laboratory 5. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2			

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
6. A woman of childbearing potential must have 2 negative serum or urine pregnancy tests at Screening, first within 10 to 14 days prior to dosing and the second within 24 hours prior to dosing 7. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 3 months after receiving the last dose of any component of the treatment regimen <u>Key Exclusion Criteria:</u> 1. Frailty index of >=2 according to Myeloma Geriatric Assessment score 2. Prior therapy for multiple myeloma other than a short course of corticosteroids (not to exceed 40 mg of dexamethasone, or equivalent per day for a maximum of 4 days, total of 160 mg dexamethasone or equivalent) 3. Prior or concurrent invasive malignancy (other than multiple myeloma) within 5 years of date of randomization (exceptions are adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix or breast, or other non-invasive lesion 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) 4. 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 5 5. Radiation therapy within 14 days of randomization			
NCT03710603[24] Characteristics (Phase of study, blinding, placebo, randomization method, randomization ratio) N= randomized ; n= treated Number of centres and number of countries= NR Patient Enrolment Dates= Still Recruiting Data cut-off: NR Study Completion Date: November 2029 Sponsored by European Myeloma Network	<u>See Below</u>	Daratumumab in combination with borteomib, lenalidomide and dexamethasone VS Lenalidomide in combination with bortezomib and low dose dexamethasone	<u>Primary:</u> - PFS <u>Secondary:</u> - Post-consolidation MRD negative rate - ORR - OS - PR - CR - Pharmacokinetic concentrations of daratumumab - incidence of anti-daratumumab antibodies - QoL
<u>Key Inclusion Criteria:</u> 1. 18 to 70 years of age, inclusive. 2. Monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy proven plasmacytoma and documented multiple myeloma satisfying at least one of the calcium, renal, anemia, bone (CRAB) criteria or biomarkers of malignancy criteria: CRAB criteria: a) Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than upper limit of normal (ULN) or >2.75 mmol/L (>11 mg/dL) b) Renal insufficiency: creatinine clearance <40 mL/min or serum creatinine >177 µmol/L (>2 mg/dL) c) Anemia: hemoglobin >2 g/dL below the lower limit of normal or hemoglobin <10 g/dL d) Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or Positron-emission tomography (PET)-CT Biomarkers of Malignancy: a) Clonal bone marrow plasma cell percentage ≥60% b) Involved: uninvolved serum free light chain (FLC) ratio ≥100 c) >1 focal lesion on magnetic resonance imaging (MRI) studies 3. Measurable disease as defined by any of the following: a) Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or b) Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin FLC ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio			

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes

c) .Newly diagnosed subjects for whom high-dose therapy and autologous stem cell transplantation (ASCT) is part of the intended treatment plan.
d) Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.
e) Clinical laboratory values meeting the following criteria during the Screening Phase (Screening hematology and chemistry tests should be repeated if done more than 3 days before C1D1)

4. Adequate bone marrow function:
   a) Hemoglobin ≥7.5 g/dL (≥4.65 mmol/L; prior red blood cell (RBC) transfusion or recombinant human erythropoietin use is permitted however transfusions are not permitted within 7 days of randomization to achieve this minimum hemoglobin count);
   b) Absolute neutrophil count (ANC) ≥1.0 x 109/L (granulocyte-colony stimulating factor (G-CSF) use is permitted);
   c) Platelet count ≥50 x 109/L if bone marrow is >50% involved in myeloma. Otherwise ≥75 x 109/L
5. Adequate liver function:
   a) Aspartate aminotransferase (AST) ≤2.5 x ULN;
   b) Alanine aminotransferase (ALT) ≤2.5 x ULN;
   c) Total bilirubin ≤1.5 x ULN (except in subjects with congenital bilirubinemia, such as Gilbert syndrome, direct bilirubin ≤1.5 x ULN)
6. Adequate renal function:
   a) Estimated creatinine clearance ≥30 mL/min. Creatinine clearance may be calculated using Cockcroft-Gault, estimated Glomerular filtration rate (eGFR) (Modified Diet in Renal Disease (MDRD)), or Chronic Kidney Disease (CKD)-epi formula
   b) Corrected serum calcium ≤13.5 mg/dL (≤3.4 mmol/L); or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L)
7. Female subjects of reproductive childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously during the Treatment Period, during any dose interruptions, and for 3 months after the last dose of any component of the treatment regimen. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. This birth control method must include one highly effective form of contraception (tubal ligation, intrauterine device (IUD), hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin 4 weeks prior to dosing. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral oophorectomy.
8. A woman of childbearing potential must have 2 negative serum or urine pregnancy tests at Screening, first within 10 to 14 days prior to dosing and the second within 24 hours prior to dosing.
9. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 3 months after receiving the last dose of any component of the treatment regimen.
10. Male subjects of reproductive potential who are sexually active with females of reproductive potential must always use a latex or synthetic condom during the study and for 3 months after discontinuing study treatment (even after a successful vasectomy).
11. Male subjects of reproductive potential must not donate sperm during the study or for 3 months after the last dose of study treatment.
12. Signed an informed consent form (ICF) (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.
13. Able to adhere to the prohibitions and restrictions specified in this protocol

<u>Key Exclusion Criteria:</u>

1. Prior or current systemic therapy or stem cell transplant (SCT) for any plasma cell dyscrasia, with the exception of emergency use of a short course (equivalent of dexamethasone 40 mg/day for a maximum 4 days) of corticosteroids before treatment.
2. 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 5.
3. Prior or concurrent invasive malignancy (other than multiple myeloma) within 5 years of date of randomization (exceptions are adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix or breast, or other non-invasive lesion 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).
4. Radiation therapy within 14 days of randomization.
5. Plasmapheresis within 28 days of randomization.

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
6. Clinical signs of meningeal involvement of multiple myeloma. 7. Chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) <50% of predicted normal (for subjects ≥65 years old FEV1 <50% or diffusing capacity of the lungs for carbon monoxide [DLCO] <50%) 8. Moderate or severe persistent asthma within the past 2 years, or currently has uncontrolled asthma of any classification. (Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study). 9. Any of the following: a) Seropositive for human immunodeficiency virus (HIV) b) Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are positive for antibodies to hepatitis B core antigen [antiHBc] and/or antibodies to hepatitis B surface antigen [antiHBs]) must be screened using real-time PCR measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (antiHBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by polymerase chain reaction (PCR). c) Seropositive for hepatitis C (HCV) (anti-HCV antibody positive or HCV-RNA quantitation positive), except in the setting of a sustained virologic response (SVR), defined as viremia at least 12 weeks after completion of antiviral therapy. 10. Concurrent medical or psychiatric condition or disease (such as but not limited to, systemic amyloidosis, POEMS, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with the study procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this study. 11. Any of the following: a) myocardial infarction within 6 months before randomization, or an unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV) b) uncontrolled cardiac arrhythmia or clinically significant electrocardiogram (ECG) abnormalities c) screening 12-lead ECG showing a baseline QT interval >470 msec d) left ventricular ejection fraction (LVEF) <40% for subjects age 65-70 years old 12. Received a strong CYP3A4 inducer within 5 half-lives prior to randomization 13. Allergy, hypersensitivity, or intolerance to boron or mannitol, corticosteroids, monoclonal antibodies or human proteins, or their excipients (refer to the Investigator's Brochure), or sensitivity to mammalian-derived products or lenalidomide. 14. Not able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder). Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. 15. Pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of any component of the treatment regimen. Or, subject is a man who plans to father a child while enrolled in this study or within 3 months after the last dose of any component of the treatment regimen. 16. Major surgery within 2 weeks before randomization or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study. Lyphoplasty or Vertebroplasty is not considered major surgery. 17. Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before randomization or is currently enrolled in an interventional investigational study. 18. Contraindications to the use of any components of the backbone treatment regimens, per local prescribing information. 19. Gastrointestinal disease that may significantly alter the absorption of oral drugs 20. Vaccination with live attenuated vaccines within 4 weeks of first study agent administration 21. Unable or unwilling to undergo antithrombotic prophylactic treatment.			
[Abbreviations]: CR – complete response; DOR – duration of response; HRQoL – health related quality of life; MRD – minimal residual disease; NR – not reported; ndMM – newly diagnosed multiple myeloma; PFS – progression free survival; ORR – overall response rate; OS – overall survival; PR – time to response; VGPR – very good partial response;			

7 SUPPLEMENTAL QUESTIONS

No supplemental questions relvant to the review were identified.

8 COMPARISON WITH OTHER LITERATURE

Three records (one abstract reporting an RCT; one abstract and one poster reporting a retrospective cohort study) were identified to support the assumption that efficacy of Cyclophosphamide, bortezomib, and dexamethasone (CyBorD) is similar to Revlimid and dexamethasone (Rd also referred to as Ld). These records provided by the submitter and through a search conducted by CADTH contained relevant information to the current review and a brief summary of the study design and results is provided below and in Table 17.

Overview of the identified literature

1. Jimenez-Zepeda et al 2017[4]: An abstract reported the findings of a RCT comparing CyBorD to Ld for the treatment of Non-Transplant Eligible MM patients in Alberta. Data were collected between January 2010 and October 2016[4]. One-hundred and thirty patients were treated with CyBorD and 71 patients were treated with Ld. The methodological details are limited as the report is in abstract form. There are no details about randomization process, detailed inclusion/exclusion criteria and no patient flow chart was provided. Patients with creatinine >250μmol/L were excluded. The CyBorD regimen was as follows: Bortezomib 1.3-1.5mg/m^2 SC or IV (3-4 weeks out of 4), cyclophosphamide 300 mg/ m^2 PO days 1, 8, 15, 22, and dexamethasone 20-40mg PO on days 1, 8, 15, and 22 with an aim to deliver a minimum of 9 cycles of treatment. The Ld regimen included: Lenalidomide 25 mg PO per day on days 1-21 of a 28-day cycle, with Dexamethasone 20-40mg PO on days 1, 8, 15, and 22. The primary outcomes were: overall response rate (ORR), progression free survival (PFS), time to second objective disease progression (PFS2). The study also reported on very good partial response (VGPR). These outcomes were presented before the median overall-survival had been reached.

2. Jimenez-Zepeda et al 2018[5,6]: 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)[5,6]. 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[5,6]. 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.

Table 17. Summary of three records provided by the submitter outlining record details[4-6]

Title	Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD) Compared to Lenalidomide and Dexamethasone (Ld) for the Treatment of Non-Transplant Eligible MM[4]		2008 Real-World Outcomes with Bortezomib-Containing Regimens and Lenalidomide Plus examethasone for the Treatment of Transplant Ineligible MM Patients: A Multi-Institutional Report from the National Myeloma Canada Research Network (MCRN) Database[5,6]			
Author	Victor Jimenez-Zepeda et al.		Victor Jimenez-Zepeda et al.			
Report Date	March 2017		December 2018			
Report Type	Abstract		Poster Abstract			
Study Design	RCT		Retrospective Cohort			
Data Cut-Off Date	01/2010 – 10/2016		2007 – 01/07/2018			
Patient Population	Non-Transplant Eligible MM		Transplant ineligible MM			
Drug of Interest	CyBorD	Ld	CyBorD/CyBorP	Ld	VMP	Vd/VP
Patient Number	130	71	423	160	204	55
Outcomes	- ORR - PFS - PFS2 - ≥ VGPR		- ORR - PFS - OS - ≥ VGPR			
Study Notes	Patients with creatinine >250µmol/L were excluded.		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; PFS2 – Time to Second Objective Disease Progression; 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-Zepada et al., 2018b[6]

Figure 5. Baseline clinical characteristics and progression-free survival outcome as reported in Jimenez-Zepeda et al. 2018 abstract[5]

Clinical Characteristics	All Patients (N=842)	CyBorD/P (N=423)	VMP (N=204)	Ld (N=160)	VD/VP (N=55)
Median Age (years)	73	71	74	75	70
Female (%)	42	39	46	44	44
Median Creat (umol/L) n=717	103	110	102	93	99
ISS Stage III (%) n=574	48	54	40	41	41
Plasma Cells (%) n=672	40	40	50	40	37
Median duration on Tx (months)	7.3	6.4	9.0	16.3	3.8

Ab: CyBorD; Cyclophosphamide, bortezomib and dexamethasone; CyBorP: cyclophosphamide,bortezomib and prednisone; VMP: bortezomib, melphalan and prednisone; VD: bortezomib and dexamethasone; VP: bortezomib and prednisone; Ld:lenalidomide and dexamethasone; Creat: Serum creatinine; N: Number of evaluable patients; Tx: Treatment

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.

Outcomes

Outcomes for all three reports are summarized in the Table 18 below:

Table 18. Summary of efficacy outcomes comparing CyBorD to Ld (also referred to as Ld)

Title	Drug	N	Median Follow-Up Time (months)	Outcomes				
				ORR (%)	Median PFS (months)	Median PFS2 (months)	≥VGPR (%)	Median OS (months)
Jimenez-Zepeda et al 2017[4]	CyBorD	130	18	84.8	22.5	45.7	56.8	Not reached
	Ld	71	39	82.8	29	39.2	54.2	Not reached
Jimenez-Zepeda et al 2018[5,6]	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

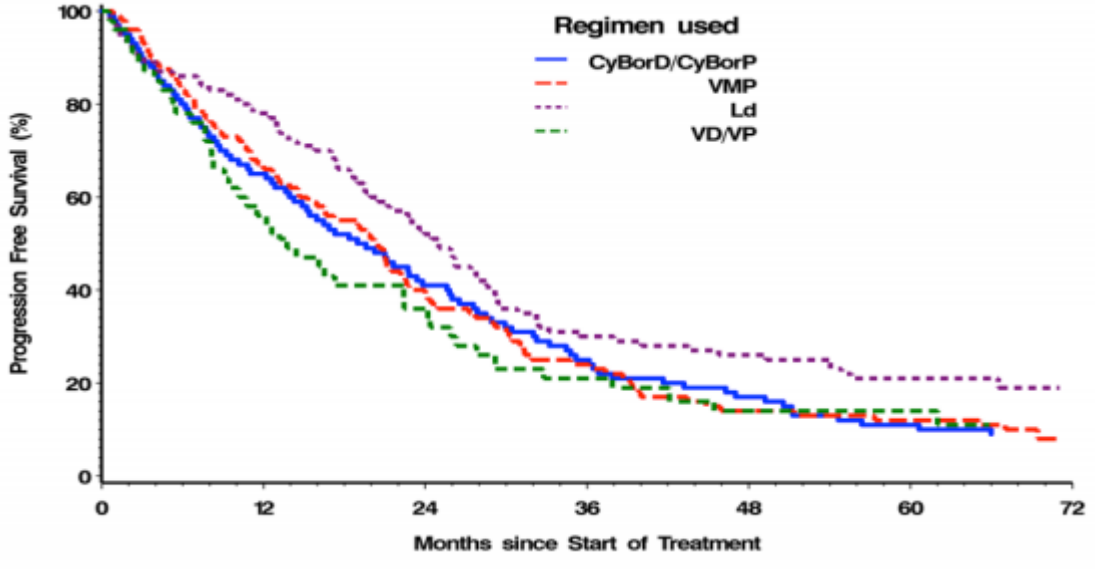
† p-value is >0.05

[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

Jimenez-Zepeda et al. 2017[4] had 130 patients treated with CyBorD and 71 patients treated with Ld with median follow-up times of 18 and 39 months, respectively. ORR and ≥VGPR rates were 84.8% and 56.8% for patients treated with CyBorD, and 82.8% and 54.2% for Ld (p=0.3). Median OS had not been reached for either group. Median PFS was 22.5 months for CyBorD and 29 months for Ld (p=0.2). Median PFS2 was 45.7 months for CyBorD and 39.2 months for Ld (p=0.8). There were no figures or tables included in the abstract.

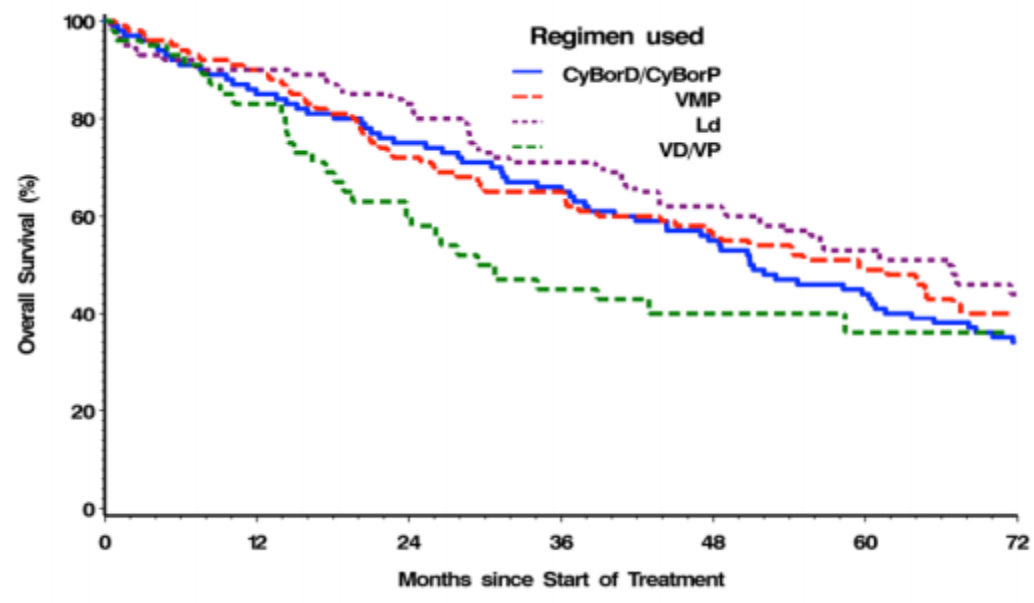
Both the poster and the abstract by Jimenez-Zepeda et al. 2018 retrospectively evaluated 842 patients[5,6]. Four-hundred and twenty-three patients were treated with CyBorD, 204 patients with VMP, 160 patients with Ld, and 55 patients with Vd/VP. For the entire cohort, median OS was 54.1 months, median 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 6 and Figure 7 are the figures as reported in Jimenez-Zepeda et al. 2018 abstract[5] and in the Jimenez-Zepeda et al. 2018 poster.[6]

Figure 6. 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 7. Overall survival clinical outcome as reported in Jimenez-Zepeda et al. 2018 abstract [5]



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.

Conclusion

Based on the three records identified, CyBorD and Ld have similar clinical outcomes. The assumption that the outcomes achieved with CyBorD could be used as markers for the otucomes achieved with Ld is likely valid.

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 Lenalidomide (Revlimid) for MM. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines.

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

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials (CCTR), Embase (1974 to present), MEDLINE All (1946 to present)

#	Searches	Results
1	exp Multiple Myeloma/ or Smoldering Multiple Myeloma/	107195
2	(myelom* or kahler disease or morbus kahler).ti,ab,kw,kf.	150679
3	((plasma* or plasmacytic or plasmocytic or plasmocyte) adj2 (cancer* or neoplas* or oncolog* or tumor* or tumour* or malignan* or leukemia* or leukaemia*)).ti,ab,kw,kf.	21130
4	or/1-3	184543
5	(RVd or VRd).ti,ab,ot,kf,kw,hw,nm.	4234
6	(Vel adj3 Rev adj3 Dex).ti,ab,ot,kf,kw,hw,nm.	3
7	("Rev/Vel/Dex" or "Vel/Rev/Dex").ti,ab,ot,kf,kw,hw,nm.	2
8	or/5-7	4235
9	Lenalidomide/	16410
10	F0P408N6V4.rn,nm.	2227
11	(Revlimid* or Revimid* or lenalidomide* or CC 5013 or CC5013 or CDC 501 or CDC501 or CDC5013 or CDC 5013 or "ENMD 0997" or ENMD0997 or IMiD 3 or IMiD3).ti,ab,ot,kf,kw,hw,nm.	22342
12	or/9-11	22342
13	Bortezomib/	32150
14	69G8BD63PP.rn,nm.	5032
15	(bortezomib* or velcade* or HSDB 7666 or LDP 341 or LDP341 or MG 341 or MG341 or MLN 341 or MLN341 or PS 341 or PS341).ti,ab,ot,kf,kw,hw,nm.	37336
16	or/13-15	37336
17	exp Dexamethasone/	191195
18	7S5I7G3JQL.rn,nm.	49351
19	(adrecort* or adrenocot* or "aeroseb-D" or "aeroseb-dex" or aflucoson* or alfalyl* or anaflogistico* or aphtasolon* or arcodexan* or artrosone* or auxiron* or azium* or bidexol* or "bisu DS" or calonat* or cebedex* or colofoam* or corsona* or corsone* or cortastat* or cortidex* or cortidexason* or cortidrona* or cortidrone* or cortisumman* or dacortina fuerte* or dacortine fuerte* or dalalone* or danasone* or "de-sone la" or decacortin* or decadeltoson* or decaderm* or decadion* or decadron* or cecaesadril* or decagel* or decaject* or decalix* or decamethason* or decasone* or decaspray* or decasterolone* or decdan* or declione* or decofluor* or dectancyl* or dekacort* or delladec* or deltafluoren* or dergramin* or deronil* or desacort* or desadrene* or desalark* or desametason* or desamethason* or desameton* or deseronil* or desigdron* or "dex-ide" or dexa mamallet* or dexa-cortidelt* or dexa-cortisyl* or dexa-scheroson* or "dexa-sine" or dexacen or dexachel* or dexacort* or dexacortal* or dexacorten* or dexacortin* or dexacortisyl* or dexadabroson* or dexadecadrol* or dexadrol* or dexadeltone* or dexafarma* or dexagel* or dexagen* or dexahelvacort* or dexakorti* or dexalien* or dexalocal* or dexalona* or dexamecortin* or dexameson* or dexametason* or dexameth*	230184

	or dexamonozon* or dexan or dexapolcort* or dexapos or dexapot* or dexaprol* or dexascheroson* or dexascherozon* or dexason or dexinolon* or dexinoral* or dexionil* or dexmethson* or dexona or dexone or DexPak or dextelan* or dextrasone* or dextenza* or dezone* or dibasona* or dinormon* or dxm or dxms or esacortene* or "ex s1" or exadion* or firmalone* or fluormethyl prednisolone* or fluormethylprednisolon* or fluormone* or fluorocort* or fluorodelta* or fortecortin* or gammacorten* or grosodexon* or hexadecadiol* or hexadecadrol* or hexadiol* or hexadrol* or "HL-dex" or isnacort* or isoptodex* or "isopto-dex" or isoptomaxidex* or "lokalison F" or loverine* or luxazone* or marvidone* or maxidex* or mediamethasone* or megacortin* or mephaseson* or metasolon* or methazon* or methazonion* or methylfluorprednisolone* or metisone lafi or mexasone* or mexidex* or millicorten* or mymethasone* or neoforderx* or nisomethasona* or novocort* or "ocu-trol" or "oftan-dexa" or opticorten* or opticortinol* or oradexan* or oradexon* or orgadrone* or ozurdex* or pidexon* or policort* or posurdex* or "predni F" or "prednisolon F" or "prednisolone F" or prodexona* or prodexone* or sanamethasone* or santeson* or sawasone* or solurex* or spoloven* or sterasone* or "sunia Sol D" or superprednol* or thilodexine* or triamcimetil* or turbinaire* or vexamet* or visumetazone* or visumethazone* or AI3-50934 or CCRIS 7067 or DXMS or HSDB 3053 or MK 125 or MK125 or NSC 34521 or NSC34521).ti,ab,ot,kf,kw,hw,nm.	
20	or/17-19	230244
21	12 and 16 and 20	6073
22	8 or 21	9969
23	4 and 22	5594
24	23 use medall	595
25	23 use cctr	404
26	Multiple Myeloma/ or Smoldering Multiple Myeloma/	106603
27	(myelom* or kahler disease or morbus kahler).ti,ab,kw,dq.	150134
28	((plasma* or plasmacytic or plasmocytic or plasmocyte) adj2 (cancer* or neoplas* or oncolog* or tumor* or tumour* or malignan* or leukemia* or leukaemia*)).ti,ab,kw,dq.	21111
29	or/26-28	184348
30	(RVd or VRd).ti,ab,kw,dq.	4222
31	(Vel adj3 Rev adj3 Dex).ti,ab,kw,dq.	3
32	("Rev/Vel/Dex" or "Vel/Rev/Dex").ti,ab,kw,dq.	2
33	or/30-32	4223
34	*lenalidomide/ or (Revlimid* or Revimid* or lenalidomide* or CC 5013 or CC5013 or CDC 501 or CDC501 or CDC5013 or CDC 5013 or "ENMD 0997" or ENMD0997 or IMiD 3 or IMiD3).ti,ab,kw,dq.	15361
35	*bortezomib/ or (bortezomib* or velcade* or HSDB 7666 or LDP 341 or LDP341 or MG 341 or MG341 or MLN 341 or MLN341 or PS 341 or PS341).ti,ab,kw,dq.	25688
36	*dexamethasone/ or (adrecort* or adrenocot* or "aeroseb-D" or "aeroseb-dex" or aflucoson* or alfalyl* or anaflogistico* or aphtasolon* or arcodexan* or artrosone* or auxiron* or azium* or bidexol* or "bisu DS" or calonat* or cebedex* or colofoam* or corsona* or corsone* or cortastat* or cortidex* or cortidexason* or cortidrona* or cortidrone* or cortisumman* or dacortina fuerte* or dacortine fuerte* or dalalone* or danasone* or "de-sone la" or decacortin* or decadeltoson* or decaderm* or decadion* or decadron* or cecaesadril* or decagel* or decaject* or decalix* or decamethason* or decasone* or decaspray* or decasterolone* or decdan* or declione* or decofluor* or dectancyl* or dekacort* or delladec* or deltafluoren* or dergramin* or deronil* or desacort* or desadrene* or desalark* or desametason* or desamethason* or desameton* or	153636

	deseronil* or desigdron* or "dex-ide" or dexa mamallet* or "dexa-cortidelt" or dexa-cortisyl* or dexa-scheroson* or "dexa-sine" or dexacen or dexachel* or dexacort* or dexacortal* or dexacorten* or dexacortin* or dexacortisyl* or dexadabroson* or dexadecadrol* or dexadrol* or dexadeltone* or dexafarma* or dexagel or dexagen* or dexahelvacort* or dexakorti* or dexalien* or dexalocal* or dexalona* or dexamecortin* or dexameson* or dexametason* or dexameth* or dexamonozon* or dexan or dexapolcort* or dexapos or dexapot* or dexaprol* or dexascheroson* or dexascherozon* or dexason* or dexinolon* or dexinoral* or dexionil* or dexmethson* or dexona* or dexone* or DexPak or dextelan* or dextrasone* or dextenza* or dezone* or dibasona* or dinormon* or dxm or dxms or esacortene* or "ex s1" or exadion* or firmalone* or fluormethyl prednisolone* or fluormethylprednisolon* or fluormone* or fluorocort* or fluorodelta* or fortecortin* or gammacorten* or grosodexon* or hexadecadiol* or hexadecadrol* or hexadiol* or hexadrol* or "HL-dex" or isnacort* or isoptodex* or "isopto-dex" or isoptomaxidex* or "lokalison F" or loverine* or luxazone* or marvidone* or maxidex* or mediamethasone* or megacortin* or mephaseson* or metasolon* or methazon* or methazonion* or methylfluorprednisolone* or metisone lafi or mexasone* or mexidex* or millicorten* or mymethasone* or neoforderx* or nisomethasona* or novocort* or "ocu-trol" or "oftan-dexa" or opticorten* or opticortinol* or oradexan* or oradexon* or orgadrone* or ozurdex* or pidexon* or policort* or posurdex* or "predni F" or "prednisolon F" or "prednisolone F" or prodexona* or prodexone* or sanamethasone* or santeson* or sawasone* or solurex* or spoloven* or sterasone* or "sunia Sol D" or superprednol* or thilodexine* or triamcimetil* or turbinaire* or vexamet* or visumetazone* or visumethazone* or AI3-50934 or CCRIS 7067 or DXMS or HSDB 3053 or MK 125 or MK125 or NSC 34521 or NSC34521).ti,ab,kw,dq.	
37	34 and 35 and 36	3039
38	33 or 37	6929
39	29 and 38	2971
40	39 use oemezd	2111
41	24 or 40	2706
42	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	1113460
43	Randomized Controlled Trial/	1006867
44	exp Randomized Controlled Trials as Topic/	286813
45	"Randomized Controlled Trial (topic)"/	156349
46	Controlled Clinical Trial/	552872
47	exp Controlled Clinical Trials as Topic/	298320
48	"Controlled Clinical Trial (topic)"/	9915
49	Randomization/	178102
50	Random Allocation/	194930
51	Double-Blind Method/	401429
52	Double Blind Procedure/	157130
53	Double-Blind Studies/	263810
54	Single-Blind Method/	76468
55	Single Blind Procedure/	33666
56	Single-Blind Studies/	78415
57	Placebos/	330328
58	Placebo/	329184

59	Control Groups/	111336
60	Control Group/	111243
61	(random* or sham or placebo*).ti,ab,hw,kf,kw.	4033379
62	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	784982
63	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	3091
64	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	2641757
65	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	95687
66	allocated.ti,ab,hw.	179094
67	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	115880
68	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	25417
69	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	965
70	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	11359
71	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	17877
72	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.	129655
73	or/42-72	5767675
74	41 and 73	879
75	25 or 74	1283
76	limit 75 to yr="2014 -Current"	860
77	limit 76 to english language	839
78	remove duplicates from 77	649

2. Literature search via PubMed

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

Search	Query	Items found
#23	Search #21 and #22	17
#22	Search publisher[sb]	543659
#21	Search #3 AND #20	602
#20	Search #7 OR #19	2073
#19	Search #8 AND #9 AND #18	640
#18	Search #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	68894
#17	Search "oftn-dexa"[tiab] OR opticorten*[tiab] OR opticortinol*[tiab] OR oradexan*[tiab] OR oradexon*[tiab] OR orgadrone*[tiab] OR ozurdex*[tiab] OR pidexon*[tiab] OR policort*[tiab] OR posurdex*[tiab] OR "predni F"[tiab] OR "prednisolon F"[tiab] OR "prednisolone F"[tiab] OR prodexona*[tiab] OR prodexone*[tiab] OR sanamethasone*[tiab] OR santeson*[tiab] OR sawasone*[tiab] OR solurex*[tiab] OR spoloven*[tiab] OR sterasone*[tiab] OR "sunia Sol D"[tiab] OR	460

Search	Query	Items found
	superprednol*[tiab] OR thilodexine*[tiab] OR triamcimetil*[tiab] OR turbinaire*[tiab] OR vexamet*[tiab] OR visumetazone*[tiab] OR visumethazone*[tiab] OR AI3-50934[tiab] OR CCRIS 7067[tiab] OR DXMS[tiab] OR HSDB 3053[tiab] OR MK 125[tiab] OR MK125[tiab] OR NSC 34521[tiab] OR NSC34521[tiab]	
#16	Search hexadrol*[tiab] OR "HL-dex"[tiab] OR isnacort*[tiab] OR isoptodex*[tiab] OR "isopto-dex"[tiab] OR isoptomaxidex*[tiab] OR "lokalison F"[tiab] OR loverine*[tiab] OR luxazone*[tiab] OR marvidone*[tiab] OR maxidex*[tiab] OR mediamethasone*[tiab] OR megacortin*[tiab] OR mephaseson*[tiab] OR metasolon*[tiab] OR methazon*[tiab] OR methazonion*[tiab] OR methylfluorprednisolone*[tiab] OR "metisone lafi"[tiab] OR mexasone*[tiab] OR mexidex*[tiab] OR millicorten*[tiab] OR mymethasone*[tiab] OR neoforderx*[tiab] OR nisomethasona*[tiab] OR novocort*[tiab] OR "ocu-trol"[tiab]	43
#15	Search dextrasone*[tiab] OR dextenza*[tiab] OR dezone[tiab] OR dibasona*[tiab] OR dinormon*[tiab] OR dxm[tiab] OR dxms[tiab] OR esacortene*[tiab] OR "ex s1"[tiab] OR exadion[tiab] OR firmalone*[tiab] OR fluormethyl prednisolone*[tiab] OR fluormethylprednisolon*[tiab] OR fluormone*[tiab] OR fluorocort*[tiab] OR fluorodelta*[tiab] OR fortecortin* OR gammacorten* OR grosodexon*[tiab] OR hexadecadiol*[tiab] OR hexadecadrol*[tiab] OR hexadiol*[tiab]	958
#14	Search dexafarma*[tiab] OR dexagel[tiab] OR dexagen*[tiab] OR dexahelvacort*[tiab] OR dexakorti*[tiab] OR dexalien*[tiab] OR dexalocal*[tiab] OR dexalona*[tiab] OR dexamecortin*[tiab] OR dexameson*[tiab] OR dexametason*[tiab] OR dexameth*[tiab] OR dexamonozon*[tiab] OR dexan[tiab] OR dexapolcort*[tiab] OR dexapos[tiab] OR dexapot[tiab] OR dexaprol*[tiab] OR dexascheroson*[tiab] OR dexascherozon*[tiab] OR dexason[tiab] OR dexinolon*[tiab] OR dexinoral*[tiab] OR dexionil*[tiab] OR dexmethson*[tiab] OR dexona[tiab] OR dexone[tiab] OR DexPak[tiab] OR dextelan*[tiab]	54160
#13	Search desametason*[tiab] OR desamethason*[tiab] OR desameton*[tiab] OR deseronil*[tiab] OR desigdron*[tiab] OR "dex-ide"[tiab] OR dexa mamallet*[tiab] OR dexa-cortidelt*[tiab] OR dexa-cortisyl*[tiab] OR dexa-scheroson*[tiab] OR "dexa-sine"[tiab] OR dexacen[tiab] OR dexachel*[tiab] OR dexacort*[tiab] OR dexacortal*[tiab] OR dexacorten*[tiab] OR dexacortin*[tiab] OR dexacortisyl*[tiab] OR dexadabroson*[tiab] OR dexadecadrol*[tiab] OR dexadrol*[tiab] OR dexadeltone*[tiab]	34
#12	Search "de-sone la"[tiab] OR decacortin*[tiab] OR decadeltoson*[tiab] OR decaderm[tiab] OR decadion*[tiab] OR decadron*[tiab] OR cecaesadril*[tiab] OR decagel*[tiab] OR decaject*[tiab] OR decalix*[tiab] OR decamethason*[tiab] OR decasone*[tiab] OR decaspray*[tiab] OR decasterolone*[tiab] OR decdan*[tiab] OR declione*[tiab] OR decofluor*[tiab] OR dectancyl*[tiab] OR dekacort*[tiab] OR delladec*[tiab] OR deltafluoren*[tiab] OR dergramin*[tiab] OR deronil*[tiab] OR desacort*[tiab] OR desadrene*[tiab] OR desalark*[tiab]	155
#11	Search adrecort*[tiab] OR adrenocot*[tiab] OR "aeroseb-D"[tiab] OR "aeroseb-dex"[tiab] OR aflucoson*[tiab] OR alfalyl*[tiab] OR anaflogistico*[tiab] OR aphtasolon*[tiab] OR arcodexan*[tiab] OR artrosone*[tiab] OR auxiron*[tiab] OR azium*[tiab] OR bidexol*[tiab] OR "bisu DS"[tiab] OR calonat*[tiab] OR cebedex*[tiab] OR colofoam*[tiab] OR corsona*[tiab] OR corsone*[tiab] OR cortastat*[tiab] OR cortidex*[tiab] OR cortidexason*[tiab] OR cortidrona*[tiab] OR cortidrone*[tiab] OR cortisumman*[tiab] OR dacortina fuerte*[tiab] OR dacortine fuerte*[tiab] OR dalalone*[tiab] OR danasone*[tiab]	172
#10	Search Dexamethasone[mh] OR 7S5I7G3JQL[rn]	49406

Search	Query	Items found
#9	Search Bortezomib[mh] OR 69G8BD63PP[rn] OR bortezomib*[tiab] OR velcade*[tiab] OR HSDB 7666[tiab] OR LDP 341[tiab] OR LDP341[tiab] OR MG 341[tiab] OR MG341[tiab] OR MLN 341[tiab] OR MLN341[tiab] OR PS 341[tiab] OR PS341[tiab]	8072
#8	Search Lenalidomide[mh] OR F0P408N6V4[rn] OR Revlimid*[tiab] OR Revimid*[tiab] OR lenalidomide*[tiab] OR CC 5013[tiab] OR CC5013[tiab] OR CDC 501[tiab] OR CDC501[tiab] OR CDC5013[tiab] OR CDC 5013[tiab] OR ENMD 0997[tiab] OR ENMD0997[tiab] OR IMiD 3[tiab] OR IMiD3[tiab]	3996
#7	Search #4 OR #5 OR #6	1477
#6	Search "Rev/Vel/Dex"[tiab] OR "Vel/Rev/Dex"[tiab]	0
#5	Search Vel[tiab] AND Rev[tiab] AND Dex[tiab]	0
#4	Search RVd[tiab] OR VRd[tiab]	1477
#3	Search #1 OR #2	138434
#2	Search (plasma[tiab] OR plasmacytic[tiab] OR plasmocytic[tiab] OR plasmocyte[tiab]) AND (cancer*[tiab] OR neoplasm* [tiab] OR tumor[tiab] OR tumors[tiab] OR tumour[tiab] OR tumours[tiab] OR oncolog*[tiab] OR leukemia*[tiab] OR leukaemia*[tiab])	76666
#1	Search Multiple myeloma[mh] OR Smoldering Multiple Myeloma[mh] OR myelom*[tiab] OR Kahler disease[tiab] OR morbus kahler[tiab]	66926

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: Revlimid (lenalidomide)/Velcade (bortezomib)/dexamethasone, 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: Revlimid (lenalidomide)/Velcade (bortezomib)/dexamethasone, 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: Revlimid (lenalidomide)/Velcade (bortezomib)/dexamethasone, multiple myeloma – last 5 years

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