CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

# pan-Canadian Oncology Drug Review
# Final Clinical Guidance Report

# Daratumumab (Darzalex) + Rd for Newly Diagnosed Multiple Myeloma

March 5, 2020

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# FUNDING

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

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# TABLE OF CONTENTS

DISCLAIMER AND FUNDING ..... ii
INQUIRIES ..... iii
TABLE OF CONTENTS ..... iv
1 GUIDANCE IN BRIEF ..... 1
1.1 Introduction ..... 1
1.2 Key Results and Interpretation ..... 1
1.2.1 Systematic Review Evidence ..... 1
1.2.2 Additional Evidence ..... 7
1.2.3 Factors Related to Generalizability of the Evidence ..... 10
1.2.4 Interpretation ..... 14
1.3 Conclusions ..... 16
2 BACKGROUND CLINICAL INFORMATION ..... 18
2.1 Description of the Condition ..... 18
2.2 Accepted Clinical Practice ..... 18
2.3 Evidence-Based Considerations for a Funding Population ..... 20
2.4 Other Patient Populations in Whom the Drug May Be Used ..... 20
3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT ..... 21
3.1 Condition and Current Therapy Information ..... 21
3.1.1 Experiences Patients have with Multiple Myeloma ..... 21
3.1.2 Patients' Experiences with Current Therapy for Multiple Myeloma ..... 23
3.1.3 Impact of Multiple Myeloma and Current Therapy on Caregivers ..... 23
3.2 Information about the Drug Being Reviewed ..... 24
3.2.1 Patient Expectations for and Experiences To Date with Daratumumab ..... 24
3.3 Additional Information ..... 28
4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT ..... 29
4.1 Currently Funded Treatments ..... 29
4.2 Eligible Patient Population ..... 29
4.3 Implementation Factors ..... 30
4.4 Sequencing and Priority of Treatment ..... 31
4.5 Companion Diagnostics ..... 31
4.6 Additional Information ..... 31
5 SUMMARY OF REGISTERED CLINICIAN INPUT ..... 32
5.1 Current Treatment(s) for Multiple Myeloma ..... 32
5.2 Eligible Patient Population ..... 33
5.3 Identify Key Benefits and Harms with Daratumumab ..... 34
5.4 Relevance of Clinical Practice ..... 34
5.5 Sequencing and Priority of Treatments with Daratumumab ..... 34
5.6 Companion Diagnostic Testing ..... 34
5.7 Additioanl Information ..... 34
6 SYSTEMATIC REVIEW ..... 36
6.1 Objectives ..... 36
6.2 Methods ..... 36
6.3 Results ..... 38
6.3.1 Literature Search Results ..... 38
6.3.2 Summary of Included Studies ..... 39
6.4 Ongoing Trials ..... 61
7 SUPPLEMENTAL QUESTIONS ..... 62
8 COMPARISON WITH OTHER LITERATURE ..... 76
9 ABOUT THIS DOCUMENT ..... 77
APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY ..... 78
REFERENCES ..... 85

# 1 GUIDANCE IN BRIEF

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

This Clinical Guidance is based on: a systematic review of the literature regarding daratumumab (Darzalex) in combination with Rd for the treatment of NDMM conducted by the Myeloma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on daratumumab (Darzalex) in combination with Rd for NDMM a summary of submitted Provincial Advisory Group Input on daratumumab (Darzalex) in combination with Rd for NDMM ,and a summary of submitted Registered Clinician Input on daratumumab (Darzalex) in combination with Rd for NDMM ,and are provided in Sections 2, 3, 4, and 5 respectively.

## 1.1 Introduction

The primary objective of this review is to evaluate the efficacy and safety of daratumumab (Darzalex) in combination with lenalidomide and dexamethasone (DRd) compared to standard of care for the treatment of patients with newly diagnosed multiple myeloma (NDMM) who are ineligible for autologous stem cell transplantation (ASCT).

Daratumumab (Darzalex) is an IgGk human monoclonal antibody (mAB) that targets the CD38 protein expressed at a high level on the surface of cells in a variety of hematological malignancies, including multiple myeloma tumour cells.[1]

The Health Canada approved indication is for the use of daratumumab in combination with lenalidomide and dexamethasone, or with bortezomib, melphalan and prednisone for the treatment of patients with NDMM who are ineligible for ASCT. Daratumumab treatment is administered intravenously. The recommended dose for daratumumab is 16mg/kg once weekly during cycles 1 and 2, every 2 weeks during cycles 3 through 6, and every 4 weeks thereafter until disease progression or unacceptable toxicities.[1]

## 1.2 Key Results and Interpretation

### 1.2.1 Systematic Review Evidence

One randomized controlled trial (RCT) was identified that met the eligibility criteria of the pCODR systematic review. MAIA[2] is a randomized, open-label, active-controlled, parallel-group, multicentre, phase III international trial, globally distributed across 14 countries in North America, Europe, the Middle East, and the Asia-Pacific region. MAIA evaluated the safety and efficacy of daratumumab in combination with lenalidomide and dexamethasone (DRd) compared to Rd. The primary endpoint was progression-free survival (PFS). Key

secondary outcomes included time to progression (TTP), minimal residual disease (MRD) negativity, overall survival (OS), response, safety and patient reported outcomes (PROs) from the EORTC QLQ-C30 and the EQ-5D-5L instruments in patients with new diagnosed multiple myeloma (NDMM) who are ineligible for autologous stem-cell transplantation (ASCT).[2]

Eligible patients were randomized in a 1:1 ratio to receive intravenous (IV) daratumumab in combination with oral lenalidomide and oral dexamethasone (daratumumab group, DRd, n=368) or oral lenalidomide and oral dexamethasone (control group, Rd, n=369). Patients were stratified by International Staging System (ISS, I vs II vs III), region (North America vs Other), and age (<75 vs ≥75).[2]

A total of 737 patients with NDMM who were ineligible for high-dose chemotherapy with stem cell transplantation due to age (≥65 years) or the presence of co-existing conditions that were likely to result in the development of unacceptable side effects were randomized into the study. Demographic and clinical characteristics appeared well balanced at baseline between the DRd and Rd treatment groups. The median age was 73 years (range 50-90) in the DRd group and 74 (range 45-89) in the control group (Rd). The majority of patients were ≥75 years (DRd - 43.5%; Rd – 43.6%) with an ECOG performance status of 0 or 1. An ECOG performance status score of ≥2 at baseline was reported in 17.1% and 16.0% of subjects in the DRd and Rd treatment groups, respectively. The majority of subjects had an ISS disease stage classification of II (44.3% DRd; 42.3% Rd) and the median time since diagnosis of MM to randomization was 0.95 (range 0.1-13.3) months in the DRd group and 0.89 (range 0-14.5) months in the Rd group. Highlights of key efficacy and safety outcomes from the MAIA trial are noted below in Table 1.[2]

Table 1: Highlights of key outcomes in the included MAIA trial.

| **Efficacy Outcomes** | MAIA[2] | |
|---|---|---|
| Treatment Groups, n | DRd, 368 | Rd, 369 |
| Analysis | First Interim Analysis | |
| Data cut-off date | September 24, 2018 | |
| Median follow-up in months | 28.0 months (range, 0 -41.4) | |
| Patients remaining on treatment, n (%)[3] | 246 | 158 |
| Number of patients who received daratumumab monotherapy, | 35 | NA |
| Median duration of single agent daratumumab | 7.3 months (0.03-31.2) | NA |
| **Primary Outcome – PFS by investigator assessment** | | |
| No. PFS events (%) | 97 (26.4) | 143 (38.8%) |
| Median PFS, months (95%CI) | Not reached | 31.9 months |
| HR* (95% CI, p-value) | 0.56 (0.43-0.73, p<0.001) | |
| **Key Secondary Outcomes** | | |
| ORR | 92.9% | 81.3% |
| p-value | <0.001 | |

| **Efficacy Outcomes** | MAIA[2] | |
|---|---|---|
| No. of patients with CR or better and VGPR or better | 47.6%<br>79.3% | 24.9%<br>53.1% |
| p-value | <0.001 | |
| Minimal Residual Disease (MRD) Negativity ** | 24.2% | 7.3% |
| P-value | <0.002 | |
| OS | | |
| No. deaths (%) | 62 (16.8%) | 76 (20.6 %) |
| Median OS, months (95% CI) | Not Reached[a] | Not Reached[a] |
| HR* (95% CI, p-value) | 0.78 (0.56-1.1) | |
| QoL | | |
| EORTC QLQ-C30 GHS | DRd showed a clinically meaningful benefit for GHS starting in Cycle 9 and sustained through cycle 12. In the Rd group the mean change from baseline in the GHS score did not meet the MID threshold at any time. The median time to worsening was 1 month longer in the D-Rd group compared to the Rd group (22.5 vs. 21.2 months), although this difference was not statistically significant. | |
| EQ-5D-5L | The EQ-5D-5L VAS score improved from baseline to Cycle 12 for both treatment groups, with a significantly greater improvement in D-Rd group compared to with Rd group at Cycle 12 (LS mean change from basesline: D-Rd, 10.1 [95% CI, 8.1-12.1] vs Rd, 4.9 [95%CI, 2.8-7.0], p=0.0002. The median time to worsening of the EQ-5D-5L VAS score was 10 months longer in the D-Rd group compared with the Rd group (32.2 months vs 22.1 months, respectively), this difference was not statistically significant and the upper bound was not evaluable at the clinical cutoff of 12 cycles. | |
| Harms Outcomes, n (%) | | |
| TEAE (any grade)[4] | [redacted][c] | [redacted] |
| Grade ≥ 3[4] | [redacted] | [redacted] |
| SAE[b] | 62.9% | 62.7% |
| AE that resulted in death | 25 (6.9) | 23 (6.3) |
| Discontinuation due to AE[b] | 7.4% | 16.2% |
| Abbreviations: NA- not applicable; AE - adverse events; CI - confidence interval; CR – complete response; EORTC QLQ - European Organization for Research and Treatment of Cancer's Core Quality of Life Questionnaire (C30) and Breast Cancer Specific Questionnaire (BR23); HR - hazard ratio, MCID – minimal clinically important difference; NE – not estimable; NR - not reported, OR - odds ratio; ORR – overall response rate; OS - overall survival, PFS - progression-free survival; PR – partial response; QOL -health-related quality of life; SAE - serious adverse event. | | |
| Notes:<br>*HR <1 favors daratumumab | | |

| Efficacy Outcomes | MAIA[2] |
|---|---|
| **At a threshold of 1 tumor cell per $10^5$ white cells<br>[a] Long term survival follow-up is ongoing<br>[b] Data is consistent with the 4 month safety analysis update (January 24, 2019)<br>[c] At least one related to daratumumab, n=[redacted] ([redacted]%)[4] | |

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

The trial met its primary outcome (crossed the pre-specified boundary for superiority) and demonstrated a statistically significant improvement in PFS (investigator assessed) such that the combination of DRd significantly prolonged PFS compared with Rd alone, HR 0.56 (95% CI, 0.43-0.73, p<0.001). At the latest data cut-off, OS data remained immature with 138 patients who had died, 62 (16.8%) in the DRd group and 76 (20.6%) in the Rd group.[2]

Key secondary endpoints, such as ORR, CR or better, MRD Negativity also demonstrated statistical significance of the DRd group versus the Rd group.[2]

The QoL data reported from PRO endpoints, including the EORTC-QLQ-C30 and EQ-5D-5L, indicated improvements in HRQoL for both treatment arms, with high compliance rates. Clinically meaningful benefit in GHS was seem for patients between cycles 9-12. Additional QoL data after cycle 12 was not available.[5]

Treatment emergent adverse events (TEAE) were experienced by >[redacted]% of patients in both treatment groups. *Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this safety information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed.* The incidence of serious adverse events (SAE) were similar between both treatment groups, 62.9% for DRd and 62.7% for Rd[2]. The 4- month safety update from January 24, 2019 reported results which were consistent with the September 24, 2018 analysis noted here. Pneumonia was the most common SAE, 13.2% of the patients in the DRd group versus 7.4% in the Rd group. Adverse events which led to the discontinuation of the trial treatment were 7.1% in the DRd group and 15.9% in the Rd group. The 4-month safety update from January 24, 2019 reported results consistent with the analysis from September 24, 2018, noted here.[2]

**Limitations**

Overall, there were no major concerns with the conduct of MAIA trial. However, the following limitations and potential sources of bias of the MAIA trial were noted by the pCODR Methods Team.

- Among these, treatment assignment in the MAIA trial was not blinded. This has the potential to introduce bias as participants would have been aware of which treatment was received.

- Additionally, according to clinician input, patients who are ≥70 years of age are considered transplant-ineligible in Canada, whereas the MAIA trial considered patients who were ≥65 years old to be transplant-ineligible. The extent to which the older aged cut-off may have influenced the results of the trial is unknown.
- he extent to which the lower median dose intensity of lenalidomide and dexamethasone in the daratumumab group compared to the control group may have influenced efficacy outcomes is also unknown.
- For patients randomized to the Rd group, [redacted]% received subsequent antimyeloma therapies, of which [redacted] patients ([redacted]%) received daratumumab as subsequent therapy. This compares with [redacted]% in the DRd group who received antimyeloma therapies and [redacted]% who received subsequent daratumumab. There will likely be confounding from subsequent use of daratumumab in the Rd arm. *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.*

- At the time of the data analysis, OS data was immature (median overall survival was not reached in either group) making the actual degree of long-term benefit of DRd compared to Rd unknown. Follow-up for long-term survival is ongoing.
- HRQoL end points were secondary and were not included in the statistical hierarchy or adjusted for multiplicity. Therefore, interpretation of HRQoL end points is limited.

**PRIMARY OUTCOME**

**Progression-free Survival (PFS)**

As of the primary analysis pre-defined cut-off date of September 24, 2018 and a median follow-up of 28.0 months (range 0-41.4), disease progression or death had occurred in 26.4% (97/368) of patients in the DRd group and 38.8% (143/369) of patients in the Rd group.[2] The Kaplan–Meier estimate of the percentage of patients who were alive without disease progression at 30 months was 70.6% (95% confidence interval [CI], 65.0 to 75.4) in the DRd group and 55.6% (95% CI, 49.5 to 61.3) in the Rd group.[2] The combination of DRd demonstrated superiority over Rd for the primary endpoint of PFS with an estimated HR of 0.56 (95% CI, 0.43 to 0.73, p<0.0001, crossing the pre-specified O'Brien-Fleming stopping boundary of p≤0.0085)[3] in favour of the DRd treatment group. The median PFS was not reached in the DRd group and was 31.9 months (95% CI, 28.9 to not reached) in the Rd group. One-, two- and three-year PFS rates were [redacted]% (95% CI, [redacted]% to [redacted]%), [redacted]% (95% CI, [redacted]% to [redacted]%), and [redacted]% (95% CI, [redacted]% to [redacted]%), in the DRd group and [redacted]% (95% CI, [redacted]% to [redacted]%), [redacted]% (95% CI, [redacted]% to [redacted]%) and [redacted]% (95% CI, [redacted]% to [redacted]%) in the Rd group, respectively.[3] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.*

**Secondary Endpoints**
**Response**

The percentage of patients with complete response (CR) or better in the ITT population was significantly higher in the DRd groups than in the Rd (47.6% vs. 24.9%), as was the percentage with very good partial or better response (79.3% vs. 53.1%) (P<0.001 for both comparisons) (Table 8).[2] A total 92.9% of patient in the DRd group and 81.3% in the Rd group had an overall response.[2] Among the patients who had a response (partial response or better), 80.3% (95% CI, 75.1 to 84.5) in the DRd group and 65.7% (95% CI, 58.6 to 71.8) in the Rd group sustained the response for 30 months.[2] The median time to the first response was 1.05 months in both groups, and the median time to a complete response or better was 10.4 months in the DRd group and 11.2 months in the Rd group.[2]

**Minimal Residual Disease (MRD) Negativity**
Based on the ITT population, the DRd group demonstrated a greater rate of MRD negativity compared with the Rd group. The MRD negativity rate, at a threshold of 1 tumor cell per $10^5$ white cells, was more than 3-fold higher in the DRd group compared with the Rd group (DRd: 24.2%, Rd: 7.3%;[2])[3].

**Overall Survival (OS)**
With a median overall follow-up of 28 months, the OS data were still immature, which is consistent with the expectation in newly diagnosed patient populations. A total of 138 deaths were observed, 62 subjects (16.8%) in the DRd group and 76 subjects (20.6%) in the Rd group. The median overall survival was not reached in either group, and follow-up for long-term survival is ongoing.[2] The hazard ratio was 0.78 (95% CI: 0.56 to 1.10).[3]

**Patient Reported Outcome (PRO) Endpoints**
PRO was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30) global health status (GHS) scale and the EuroQol 5-dimensional descriptive system (EQ-5D-5L). PRO analyses, with data available from baseline through to cycle 12, were descriptive and included patients in the ITT population. All PRO measures were collected prior to the administration of study intervention or study assessments on that visit within 21 days of randomization and on Day 1 of Cycles 3, 6, 9, and 12 in year 1, and every sixth cycle thereafter until PD, [redacted].[4] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by sponsor that it can be publicly disclosed.*

***EORTC QLQ-C30***
Perrot et al[5] reported that GHS improved in both treatment groups across all time points, with significantly greater improvement from baseline to Cycle 3 in the DRd group versus the Rd group (least squares [LS] mean change from baseline: DRd, 4.5 [95% CI, 2.4-6.6] vs Rd, 1.5 [95% CI, –0.7-3.7]; between-arm difference in LS mean change from baseline: 3.0 [95% CI, 0.1-5.9]; *P* = 0.0454). In the DRd group, a clinically meaningful benefit was observed for GHS starting in Cycle 9 and sustained through Cycle 12.[5] The mean change from baseline in the GHS score did not meet the MID threshold at any time for the Rd group.

***EuroQol EQ-5D-5L***
Analysis of the ITT population showed that, VAS score improved from baseline to Cycle 12 for both treatment groups, with significantly greater improvement in

the DRd group compared with the Rd group at Cycle 12 (LS mean change from baseline: DRd, 10.1 [95% CI, 8.1-12.1] vs Rd, 4.9 [95% CI, 2.8-7.0]; between-arm difference in LS mean change from baseline: 5.2 [95% CI, 2.4-8.0]; *P* = 0.0002).[5] In the DRd group, the VAS score had clinically meaningful improvement from baseline starting at Cycle 3 and sustained through Cycle 12; the Rd group crossed the MID threshold of clinically meaningful benefit at Cycle 9, but this was not sustained through Cycle 12. The median time to worsening of the EQ-5D-5L VAS score was 10 months longer in the DRd group compared with the Rd group (32.2 months vs 22.1 months, respectively), although this difference was not statistically significant and the upper bound was not evaluable at the clinical cut off.[5]

***Safety Outcomes***

A total of 364 patients in the DRd group and 365 patients in the RD group received at least one dose of study treatment and were included in the safety analysis. With a median treatment duration of 25.3 months in the DRd treatment group and 21.3 months in the Rd treatment group,[3]daratumumab in combination with Rd resulted in higher incidences of any grade and grade 3 or 4 neutropenia and pneumonia in elderly patients with newly diagnosed multiple myeloma. The most common adverse events of grade 3 or 4 were neutropenia (50.0% in the DRd group and 35.3% in the Rd group), anemia (11.8% and 19.7%), lymphopenia (15.1% and 10.7%), pneumonia (13.7% and 7.9%), and leukopenia (11.0% and 4.9%).[2] The incidence of infections of any grade was 86.3% in the DRd group and 73.4% in the Rd group; the incidence of grade 3 or 4 infections was 32.1% in the DRd group and 23.3% in the Rd group.[2] Serious treatment-emergent adverse events (TEAEs) were reported at comparable incidences in the DRd group.

Discontinuation of study treatment due to TEAEs was reported at a lower incidence in the DRd group (7.1%) compared with the Rd group (15.9%). Discontinuation of the trial treatment owing to an infection occurred in 0.5% of the patients in the DRd group and in 1.4% of the patients in the Rd group; no patients in the DRd group, as compared with 1 patient (0.3%) in the Rd group, discontinued treatment because of neutropenia.

Adverse events that resulted in death were observed in 25 patients (6.9%) in the daratumumab group and in 23 patients (6.3%) in the control group; the most common such event was pneumonia, which resulted in death in 0.5% and 0.8% of the patients, respectively.[2] Of the 364 subjects who received daratumumab, 40.9% experienced an infusion-related reaction (IRR). Infusion-related reactions usually occurred during administration of the first dose (in 98.0% of the patients who had such reactions), and only one patient (with grade 4 hypertension) discontinued daratumumab treatment due to an infusion-related reaction.[2]

### 1.2.2 Additional Evidence

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

### *Patient Advocacy Group Input*

One patient advocacy group, Myeloma Canada provided input on daratumumab in combination with lenalidomide and dexamethasone (Rd) as a first-line treatment for newly diagnosed multiple myeloma (MM) patients who do not qualify for autologous stem cell transplant. A total of 7 patients and four caregivers had experience with the daratumumab and Rd combination under review and such patients were ineligible for autologous stem cell transplant.

From the patient perspective, infections were reported to be the most important MM symptom to control followed by kidney problems, mobility, pain and fatigue, neuropathy (pain, numbness, tingling, swelling or muscle weakness), and shortness of breath. Overall, six respondents reported that the common side effects of daratumumab and Rd were generally tolerated. Among the side effects associated with currently available treatments, pain was most commonly rated (24%) as "most important to avoid"; alternatively, shortness of breath was most commonly rated (21%) as "least important to avoid". Overall, key patient values included improving quality of life, the ability to have a normal life, to have more treatment options, disease control, and manageable side effects.

### *Provincial Advisory Group (PAG) Input*

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:

- Additional resources for preparation, administration, and monitoring

### *Registered Clinician Input*

Two joint clinician inputs were submitted on behalf of the Myeloma Canada Research Network (three clinicians) and Cancer Care Ontario Hematology DAC (two clinicians), which constituted input from a total of five clinicians.

The clinicians reported improvements of treatment tolerability, safety, and effectiveness with DRd compared to currently available therapies. Overall, clinicians were satisfied with the results from the phase III randomized, open-label, active-controlled clinical trial (NCT02252172). Namely, a superior progression-free survival (PFS) and minimal toxicity were highlighted as key benefits of the treatment combination. In addition, the clinicians noted that the discontinuation rate due to toxicity of DRd was reported to be lower compared to other treatments such as lenalidomide/ bortezomib/ dexamethasone (RVd).

There was general agreement that DRd would be administered as first-line treatment. However, one clinician noted that the use of DRd in high-risk patients should be investigated since they may be more suited to VRd therapy.

### *Summary of Supplemental Questions*

The following Supplemental Questions were identified while developing the review protocol as relevant to the pCODR review of daratumumab in combination with lenalidomide and dexamethasone:

- Part 1: Critical appraisal of the Sponsor's submitted network meta-analysis (NMA) comparing daratumumab (Darzalex) in combination with lenalidomide and dexamethasone (DRd) to bortezomib/melphalan/prednisone (VMP), daratumumab/bortezomib/melphalan/prednisone (D-VMP), melphalan/prednisone/thalidomide (MPT), bortezomib/thalidomide/dexamethasone (VTD), cyclophosphamide/thalidomide/dexamethasone (CTD), melphalan/prednisone (MP), and thalidomide/dexamethasone (TD) among others in patients with NDMM who are ineligible for ASCT.

  The Sponsor submitted an NMA comparing DARA-based regimens to other pharmacological interventions for patients with Newly Diagnosed Multiple Myeloma (NDMM) who are ineligible for ASCT. Results of the NMA have been published (conference posted) for the primary outcome PFS, as well as for ORR.[5] Additional details from the ITC were obtained from the Sponsors full NMA report provided to CATDH. The results of this NMA were used to inform the Sponsors economic evaluation, with respect to the comparisons with CyBorD and VMP. The NMA was summarized and critically appraised using the ISPOR Task Force Indirect Comparison/Network Meta-analysis Study Questionnaire.[6]

  The NMA was conducted using a Bayesian framework. This NMA indicates that both daratumumab with Rd (DRd) or with VMP (D-VMP) are the best treatment options for NDMM patients who are ineligible for ASCT. The results of the NMA shows that DRd has the highest probability of being the best treatment option in OS, PFS and ORR, followed by D-VMP.

  The main limitations of the NMA are such that the definition of progression-free survival, overall survival and the criteria used to define ORR and ≥CR varied among trials. The differences in the trials' duration of follow-up and other trial characteristics may have also affected the treatment effects observed in each trial. Finally, the submitted NMA did not explore QOL between DARA-based regimens and other therapies. Considering all these uncertainties and limitations, the conclusions drawn from the NMA should be interpreted with caution.

- Part 2: Critical appraisal of the Sensitivity Analysis of the Sponsor's submitted NMA for the addition of VRd (Bortezomib-Lenalidomide-Dexamethasone)

  The Sponsor's submitted NMA excluded the SWOG S0777 study which examined VRd vs. Rd. As a result, VRd was not included in the Sponsor's submitted NMA. The CGP noted that VRd has received a positive reimbursement recommendation from CADTH for the treatment of newly diagnosed multiple myeloma patients in whom stem cell transplantation is not intended and as such should be considered as a relevant comparator. CADTH requested the Sponsor to update their NMA with the inclusion of the SWOG-S0777 trial. In response to CADTH's request, the Sponsor noted that the SWOG-S0777 study enrolled both

both transplant-eligible (TE) and TIE (transplant ineligible) patients, and data for patients who are TIE only (~50% [aged ≥65 y and frail]) were unavailable. At a subsequent request of CADTH, the Sponsor provided a sensitivity analysis of the previously-conducted NMA including all patients who received VRd in SWOG S0777 to offer a comprehensive view of the comparative effectiveness of DARA-based treatments in transplant ineligible newly diagnosed multiple myeloma (NDMM).

The sensitivity analysis that included VRd, demonstrated favorable efficacy outcomes for DARA-based regimens versus other relevant frontline options for patients with NDMM who are transplant ineligible. However, there are several limitations to note. These include lack of comparative trial data and demographic differences between patients from SWOG-S0777 and patients from trials of other treatments for patients with NDMM who are ineligible for ASCT which are included in the network. In addition, the majority of SWOG S0777 patients are transplant eligible (<65 y), who often have better prognoses than transplant ineligible patients (≥65 y). These differences result in a violation of the similarity assumption of analysis and therefore represent a significant limitation in comparing efficacy outcomes of the SWOG-S0777 and MAIA trials. As such, results of the sensitivity analysis should be interpreted with caution.

See Section 7 for more information.

***Comparison with Other Literature***

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

### 1.2.3 Factors Related to Generalizability of the Evidence

Table 1. Addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

**Table 1. Assessment of generalizability of evidence for daratumumab in combination with lenalidomide and dexamethasone in patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant**

| Domain | Factor | Evidence (MAIA trial) | Generalizability Question | CGP Assessment of Generalizability |
|---|---|---|---|---|
| **Population** | Patients with monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma, primary amyloidosis, and radiation therapy within 14 days of randomization. | The MAIA trial excluded patients with a diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma as well as those who had radiation therapy within 14 days of randomization.<br><br>PAG is seeking guidance on these patients as in practice, multiple myeloma regimens are generalized to patients with primary amyloidosis.<br><br>PAG is also seeking clarity on whether patients who receive urgent radiation prior to starting DRd treatment as well as patients who present with renal failure, would be eligible. | Are the trial results generalizable to patients with primary monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, primary amyloidosis, or patients who had radiation therapy within 14 days of randomization? | The results of this trial are not generalizable to patients with MGUS, smoldering myeloma or amyloidosis. Patients treated with radiation would no impact patient eligibility for this regimen, and a 14-day post-treatment window would not impact choice of regimen used. |
| | ECOG Performance Status | **DRd (N = 368)** / **Rd (N = 369)**<br>ECOG PS— no. (%)<br>0: 127 (34.5) / 123 (33.3)<br>1: 178 (48.4) / 187 (50.7)<br>2: 63 (17.1) / 59 (16.0) | Are the trial results generalizable to patients with an ECOG score of greater than 2? | For patients with ECOG of 2 or greater secondary to myeloma, this regimen could still be used as performance status typically improves with the initiation of myeloma therapy. |

| Domain | Factor | Evidence (MAIA trial) | Generalizability Question | CGP Assessment of Generalizability |
|---|---|---|---|---|
| | | The majority of patients in the DRd group and Rd group had an ECOG performance score of 1 (48.4% and 50.7% respectively) and 17% in the DRd group and 16% in the Rd had a performance status of 2.[2] | | |
| **Intervention** | Dosage | PAG noted that the recommended dosing/schedule for DRd in this setting differs from other daratumumab-based regimens for multiple myeloma (e.g., D-CyBorD, DVMP or DRd). The dosing for daratumumab in D-VMP for newly diagnosed multiple myeloma is 16mg/kg in cycle 1, then every 3 weeks in cycles 2-9, and every 4 weeks thereafter (cycles are 42 days in length). The dosing od daratumumab for D-Rd in the relapsed/refractory setting is 16 mg/kg per week in cycles 12, every 2 weeks in cycles 3-6 and every 4 weeks thereafter (cycles are 28 days in length). The daratumumab dosage in the MAIA trial for DRd was 16mg/kg once weekly in cycles 1-2, then every 2 weeks in cycles 3-6 and then | Is the MAIA trial dosage for daratumumab generalizable to patients in Canada? | Yes. The dosing for DRd for patients with newly diagnosed is generalizable to patients in Canada and is currently approved and is the same as what is used for daratumumab in the relapsed/refractory setting. |

| Domain | Factor | Evidence (MAIA trial) | Generalizability Question | CGP Assessment of Generalizability |
|---|---|---|---|---|
| | | every 4 weeks thereafter (cycles are 28 days in length). | | |
| **Comparator** | Rd | Although the comparator of Rd in the MAIA trial is a funded option, PAG is also seeking comparative information on DRd compared with CyBorD. | Are the results of the trial applicable given that other treatment regimens are available in the Canadian setting? | Yes. Rd is a treatment option in Canada. CyBorD is a more common first line treatment option but the efficacies are felt to be similar.[7]<br><br>The CGP also noted that additional comparators relevant to this review include VRd, D-CyBorD and D-VMP. CADTH has conditionally recommended to reimburse both VRd and D-VMP in the newly diagnosed transplant in-eligible population; however, there are no head to head trials evaluating the efficacy and safety of these agents. |
| **Abbreviations** ECOG = Eastern Cooperative Oncology Group; DRd = daratumumab in combination with lenalidomide and dexamethasone; Rd = lenalidomide and dexamethasone; PAG = Provincial Advisory Group | | | | |

### 1.2.4 Interpretation

***NEED AND BURDEN OF ILLNESS:***

It is estimated that 3000 patients are diagnosed with myeloma annually in Canada. Despite recent advances in treatment, myeloma remains an incurable disease, and approximately 1500 patients die every year from this disease. There is ongoing need for improved treatment to control the disease, and eventually find a cure. The impact of this disease on patients and families is profound, and it is imperative that we find well tolerated treatments that allow patients to maintain a good quality of life for as long as possible. With currently available therapies, patients typically run out of options and die of their disease. As a result, there is an ongoing need for therapies that can prolong the progression free interval for as long as possible, until such time as a cure is discovered.

***EFFECTIVENESS:***

Progression-free Survival:

The MAIA study demonstrated that the combination of daratumumab, lenalidomide and dexamethasone (DRd) is a highly effective treatment regimen for transplant ineligible patients with myeloma. Although an overall survival benefit has yet to be seen, probably due to immature data and short follow-up, the initial results of progression-free survival indicate the DRd regimen is highly effective and provides a clinically meaningful improvement in outcome. In the MAIA study, the median PFS for the DRd group has yet to be reached, compared to 31.9 months for Rd. The three-year progression free survival is estimated to be [redacted]% for the DRd group, compared to [redacted]% for the Rd group. *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.* This 31% absolute improvement in PFS after three years (HR 0.56 (95%CI 0.43-0.73; P<0.007) is clinically significant. In a subgroup analysis, the PFS benefit was seen across all subgroups favoring DRd including ECOG performance status greater than 2, high risk cytogenetics, and age greater than 75. The only subgroup that did not favor DRd was in patients with hepatic impairment. However, this analysis only included 29 patients. Therefore, the clinical relevance of this observation is unclear due to the small sample size.

Overall Survival:

With a median follow-up of 28 months, data are immature for determination of overall survival. Further time is necessary to determine the impact of the improvement in PFS on the overall survival rate.

Minimal Residual Disease:

The clinical utility of assessment of the bone marrow for minimal residual disease remains unclear for myeloma and it remains to be a proven surrogate for PFS and OS. However, there is a growing body of evidence linking MRD negativity with improvement in PFS and OS.[8] Although assessing MRD still remains part of clinical trials, and is not yet used for clinical decision-making, it can be a powerful predictor of outcome. In Munshi et al's meta-analysis of its impact on overall survival, achieving MRD negativity reduced the HR for death to 0.56 compared to retention of MRD positivity. In the MAIA study,

the MRD negative rate was 24.2% in the DRd group, and 7.3% in the Rd group (odds ratio: [redacted]; 95% CI: [redacted]; p<[redacted]). *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.* This statistically significant difference is consistent with the PFS findings and strongly suggests there may be a long-term overall survival benefit for those who achieve this level of disease control.

***SAFETY:***

The rates of adverse events were similar in the DRd arm compared to the Rd arm of the MAIA trial apart from neutropenia and pneumonia. The incidence of grade 3 or 4 infections was 32.1% in the DRd arm, compared to 23.3% in the Rd group, and more specifically, the rate of pneumonia was 13.7% compared to 7.9%, respectively. Despite this high incidence, the rate of discontinuation of treatment because of infection was low (0.5% in the DRd group, and 1.4% in the Rd group). The incidence of grade 3 or 4 neutropenia was 50% in the DRd arm, and 35.3% in the Rd arm. Although this was the most common toxicity seen, the clinical significance of the neutropenia and its contribution to the infection rate and the rate of febrile neutropenia requiring admission is unclear. When comparing serious Treatment Emergent Adverse Events (TEAE), the two groups were equally balanced. This was consistent across age groups, with patients over the age of 75 reporting serious TEAE in 65.5% of patients in the DRd group, and 70.4% in the Rd group. For patients under the age of 75 the rates were 60.9% and 56.8% respectively. The frequencies of adverse events resulting in death were similar between the daratumumab group, and the control group (6.9% vs. 6.3%, respectively). Second primary cancers were also balanced with an incidence of 3.3% in the DRd group and 3.6% in the Rd group.

Infusion-related reactions were common in the daratumumab arm. Just over 40% of patients had a reaction, and 98% of these reactions occurred during administration of the first dose. Only one patient discontinued daratumumab due to infusion-related reactions. Although common, the infusion related reactions did not have an impact on the ability to give subsequent cycles of daratumumab or lenalidomide.

For lenalidomide, patients were started on a dose of 25 mg daily for 21 or 28 days. Dose reductions or missed doses of lenalidomide were frequent in both arms of the trial. In the DRd group, 168 patients (46%) required a dose modification in the first 2 cycles, only modestly greater than the proportion requiring dose modifications in the Rd arm, (129 patients; 35.3%). The relative dose intensity for lenalidomide was lower in the DRd arm, compared to the Rd arm (76.2% vs. 91.4% respectively), suggesting that lenalidomide at the 25 mg dose is difficult to tolerate with or without daratumumab, and dose modifications are common and necessary due to adverse events.

Patients with renal failure would preferentially used a bortezomib based regimen such as Daratumumab/Bortezomib/Dexamethasone. There may be a small minority of patients who may be treated with dose reduced lenalidomide if there was a contraindication to the use of a proteasome inhibitor in patients with renal failure, and GFR less than 30.

***PATIENT REPORTED OUTCOMES:***

Both the EORTC QLQ-C30 and the EuroQol-5D-5L were used to assess HRQoL. Compared to baseline, both the DRd and the Rd groups had improvement in QoL assessments. The mean change from baseline in the Global Health Assessment did not meet the MID threshold at any time for the Rd group. For the EORTC QLQ-C30 Global Health

Assessment, the DRd group reached the threshold for clinically meaningful benefit only from cycles 9 to 12. The significance of this transient improvement is unclear. Similarly, for the EorQol-5D-5L, there was overall improvement in both treatment groups at all time points. In the DRd group, there was a clinically meaningful improvement from cycle 3 through 12. In the Rd group, this threshold was only transiently met at cycle number 9. In totality, the treatment groups were not significantly different from one another at any time. Both assessment tools confirm that the addition of daratumumab to lenalidomide and dexamethasone, at a minimum, does not worsen the quality of life, and may be associated with an improvement.

## 1.3 Conclusions

The CGP concluded that there is a net overall clinical benefit to the combination of daratumumab, lenalidomide, and dexamethasone in the treatment of patients with newly diagnosed, transplant ineligible myeloma based on one high-quality randomized controlled trial that demonstrated a clinically and statistically significant benefit in PFS compared with lenalidomide and dexamethasone alone. Myeloma remains in incurable disease with a finite number of treatment options, and a 3-year PFS of almost [redacted]% in the daratumumab group compared to [redacted]% without daratumumab is clinically meaningful and a major advance in myeloma therapy. *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.* Further follow-up is necessary to see the impact of this improved disease control on overall survival. Although the rate of adverse events was high in both arms, the complications were manageable, and not unexpected based on past experience with monoclonal antibody therapy and lenalidomide.

The CGP also considered:

- In Canada, cyclophosphamide, bortezomib and dexamethasone (CyBorD) or Rd is the most commonly used current therapy in the first line setting for the treatment of myeloma in transplant ineligible patients. Although there are no data comparing DRd with CyBorD, using Rd is a reasonable and appropriate comparator.
- Rd and CyBorD have previously been shown to have similar efficacy [7]. Since DRd has demonstrated superior PFS over Rd, 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.
- The results of the MAIA study are consistent with the patient advocacy feedback of improvement in quality of life, and prolonged disease control.
- As familiarity with the infusion of daratumumab rises, changing the duration of infusion to 90 minutes for doses beyond week 1 is likely to occur since, thus far, studies continue to report no increased patient safety concerns.[9]
- Whether addition of cyclophosphamide to the DRd daratumumab-based regimen might improve efficacy has not been examined in clinical trials; therefore, no valid conclusions about this possibility can be drawn.
- There are no evidence-based criteria for deciding subsequent therapies after daratumumab, lenalidomide and dexamethasone. There are many potential

treatment options to be considered based on patient comorbidities, tolerance to past therapy, and efficacy of previous regimens. The most appropriate next line of therapy will need to be individualized to the patient's circumstances.

- It is likely that daratumumab-containing regimens will become the new standard first line therapy for myeloma in Canada. For patients currently on therapy with regimens not containing daratumumab, or if daratumumab had not been used in the first line setting, then using it in second line would be an attractive alternative.
- In the absence of direct comparison studies, the network meta-analysis (NMA) for first line therapy in transplant ineligible supports the addition of daratumumab to either a bortezomib based regimen or lenalidomide based regimen, compared to regimens without this monoclonal antibody. Treatment will need to be individualized to the patient's circumstances.

  DRd cannot be usefully compared to bortezomib, lenalidomide and dexamethasone (VRd) as delivered in the SWOG S0777 trial due to the younger population enrolled in the latter study. However, based on the NMA, the results still favor a daratumumab-based regimen despite the potential bias in study design that would typically favor the VRd group. It is important to note that the sensitivity analysis of the NMA which compared VRd to DRd violated the similarity assumption, and results should be interpreted with caution.

# 2 BACKGROUND CLINICAL INFORMATION

# BACKGROUND CLINICAL INFORMATION

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

## 2.1 Description of the Condition

Multiple myeloma is a neoplasm of malignant plasma cells. These cells usually reside in the bone marrow and for this reason the disease is based in bones. Plasma cells secrete immunoglobulin proteins and multiple myeloma is characterized by detection of a serum clonal immunoglobulin protein (paraprotein) or increased levels of one of the subunits of these paraproteins – serum immunoglobulin free light chains. Myeloma is diagnosed when a bone marrow shows greater than 10% clonal plasma cells. The disease requires treatment when the proliferation of these plasma cells causes "end-organ" damage-either boney lytic lesions, anemia, hypercalcemia or renal dysfunction secondary to the deposition of the myeloma paraprotein in the kidney. More recently these criteria have been modified to include three other indications for treatment: high levels of the serum free light chains (ratio >100), detection of two or more lesions in the bone or bone marrow on magnetic resonance imaging, or a bone marrow showing 60% or greater clonal plasma cells.[10] Multiple myeloma is not curable and the overall prognosis of multiple myeloma is approximately 6 years,[11] but patients who can undergo autologous stem cell transplantation (ASCT) have an expected median survival of 8 years.[12] Elderly patients greater than age 75 have an expected median survival of 5 years.
In Canada there were approximately 2,900 new myeloma cases in 2017.[13] Of these, there were 1,700 in men, and 1,200 new cases of myeloma in women. There were 1,450 deaths from myeloma in 2017 accounting for approximately 4 deaths for every 100,000 people. Interestingly, myeloma is one of the few cancers where there has been a statistical increase in the age standardized 5-year relative survival rates comparing the period of 1992 to 1994 to 2006-2008. The prevalence of myeloma is about 3.5 times the incidence. The median age for diagnosis of myeloma is age 65.

Staging of myeloma can separate patients into different prognostic groups. The International Myeloma working group (IMWG) staging is based on the values of serum albumin and beta 2 microglobulin (B2M). Stage 1 includes patients whose values of these two tests are both normal. Stage 3 includes patients whose B2M is greater than 5.5 mg/L and stage 2 includes patients who do not fit into either of these. The recent "revised IMWG staging criteria" includes the results of cytogenetics or LDH and defines t(4:14), t(14;16), or deletion of 17p as high-risk genetics changes. The median overall survival of IWMG stage 1 is 62 months, stage 2 is 44 months and stage 3 is 29 months.[14] Using the revised IMWG criteria, stage 1 disease has a median survival that was not reached, 83 months for stage 2, and 43 months for stage 3.[15]

## 2.2 Accepted Clinical Practice

Treatment is initiated once a diagnosis of symptomatic multiple myeloma is made. Treatment is dependent on whether a patient is eligible for ASCT and the risk profile of the patient as defined by the revised IMWG criteria. Patients generally under age 70 and without significant co-morbidities may be candidates for ASCT. These patients will undergo 3-4 cycles of induction therapy prior to stem cell harvest and then undergo high dose therapy and stem cell transplantation. Tandem transplants may be offered to high-risk patients with revised IMWG stage 3.[16] Post ASCT, patients will benefit from maintenance therapy with lenalidomide with

increased PFS and OS as shown in a recent meta-analysis.[17] They will also benefit from two years of bisphosphonate therapy particularly if they have documented lytic bone disease.[18] Induction regimens can include bortezomib –containing regimens, lenalidomide and low dose dexamethasone regimens, carfilzomib-lenalidomide regimens or other multi-drug combinations. Whereas in the US, bortezomib, lenalidomide and dexamethasone has become the current standard of care, in Canada the regimen used most often is CyBorD (cyclophosphamide, bortezomib, dexamethasone).[19] The optimal induction regimen pre-transplant is unknown. To address this issue, a recent study showed that outcomes were similar regardless of which modern induction regimen was used.[28]

Patients who are not eligible for ASCT may be treated with any of the regimens described above for the transplant group. Historical treatment with melphalan and prednisone has been replaced by triplet therapy. The addition of thalidomide to melphalan and prednisone (MPT) was superior to melphalan and prednisone (MP) based on the results of several randomized trials. A meta-analysis showed superior response rates, PFS and OS.[20] VMP (Bortezomib, Melphalan and prednisone) also has superior OS to MP.[21,22] Based on these results, CyBorD (cyclophosphamide, bortezomib and dexamethasone), a Canadian standard therapy for transplant ineligible myeloma, arose with the substitution of the alkylator from melphalan to cyclophosphamide. CyBorD has been predominantly studied as an induction regimen prior to transplant. In a phase 2 study, 63 patients were treated with this induction regimen. [6] The ORR was 89% with 62% achieving a very good partial response (VGPR). The median PFS was 40 months and the 5-year PFS and OS were 42% and 70%. In a non clinical trial setting, 109 newly diagnosed patients with multiple myeloma were treated with the CyBorD combination in preparation of ASCT.[19] The ORR was 98% including a 79% VGPR post ASCT. This is well tolerated with no severe peripheral neuropathy and minimal hematologic toxicity. Based on these response rates and tolerability, CyBorD has become a Canadian standard for the transplant ineligible patients as well. The appropriateness of CyBorD as first line therapy in this population was recently confirmed showing similar OS as Rd, another standard therapy in Canada.[23]

Lenalidomide and dexamethasone (Rd) was compared to the melphalan-containing regimen MPT (melphalan, prednisone and thalidomide) for transplant ineligible patients. In this trial, PFS was superior for continuous Rd versus MPT or Rd stopped after 18 months.[24] The median PFS for continuous Rd was 25.5 months, 20.7 months for 18 months of Rd, and 21.2 months for MPT ($p<0.001$). OS was not significantly different (59%, 56% and 51% at 4 years, respectively). Lenalidomide and dexamethasone is a regimen that has the advantages of being given entirely orally and is usually well tolerated in the elderly but may be difficult in patients with renal compromise. More recently, VRd was studied in the transplant ineligible groups and has shown both a statistically significant PFS and an OS benefit over Rd based on the SWOG S0777 trial.[11] The median PFS was 43 months with VRd versus 30 months in Rd ($p=0.0018$; HR of 0.712). The median OS was significantly improved with an OS of 75 months in VRd versus 64 months in Rd ($p=0.025$ and HR 0.709). Although improved efficacy, toxicities were greater with VRd and more than twice as many patients (23% versus 10%) discontinued therapy due to side effects. This regimen was recently approved by pCODR pending the assessment of feasibility of adoption (budget impact).

Daratumumab is a monoclonal antibody to CD38 expressed on the surface of myeloma cells. It has direct antitumor and immunomodulatory activity. This drug has been approved for use in Canada in the relapsed setting in combination with either bortezomib and dexamethasone, or lenalidomide and dexamethasone. The addition of daratumumab in both of these regimens significantly improved response rate and progression free survival.[25,26] With this success in the relapsed setting, trials were undertaken to combine daratumumab with standard first line therapy in transplant ineligible patients. In a phase 3 study, daratumumab plus VMP

(bortezomib, melphalan, and prednisone) was compared with VMP.[27] The 18-month progression-free survival rate was 71.6% (95% confidence interval [CI], 65.5 to 76.8) in the daratumumab + VMP group and 50.2% (95% CI, 43.2 to 56.7) in the VMP control group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.38 to 0.65; P<0.001). Based on this study, the initial recommendation from pCODR was favorable pending budget impact assessment. The corresponding phase 3 study comparing daratumumab, lenalidomide and dexamethasone, with lenalidomide and dexamethasone is the focus of this review.[2]

The landscape of myeloma treatment becomes increasingly complicated as new drugs are discovered leading to seemingly endless possible combinations. Despite these advances, myeloma remains an incurable cancer. This results in an ongoing need to find therapies that will control the disease for as long as possible, with acceptable toxicity and preservation of quality of life.

## 2.3 Evidence-Based Considerations for a Funding Population

There are several options for first-line therapy for transplant ineligible myeloma. Which regimen to choose would depend on patient-specific factors and ability to tolerate the treatment. For patients treated with daratumumab and lenalidomide until disease progression, the patient would not be eligible for these therapies at the time of relapse.

## 2.4 Other Patient Populations in Whom the Drug May Be Used

For patients with primary amyloidosis, there is insufficient evidence to support the use of first-line daratumumab, lenalidomide and dexamethasone, and use of this regimen in this patient population should be reserved for clinical trials. Similarly, patients with asymptomatic myeloma, or smoldering myeloma would not be considered appropriate for therapy with this a daratumumab-containing regimen.

# 3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The patient advocacy group Myeloma Canada provided input on daratumumab in combination with lenalidomide and dexamethasone (Rd) as a first-line treatment for newly diagnosed multiple myeloma (MM) patients who do not qualify for autologous stem cell transplant. The input from Myeloma Canada is summarized below.

Myeloma Canada's input was based on information gathered from two online surveys that asked respondents about MM experiences and respective treatments; one was addressed to MM patients and the other to caregivers. Survey responses were collected from a total of 214 patients and 96 caregivers. Among the 214 patient respondents, there was representation of each province with at least two respondents but none of the territories. Among the 96 caregiver respondents, there was representation of each province with at least one individual, two individuals from the USA, and no representation of the territories. Notably, only seven patients and four caregivers had experience with the daratumumab and Rd combination under review and such patients were ineligible for autologous stem cell transplant. The survey was administered in English and French and made available from June 19th to July 12th, 2019 and July 8th to 12th, 2019 in Quebec respectively.

From the patient perspective, infections were reported to be the most important MM symptom to control followed by kidney problems, mobility, pain and fatigue, neuropathy (pain, numbness, tingling, swelling or muscle weakness), and shortness of breath. Among the side effects associated with currently available treatments, pain was most commonly rated (24%) as "most important to avoid"; alternatively, shortness of breath was most commonly rated (21%) as "least important to avoid". Overall, key patient values included improving quality of life, the ability to have a normal life, to have more treatment options, disease control, and manageable side effects.

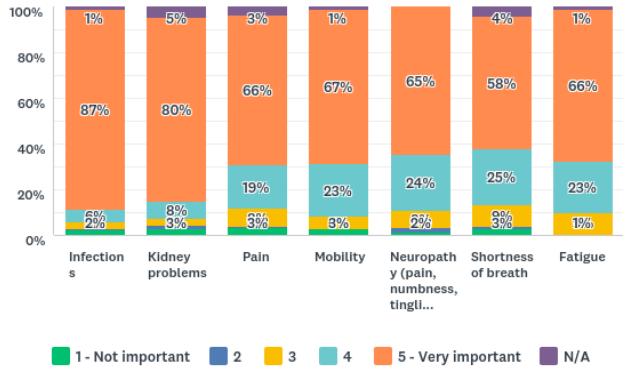
Please see below for a summary of specific input received from the patient advocacy groups.

## 3.1 Condition and Current Therapy Information

### 3.1.1 Experiences Patients have with Multiple Myeloma

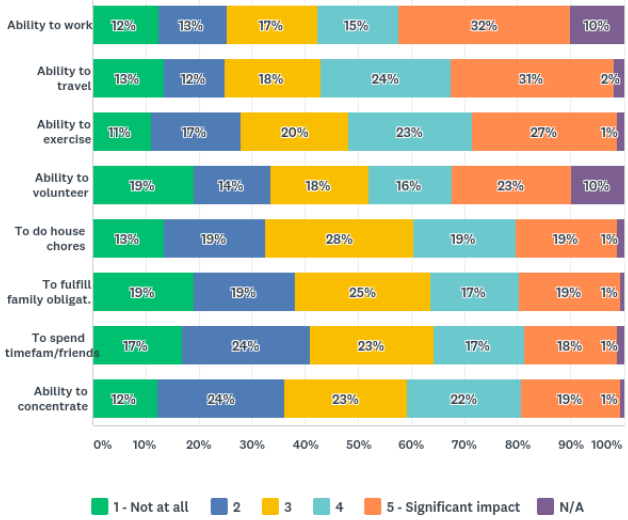
Patients were asked to rate the importance of controlling key symptoms of MM on a scale from 1 to 5 representing "not important" and "very important" respectively. Among 174 respondents, infections (87%) were reported by the greatest number of patients to be a key MM that is very important to control, followed by kidney problems (80%), mobility (67%), pain (66%) and fatigue (66%), neuropathy (pain, numbness, tingling, swelling or muscle weakness) (65%), and shortness of breath (58%) (Figure 1).

Figure 1. Patient Perspective of the Importance of Controlling Key MM Symptoms, Myeloma Canada




Patients were also asked to report the impact that MM symptoms have on their activities of daily living (ADL) and quality of life (QOL) on a scale from 1 to 5 representing "not at all" and "significant impact" respectively. Among 173 patient respondents, MM was reported to have a significant impact on the ability to work (32%), ability to travel (31%), ability to exercise (27%), ability to volunteer (23%), ability to do house chores (19%), ability to fulfill family obligations (19%), ability to concentrate (19%), and ability to spend time with friends and family (18%) (Figure 2). The ability to work (32%) was most commonly reported to be significantly impacted by MM; however, the ability to volunteer (19%) and to fulfill family obligations (19%) were most commonly reported to be "not at all" impacted by the disease (Figure 2).

Figure 2. Effect of MM Symptoms on Patients' ADL and QOL, Myeloma Canada

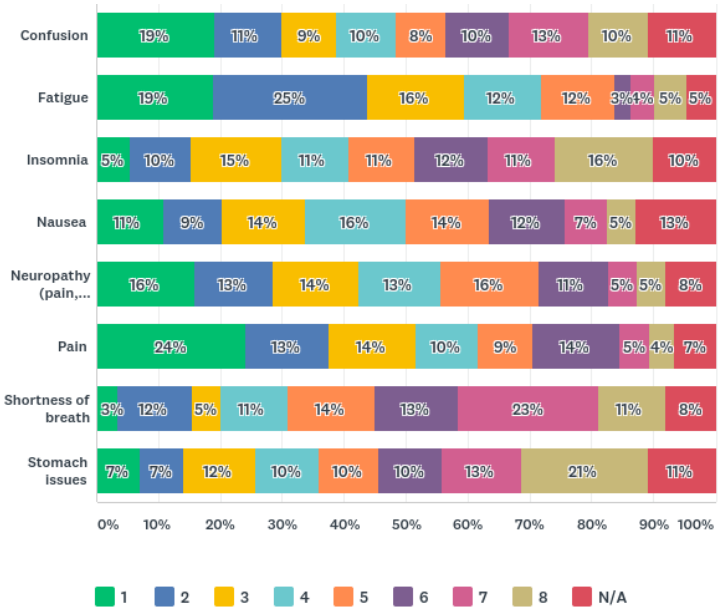



Furthermore, patients were asked *"what is most important to you when it comes to treating your myeloma"*. Among 147 respondents, quality of life/normal life was most commonly reported as indicated by 32 patients (22%); followed by treatment options/plan as indicated by 24 patients (16%), disease control as indicated by 23 patients (16%), manageable side effects as indicated by 18 patients (12%), pain control as indicated by 13 patients (9%), remission as indicated by 11 patients (7%), more information as indicated by 9 patients (6%), prolonged life as indicated by 8 patients (5%), a cure as indicated by 7 patients (5%), more care or support as indicated by 5 patients (3%), better or closer relationship with the doctor as indicated by 2 patients (1%), and cost and how to deal with family members as indicated by 1 patient (<1%) each. Notably, some respondents stated more than one item.

### 3.1.2 Patients' Experiences with Current Therapy for Multiple Myeloma

Patients were asked to rate the importance of avoiding particular treatment side effects on a scale from 1 to 8 representing "the most important to avoid" and "the least important to avoid" respectively. Among 166 respondents, pain (24%) was most commonly rated to be "the most important to avoid" (Figure 3). Followed by, confusion (19%) and fatigue (19%), neuropathy (pain, numbness, tingling, swelling or muscle weakness) (16%), nausea (11%), stomach issues (7%), insomnia (5%), and shortness of breath (3%) (Figure 3). Alternatively, stomach issues were most commonly rated as the least important side effect to avoid (21%) (Figure 3).

Figure 3. Patient Perspective of the Importance of Avoiding Particular Side Effects, Myeloma Canada

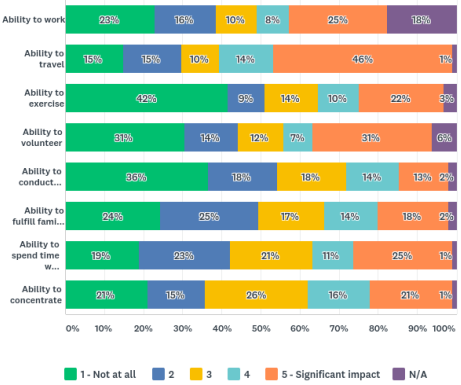



In addition, 162 patients selected their primary financial implication related to their treatment from a list of options. Drug costs were selected by 23 patients (14%), parking costs and lost income due to absence from work were both selected by 21 patients (13%), travel costs were selected by 13 patients (8%), and accommodation and medical supply costs were both selected by 3 patients (2%). Notably, some patients chose more than one option. Conversely, 48 patients (30%) reported that they had no financial implications related to their myeloma treatment.

### 3.1.3 Impact of Multiple Myeloma and Current Therapy on Caregivers

Caregivers were asked to report the impact that caring for someone with MM has on their ADL and QOL on a scale from 1 to 5 representing "not at all" and "significant impact" respectively. Among 96 caregiver respondents, ability to travel (46%) was most commonly reported to be significantly impacted by the caregiver role (Figure 4). Followed by, ability to volunteer (31%), ability to work (25%) and ability to spend time with friends and family (25%), ability to exercise (22%), ability to concentrate (21%), ability to fulfil family obligations (18%), and ability to conduct house chores (13%) (Figure 4). Conversely, the ability to exercise (42%) was most commonly reported to be "not at all" impacted by the caregiver role (Figure 4).

Figure 4. Impact of the Caregiver Role on their ADL and QOL, Myeloma Canada

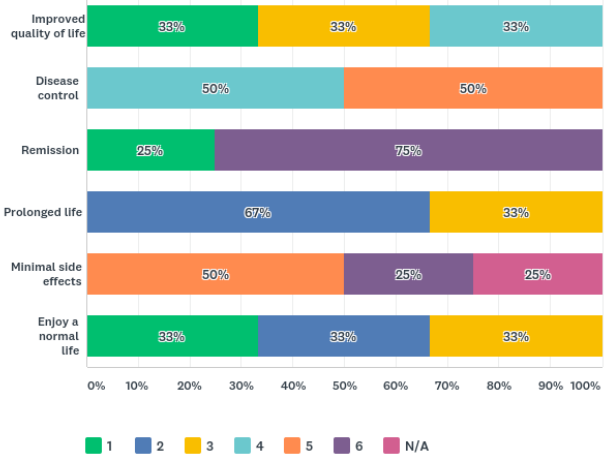



## 3.2 Information about the Drug Being Reviewed

### 3.2.1 Patient Expectations for Daratumumab and Rd

Overall, majority of respondents (99% or 162/164) reported that it is very important to have access to effective treatments for MM and 91% (148/163) reported that it is very important to improve quality of life when taking a drug or considering taking a drug for MM. Among all the patient respondents, seven had experience with the daratumumab and Rd treatment combination and were ineligible for autologous stem cell transplant. Patients were asked to rank their expectations of daratumumab and Rd from most to least important. Among five responses, improved quality of life, remission, and to enjoy a normal life were the only items rated a score of 1—most important (Figure 5). Of note, N/A was an optional section that was selected to indicate that the question did not apply to the respondent.

Figure 5. Patient Expectations of Daratumumab and Rd, Myeloma Canada



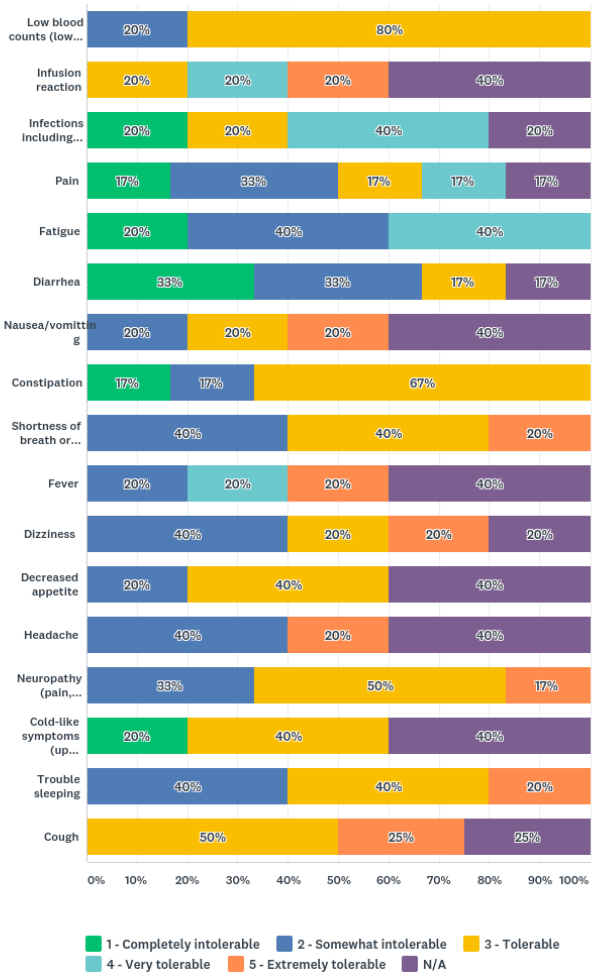

### 3.2.2 Patient Experiences to Date with Daratumumab and Rd

Myeloma Canada collected responses from seven patients who had experience with daratumumab and Rd as first-line therapy and no prior stem cell transplant; however, only five completed majority of the questions. Patients were asked to rate the combined effectiveness of the daratumumab combination with a graded scale from 1 to 5, representing not effective, fairly effective, effective, very effective, and extremely effective, in increasing respective order. No agreement regarding the effectiveness of the treatment combination was reported among the six patients. Two (33%) patients rated the treatment combination as fairly effective

and scores indicating that the treatment combination is effective, very effective, extremely effective or N/A received one patient (17%) vote each. Patients were also asked if the treatment combination met their expectation of treating their MM; of the six respondents, one (17%) patient responded “yes”, three patients (50%) responded “no”, and two patients selected the “please explain” option but the responses were not provided. Furthermore, patients were asked to indicate specific expectations that had been fulfilled by the daratumumab combination. Among six patient respondents, expectations of improved quality of life, disease control, remission, and prolonged life were fulfilled for three patients (50%); however, minimal side effects and to enjoy a normal life were only fulfilled for two patients (33%). Notably, “Other (please specify)” was selected by one patient who specified that they “Just started treatments.”

Additionally, when patients were asked whether administration of the daratumumab combination had a negative effect; four answered “no” (majority) and two answered “yes”. Of note, one comment mentioned that a patient had an infection very early in the study and another comment stated no problems. Overall, six respondents reported that the common side effects of daratumumab and Rd were generally tolerated. In regard to specific side effects, patients rated their tolerability on a graded scale from 1 to 5 with labels representing completely intolerable, somewhat intolerable, tolerable, very tolerable, and extremely tolerable in increasing respective order. Diarrhea was most commonly voted to be “completely intolerable” (33%). Followed by cold-like symptoms (upper respiratory infection) (20%), fatigue (20%), and infections including pneumonia (20%); subsequently, pain (17%) and constipation (17%) (Figure 6). Conversely, cough was the most commonly reported side effect to be “extremely tolerable” (Figure 6).

Figure 6. Patient Rating of the Tolerability of Daratumumab and Rd Side Effects, Myeloma Canada




Moreover, patients were asked to rate their quality of life since starting the daratumumab and Rd combination on a graded scale from 1 to 5 with labels representing poor, fair, good, very good, and excellent quality of life in increasing respective order. Among the six respondents, two patients rated their quality of life to be fair, two rated their quality of life to be good, one rated their quality of life to be very good, and one rated their quality of life to be excellent (Figure 7). Patients were asked to rate the impact of MM symptoms on specific activities since taking the daratumumab and Rd using a scale of 1 to 5 representing "not at all" and "significant impact" respectively. Volunteering was voted by the greatest percentage among five respondents to be the most significantly impacted (40%) followed by the ability to work (20%) and travel (20%) (Figure 8). Additionally, when asked "*if the treatment combination improved their health and well-being and long-term health outlook*?", two patients (2/6) responded "yes", one patient (1/6) responded "no", and three patients (3/6) responded that it is "too soon to tell".

Figure 7. Patient Rating of QOL Since Starting Daratumumab and Rd, Myeloma Canada

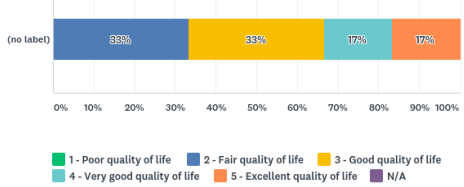
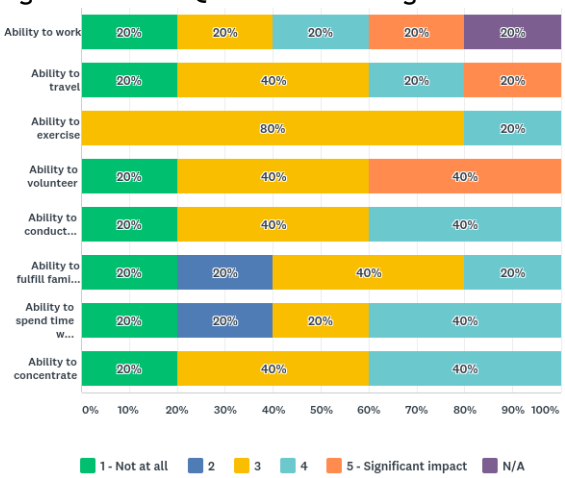


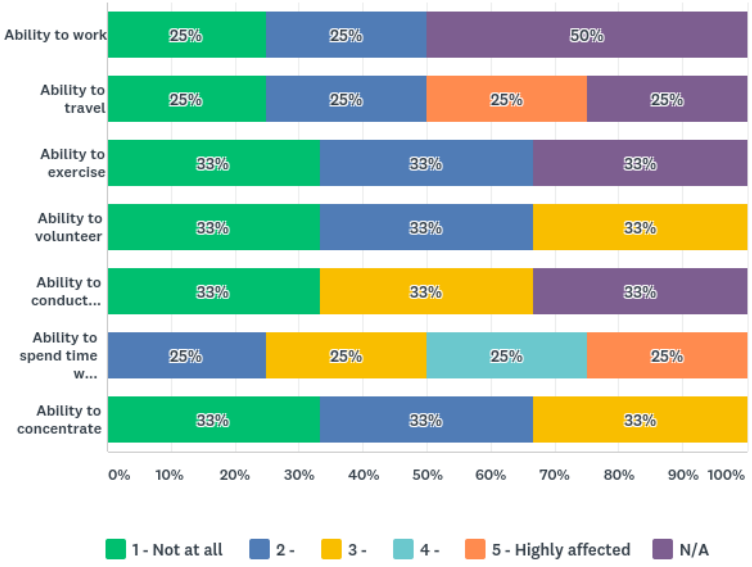

Figure 8. Patient Rating of ADL and QOL since Starting Daratumumab and Rd, Myeloma Canada




### 3.2.3 Caregiver Expectations for and Experiences to Date with Daratumumab and Rd

Four caregivers reported on how their activities of daily living were affected while helping to manage the side effects of daratumumab and Rd. When asked "*if they experienced any challenges while helping to manage side effects of the treatment combination under review for the person they are caring for?*", *the* majority responded "no" (3/4). One caregiver noted that "After 4 weeks into the treatment there do not appear to be any side effects other than pain. The treatment itself is taking up a lot of time at present as I always accompany him for his treatments." Furthermore, the impact on the caregiver to participate in specific activities due to caregiver responsibilities associated with daratumumab and Rd side effects was assessed with a scale from 1 to 5 representing "not at all" and "highly affected" respectively. The ability to travel and to spend time with friends and family were both reported by one respondent (1/4) to be highly affected (score of 5) (Figure 9). Notably, the ability to spend time with friends and family was the only activity that received scores greater than 1, which highlights the impact of the caregiver role on the ability to spend time with friends and family (Figure 9).

Figure 9. Impact of Caregiver Responsibilities Due to Managing Daratumumab and Rd Side Effects on Caregiver's ADL and QOL, Myeloma Canada




## 3.3 Additional Information

None to report.

# 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:

- Additional resources for preparation, administration, and monitoring

Please see below for more details.

## 4.1 Currently Funded Treatments

Bortezomib/melphalan/prednisone (VMP), cyclophosphamide/bortezomib/dexamethasone (CyBorD), and lenalidomide/dexamethasone (Rd) are funded in almost all the provinces for patients with newly diagnosed multiple myeloma who are not suitable for autologous stem cell transplant. Lenalidomide/bortezomib/dexamethasone (VRd) was recently reviewed at pCODR and received a positive conditional reimbursement recommendation.

PAG noted that Rd and CyBorD are current treatments of choice for patients with newly diagnosed multiple myeloma that are transplant ineligible. Although the comparator of Rd in the MAIA trial is a funded option, PAG is also seeking comparative information on DRd compared with CyBorD.

## 4.2 Eligible Patient Population

The MAIA trial excluded patients with a diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma as well as those who had radiation therapy within 14 days of randomization. PAG is seeking guidance on these patients as in practice, multiple myeloma regimens are generalized to patients with primary amyloidosis. PAG is also seeking clarity on whether patients who receive urgent radiation prior to starting DRd treatment as well as patients who present with renal failure, would be eligible.

PAG is seeking guidance on the definition of “transplant ineligible” as they may vary (e.g., different age cut-offs).

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

- Patients currently treated for newly diagnosed multiple myeloma not eligible for transplant (e.g., Rd, CyBorD, or VMP)

- Patients who recently completely Rd and who have not yet experienced progression.

If switching to DRd or adding daratumumab to Rd is appropriate in these patients, PAG is seeking guidance on the dosing schedule administered and when in treatment daratumumab addition can be considered (e.g., first or second cycle of CyBord).

Patients eligible for transplant and use of DRd as induction therapy to transplant are considered out of scope of the current pCODR review.

## 4.3 Implementation Factors

The weekly dosing schedule in weeks 1 to 8, the every two weeks in weeks 9 to 24, and the every four weeks from week 25 until progression is difficult for many patients, especially those who would have to travel far to and from cancer centres with the resources to administer and monitor daratumumab infusions. The recommended dosing/schedule for DRd in this setting differs from other daratumumab-based regimens for multiple myeloma (e.g., D-CyBorD, DVMP or DRd), PAG noted this may lead to potential dosing errors. PAG noted that processes would need to be in place, prior to implementation of daratumumab in this setting, to minimize dosing errors and patient confusion.

Daratumumab can affect immunofixation on the SPEP and laboratories need to be aware if patients are on daratumumab to correctly interpret the results.

PAG is seeking guidance on whether clinicians would support the adoption of rapid infusion daratumumab (ninety-minute infusion with 20% dose over 30 minutes followed by 80% dose over 60 minutes).

PAG is also seeking guidance on whether clinicians would add cyclophosphamide to DRd upon biochemical progression. Also, if there is evidence to inform whether patients could have a treatment break from daratumumab after a maximum response is achieved, then continue on Rd Maintenance, and re-initiate daratumumab at the time of disease progression on Rd.

PAG is seeking guidance on treatment duration and discontinuation criteria.

Additional resources will be required for pre-medication, drug preparation, administration time and close monitoring for multiple severe adverse effects including infusion reactions. PAG identified that one to one nurse to patient may be required given the high rate of infusion reactions and the frequency of infusion rate adjustments. As daratumumab interferes with cross-matching for blood transfusions, patients would also need to have RBC phenotyping prior to starting daratumumab. PAG noted that the significantly increased chair time compared to current treatment is a barrier to implementation, given the additional resources needed as well as slower infusion time to reduce the risk of infusion reactions with daratumumab. Additional hospital resources may be required if patients have an infusion related reaction that requires in-patient hospital admission for management/monitoring or to complete the reminder of the infusion post reaction (infusion time beyond hours of operation of ambulatory chemotherapy suite).

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

The high cost of daratumumab, as an add-on therapy, is a barrier to implementation. As daratumumab is an intravenous infusion that is an add-on to an oral treatment regimen, PAG noted that an intravenous infusion may not be as acceptable or as accessible geographically as oral therapy for some patients.

## 4.4 Sequencing and Priority of Treatments

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

- What would be the best treatment (e.g., novel doublet or triplet regimens such as Kd or PVd) after progression following DRd?
- Sequencing of subsequent second- and third-line therapies such as carfilzomib-based regimens (e.g., KRd), bortezomib-based regimens, pomalidomide, and re-treatment with lenalidomide-based regimens
- Clarity on whether patients would be ineligible for re-treatment with daratumumab-based regimens in subsequent lines of therapy.

PAG is seeking guidance on the preferred first-line treatment option in this setting (e.g., Rd, RVd, CyBorD, D-VMP, D-CyBorD, or DRd). In what clinical scenarios would DRd be the preferred first-line setting and in what clinical scenarios would DRd not be used in the first-line setting?

PAG noted that daratumumab for the treatment of patients with multiple myeloma who have received at least one prior therapy, is funded in some jurisdictions or under provincial consideration. PAG is seeking guidance on the optimal use of daratumumab and preference to use daratumumab in the first-line setting or reserve daratumumab for downstream treatment.

Daratumumab in combination with VMP, for the treatment of patients with newly diagnosed multiple myeloma who are not suitable for autologous stem cell transplant, is currently under review at pCODR. PAG is seeking guidance on preference for daratumumab in combination with Rd or VMP.

## 4.5 Companion Diagnostic Testing

None.

## 4.6 Additional Information

PAG noted there have been recent publications for subcutaneous daratumumab. PAG is seeking guidance on the timeline for subcutaneous daratumumab availability.

# 5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two joint clinician inputs were submitted on behalf of the Myeloma Canada Research Network (three clinicians) and Cancer Care Ontario Hematology DAC (two clinicians), which constituted input from a total of five clinicians on the pCODR review of daratumumab with lenalidomide and dexamethasone (DRd) for newly diagnosed multiple myeloma (MM) patients who are ineligible for autologous stem cell transplant (ASCT).

The clinicians reported improvements of treatment tolerability, safety, and effectiveness with DRd compared to currently available therapies. Overall, clinicians were satisfied with the results from the phase III randomized, open-label, active-controlled clinical trial (NCT02252172). Namely, a superior progression-free survival (PFS) and minimal toxicity were highlighted as key benefits of the treatment combination. For instance, the discontinuation rate due to toxicity of DRd was reported to be lower compared to other treatments such as lenalidomide/ bortezomib/ dexamethasone (RVd). One clinician emphasized the novelty of DRd to integrate immunotherapy into first-line treatment of MM; particularly as DRd has been demonstrated in the relapsed setting to dramatically improve the outcome of MM compared to treatments that have been available over the past decade. In general, clinicians felt that DRd would meet the clinical unmet need of providing better treatment options other than lenalidomide and dexamethasone (Rd) or bortezomib based therapies such as bortezomib/cyclophosphamide/dexamethasone (CyBorD) and bortezomib/melphalan/prednisone (VMP) for transplant ineligible patients. The unmet need arises from toxicity concerns in addition to availability of treatment options. Notably, no DRd-related harms were explicitly stated and no contraindications for DRd were identified. Furthermore, one clinician noted that the creatinine clearance cut-off of the pivotal trial was too limiting since there is extensive and reassuring accounts of using lenalidomide and daratumumab in cases of renal failure. Accordingly, all the clinicians felt that there was no particular subgroup that DRd should be limited to.

All the clinicians agreed that DRd would be implemented as first-line therapy to treat transplant ineligible MM patients; thus, DRd would replace current first-line therapies such as Rd and CyBorD in Ontario and RVd in Alberta. Moreover, bortezomib and pomalidomide based regimens were most commonly agreed to be utilized in the second- and third-line setting, respectively. Furthermore, there was general support for the adoption of rapid infusion daratumumab into clinical practice, which is part of standard clinical care in Ontario. In regard to adding cyclophosphamide to DRd upon biochemical progression; three clinicians supported this practice but one clinician would add cyclophosphamide to a different treatment combination and another felt that quadruplet therapy is harder for older patients so they would rather administer another regimen. Moreover, all clinicians noted that there is no current evidence to inform patients of a treatment break after a maximum response to daratumumab, and to subsequently continue on Rd but re-initiate daratumumab upon disease progression. Notably, two clinicians highlighted that the reason for this treatment break is different from clinical practice as treatment breaks are implemented for toxicity and psychosocial reasons.

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

## 5.2 Current Treatment(s) for this Type of Cancer

VMP, CyBorD, and Rd are currently funded in almost all provinces for patients that are newly diagnosed with MM and not eligible for ASCT. VMP, CyBorD, and Rd are used in standard care among clinicians practicing in Ontario; one clinician noted that Rd is the preferred therapy for the majority of patients who are ineligible for transplant while CyBorD is most often used in the setting of renal failure or high-risk cytogenetics. However, RVd serves as first-line therapy in Alberta; in the absence of RVd, Rd and bortezomib based therapies (CyBorD/VMP) become

options for first-line therapy with the majority of clinicians preferring Rd over CyBorD/VMP.

Overall, Rd was identified as the most appropriate comparator. One clinician from Ontario noted the use of Rd as a comparator based on treatment durations. As explained, Rd is administered continuously until progression as opposed to currently funded bortezomib-based treatments such as CyBorD/VMP, which are administered with fixed-duration regimens. Thus, Rd is the reasonable and appropriate comparator since its administration matches the continuous regimen of DRd. The clinician from Alberta expressed the need to identify whether DRd is preferable to RVd (first-line therapy in Alberta); however, the preference of Rd over CyBorD/VMP deems it as a reasonable and appropriate comparator.

## 5.3 Eligible Patient Population

There was consensus among the clinicians that the patient population in the reimbursement request aligns with the needs of patients in clinical practice. Specifically, one clinician stated that there is an important clinical unmet need for better treatment other than Rd or CyBorD/VMP for MM patients who are ineligible for transplant. They noted that the need is not only related to treatment availability but also toxicity effects. For instance, the discontinuation rate due to toxicity of DRd was reported to be lower compared to potentially available treatments such as RVd.

In general, there was agreement of the inclusion and exclusion criteria from the pivotal trial being reasonable and applicable to clinical practice; however, one clinician noted that DRd does not need to be limited to patients with a creatinine clearance over 30 mL/min, as implemented in the clinical trial, due to extensive and reassuring accounts of lenalidomide and daratumumab administration in cases of renal failure. Additionally, another clinician mentioned that frail patients that are ineligible for transplant as assessed with the International Myeloma Working Group frailty score are fit for treatment with DRd but only if the frailty is due to multiple myeloma. Furthermore, it was agreed that there is no particular subgroup that DRd should be limited to.

## 5.4 Relevance to Clinical Practice

All five of the clinicians reported having experience administering the DRd combination under review and supported early use of DRd as opposed to administering the treatment combination for subsequent lines of therapy. Of note, three clinicians expressed their positive impression of the data as the reported results are unprecedented and exhibit minimal toxicity and good PFS. One clinician stated they would administer DRd to most of their patients currently prescribed Rd and another noted they would administer DRd in the same fashion as outlined in the presented study but implement dose modifications for efficacy and toxicity. Furthermore, one clinician reported specifically on the administration of DRd for older patients since they often receive one or two lines of treatment; thus, they would want to use the best treatment upfront, which they stated is DRd.

The reported differences between DRd and currently available treatments highlighted beneficial differences in regard to efficacy, safety, and tolerability. One clinician commented on the superior PFS of DRd, which in most cases is associated with an improved quality of life and potentially overall survival. Another clinician commented on the novelty of integrating immunotherapy into the initial treatment of MM through DRd. Especially in the relapsed setting, DRd has shown potential to dramatically improve the outcome of MM as compared to available treatments over the previous decade. Moreover, no contraindications to DRd were identified. Notably, when

asked if there are contraindications to using DRd, one clinician articulated the favourability of using better medicines upfront rather than later since delayed administration of favourable drugs can increase mortality risk and drug toxicity. Alternatively, bortezomib based regimens, which are the current alternative to Rd based regimens are contraindicated in patients with significant peripheral neuropathy.

## 5.5 Sequencing and Priority of Treatments with New Drug Under Review

There was general agreement that DRd would be administered as first-line treatment. However, one clinician noted that the use of DRd in high-risk patients should be investigated since they may be more suited to RVd therapy. In addition, another clinician expects a split between DRd and dexamethasone/ bortezomib/ melphalan/ prednisone as the preferred regimen for the initial treatment of transplant ineligible patients with MM. Moreover, the majority of clinicians mentioned a bortezomib based-regimen as the second-line therapy; however, alternative suggestions for second-line therapy included carfilzomib/dexamethasone and pomalidomide/ bortezomib/dexamethasone upon availability. Moreover, there was a general agreement that a pomalidomide based regimen should be implemented as the third-line therapy with the dexamethasone combination being the most commonly mentioned. Notably, two clinicians highlighted the tolerability of DRd in elderly patients but one clinician stated that treatment selection is ultimately based on patient preference, comorbidities, and psychosocial considerations.

## 5.6 Companion Diagnostic Testing

No companion diagnostic testing is currently available or needed for eligibility for DRd. Notably, the clinicians from Cancer Care Ontario Hematology DAC mentioned that red blood cell phenotyping should be flagged to Canadian Blood Services to facilitate blood transfusions, which are typically required by MM patients.

## 5.7 Additional Information

No additional information provided.

## 5.8 Implementation Questions

### 5.8.1 There have been recent publications for rapid infusion daratumumab (ninety-minute infusion with 20% dose over 30 minutes followed by 80% dose over 60 minutes). In clinical practice, is there support for adoption of rapid infusion daratumumab?

Overall, there was general support for the adoption of rapid infusion daratumumab into clinical practice. In particular, this already has been adopted into standard clinical care in Ontario. The clinician from Alberta noted that rapid infusion could be adopted in an individualized manner and it would likely be implemented after one cycle of daratumumab; however, the possibility of subcutaneous daratumumab may make this practice subject to debate.

### 5.8.2 In clinical practice, would clinicians add cyclophosphamide to DRd upon biochemical progression?

Three clinicians supported adding cyclophosphamide to DRd upon biochemical progression; one clinician would implement it as a bridge to second-line therapy. However, two of these clinicians noted that it would be difficult to justify funding cyclophosphamide for DRd alone and not other regimens. Alternatively, two other clinicians responded "probably not"; one clinician mentioned their preference to save cyclophosphamide for another combination and the other indicated that quadruplet therapy is hard for older patients so they would rather administer another regimen.

### 5.8.3 Is there evidence to inform whether patients could have a treatment break from daratumumab after a maximum response is achieved, then continue on Rd Maintenance, and re-initiate daratumumab at the time of disease progression on Rd?

All clinicians noted that there is no current evidence to inform patients of a treatment break after a maximum response to daratumumab, and to subsequently continue on Rd but re-initiate daratumumab upon disease progression. One clinician noted that this should be studied in Canada and another commented that reaching the minimal residual disease may serve as evidence, but they were not certain in their response. However, two clinicians mentioned that the reason for this treatment break is different from clinical practice. For instance, one clinician mentioned that treatment breaks are implemented due to toxicity and psychosocial reasons. Another clinician noted their reluctance to interrupt effective therapy based on published data and anecdotal experience. They explained that published data reports the infrequent recapture response after restarting previous agents, which is presumably attributed to myeloma subclone(s) that emerge(s) at relapse exhibiting resistance to the previous agent. Thus, they try to maintain an acceptable toxicity profile from the initiation of a treatment regimen so that interruptions are not needed.

## 6.1 Objectives

The primary objective of this review is to evaluate the efficacy and safety of daratumumab (Darzalex) in combination with lenalidomide and dexamethasone (DRd) in patients with newly diagnosed multiple myeloma (NDMM) who are ineligible for autologous stem cell transplantation (ASCT).

Note: Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

- Part 1: Critical appraisal of the Sponsor's submitted network meta-analysis (NMA) comparing daratumumab (Darzalex) in combination with lenalidomide and dexamethasone (DRd) to bortezomib/melphalan/prednisone (VMP), daratumumab/bortezomib/melphalan/prednisone (D-VMP), melphalan/prednisone/thalidomide (MPT), bortezomib/thalidomide/dexamethasone (VTD), cyclophosphamide/thalidomide/dexamethasone (CTD), melphalan/prednisone (MP), and thalidomide/dexamethasone (TD) among others in patients with NDMM who are ineligible for ASCT.
- Part 2: Critical appraisal of the Sensitivity Analysis of the Sponsor's submitted NMA for the addition of VRd (Bortezomib-Lenalidomide-Dexamethasone)

## 6.2 Methods

### Review Protocol and Study Selection Criteria

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

**Table 2. Selection Criteria**

| Clinical Trial Design | Patient Population | Intervention‡ | Appropriate Comparators | Outcomes |
|---|---|---|---|---|
| Published and unpublished RCTs.<br><br>In the absence of RCTs, fully published non-comparative clinical trials investigating efficacy and safety of daratumumab | Patients with newly diagnosed multiple myeloma (NDMM) who are ineligible for autologous stem cell transplant (ASCT) | 28-day cycle of IV daratumumab (16mg/kg once weekly during cycles 1 and 2, every 2 weeks during cycles 3 through 6, and every 4 weeks thereafter) + oral lenalidomide (25 mg on days 1 through 21) and oral dexamethasone (40 mg on days 1,8,15 and 22) | All appropriate treatment regimens including but not limited to:<br>• bortezomib/melphalan/ prednisone (VMP)<br>• cyclophosphamide/bortezomib/dexamethasone (CyBorD)<br>• lenalidomide/dexamethasone (Rd)<br>• lenalidomide/bortezomib/ dexamethasone (VRd)*<br>• daratumumab + bortezomib/ melphalan/prednisone (D-VMP)* | <u>Efficacy</u><br>• **PFS**<br>• TTP<br>• ORR<br>• VGPR<br>• **CR**<br>• sCR<br>• PR<br>• SD<br>• PD<br>• **OS**<br>• PFS2<br>• MRD negative rate<br>• **HRQoL**<br><br><u>Safety & tolerability</u><br>• **AEs**<br>• TEAEs<br>• SAEs<br>• Secondary malignancies<br>• time required for daratumumab infusion |

[Abbreviations] AE = adverse events; ASCT = autologous stem cell transplantation; CI = confidence interval; CR = complete response; DRd = daratumumab, lenalidomide and dexamethasone; HRQoL = health-related quality of life; IV = intravenously; MRD = minimal residual disease; NDMM = newly diagnosed multiple myeloma; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PR = partial response; PD = progressive disease; RCT = randomized controlled trial; Rd = lenalidomide and dexamethasone; SAE = serious adverse events; sCR = stringent complete response; SD = stable disease; TEAE = treatment-emergent adverse event; TTP = time to disease progression; VGPR = very good partial response; Bold outcomes were identified as important by patients' input.

‡Dosages listed are according to the trial and may be adjusted

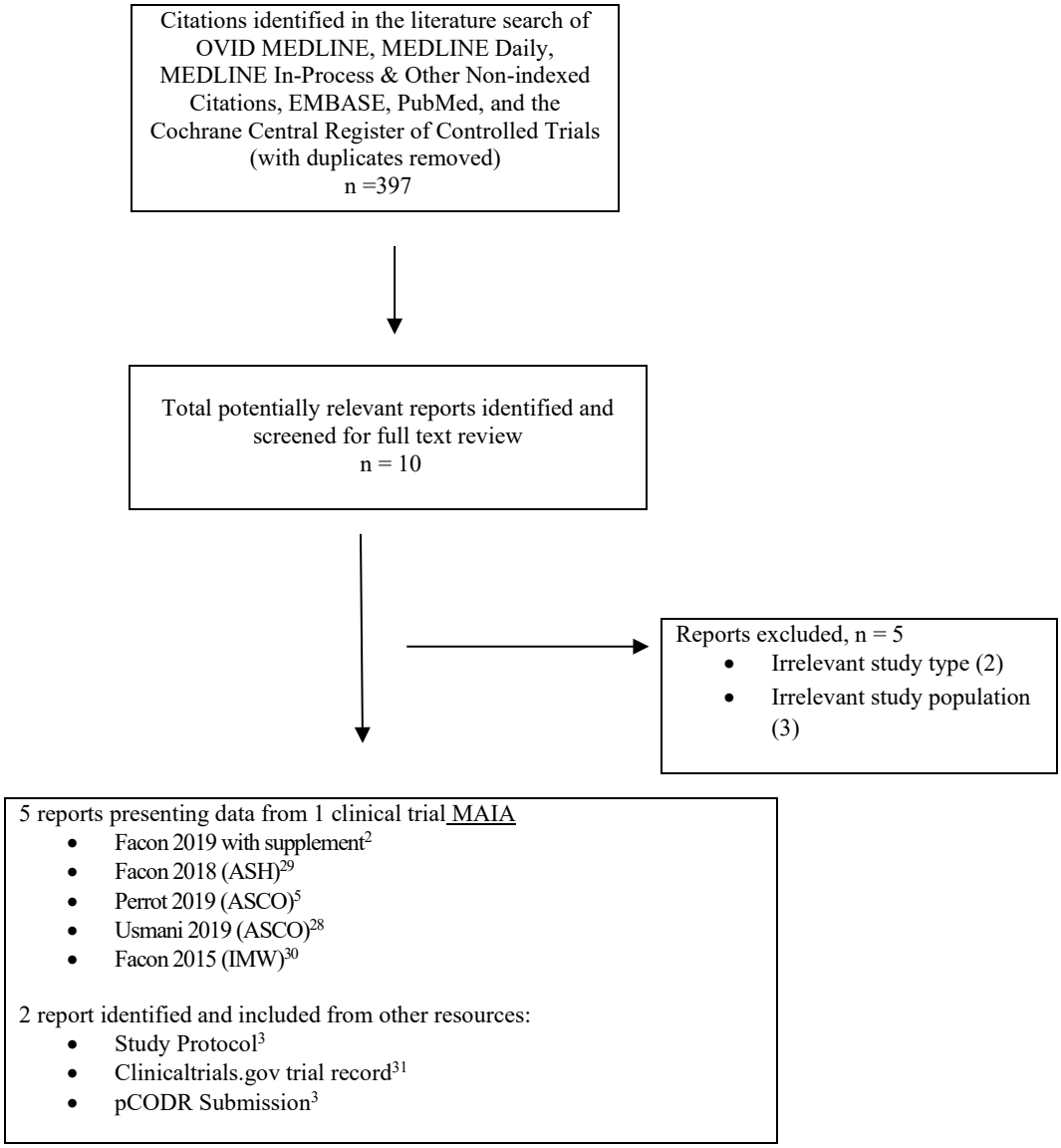
*Recently recommended for reimbursement but not currently available in Canadian jurisdictions

## 6.3 Results

### Literature Search Results

Of the 397 potentially relevant reports identified, one trial[2] with data presented in 5 reports[2,5,28-30] was included in the pCODR systematic review. A total of 5 studies reviewed in full text were excluded. Reasons for exclusion are provided in the Figure 1 below.

**Figure 1. Sample PRISMA Flow Diagram for Inclusion and Exclusion of studies**




**Note: Additional data related to study MAIA were also obtained from documents provided in the pCODR submission, and through requests to the Sponsor by pCODR.*

## Summary of Included Studies

One clinical trial was identified that met the eligibility criteria and is included in this systematic review (Table 3). MAIA[2] is a randomized, international, multicentre, open-label, active-controlled, parallel-group phase III trial that evaluated the efficacy and safety of daratumumab + lenalidomide and dexamethasone versus lenalidomide and dexamethasone (Rd) in patients with newly diagnosed multiple myeloma (NDMM) who are ineligible for autologous stem cell transplantation (ASCT). Quality characteristics of this trial are reported in Table 4.

### Detailed Trial Characteristics

**Table 3: Summary of Trial Characteristics of the Included Studies.**

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| MAIA<br>NCT02252172<br>CR104762<br><br>Randomized, controlled, open-label Phase III study<br><br>737 randomized (daratumumab + lenalidomide and dexamethasone (DRd) n=368; lenalidomide and dexamethasone (Rd) n=369).<br>729 patients (DRd n=364, Rd n=365) received at least one dose of trial treatment<br><br>176 sites in 14 countries from Europe, North America, the Middle East and the Asia-Pacific region.<br><br>Patient Enrolment Dates: March 2015 to January 2017<br><br>Data cut-off dates:<br>Clinical data cutoff for the primary analysis (second interim) - September 24, 2018<br><br>4 Month Safety Update: January 24, 2019<br><br>Final analysis: For OS is planned to be performed after 330 deaths have been reported<br><br>Estimated study completion date: March 30, 2024<br><br>Funding: Janssen Research and Development | <u>Key Inclusion Criteria:</u><br>• newly diagnosed multiple myeloma<br>• ineligible for high-dose chemotherapy with stem cell transplantation (STC) owing to age (≥65 years) or to the presence of coexisting conditions that were likely to result in the development of unacceptable side effects<br>• ECOG performance status of 0-2<br>• Adequate hematologic, hepatic, renal and cardiac function<br>• hemoglobin level of ≥7.5 g per deciliter, an absolute neutrophil count of 1000 or more per cubic millimeter, platelet count of 70,000 or more per cubic millimeter (>50,000 per cubic millimeter if ≥50% of nucleated bone marrow cells were plasma cells)<br>• aspartate aminotransferase and alanine aminotransferase levels no more than 2.5 times the upper limit of the normal range<br>• total bilirubin level no more than 2.0 times the upper limit of the normal range<br>• creatinine clearance of 30 ml or more per minute<br>• a corrected serum calcium level of ≤14 mg per deciliter (≤3.5 mmol per liter)<br><br><u>Key Exclusion Criteria:</u>[2]<br>• Patients with monoclonal gammopathy of undetermined significance<br>• smoldering multiple myeloma<br>• primary amyloidosis | <u>Intervention:</u><br>28-day cycle of IV daratumumab (16mg/kg once weekly during cycles 1 and 2, every 2 weeks during cycles 3 through 6, and every 4 weeks thereafter) + oral lenalidomide (25 mg on days 1 through 21) and oral dexamethasone (40 mg on days 1,8,15 and 22)<br><br><u>Comparator:</u><br>28-day cycle of oral lenalidomide (25 mg on days 1 through 21) and oral dexamethasone (40 mg on days 1,8,15 and 22) | <u>Primary:</u><br>PFS<br><br><u>Secondary:</u><br>TTP<br>SCR<br>MRD negativity<br>OR<br>VGPR<br>OS<br>Percentage of patients with CR<br>Time to response<br>Efficacy in subgroup of patients with high-risk cytogenic profile<br>Safety<br>HRQoL |

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| | • Waldenström's macroglobulinemia<br>• plasma cell leukemia or POEMS syndrome<br>• prior systemic therapy including stem-cell transplantation for treatment of myeloma<br>• malignancy within 5 years of randomization | | |

**Abbreviations**: ASCT = autologous stem cell transplantation; ECOG = Eastern Cooperative Oncology Group; CR = complete response; DRd = daratumumab, lenalidomide and dexamethasone; HRQoL = health-related quality of life; IV = intravenously; MRD = minimal residual disease; NDMM = newly diagnosed multiple myeloma; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PR = partial response; PD = progressive disease; RCT = randomized controlled trial; Rd = lenalidomide and dexamethasone; SAE = serious adverse events; sCR = stringent complete response; SD = stable disease; TEAE = treatment-emergent adverse event; TTP = time to disease progression; VGPR = very good partial response;

**Table 4: Select quality characteristics of the MAIA trial of daratumumab + lenalidomide and dexamethasone in patients with NDMM who are ineligible for ASCT**

| Study | Treatment vs. Comparator | Primary outcome | Required sample size | Sample size | Randomization method | Allocation concealment | Blinding | ITT Analysis | Final analysis | Early termination | Ethics Approval |
|---|---|---|---|---|---|---|---|---|---|---|---|
| MAIA | Daratumumab + lenalidomide and dexamethasone (DRd)<br><br>vs.<br><br>lenalidomide and dexamethasone (Rd) | PFS | The first analysis for safety was conducted after 100 patients had received at least 8 weeks of treatment or had discontinued treatment. The second analysis reported here, assessed safety and efficacy after 240 events of disease progression or death had occurred (i.e., 62% of the 390 planned events for the primary analysis).<br><br>The final OS analysis will be performed after 330 deaths have been reported, which will provide 80% power to detect a risk of disease progression or death that was 25% lower with DRd than with Rd, using a log-rank test at a two-sided alpha level of 0.05. | DRd (368)<br><br>Rd (369) | IWRS | Yes | No | Yes | **No** | No | Yes |

Abbreviations: RFS = relapse-free survival; HR = hazard ratio; IWRS = interactive web-response system; OS = overall survival; PFS = progression-free survival; vs. = versus; ITT = intention to treat.

### *a) Trials*

MAIA[2] is a randomized, open-label, active-controlled, parallel-group, multicenter, phase III international trial, globally distributed across 14 countries in North America, Europe, the Middle East, and the Asia-Pacific region. MAIA evaluates whether daratumumab in combination with lenalidomide and dexamethasone (DRd) compared to Rd improves progression-free survival (PFS), time to progression (TTP), minimal residual disease (MRD) negativity, overall survival (OS) and response in patients with new diagnosed multiple myeloma (NDMM) who are ineligible for autologous stem-cell transplantation (ASCT). The trial design was developed by the authors in collaboration with the sponsor, Janssen Research and Development. Data were compiled and maintained by Janssen. The majority of the authors declared receiving grant support or having a consulting or advisory role with the Sponsor.

Eligible patients were randomized to receive intravenous (IV) daratumumab in combination with oral lenalidomide and oral dexamethasone (daratumumab group, DRd, n=368) or oral lenalidomide and oral dexamethasone (control group, Rd, n=369). Patients were stratified by International Staging System (ISS, I vs II vs III), region (North America vs Other), and age (<75 vs ≥75).

**Outcomes**

The primary efficacy endpoint of this study was progression-free survival (PFS), which was defined as the time from randomization to either disease progression in accordance with the International Myeloma Working Group or death from any cause. For patients who had not progressed, data were censored at the date of the disease evaluation before the start of any subsequent anti-myeloma therapy.[2] The analysis of PFS was based on the ITT population.

A key secondary efficacy endpoint was time to progression (TTP), defined as the time from the date of randomization to the date of first documented evidence of disease progression.[2] Another secondary endpoint, the rate of negative status for minimal residual disease, was defined as the proportion of patients assessed as having negative status for minimal residual disease at any time point after the date of randomization.[2] Complete response rate, defined as the percentage of patients achieving a complete response, was defined by negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and less than 5% plasma cells in bone marrow.[2] For patients with negative serum M-protein quantitation by electrophoresis and suspected daratumumab interference on immunofixation, a reflex assay using an anti-idiotype antibody was utilized to confirm daratumumab interference and to rule out false positive immunofixation.[2] Patients with confirmed daratumumab interference who met all other clinical criteria for complete response or stringent complete response were considered as having complete response or stringent complete response.

Progression-free survival on the next line of therapy (PFS2) was defined as the time from randomization to progression on the next line of treatment or death, whichever occurred first.[2] Disease progression was based on investigator judgment. For patients who were still alive and had not yet progressed on the next line of treatment, data were censored on the last date of follow-up.

Overall survival was measured from the date of randomization to the date of the patient's death.[2] If the patient was alive or the vital status was unknown, the patient's data was censored at the date the patient was last known to be alive.

Stringent complete response rate was defined as the percentage of patients achieving complete response in addition to having a normal free light-chain ratio and absence of clonal cells in bone marrow, as assessed by immunohistochemical analysis, immunofluorescence analysis, or two- to four-color flow cytometry.[2]

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

Proportion of patients who achieved very good partial response or better was defined as the proportion of patients achieving very good partial response and complete response (including stringent complete response), according to International Myeloma Working Group criteria, during or after the trial treatment at the time of data cutoff.[2]

Time to response was defined as the time between randomization and the first efficacy evaluation at which the patient met all criteria for either complete response/stringent complete response or partial response, as applicable.[2] For patients without response, data were censored either at the date of progressive disease or, in the absence of progressive disease, at the last disease evaluation before the start of subsequent anti-myeloma therapy.

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

PRO endpoints were assessed via the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30) global health status (GHS) scale and the EuroQol 5-dimensional descriptive system (EQ-5D-5L). All PRO measures were collected prior to the administration of study intervention or study assessments on that visit within 21 days of randomization and on day 1 of cycles 3, 6, 9, and 12, and every sixth cycle thereafter. PRO analyses were descriptive and included patients in the ITT population.[5]

Safety was assessed by monitoring and recording all reported adverse events with onset during the treatment phase (i.e., treatment-emergent adverse events, and adverse events that have worsened since baseline) using the NCI CTCAE version 4.0. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.[3]

**Disease Assessment**

Samples for efficacy assessment, evaluated at a central laboratory, were obtained every 28 days for 2 years and then every 8 weeks there-after until disease progression.[2] Bone marrow aspirate obtained at baseline, at the time of suspected complete or stringent complete response, and at 12, 18, 24, and 30

months after the first dose in patients who had a complete response or better was used to assess MRD.[2] Response to study treatment and progressive disease was evaluated by a validated computer algorithm. Safety assessments included the evaluation of adverse events, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4), electrocardiography, clinical laboratory testing, physical examinations, and vital signs.

A pre-planned sensitivity analysis that evaluated potential bias arising from missed disease assessments was conducted. Missing a disease assessment could impact the PFS results if a subject missed one or more disease assessments and on the next performed assessment there was initial evidence of progression (i.e., disease progression potentially developed during the time when no disease assessment took place). In this case, the timing of PD may be artificially postponed resulting in a prolonged PFS calculation for that subject. There would be no impact on PFS results if a subject missed one or more disease assessments but on the next performed assessment there was no evidence of progression. As disease assessments were to be collected every 28 days for the first 2 years of study, missing one disease assessment would have minimal impact on the PFS analysis as the median PFS was greater than 30 months in either group.[3] Among the 197 patients (108 in DRd and 89 in Rd) who missed at least one disease assessment within the first 2 years, 188 (95%) of them did not have initial evidence of progression immediately after the missed assessment.[3] Nine subjects (6%) had one or more missed disease assessments followed by an assessment with evidence of progression, with a numerically higher number in the Rd group (6 subjects) compared to the DRd group (3 subjects).[3] As such, the imbalance in the proportion of patients who missed at least one disease assessment followed by an assessment with evidence of progression is unlikely to bias the efficacy results in favour of the DRd arm, as this occurred in more patients in the Rd arm.

Subjects who missed multiple disease assessments would have a greater impact on the PFS results. To account for extreme cases, the pre-planned sensitivity analysis censored any PFS events (PD or death) that occurred after >70 days (2.5 times 28-day cycles) since the subject's last assessment).[3] Nine PFS events (7 in Rd and 2 in DRd group) were censored, however the results still showed significant improvement in PFS for subjects in the DRd group compared with the Rd group (HR=0.57; 95% CI: 0.44, 0.74; p<0.0001)and are consistent with the primary PFS analysis (HR=0.56; 95% CI: 0.43, 0.73; p<0.0001).[3]

**Statistical Data Analyses**

The MAIA study incorporated 2 pre-planned interim analyses and utilized an Independent Data Monitoring Committee (IDMC).[3] The first interim analysis evaluated safety and was performed after a total of approximately 100 subjects had been treated for at least 8 weeks or discontinued the study treatment. The second interim analysis, with a purpose to evaluate cumulative interim safety and efficacy of DRd (data cut-off September 24, 2018), was performed when approximately 234 PFS events, which is 60% of the total planned events (390 PFS events), had been accumulated.[2] The significance level at this interim analysis to establish the superiority of DRd over Rd with regard to PFS was determined based on the observed number of PFS events at the interim analysis, using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending

method.[2] Assuming 234 PFS events are observed at the second interim analysis, the alpha to be spent was 0.0076 (2-sided) for the interim analysis and 0.0476 (2-sided) for the primary PFS analysis (390 PFS events occur).[2] A hierarchical testing procedure was used in the analysis of the primary endpoint and key secondary endpoints to achieve strong control of the overall familywise Type I error rate of 0.05.[3] The significance level was determined according to the alpha-spending function specific to each end point. For the evaluation of overall survival, a modified linear alpha-spending function was used to determine the alpha level at the time of each of three analyses (the second interim analysis, the primary PFS analysis, and the final OS analysis). The final OS analysis is planned to be performed after 330 deaths have been reported. A sample of 730 patients was estimated to provide the trial with 80% power to detect a risk of disease progression or death that was 25% lower with DRd than with Rd, using a log-rank test at a two-sided alpha level of 0.05.[3]

The Kaplan–Meier method was used to estimate the distribution of overall PFS for each treatment group.[3] Hazard ratios with corresponding two-sided 95% CIs for all time-to-event efficacy endpoints, including TTP, PFS2, OS, and time to subsequent anti-myeloma treatment were calculated with the use of a stratified Cox regression model with treatment as the sole explanatory variable. Comparison between the 2 treatment groups for overall response rates, VGPR rate, and other binary endpoints was conducted using the stratified Cochran Mantel Haenszel test.[3] Duration of response was provided descriptively without formal statistical comparison.

To assess homogeneity and consistency of the safety and treatment effects across pre-defined patient subsets, subgroup analyses for efficacy and safety endpoints were performed in subgroups on the basis of sex, age, race, baseline renal function, baseline hepatic function, geographic region, ISS, type of multiple myeloma, cytogenetic risk, and Eastern Cooperative Oncology Group (ECOG) performance score.[3]

HRQoL, assessed by the EQ-5D-3L (utility score and visual analogue scale [VAS]) and the EORTC QLQ-C30, was a secondary endpoint in the MAIA trial. The EQ-5D-3L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels: no problems, some problems, extreme problems. The minimally important difference (MID) threshold was defined as 0.075 point for the EQ-5D-3L.[5] The EQ VAS records the respondent's self-rated health on a vertical VAS where the endpoints are labelled 'best imaginable health state' and 'worst imaginable health state', with a difference of 7.5 points required to meet the criteria for MID.[5] The EORTC QLQ-C30 includes 30 items from 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), a GHS scale, 3 symptom scales (fatigue, nausea and vomiting, and pain) and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scores are transformed to a scale ranging from 0 to 100, with a MID threshold of 8 points[5]: for the functional and GHS domains, a higher score represents better functioning and HRQoL; for the symptom domains, a higher score indicates greater symptom severity. Descriptive analyses followed by a mixed-model, repeated-measures analysis was used to assess differences in mean scores.[3]

### *b) Populations*

The primary analysis was performed in the intention to treat population, which included all patients who underwent randomization. A total of 737 patients with NDMM who were ineligible for high-dose chemotherapy with stem cell transplantation due to age (≥65 years) or the presence of co-existing conditions that were likely to result in the development of unacceptable side effects were randomized into the study. Specifically, subjects had documented multiple myeloma satisfying CRAB criteria (calcium elevation, renal insufficiency, anemia, and bone abnormalities), had bone marrow with at least 10% plasma cells or a biopsy proven plasmacytoma, and had evidence of measurable secretory disease. Enrollment was limited to subjects who did not receive prior therapy for multiple myeloma and who were not considered candidates for HDT and ASCT.[2] Subjects with a poor ECOG performance status score (i.e., ECOG performance status score of 3 or worse) or with a CrCL <30mL/min were excluded for safety reasons, as this population of patients generally has a greater risk for toxicity.[2]

Demographic and clinical characteristics appeared well balanced at baseline between the DRd and Rd treatment groups (Table 5). The median age was 73 years (range 50-90) in the DRd group and 74 (range 45-89) in the control group (Rd). The majority of patients were ≥75 years (DRd - 43.5%; Rd – 43.6%) with an ECOG performance status of 0 or 1. An ECOG performance status score of ≥2 at baseline was reported in 17.1% and 16.0% of subjects in the DRd and Rd treatment groups, respectively. The majority of subjects had an ISS disease stage classification of II (44.3% DRd; 42.3% Rd) and the median time since diagnosis of MM to randomization was 0.95 (range 0.1-13.3) months in the DRd group and 0.89 (range 0-14.5) months in the Rd group. The majority of subjects had serum measurable disease, with IgG the most common immunoglobulin isotype (61.1% DRd; 62.6% Rd). Of the 642 subjects who had baseline cytogenetic data reported, 15.0% in the DRd group and 13.6% in the Rd group had a high-risk cytogenetic abnormality, as defined by del17p, t(14;16) or t(4;14) determined by fluorescent in situ hybridization (FISH) or karyotype testing.

**Table 5: Demographics and baseline characteristics of patients in the MAIA trial.**

| Characteristic | Daratumumab Group (N=368) | Control Group (N=369) |
|---|---|---|
| Median age (range) — yr | 73.0 (50–90) | 74.0 (45–89) |
| Age category — no. (%) | | |
| <65 yr | 4 (1.1) | 4 (1.1) |
| 65 to <70 yr | 74 (20.1) | 73 (19.8) |
| 70 to <75 yr | 130 (35.3) | 131 (35.5) |
| ≥75 yr | 160 (43.5) | 161 (43.6) |
| ECOG performance status — no. (%)† | | |
| 0 | 127 (34.5) | 123 (33.3) |
| 1 | 178 (48.4) | 187 (50.7) |
| 2‡ | 63 (17.1) | 59 (16.0) |
| ISS disease stage — no. (%)§ | | |
| I | 98 (26.6) | 103 (27.9) |
| II | 163 (44.3) | 156 (42.3) |
| III | 107 (29.1) | 110 (29.8) |
| Type of measurable disease — no. (%) | | |
| IgG | 225 (61.1) | 231 (62.6) |
| IgA | 65 (17.7) | 66 (17.9) |
| Other¶ | 9 (2.4) | 10 (2.7) |
| Detected in urine only | 40 (10.9) | 34 (9.2) |
| Detected as serum free light-chain only | 29 (7.9) | 28 (7.6) |
| Cytogenetic profile — no./total no. (%)‖ | | |
| Standard risk | 271/319 (85.0) | 279/323 (86.4) |
| High risk | 48/319 (15.0) | 44/323 (13.6) |
| Median time since initial diagnosis of multiple myeloma (range) — mo | 0.95 (0.1–13.3) | 0.89 (0–14.5) |

* The intention-to-treat population included all patients who underwent randomization. Post hoc analyses showed no significant differences between the two groups in the characteristics evaluated at baseline.
† Eastern Cooperative Oncology Group (ECOG) performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability.
‡ Two patients had a score of greater than 2 (one patient had a score of 3, and another patient had a score of 4).
§ The International Staging System (ISS) disease stage, which is derived on the basis of the combination of serum $\beta_2$-microglobulin and albumin levels, consists of three stages. Higher stages indicate more severe disease.
¶ This category includes IgD, IgE, IgM, and biclonal.
‖ Cytogenetic risk was based on fluorescence in situ hybridization or karyotype analysis; patients who had a high-risk cytogenetic profile had at least one high-risk abnormality (del17p, t[14;16], or t[4;14]).

Source: From the New England Journal of Medicine, Facon T, et al., Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma 380, 2104-15. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

### *c) Interventions*

Patients were randomized in a 1:1 ratio to receive either a 28-day cycle of IV daratumumab (16mg/kg once weekly during cycles 1 and 2, every 2 weeks during cycles 3 through 6, and every 4 weeks thereafter) + oral lenalidomide (25 mg on days 1 through 21) and oral dexamethasone (40 mg on days 1,8,15 and 22) or oral lenalidomide (25 mg on days 1 through 21) and oral dexamethasone (40 mg on days 1,8,15 and 22).[2]

Patients in both groups were to continue receiving treatment until disease progression, unacceptable toxic effects or study end. Dose modifications or interruptions were permitted during the trial for certain patients who were unable to tolerate the protocol-specified dosing scheme. For patients who had a creatinine clearance between 30 and 50 ml per minute, a reduced dose of lenalidomide (10 mg) was recommended. For cases of neutropenia and thrombocytopenia, adjustment of the dose of lenalidomide was recommended. Patients who were older than 75 years of age or who had a body-mass index <18.5 received dexamethasone at a dose of 20 mg once weekly.

Per protocol, patients in both treatment groups were to receive 25 mg lenalidomide (days 1-21 of a 28-day cycle) until disease progression or unacceptable toxicity. Patients with a creatinine clearance of 30-50 mL/min were recommended a reduced lenalidomide dose of 10 mg (210 mg lenalidomide per cycle). In addition, lenalidomide dose adjustments were recommended for patients who experienced treatment emergent adverse events (TEAEs), such as neutropenia and thrombocytopenia.

In the safety population, defined as subjects who have received at least one administration of any study treatment (daratumumab, lenalidomide, or dexamethasone), subjects in the DRd group received a median of 27 (range 1-44) treatment cycles while subjects in the Rd group received a median of 22 (range 1-43) treatment cycles, at the time of the clinical cut-off (September 24, 2018). In the updated safety analysis (Jan 24, 2019), median treatment cycles were [redacted] and [redacted] in the DRd and Rd groups, respectively.[4] *Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.* Consequently, the median duration of treatment was longer for the DRd treatment group (25.3 months, range 0.1-40.4) than for the Rd treatment group (21.3 months, range 0.03-40.6).[2] The median relative dose intensity of lenalidomide (76.2%) and dexamethasone (84.2%) was lower for the daratumumab group than the control group (91.4% and 90.7%, respectively).[2] [redacted]).[3] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.*

According to the sponsor, [redacted].[4] *Non-disclosable*

*information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier*

**Table 6: Reasons for Lenalidomide Dose Modifications (MAIA; MMY3008)[4]**

| Lenalidomide dose modification | DRd n (%) | Rd n (%) |
|---|---|---|
| Analysis Set (safety) | [redacted] | [redacted] |
| Skipped doses | [redacted] | [redacted] |
| Dose reductions | [redacted] | [redacted] |
| Dose delays | [redacted] | [redacted] |

DRd = daratumumab + lenalidomide + dexamethasone; Rd = lenalidomide + dexamethasone

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

Adverse events were the most common reason for both lenalidomide skipped doses and dose reductions. Dose modifications for lenalidomide were permitted per protocol in response to toxicity observed attributed to lenalidomide and according to the lenalidomide label. Specifically, [redacted].[4] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.* Of note, as per the review protocol, daratumumab dose reductions were not allowed, patients could only delay or skip infusions. The most common reason for a skipped dose was TEAE.

**Pre- and Post-infusion Medication**

During daratumumab infusion days, patients received acetaminophen 650 to 1,000 mg intravenously or orally, diphenhydramine 25 to 50 mg (or equivalent) intravenously or orally, and dexamethasone 40 mg intravenously or orally approximately 1 hour prior to daratumumab infusion.[2] For patients older than 75 years of age or with body mass index less than 18.5 kilograms per square meter, dexamethasone was administered at a dose of 20 mg once weekly.[2]

Post-infusion medications were administered for patients with higher risk of respiratory complications (i.e., those with mild asthma or patients with chronic obstructive pulmonary disease who have forced expiratory volume in 1 second <80%); these medications included diphenhydramine (or equivalent), short-acting ß2 adrenergic receptor agonists such as salbutamol aerosol, and control medications for lung disease (e.g., inhaled corticosteroids ± long-acting ß2 adrenergic receptor agonists for patients with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for patients with chronic obstructive pulmonary disease).[2]

**Subsequent Therapy**

Based on the safety dataset, which includes all patients who received at least one dose of randomized treatment, [redacted].[4] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.*

[redacted][4] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.*

[redacted][4] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.*

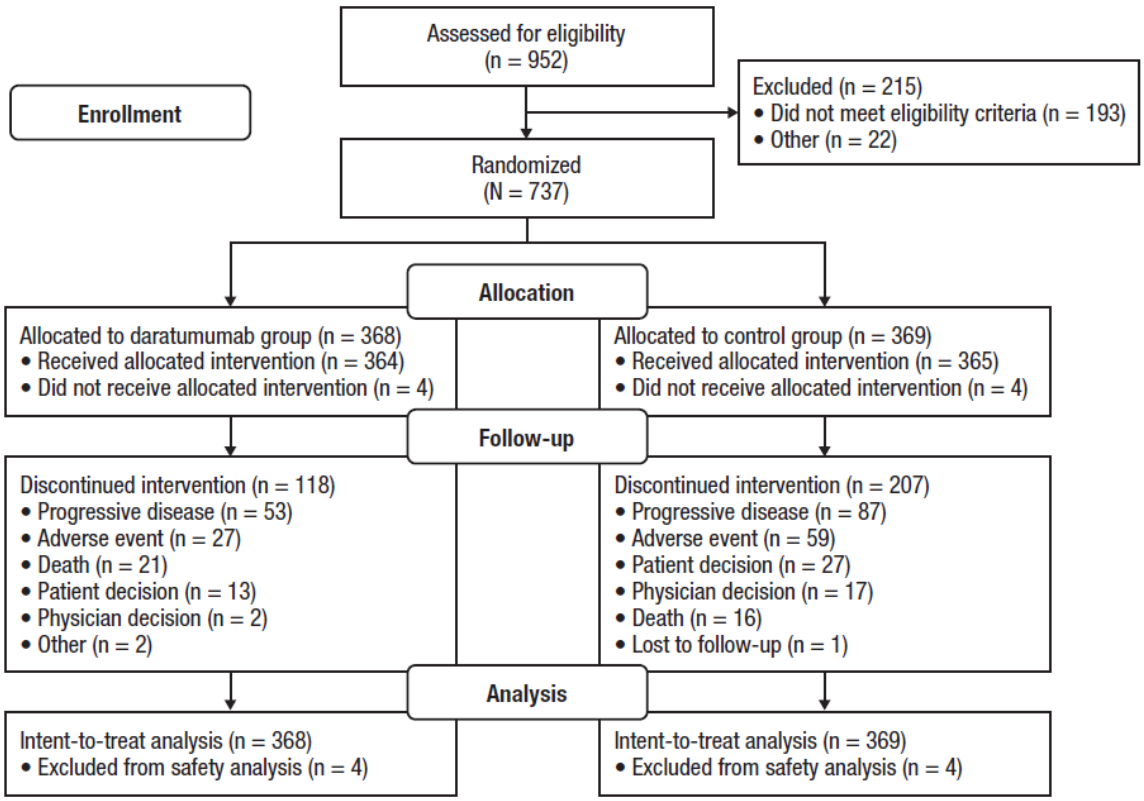
### *d) Patient Disposition*

Among the 737 patients who underwent randomization,729 patients (364 in the DRd group and 365 in the Rd group) received at least one dose of the trial treatment. Eight subjects (4 subjects in each treatment group) were randomized but did not receive treatment. Of these subjects, two, who were both in the DRd group, died of an adverse event before receiving treatment and the remaining 6 subjects were not treated as they withdrew from the study prior to Cycle 1 Day 1.[3]

At the time of the clinical data cutoff for the primary analysis (September 24, 2018), a total of 118 patients (32.4%) in the DRd group and 207 patients (56.7%) in the Rd group had discontinued treatment.[2] Results of an updated analysis for safety through to 24 January 2019 were consistent with the primary analysis[4] The most common reason for treatment discontinuation in both the primary and updated safety analyses was progressive disease (14.6% in the DRd group and 23.8% in the Rd group) and adverse events (7.4% and 16.2%, respectively).[2] Discontinuation due to physician decision was 0.5% in the DRd group and 4.6% in the Rd group.[2] Patients who discontinued treatment for reasons other than

disease progression and remained in the trial were followed for the primary end point.

**Figure 2: Patient disposition in the MAIA trial.**




Source: Facon et al 2019 Suppl (Figure S2)

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Information on the protocol deviations that occurred during the trial was not provided in the pCODR submission. A request was made to the Sponsor for this information and they indicated that major protocol deviations were generally low for both groups. Specifically, major protocol deviations were reported for [redacted] subjects ([redacted]%) across both treatment groups: [redacted] subjects ([redacted]%) in the DRd group and [redacted] subjects ([redacted]%) in the Rd group.[4] The majority of these included efficacy assessment deviations ([redacted]% in DRd group and [redacted]% in Rd group) and entered in study but did not satisfy criteria ([redacted] in both groups).[4] [redacted][4] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.*

### e) *Limitations/Sources of Bias*

Overall, there were no major concerns with the conduct of MAIA trial. The randomization method and sample size were adequate, and the efficacy analysis

was conducted according to the intention-to-treat principal. The study protocol was approved by institutional review boards or independent ethics committees at each study center and the trial was conducted in accordance with Good Clinical Practice guidelines.

However, the following limitations and potential sources of bias of the MAIA trial were noted by the pCODR Methods Team:

- With an open-label study design, treatment assignment in the MAIA trial was not blinded. This has the potential to introduce bias as participants would have been aware of which treatment was received.
- According to clinician input, patients who are ≥70 years of age are considered transplant-ineligible in Canada, whereas the MAIA trial considered patients who were ≥65 years old to be transplant-ineligible. The extent to which the older aged cut-off may have influenced the results of the trial is unknown.
- The extent to which the lower median dose intensity of lenalidomide and dexamethasone in the daratumumab group compared to the control group may have influenced efficacy outcomes is unknown.
- For patients randomized to the Rd group, [redacted]% received subsequent antimyeloma therapies, of which [redacted] patients ([redacted]%) received daratumumab as subsequent therapy. This compares with [redacted]% in the DRd group who received antimyeloma therapies and [redacted]% who received subsequent daratumumab. *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.* There will likely be confounding from subsequent use of daratumumab in the Rd arm.
- At the time of the data analysis, OS data was immature (median overall survival was not reached in either group) making the actual degree of long-term benefit unknown. Follow-up for long-term survival is ongoing.
- HRQoL end points were secondary and were not included in the statistical hierarchy or adjusted for multiplicity. Furthermore, selection bias over time should be considered when interpreting results of the HRQoL assessment, as the long-term responders tend to be the healthier patients. Overall, interpretation of HRQoL end points is limited as data was only collected for up to 12 cycles and additional data for the subsequent cycles was not available.
- A number of relevant comparators were noted by the Clinical Guidance Panel and PAG, including DVMP and VRd. There were not head to head trials identified in the systematic review that evaluated DRd to these comparators. The comparison for DVMP was provided as part of the network meta-analysis (NMA) submitted by the Sponsor; however, a comparison to VRd was not included in the NMA. Therefore, the review team requested the Sponsor to provide an updated ITC for the comparison of DRd to these relevant comparators. To address this request, the Sponsor provided a sensitivity analysis which included VRd in the NMA. A critical appraisal of the NMA can be found in Section 7.
- The sponsor, Janssen Research and Development supported the trial and were involved in the design of the study, data collection, performing data analysis, and interpreting results. The extent to which the Sponsor's involvement may have influenced the results and reporting of the trial is unknown.

## Detailed Outcome Data and Summary of Outcomes
### *Efficacy Outcomes*

**PRIMARY OUTCOME**
**Progression-free Survival (PFS)**

As of the primary analysis pre-defined cut-off date of September 24, 2018 and a median follow-up of 28.0 months (range 0-41.4), disease progression or death had occurred in 26.4% (97/368) of patients in the DRd group and 38.8% (143/369) of patients in the Rd group.[2] The Kaplan–Meier estimate of the percentage of patients who were alive without disease progression at 30 months was 70.6% (95% confidence interval [CI], 65.0 to 75.4) in the DRd group and 55.6% (95% CI, 49.5 to 61.3) in the Rd group.[2] The combination of DRd demonstrated superiority over Rd for the primary endpoint of PFS with an estimated HR of 0.56 (95% CI, 0.43 to 0.73, p<0.0001, crossing the pre-specified O'Brien-Fleming stopping boundary of p≤0.0085)[3] in favour of the DRd treatment group. The Kaplan-Meier plot of PFS shows early separation of the curves favoring DRd, which continued to widen over time (Figure 3). The median PFS was not reached in the DRd group and was 31.9 months (95% CI, 28.9 to not reached) in the Rd group. One-, two- and three-year PFS rates were [redacted]% (95% CI, [redacted]% to [redacted]%), [redacted]% (95% CI, [redacted]% to [redacted]%), and [redacted]% (95% CI, [redacted]% to [redacted]%), in the DRd group and [redacted]% (95% CI, [redacted]% to [redacted]%), [redacted]% (95% CI, [redacted]% to [redacted]%) and [redacted]% (95% CI, [redacted]% to [redacted]%) in the Rd group, respectively.[3]

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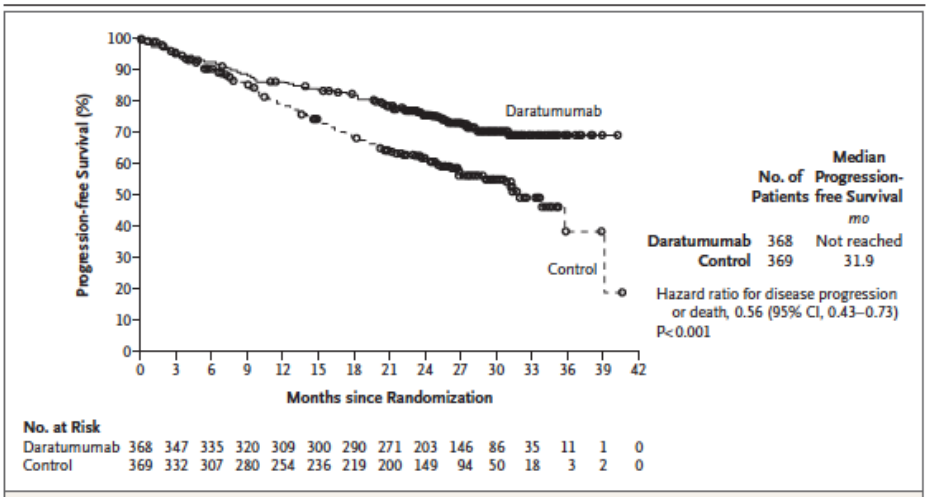
**Figure 3. Progression-free survival**




Shown are the results of the Kaplan–Meier estimates of progression-free survival among patients in the ITT population. The daratumumab group received treatment with daratumumab, lenalidomide, and dexamethasone; the control group received treatment with lenalidomide and dexamethasone. The interim analysis of PFS was performed after 240 events of disease progression or death had occurred (62% of the planned 390 events for the final analysis).

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### Sensitivity Analyses of PFS

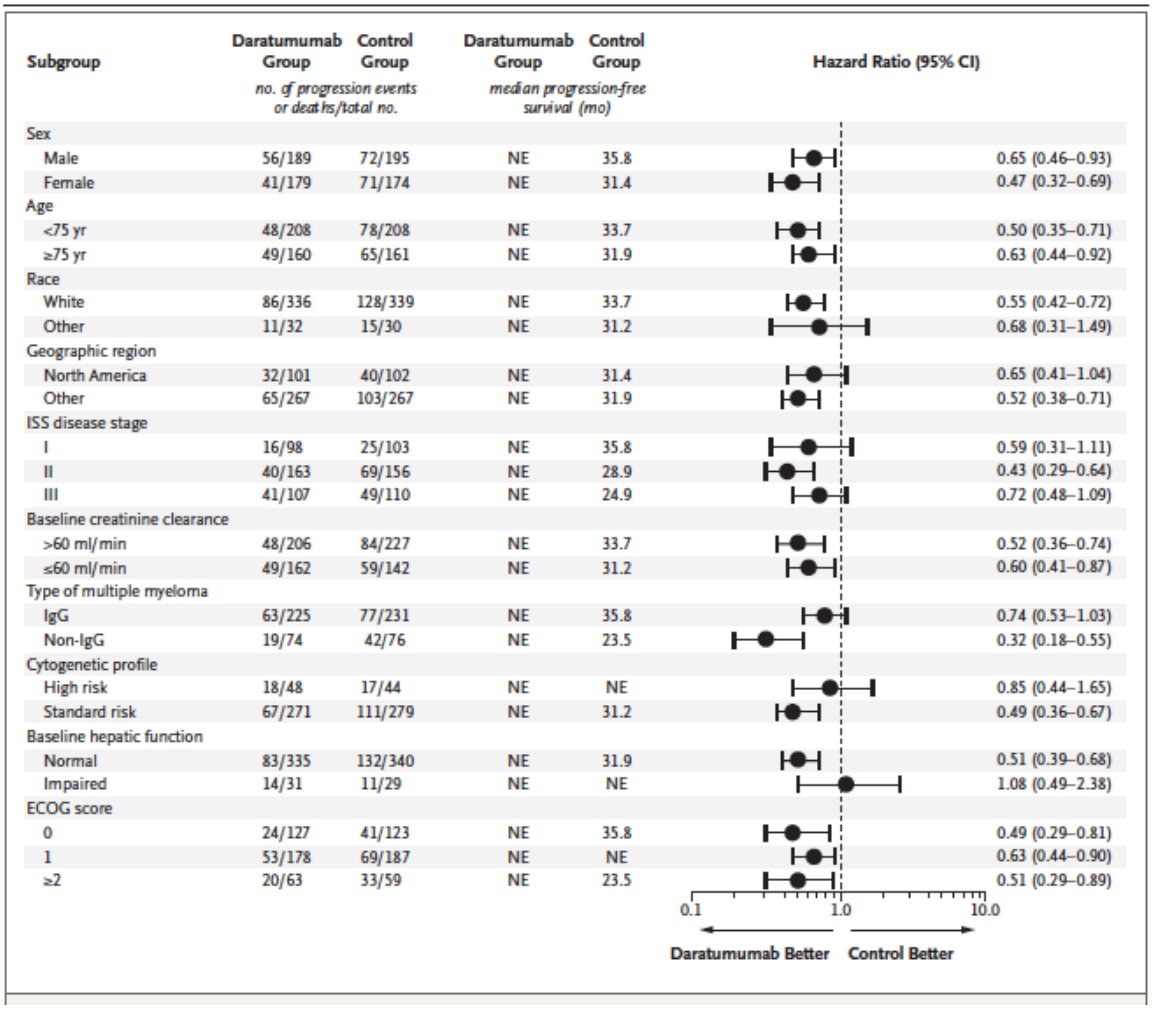
A sensitivity analysis using disease progression by investigator assessment was consistent with the primary analysis assessed by computer algorithm. By investigator assessment, [redacted] subjects ([redacted]%) in the DRd group and [redacted] subjects ([redacted]%) in the Rd group had progressive disease or died and the results (HR=[redacted]; 95% CI: [redacted]) were consistent with the main analysis.[3] *Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.*

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

### Subgroup Analyses of PFS

Pre-specified subgroup analyses of PFS consistently showed HRs<1 in favour of the DRd treatment group across clinically relevant subgroups, including subjects 75 years of age or older (HR 0.63; 95% CI, 0.44 to 0.92), and subjects with a poor prognosis such as those with renal impairment (HR 0.60; 95% CI, 0.41 to 0.87) or ECOG performance status of 2 or greater (HR 0.51; 95% CI, 0.29 to 0.89).[2] The only exception was the subgroup of subjects with impaired hepatic function at baseline, which had a small sample size (31 and 29 subjects in the DRd and Rd groups, respectively) thereby limiting the interpretation of the results (Figure 4).[2]

**Figure 4. Forest plot of hazard ratios for PFS according to pre-specified patient subgroups in the MAIA trial**




Shown are the results of an analysis of progression-free survival in prespecified subgroups in the intention-to-treat population. The daratumumab group received treatment with daratumumab, lenalidomide, and dexamethasone; the control group received treatment with lenalidomide and dexamethasone. The International Staging System (ISS) disease stage, which is derived on the basis of the combination of serum β2-microglobulin and albumin levels, consists of three stages, with higher stages indicating more advanced disease. The subgroup analysis for the type of myeloma was performed on data from patients who had measurable disease in serum. A high-risk cytogenetic profile was defined by the detection of a del17p, t(14;16), or t(4;14) cytogenetic abnormality (or a combination of these) on fluorescence in situ hybridization or karyotype analysis. Impaired baseline hepatic function includes mild impairment (total bilirubin level less than or equal to the upper limit of the normal range [ULN] and aspartate aminotransferase level higher than the ULN, or total bilirubin level higher than the ULN and ≤1.5 times the ULN), moderate impairment (total bilirubin level >1.5 times and ≤3 times the ULN), and severe impairment (total bilirubin level >3 times the ULN). Eastern Cooperative Oncology Group (ECOG) performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability. NE denotes could not be estimated.

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**Secondary Endpoints**

**Response**

The percentage of patients with complete response or better in the ITT population was significantly higher in the DRd groups than in the Rd (47.6% vs. 24.9%), as was the percentage with very good partial or better response (79.3% vs. 53.1%) (P<0.001 for both comparisons) (Table 8).[2] A total 92.9% of patient in the DRd group and 81.3% in the Rd group had an overall response.[2] These response outcomes favouring patients in the DRd group over Rd group was true for both in patients aged ≥75 years and those <75 years.[28] The VGPR or better rate was 79.3% in the DRd treatment group compared with 53.1% in the Rd treatment group The CR or better rate was significantly higher in the DRd treatment group (47.6%) compared with the Rd treatment group (24.9%)

Among the patients who had a response (partial response or better), 80.3% (95% CI, 75.1 to 84.5) in the DRd group and 65.7% (95% CI, 58.6 to 71.8) in the Rd group sustained the response for 30 months.[2] The median time to the first response was 1.05 months in both groups, and the median time to a complete response or better was 10.4 months in the DRd group and 11.2 months in the Rd group.[2]

**Minimal Residual Disease (MRD) Negativity**

Based on the ITT population, the DRd group demonstrated a greater rate of MRD negativity compared with the Rd group. The MRD negativity rate, at a threshold of 1 tumor cell per $10^5$ white cells, was more than 3-fold higher in the DRd group compared with the Rd group (DRd: 24.2%, Rd: 7.3%;[2]; p<0.0001)[1] . The MRD-negativity rate was increased with DRd versus Rd both in patients aged ≥75 years and those <75 years. Negative status for MRD was associated with longer progression-free survival than positive status, regardless of the treatment group. All the patients who were negative for minimal residual disease had a complete response or better.

**Table 8: Summary of Response Rates and Minimal Residual Disease Status in the Intention-to-Treat Population.***

| Variable | Daratumumab Group (N=368) | Control Group (N=369) | P Value |
|---|---|---|---|
| Overall response — no. (% [95% CI]) | 342 (92.9 [89.8–95.3]) | 300 (81.3 [76.9–85.1]) | <0.001† |
| Best overall response — no. (%) | | | |
| Complete response or better | 175 (47.6) | 92 (24.9) | <0.001† |
| Stringent complete response‡ | 112 (30.4) | 46 (12.5) | — |
| Complete response | 63 (17.1) | 46 (12.5) | — |
| Very good partial response or better | 292 (79.3) | 196 (53.1) | <0.001† |
| Very good partial response | 117 (31.8) | 104 (28.2) | — |
| Partial response | 50 (13.6) | 104 (28.2) | — |
| Stable disease | 11 (3.0) | 56 (15.2) | — |
| Progressive disease | 1 (0.3) | 0 | — |
| Response could not be evaluated | 14 (3.8) | 13 (3.5) | — |
| Negative status for minimal residual disease — no. (%)§ | 89 (24.2) | 27 (7.3) | <0.001¶ |

* Response was assessed on the basis of International Myeloma Working Group recommendations (details on the crite- ria for disease responses are provided in the protocol). The following secondary end points were tested sequentially, each with an overall two-sided alpha level of 0.05, with the use of a

hierarchical testing approach: complete response or better, very good partial response or better, negative status for minimal residual disease, and overall response.
† The P value was calculated with the use of the Cochran–Mantel–Haenszel chi-square test.
‡ Criteria for a stringent complete response include the criteria for a complete response plus a normal free light-chain ratio and absence of clonal plasma cells, as assessed by immunofluorescence or immunohistochemical analysis or by two-color to four-color flow cytometry.
§ The threshold for minimal residual disease was defined as 1 tumor cell per $10^5$ white cells. Status regarding minimal residual disease is based on a post randomization assessment performed on bone marrow samples with the use of a validated next-generation sequencing assay (clonoSEQ Assay, version 2.0; Adaptive Biotechnologies) in accordance with International Myeloma Working Group guidelines on assessment of minimal residual disease.[23]
¶The P value was calculated with the use of the Fisher's exact test.

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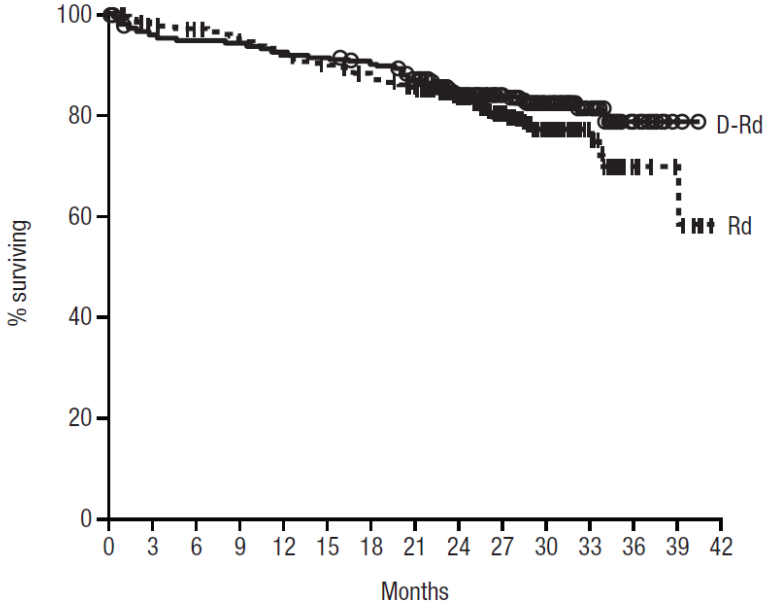
### Overall Survival (OS)

With a median overall follow-up of 28 months, the OS data were still immature, which is consistent with the expectation in newly diagnosed patient populations. A total of 138 deaths were observed, 62 subjects (16.8%) in the DRd group and 76 subjects (20.6%) in the Rd group. The median overall survival was not reached in either group, and follow-up for long-term survival is ongoing (see Figure 5).[2] The hazard ratio was 0.78 (95% CI: 0.56 to 1.10).[3]

**Figure 5. Overall Survival in the Intention-to-Treat Analysis Set.**

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**Patient Reported Outcome (PRO) Endpoints**

PRO endpoints included change from baseline in HRQoL according to the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30) global health status (GHS) scale and the EuroQol 5-dimensional descriptive system (EQ-5D-5L). All PRO measures were collected prior to the administration of study intervention or study assessments on that visit within 21 days of randomization and on day 1 of cycles 3, 6, 9, and 12, and every sixth cycle thereafter. PRO analyses, were descriptive and included patients in the ITT population.[5] PRO data was only available from baseline to cycle 12.

The EORTC QLQ-C30 includes 30 items from 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), a GHS scale, 3 symptom scales (fatigue, nausea and vomiting, and pain) and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scores are transformed to a scale ranging from 0 to 100: for the functional and GHS domains, a higher score represents better functioning and HRQoL; for the symptom domains, a higher score indicates greater symptom severity. A change from baseline of 8 points in the GHS was considered a minimally important difference.[5]

The EQ-5D-5L includes 5 domains of utility (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), presented in the range of 0 to 1, with a high score indicating a high level of utility. A visual analog scale (VAS) rating "health today," ranges from 0 to 100, with a high score indicating a high level of self-evaluated health status.[5]

PRO compliance rates for the first 12 cycles, as a percentage of available patients at the time of assessment reported from baseline through to cycle 12, were high and comparable in both treatment groups, with rates >90% at baseline (EORTC QLQ-C30: DRd – 96.2%, Rd – 94.3%; EQ-5D-5L: DRd – 94.8%, Rd – 93.8%) and >80% at Cycle 12 (EORTC QLQ-C30: DRd – 86.7%, Rd – 86.9%; EQ-5D-5L: DRd – 83.1%, Rd – 85.3%).[5] PRO compliance rates after the first 12 cycles are unknown.

***EORTC QLQ-C30***

Mean baseline values for the EORTC QLQ-C30 scores were comparable between the DRd (56.7) and Rd (56.2) groups and between patients ≥75 (DRD: 56.9, Rd: 55.7) and those <75 years of age (DRD: 56.6, Rd: 56.5). Perrot et al[5] reported that GHS improved in both treatment groups across all time points, with significantly greater improvement from baseline to Cycle 3 in the DRd group versus the Rd group (least squares [LS] mean change from baseline: DRd, 4.5 [95% CI, 2.4-6.6] vs Rd, 1.5 [95% CI, −0.7-3.7]; between-arm difference in LS mean change from baseline: 3.0 [95% CI, 0.1-5.9]; *P* = 0.0454). In the DRd group, a clinically meaningful benefit was observed for GHS starting in Cycle 9 and sustained through Cycle 12.[5] The mean change from baseline in the GHS score did not meet the MID threshold at any time for the Rd group. The median time to worsening was 1 month longer in the DRd group compared with the Rd group (22.5 vs 21.2 months), although this difference was not statistically significant.[5]

***EORTC QLQ-C30 GHS by Age Subgroups***

The baseline GHS values were similar across age groups (≥75 years and <75 years) and treatment groups. Results from the cancer-specific EORTC-QLQ-C30 indicated improvements in health-related quality of life in subjects ≥75 years and <75 years in both the DRd and Rd groups, however the treatment groups in both age groups were not significantly different from one another at any time point. Patients ≥75 years of age in the DRd group had improved EORTC QLQ-C30 GHS scores across all time points, while improvements from baseline for patients ≥75 years of age in the Rd group occurred in Cycles 6 through 12. For patients ≥75 years of age, the magnitude of improvements from baseline in EORTC QLQ-C30 GHS scores was greatest in the DRd group compared with the Rd group; however, the between-arm differences in GHS scores for this age subgroup were not significantly different at any time point. Among patients ≥75 years of age in the DRd group, a clinically meaningful benefit was observed for GHS in Cycle 9, exceeding the MID threshold; in the Rd group, the GHS score did not meet the MID threshold at any time. Among patients <75 years of age, both treatment groups had improved GHS scores from baseline at all time points; the treatment groups were not significantly different from one another at any time point.[5] A clinically meaningful benefit in GHS was seen for patients <75 years of age in the DRd group at Cycles 9 through 12, and at Cycle 9 in the Rd group.[5]

***EuroQol EQ-5D-5L***

Mean baseline values for the utility (DRD: 0.58, Rd: 0.6) and VAS scores (DRD: 62.6, Rd: 62.7) were similar between the two treatment groups. Analysis of the ITT population showed that, VAS score improved from baseline to Cycle 12 for both treatment groups, with significantly greater improvement in the DRd group compared with the Rd group at Cycle 12 (LS mean change from baseline: DRd, 10.1 [95% CI, 8.1-12.1] vs Rd, 4.9 [95% CI, 2.8-7.0]; between-arm difference in LS mean change from baseline: 5.2 [95% CI, 2.4-8.0]; $P = 0.0002$).[5] In the DRd group, the VAS score had clinically meaningful improvement from baseline starting at Cycle 3 and sustained through Cycle 12; the Rd group crossed the MID threshold of clinically meaningful benefit at Cycle 9, but this was not sustained through Cycle 12. The median time to worsening of the EQ-5D-5L VAS score was 10 months longer in the DRd group compared with the Rd group (32.2 months vs 22.1 months, respectively), although this difference was not statistically significant and the upper bound was not evaluable at the clinical cut off.[5] Clinically meaningful improvements in the EQ-5D-5L utility score occurred in both treatment arms at all time points; however, the treatment groups were not significantly different from one another at any time.

***Safety Outcomes***

A total of 364 patients in the DRd group and 365 patients in the RD group received at least one dose of study treatment and were included in the safety analysis. With a median treatment duration of 25.3 (01-40.4) months in the DRd treatment group and 21.3 (0.03-40.6)[3] months in the Rd treatment group,[3] daratumumab in combination with Rd resulted in higher incidences of any grade and grade 3 or 4 neutropenia and pneumonia in elderly patients with newly diagnosed multiple myeloma. The most common adverse events of grade 3 or 4 were neutropenia (50.0% in the DRd group and 35.3% in the Rd group), anemia (11.8% and 19.7%), lymphopenia (15.1% and 10.7%), pneumonia (13.7% and 7.9%), and leukopenia (11.0% and 4.9%).[2] The incidence of infections of any grade was 86.3% in the DRd group and 73.4% in the Rd group; the incidence of

grade 3 or 4 infections was 32.1% in the DRd group and 23.3% in the Rd group.[2] Table 9 shows the most common adverse events during treatment in the safety population at the time of cutoff for the primary analysis (September 24, 2018).

Serious treatment-emergent adverse events (TEAEs) were reported at comparable incidences in the DRd group (62.9%) and the Rd group (62.7%). Pneumonia was the most common serious adverse event, occurring in 13.2% of the patients in the DRd group and in 7.4% of the patients in the Rd group. Grade 3/4 TEAEs were reported in 94.3% and 88.7% of patients aged ≥75 years receiving DRd and Rd, respectively, and in 86.5% and 77.7% of patients aged <75 years receiving DRd and Rd, respectively.[28] Serious TEAEs were reported in 65.6% and 70.4% of patients aged ≥75 years receiving DRd and Rd, respectively, and in 60.9% and 56.8% of patients aged <75 years receiving DRd and Rd, respectively.[28] In the updated safety analysis (Jan 24, 2019), the TEAEs reported for daratumumab in combination with Rd were consistent with those reported in the primary analysis. The proportion of subjects with TEAEs of any grade did not differ by more than 2% between the safety update and the primary analysis.

Discontinuation of study treatment due to TEAEs was reported at a lower incidence in the DRd group (7.1%) compared with the Rd group (15.9%). Discontinuation of the trial treatment owing to an infection occurred in 0.5% of the patients in the DRd group and in 1.4% of the patients in the Rd group; no patients in the DRd group, as compared with one patient (0.3%) in the Rd group, discontinued treatment because of neutropenia. In patients aged ≥75 years, the incidence of treatment discontinuations due to TEAEs was 10.2% and 20.8% in those receiving DRd and Rd, respectively.[28] This compared to 4.8% and 12.1% of patients aged <75 years receiving DRd and Rd, respectively.[28]

Adverse events that resulted in death were observed in 25 patients (6.9%) in the daratumumab group and in 23 patients (6.3%) in the control group; the most common such event was pneumonia, which resulted in death in 0.5% and 0.8% of the patients, respectively.[2] Invasive second primary cancers occurred in 12 patients (3.3%) in the DRd group (solid tumors in 2.7% and hematologic cancers in 0.5%) and in 13 patients (3.6%) in the Rd group (solid tumors in 3.0% and hematologic cancers in 0.5%). [redacted] additional subjects in the DRd treatment group and [redacted] additional subjects in the Rd treatment group died by the clinical cut-off for the safety update (DRd: [redacted] subjects [redacted%]; Rd: [redacted] subjects [redacted%]).[4] [redacted]

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

Of the 364 subjects who received daratumumab, 40.9% experienced an infusion-related reaction (IRR). IRRs usually occurred during administration of the first dose (in 98.0% of the patients who had such reactions), and only one patient (with grade 4 hypertension) discontinued daratumumab treatment due to an infusion-related reaction. In the DRd arm, infusion-related reactions were

observed in 35.7% (1.9% grade 3, 0.6% grade 4) of patients aged ≥75 years and 44.9% (2.9% grade 3, 0% grade 4) of patients aged <75 years.

**Table 9. Most Common Adverse Events and Second Primary Cancers Reported during Treatment in the Safety Population.***

| Event | Daratumumab Group (N=364) | | Control Group (N=365) | |
|---|---|---|---|---|
| | Any Grade | Grade 3 or 4 | Any Grade | Grade 3 or 4 |
| | *number of patients (percent)* | | | |
| Hematologic adverse events | | | | |
| Neutropenia | 207 (56.9) | 182 (50.0) | 154 (42.2) | 129 (35.3) |
| Anemia | 126 (34.6) | 43 (11.8) | 138 (37.8) | 72 (19.7) |
| Leukopenia | 68 (18.7) | 40 (11.0) | 34 (9.3) | 18 (4.9) |
| Lymphopenia | 66 (18.1) | 55 (15.1) | 45 (12.3) | 39 (10.7) |
| Nonhematologic adverse events | | | | |
| Infections | 314 (86.3) | 117 (32.1) | 268 (73.4) | 85 (23.3) |
| Pneumonia | 82 (22.5) | 50 (13.7) | 46 (12.6) | 29 (7.9) |
| Diarrhea | 207 (56.9) | 24 (6.6) | 168 (46.0) | 15 (4.1) |
| Constipation | 149 (40.9) | 6 (1.6) | 130 (35.6) | 1 (0.3) |
| Fatigue | 147 (40.4) | 29 (8.0) | 104 (28.5) | 14 (3.8) |
| Peripheral edema | 140 (38.5) | 7 (1.9) | 107 (29.3) | 2 (0.5) |
| Back pain | 123 (33.8) | 11 (3.0) | 96 (26.3) | 11 (3.0) |
| Asthenia | 117 (32.1) | 16 (4.4) | 90 (24.7) | 13 (3.6) |
| Nausea | 115 (31.6) | 5 (1.4) | 84 (23.0) | 2 (0.5) |
| Second primary cancer† | 32 (8.8) | NA | 26 (7.1) | NA |
| Invasive second primary cancer | 12 (3.3) | NA | 13 (3.6) | NA |
| Any infusion-related reaction | 149 (40.9) | 10 (2.7) | NA | NA |

* The safety population included all patients who received at least one dose of the trial treatment. Adverse events of any grade that were reported in more than 30% of patients in either treatment group and grade 3 or 4 adverse events that were reported in more than 10% of patients in either treatment group are listed. NA denotes not applicable.

† The presence of a second primary cancer was prespecified in the statistical analysis plan as an adverse event of clinical interest.

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## 6.4 Ongoing Trials

No ongoing trials were identified as being relevant to this review.

# 7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of daratumumab (Darzalex) in combination with lenalidomide and dexamethasone (DRd) :

- Part 1: Critical appraisal of the Sponsor submitted network meta-analysis (NMA) comparing daratumumab in combination with lenalidomide and dexamethasone (DRd) to bortezomib/melphalan/prednisone (VMP), daratumumab/bortezomib/melphalan/prednisone (D-VMP), melphalan/prednisone/thalidomide (MPT), bortezomib/thalidomide/dexamethasone (VTD), cyclophosphamide/thalidomide/dexamethasone (CTD), melphalan/prednisone (MP), and thalidomide/dexamethasone (TD) among others in patients with NDMM who are ineligible for ASCT.
- Part 2: Critical appraisal of the Sensitivity Analysis of the Sponsor's submitted NMA for the addition of VRd (Bortezomib-Lenalidomide-Dexamethasone)

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

## Part1: Critical Appraisal of the Sponsor's Submitted ITC and NMA[32]

### 7.1.1 Background and Objective

In the absence of randomized control trials (RCTs) directly comparing daratumumab combination treatment with other currently funded therapies in Canada in NDMM patients who are ineligible for ASCT, the Sponsor conducted a network meta-analysis (NMA) . In Canada, bortezomib, cyclophosphamide and dexamethasone/prednisone (CyBorD/P) and bortezomib-melphalan-prednisone (VMP) are current treatments of choice for patients with newly diagnosed multiple myeloma that are transplant ineligible. The efficacy of CyBorD was assumed to be equivalent to that of VMP for the purpose of this NMA.[3]

The aim of the NMA was to evaluate and compare the relative efficacy and safety of daratumumab – based regimens versus other selected regimens for the treatment of NDMM who are ineligible for transplantation. The outcomes of interest were progression-free survival (PFS), overall survival (OS), overall response rate (ORR), complete response or greater (≥CR), time to progression (TTP) and safety outcomes.

The objective of this section is to summarize and critically appraise the methods and results of the performed NMA, in NDMM patients who are ineligible for ASCT, in order to inform the pCODR clinical and economic evaluations of daratumumab in combination with lenalidomide and dexamethasone.

### 7.1.2 Methods

#### Systematic Review

The evidence informing the NMA was identified through a systematic review conducted in front-line MM to discover available treatments for this indication in June 2017. An update of

the SLR was conducted in June 2018 (conference abstracts September 2018) and a second update January 2019. The following databases were searched: PubMed, EMBASE, Cochrane, The American Society of Haematology (ASH), American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO). Additional meta-analyses/reviews and ClinicalTrials.gov were further searched for potential publications that were not included in the search engines. The original SLR and SLR update identified 77 studies covering 34 trials. For the NMA reported in this document, only trials that have reported efficacy and safety data in manuscripts have been included. Hence, trials for which results were only reported conference proceedings were excluded in the NMA. Not all studies observed in the SLR were by default included in NMA. Rationale for that could be disconnectivity to the network, or not reporting from the endpoints or interest.

The methods used for the systematic review followed PRISMA guidelines for reporting and appeared comprehensive. Details were provided on the inclusion criteria used for the review and the specific evidence sources searched (i.e., data bases, conference proceedings, hand searches). However, information on the literature search strategies, the methods used for trial selection (i.e., independent reviewers, with discrepancies adjudicated by a third reviewer) and information on data extraction (i.e., prospectively determined data fields) were not included within the submitted report. The quality of the observed trials in the SLR was assessed by the Cochrane risk of bias tool and the ISPOR questionnaire and the results of these assessments were provided.

**NMA methodology**

A Bayesian NMA was conducted based on the studies collected in the SLR for which trial results were reported in a full publication. The NMA analyses use the ALCYONE[27] data-cut from June 2018, and the MAIA data-cut from November 2018.[32] All NMAs were conducted in BUGS (WinBUGS, OpenBUGS or MultiBUGS), and the $I^2$- tests were conducted in Cran-R.[32] Homogeneity, similarity, and consistency were tested and both fixed (FE) and random effects (RE) models were considered for all the outcomes. The choice between fixed and random effects models was based on deviance information criterion (DIC) score and/or the presence of observed heterogeneity in the network. The random effects model for PFS and OS were selected because of the heterogeneity observed in the networks. [redacted]

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**NMA Results**

A total of 77 publications, describing 34 RCTS were identified in the Systematic review. The Sponsor has noted that though Bortezomib plus Rd (VRd) is recommended as a preferred treatment option for Newly diagnosed MM patients, data on exclusively transplant ineligible population is not currently available and therefore it was not included in the NMA. Upon

request from CADTH, the Sponsor provided a sensitivity analysis with VRd included. The information can be found in section 7.2.

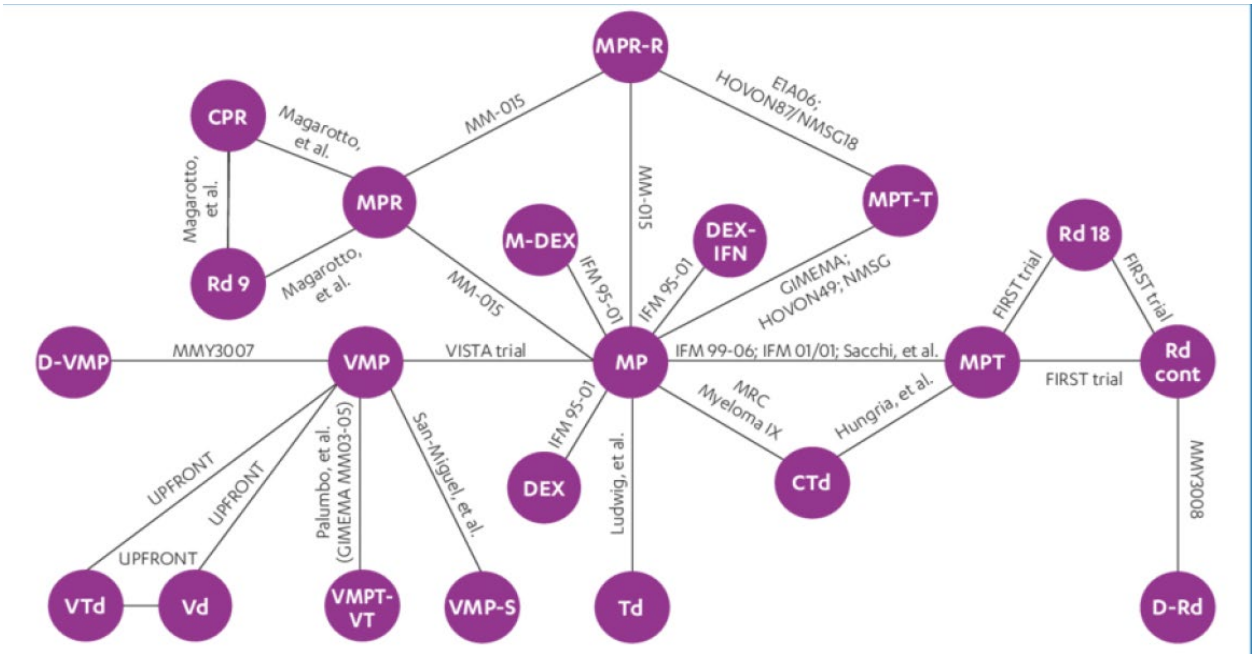
## Efficacy

### Progression-free survival (PFS)

PFS data were reported in 21 trials and Figure 6 shows the PFS evidence network diagram.[33] While the definitions of PFS varied slightly among the trials, the authors noted this to have little impact on the results.

Daratumumab based regimens were noted to have the highest probabilities of being more effective than Rd continuous (Figure 7). Specifically, DRd showed a HR of 0.55 (95% CrI, 0.31-0.97) and D-VMP an HR of 0.59 (95% CrI, 0.2-1.64). DARA-based regimens had the highest probabilities of being more effective than Rd continuous.

**Figure 6. NMA network diagram for PFS**

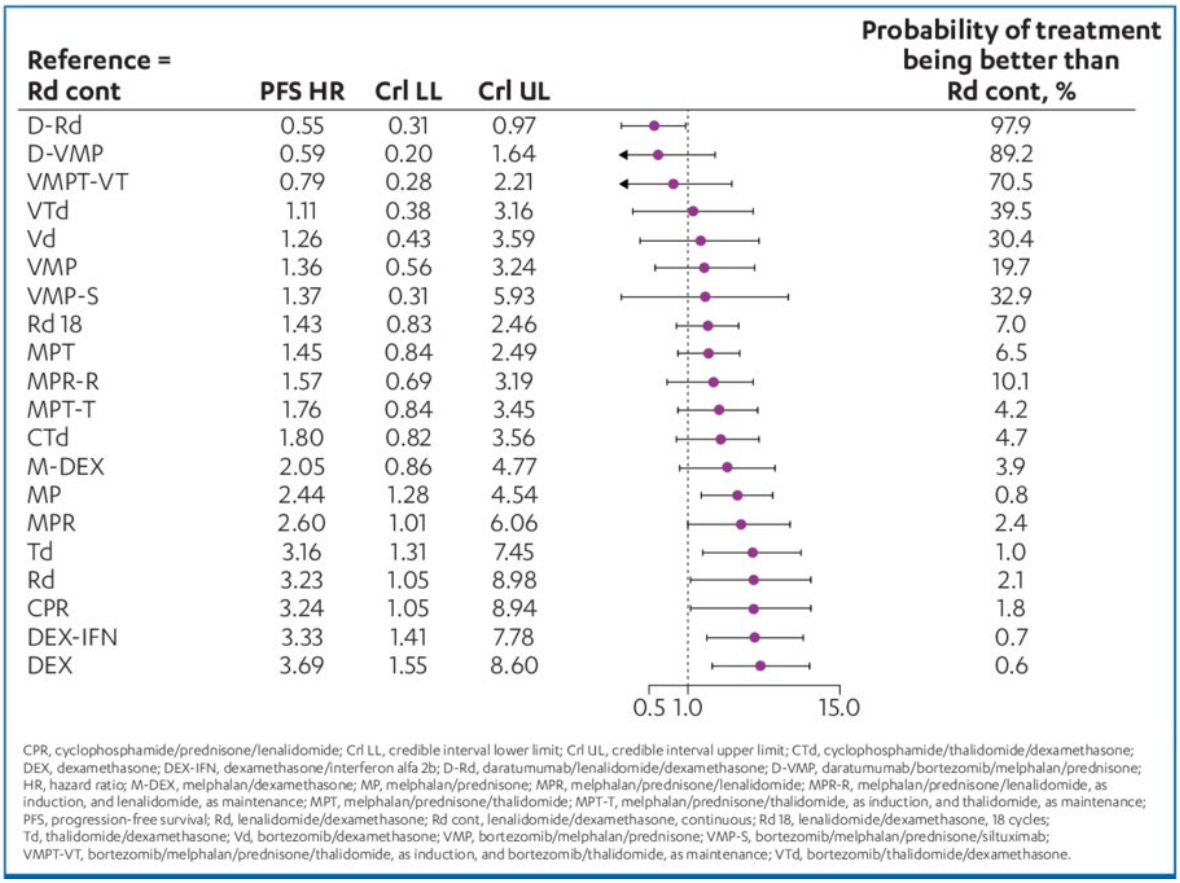



CPR, cyclophosphamide/prednisone/lenalidomide; CTd, cyclophosphamide/thalidomide/dexamethasone; DEX, dexamethasone; DEX-IFN, dexamethasone/interferon alfa 2b; D-Rd, daratumumab/lenalidomide/dexamethasone; D-VMP, daratumumab/bortezomib/melphalan/prednisone; M-DEX, melphalan/dexamethasone; MP, melphalan/prednisone; MPR, melphalan/prednisone/lenalidomide; MPR-R, melphalan/prednisone/lenalidomide, as induction, and lenalidomide, as maintenance; MPT, melphalan/prednisone/thalidomide; MPT-T, melphalan/prednisone/thalidomide, as induction, and thalidomide, as maintenance; PFS, progression-free survival; Rd cont, lenalidomide/dexamethasone, continuous; Rd 9, lenalidomide/dexamethasone, 9 cycles; Rd 18, lenalidomide/dexamethasone, 18 cycles; Td, thalidomide/dexamethasone; Vd, bortezomib/dexamethasone; VMP, bortezomib/melphalan/prednisone; VMP-S, bortezomib/melphalan/prednisone/siltuximab; VMPT-VT, bortezomib/melphalan/prednisone/thalidomide, as induction, and bortezomib/thalidomide, as maintenance; VTd, bortezomib/thalidomide/dexamethasone.

**Figure 1. Evidence network for PFS.**

Source: Janssen's Inc. NMA[33]

**Figure 7. Results of NMA for PFS[33]**




Source: Janssen's Inc. NMA[33]

## Overall Survival (OS)

Twenty-one trials were included in the analysis and the network of evidence for OS is presented in Figure 8.[32] Compared to reference treatment Rd continuous, DRd showed an HR of [redacted][CrI95% [redacted]] and D-VMP a HR of [redacted][CrI95% [redacted]][32] (Figure 9). *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.*

## Figure 8. NMA network diagram for OS

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

## Figure 9. Results of NMA for OS [32]

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

Source: Janssen's Inc. NMA[33]

### Overall Response Rate (ORR)

For ORR, 21 trial were included in the analysis. Figure 10 shows the ORR evidence network diagram. DARA-based regimens had the highest probabilities of being more effective than Rd continuous. DRd has the highest probability to be the best treatment option followed by D-VMP. Compared to reference treatment Rd continuous, DRd showed an OR of 3.05 [CrI95% 1.91-4.99] and D-VMP a OR of 1.83 [CrI95% 0.92-3.67][33] (Figure 11). [redacted]

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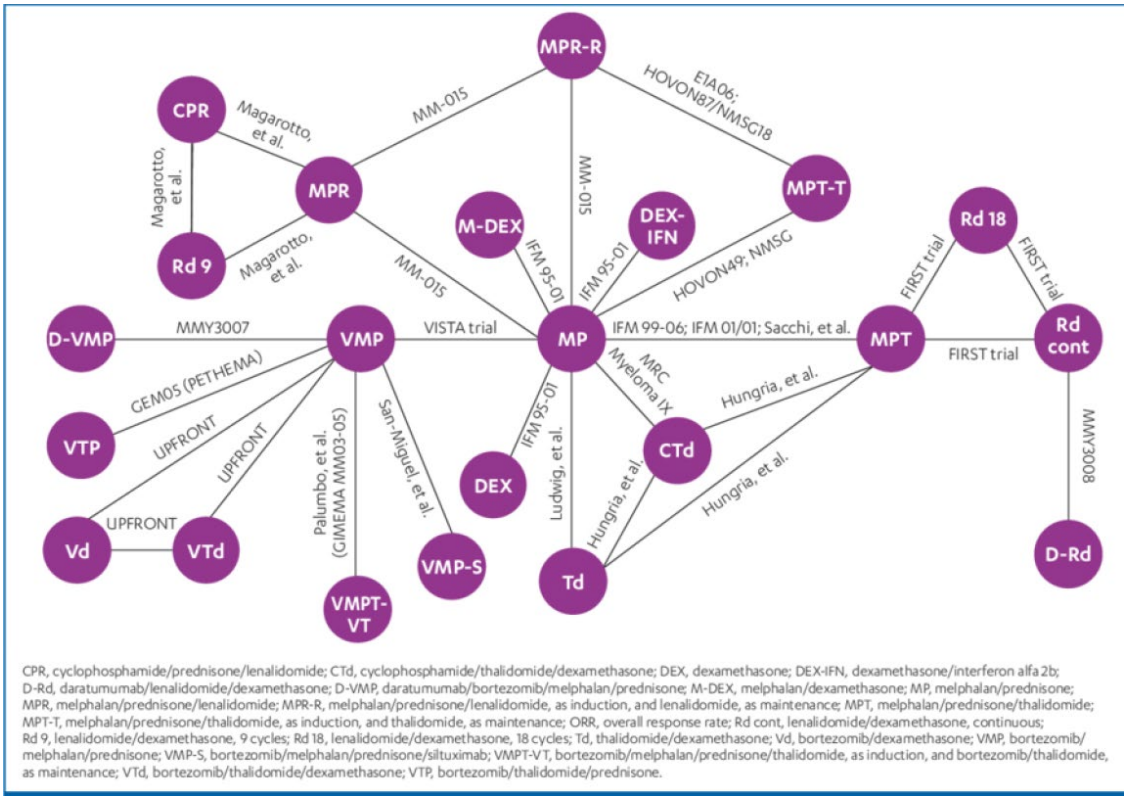
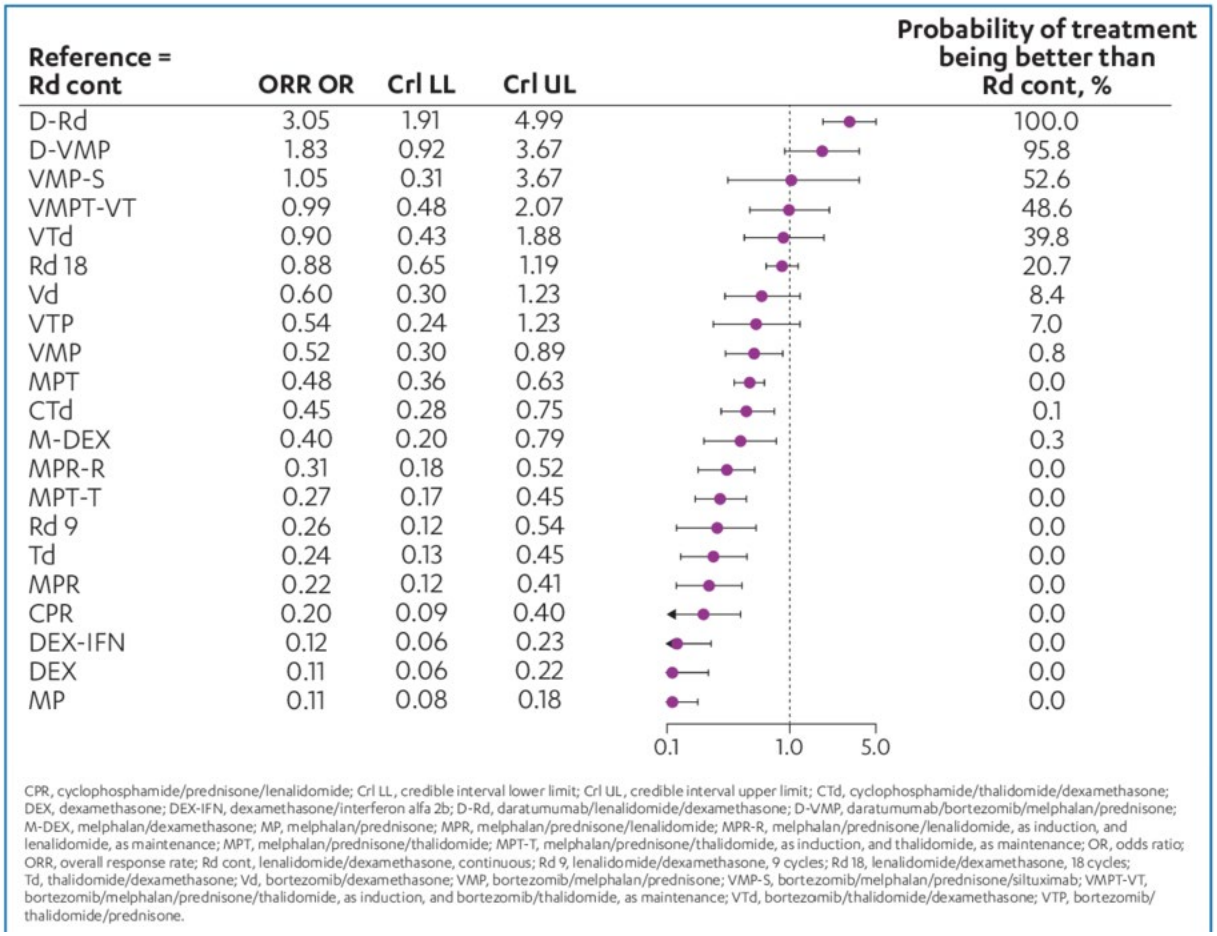
**Figure 10. NMA network diagram for ORR[33]**




CPR, cyclophosphamide/prednisone/lenalidomide; CTd, cyclophosphamide/thalidomide/dexamethasone; DEX, dexamethasone; DEX-IFN, dexamethasone/interferon alfa 2b; D-Rd, daratumumab/lenalidomide/dexamethasone; D-VMP, daratumumab/bortezomib/melphalan/prednisone; M-DEX, melphalan/dexamethasone; MP, melphalan/prednisone; MPR, melphalan/prednisone/lenalidomide; MPR-R, melphalan/prednisone/lenalidomide, as induction, and lenalidomide, as maintenance; MPT, melphalan/prednisone/thalidomide; MPT-T, melphalan/prednisone/thalidomide, as induction, and thalidomide, as maintenance; ORR, overall response rate; Rd cont, lenalidomide/dexamethasone, continuous; Rd 9, lenalidomide/dexamethasone, 9 cycles; Rd 18, lenalidomide/dexamethasone, 18 cycles; Td, thalidomide/dexamethasone; Vd, bortezomib/dexamethasone; VMP, bortezomib/melphalan/prednisone; VMP-S, bortezomib/melphalan/prednisone/siltuximab; VMPT-VT, bortezomib/melphalan/prednisone/thalidomide, as induction, and bortezomib/thalidomide, as maintenance; VTd, bortezomib/thalidomide/dexamethasone; VTP, bortezomib/thalidomide/prednisone.

Source: Janssen's Inc. NMA[33]

**Figure 11. Results of NMA for ORR[33]**



| Reference = Rd cont | ORR OR | CrI LL | CrI UL | Probability of treatment being better than Rd cont, % |
|---|---|---|---|---|
| D-Rd | 3.05 | 1.91 | 4.99 | 100.0 |
| D-VMP | 1.83 | 0.92 | 3.67 | 95.8 |
| VMP-S | 1.05 | 0.31 | 3.67 | 52.6 |
| VMPT-VT | 0.99 | 0.48 | 2.07 | 48.6 |
| VTd | 0.90 | 0.43 | 1.88 | 39.8 |
| Rd 18 | 0.88 | 0.65 | 1.19 | 20.7 |
| Vd | 0.60 | 0.30 | 1.23 | 8.4 |
| VTP | 0.54 | 0.24 | 1.23 | 7.0 |
| VMP | 0.52 | 0.30 | 0.89 | 0.8 |
| MPT | 0.48 | 0.36 | 0.63 | 0.0 |
| CTd | 0.45 | 0.28 | 0.75 | 0.1 |
| M-DEX | 0.40 | 0.20 | 0.79 | 0.3 |
| MPR-R | 0.31 | 0.18 | 0.52 | 0.0 |
| MPT-T | 0.27 | 0.17 | 0.45 | 0.0 |
| Rd 9 | 0.26 | 0.12 | 0.54 | 0.0 |
| Td | 0.24 | 0.13 | 0.45 | 0.0 |
| MPR | 0.22 | 0.12 | 0.41 | 0.0 |
| CPR | 0.20 | 0.09 | 0.40 | 0.0 |
| DEX-IFN | 0.12 | 0.06 | 0.23 | 0.0 |
| DEX | 0.11 | 0.06 | 0.22 | 0.0 |
| MP | 0.11 | 0.08 | 0.18 | 0.0 |



CPR, cyclophosphamide/prednisone/lenalidomide; CrI LL, credible interval lower limit; CrI UL, credible interval upper limit; CTd, cyclophosphamide/thalidomide/dexamethasone; DEX, dexamethasone; DEX-IFN, dexamethasone/interferon alfa 2b; D-Rd, daratumumab/lenalidomide/dexamethasone; D-VMP, daratumumab/bortezomib/melphalan/prednisone; M-DEX, melphalan/dexamethasone; MP, melphalan/prednisone; MPR, melphalan/prednisone/lenalidomide; MPR-R, melphalan/prednisone/lenalidomide, as induction, and lenalidomide, as maintenance; MPT, melphalan/prednisone/thalidomide; MPT-T, melphalan/prednisone/thalidomide, as induction, and thalidomide, as maintenance; OR, odds ratio; ORR, overall response rate; Rd cont, lenalidomide/dexamethasone, continuous; Rd 9, lenalidomide/dexamethasone, 9 cycles; Rd 18, lenalidomide/dexamethasone, 18 cycles; Td, thalidomide/dexamethasone; Vd, bortezomib/dexamethasone; VMP, bortezomib/melphalan/prednisone; VMP-S, bortezomib/melphalan/prednisone/siltuximab; VMPT-VT, bortezomib/melphalan/prednisone/thalidomide, as induction, and bortezomib/thalidomide, as maintenance; VTd, bortezomib/thalidomide/dexamethasone; VTP, bortezomib/thalidomide/prednisone.

Source: Janssen's Inc. NMA[33]

## Discontinuation due to Adverse Events

Regarding the outcome of discontinuation due to adverse events, D-VMP showed the highest probability of being the best treatment option followed by VD. DRd scored third best in terms of discontinuation due to adverse events, with a probability of being ranked first of approximately [redacted].The Odds Ratio (OR) of DRd compared to Rd continuous is [redacted][32] . Peripheral neuropathy grade 3 -4, anemia grade 3-4, thrombocytopenia grade 3-4, pneumonia grade 3-4, neutropenia grade 3-4, and neutropenia grade 3-4 were noted as specific AEs of interest. *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30,, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.*

Based on the NMA ranking, [redacted]. *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.*

[redacted][32] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.*

[redacted].[32] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.*

[redacted].[32] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.*

## Critical Appraisal of NMA

The quality of the Sponsor-submitted NMA was assessed according to the 2014 ISPOR (International Society of Pharmacoeconomics and Outcomes Research) Task Force Indirect Comparison/Network Meta-analysis Study Questionnaire. [6] The questionnaire items were scored with yes/no/not reported or applicable and discussed in a narrative summary. A summary of the quality assessment is provided in Table 10.

Overall, the reporting of the methods used to conduct both the systematic review and meta-analyses were, for the most part, clear and comprehensive. Both FE and RE models were fitted on the available data per endpoint, although both are not presented in the report. The goodness of fit was assessed using the deviance information criterion (DIC). The model with the lowest DIC score was considered as the best fit on the data [redacted] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.*

For the NMAs on OS and PFS, the PH assumption was assumed to hold. [redacted].[33] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.*, the current results should be interpreted with caution.

**Table 10. ISPOR Questionnaire[6] to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis.[†]**

| ISPOR Questions[†] | Details and Comments |
|---|---|
| 1. Is the population relevant? | **Yes.** [redacted] |
| 2. Are any critical interventions missing? | **Yes.** [redacted] |
| 3. Are any relevant outcomes missing? | **Yes.** [redacted] |
| 4. Is the context (e.g., settings and circumstances) applicable to your population? | **Yes.** |
| 5. Did the researchers attempt to identify and include all relevant randomized controlled trials? | **Yes.** [redacted] |
| 6. Do the trials for the interventions of interest form one connected network of randomized controlled trials? | **Yes.** |
| 7. Is it apparent that poor quality studies were included thereby leading to bias? | **Unclear.** [redacted] |
| 8. Is it likely that bias was induced by selective reporting of outcomes in the studies? | **No.** [redacted] |
| 9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network? | **Yes.** [redacted] |
| 10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results? | [redacted] |
| 11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons) | **Yes.** [redacted] |
| 12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in | **Yes.** |

| ISPOR Questions† | Details and Comments |
|---|---|
| treatment effects (i.e. consistency) evaluated or discussed? | |
| 13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis? | **Yes.** |
| 14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis? | **Unclear.** [redacted] |
| 15. Was a valid rationale provided for the use of random effects or fixed effect models? | **No.** [redacted] |
| 16. If a random effects model was used, were assumptions about heterogeneity explored or discussed? | **No.** [redacted] |
| 17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed? | **No.** |
| 18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison? | **Yes.** |
| 19. Are the individual study results reported? | **Yes.** [redacted] |
| 20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis? | **Yes.** |
| 21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty? | **Yes.** [redacted] |
| 22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome? | **Yes.** [redacted] |
| 23. Is the impact of important patient characteristics on treatment effects reported? | **Yes,** [redacted] |
| 24. Are the conclusions fair and balanced? | **Yes.** [redacted] |
| 25. Were there any potential conflicts of interest? | **Unclear** |

| ISPOR Questions† | Details and Comments |
|---|---|
| 26. If yes, were steps taken to address these? | **Unclear** |
| † Adapted from Jansen et al. Indirect Treatment Comparison/Network Meta-Analysis Study Questionnaire to Assess Relevance and Credibility to Inform Health Care Decision Making: An ISPOR-AMCP-NPC Good Practice Task Force Report. | |

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

### 7.1.3 Summary

The network meta-analysis provided by the Sponsor investigated DARA-based regimens compared to other pharmacological interventions for patients with NDMM who are ineligible for ASCT. The Sponsor used these results to estimate the clinical effect between treatments that were not directly compared in RCTs. The results of this NMA were used to inform the Sponsors' economic evaluation. It was summarized and critically appraised using the ISPOR Task Force Indirect Comparison/Network Meta-analysis Study Questionnaire.[6]

[redacted] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.* Considering all these uncertainties and limitations, the conclusions drawn from the NMA should be interpreted with caution.

The NMA was conducted using a Bayesian framework. [redacted]. (Table 11) *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 30, 2020 or until notification by sponsor that it can be publicly disclosed, whichever is earlier.*

**Table 11: Summary of results[32]**

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

## 7.2 Critical Appraisal of Sensitivity Analysis of the previously-conducted NMA[33]

The Sponsor submitted NMA examined D-VMP and D-Rd vs comparators, excluding the SWOG S0777 study (bortezomib/lenalidomide/dexamethasone [VRd]; Durie BG, et al. *Lancet* 2017) as it enrolled both transplant-eligible (TE) and TIE (transplant ineligible) pts, and data for pts

who are TIE only (~50% [aged ≥65 y and frail]) were unavailable. VRd recently received EMA approval for treatment of TIE NDMM based on SWOG S0777, but results specific to TIE patients remain unavailable. At the request of CADTH, the Sponsor provided a sensitivity analysis of the previously-conducted NMA including all pts who received VRd in SWOG S0777 to offer a comprehensive view of the comparative effectiveness of DARA-based treatments in TIE NDMM.

**Methods:**

Based on a systematic literature review conducted through January 2019, both PFS and OS were extracted and synthesized in Bayesian NMAs. Choice of fixed- or random-effects model was based on lowest deviance information criterion (DIC) and/or presence of heterogeneity in the network. Rd continuous was selected as reference, as it was commonly included in guidelines across regions. For PFS and OS, HR <1 indicates the comparison is not in favor of Rd continuous.

**Results:**

Both PFS and OS are reported using the RE model. PFS HR for VRd in the sensitivity analysis was 0.74 (95% credible interval [CrI], 0.42-1.30) compared with Rd continuous, which was consistent with SWOG S0777 (0.71; [96% Wald confidence interval [CI], 0.56-0.91]) and higher than HRs for DRd (0.55; 95% CrI, 0.31-0.97) and D-VMP (0.58; 95% CrI, 0.20-1.62; Table 12). The SWOG S0777 OS HR estimated by Guyot algorithm for patients aged ≥65 y was 0.80 (95% CI, 0.56-1.16). OS HR for VRd in the sensitivity analysis was 0.80 (95% CrI, 0.51-1.26) compared with Rd continuous, which was similar to SWOG S0777 and higher than DRd (0.78; 95% CrI, 0.51-1.18).

**Conclusions and limitations:**

While this updated NMA, with a sensitivity analysis that included VRd, demonstrated favorable efficacy outcomes for DARA-based regimens vs other relevant frontline options for pts with NDMM who TIE are, there are several limitations to note. These include lack of comparative trial data and demographic differences between patients from SWOG-S0777 and those trials of other treatments for patients with NDMM who are ineligible for ASCT that are included in the network. The majority of SWOG S0777 pts are TE (<65 y), who often have better prognoses than TIE pts (≥65 y). These differences result in a violation of the similarity assumption of analysis and therefore represent a significant limitation in comparing efficacy outcomes of the SWOG-S0777 and MAIA trials. As such, results of the sensitivity analysis should be interpreted with caution.

**Table 12: Comparison of PFS and OS Across Treatments[a]**

| Global NMA[b] | | |
|---|---|---|
| | PFS[c]<br>HR (95% CrI) | OS[d]<br>HR (95% CrI) |
| D-Rd | 0.55 (0.31-0.97) | 0.78 (0.51-1.18) |
| D-VMP | 0.58 (0.20-1.62) | NA |
| VRd | 0.74 (0.42-1.30) | 0.80 (0.51-1.26) |
| VMPT-VT | 0.79 (0.27-2.18) | 0.91 (0.47-1.76) |
| Rd18 | 1.43 (0.83-2.45) | 0.98 (0.73-1.32) |
| MPT | 1.45 (0.85-2.47) | 1.28 (0.95-1.74) |
| VMP | 1.35 (0.56-3.20) | 1.29 (0.76-2.22) |

| Global NMA[b] | | |
|---|---|---|
| | PFS[c]<br>HR (95% CrI) | OS[d]<br>HR (95% CrI) |
| VMP-S | 1.35 (0.30-5.76) | NA |
| VTd | 1.10 (0.38-3.09) | 1.42 (0.72-2.79) |
| Vd | 1.25 (0.43-3.51) | 1.44 (0.72-2.84) |
| M-DEX | 2.04 (0.86-4.74) | 1.70 (1.00-2.89) |
| CTd | 1.79 (0.83-3.53) | 1.72 (1.08-2.69) |
| MPR-R | 1.57 (0.70-3.18) | 1.81 (1.15-2.91) |
| MPT-T | 1.75 (0.85-3.42) | 1.92 (1.26-2.93) |
| MP | 2.43 (1.29-4.50) | 2.01 (1.37-2.93) |
| DEX-IFN | 3.33 (1.42-7.68) | 2.07 (1.22-3.52) |
| DEX | 3.68 (1.56-8.49) | 2.16 (1.28-3.62) |
| MPR | 2.61 (1.05-6.09) | 2.36 (1.34-4.17) |
| CPR | 3.28 (1.13-9.04) | 2.75 (1.36-5.50) |
| Rd9 | 3.26 (1.11-9.04) | 2.94 (1.50-5.78) |
| Td | 3.16 (1.32-7.41) | 3.11 (1.74-5.57) |

[a]Presented in order of increasing HR for OS

[b]Reference treatment = Rd continuous.

[c]ITT population.

[d]≥65 years population.

CPR, cyclophosphamide/prednisone/lenalidomide; CrI, credible interval; CTd, cyclophosphamide/thalidomide/dexamethasone; DEX, dexamethasone; DEX-IFN, dexamethasone/interferon alfa 2b; D-Rd, daratumumab/lenalidomide/dexamethasone; D-VMP, daratumumab/bortezomib/melphalan/prednisone; HR, hazard ratio; M-DEX, melphalan/dexamethasone; MP, melphalan/prednisone; MPR, melphalan/prednisone/lenalidomide; MPR-R, melphalan/prednisone/lenalidomide, as induction, and lenalidomide as maintenance; MPT, melphalan/prednisone/thalidomide; MPT-T, melphalan/prednisone/thalidomide, as induction, and thalidomide as maintenance; NA, not available; OS, overall survival; PFS, progression-free survival; Rd9, lenalidomide/dexamethasone, 9 cycles; Rd18, lenalidomide/dexamethasone, 18 cycles; Td, thalidomide/dexamethasone; Vd, bortezomib/dexamethasone; VMP, bortezomib/melphalan/prednisone; VMP-S, bortezomib/melphalan/prednisone/siltuximab; VMPT-VT, bortezomib/melphalan/prednisone/thalidomide, as induction, and bortezomib/thalidomide as maintenance; VRd, bortezomib/lenalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone.

# 8 COMPARISON WITH OTHER LITERATURE

None identified.

# 9 ABOUT THIS DOCUMENT

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

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. The sponsor, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

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

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

# APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

## 1. Literature search via Ovid platform

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

Search Strategy:

| Line # | Search Strategy |
|---|---|
| 1 | (daratumumab* or darzalex* or HuMax-CD38 or HuMaxCD38 or JNJ 54767414 or JNJ54767414 or 4Z63YK6E0E).ti,ab,ot,kf,kw,hw,rn,nm. |
| 2 | exp lenalidomide/ |
| 3 | (revimid* or revlimid* or lenalidomid* or CC-5013 or CC5013 or CDC-501 or CDC501 or "ENMD 0997" or ENMD0097 or HSDB 8220 or HSDB8220 or IMiD 3 or IMiD3 or F0P408N6V4).ti,ab,ot,kf,kw,hw,rn,nm. |
| 4 | 2 or 3 |
| 5 | exp dexamethasone/ |
| 6 | 7S5I7G3JQL.rn,nm. |
| 7 | (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* 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. |
| 8 | 5 or 6 or 7 |
| 9 | 1 and 4 and 8 |
| 10 | (DARADEXALENA or (Rev adj2 Dex)).ti,ab. |
| 11 | (daratumumab* or darzalex* or DARA or DRd or Rd).ti,ab. |
| 12 | (revlimid-dexamethasone or lenalidomide-dexamethasone or len-dex or rev-dex).ti,ab. |
| 13 | 11 and 12 |
| 14 | 10 or 13 |
| 15 | 9 or 14 |
| 16 | 15 use cctr |
| 17 | 15 use medall |
| 18 | 16 or 17 |
| 19 | *daratumumab/ |
| 20 | (daratumumab* or darzalex* or HuMax-CD38 or HuMaxCD38 or JNJ 54767414).ti,ab,kw,dq. |
| 21 | 19 or 20 |
| 22 | *lenalidomide/ |
| 23 | (revimid* or revlimid* or lenalidomide* or CC-5013 or CC5013 or CDC-501 or CDC501 or "ENMD 0997" or ENMD0097 or HSDB 8220 or HSDB8220 or IMiD 3 or IMiD3).ti,ab,kw,dq. |
| 24 | 22 or 23 |
| 25 | *dexamethasone/ |

| | |
|---|---|
| 26 | (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* 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. |
| 27 | 25 or 26 |
| 28 | (DARADEXALENA or (Rev adj2 Dex)).ti,ab. |
| 29 | (daratumumab* or darzalex* or DARA or DRd or Rd).ti,ab. |
| 30 | (revlimid-dexamethasone or lenalidomide-dexamethasone or len-dex or rev-dex).ti,ab. |
| 31 | 29 and 30 |
| 32 | 28 or 31 |

| | |
|---|---|
| 33 | 21 and 24 and 27 |
| 34 | 32 or 33 |
| 35 | 34 use oemezd |
| 36 | 35 not conference abstract.pt. |
| 37 | 18 or 36 |
| 38 | remove duplicates from 37 |
| 39 | 35 and conference abstract.pt. |
| 40 | limit 39 to yr="2014 -Current" |
| 41 | 38 or 40 |
| 42 | limit 41 to english language |

## 2. Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

| Search | Query |
|---|---|
| #18 | Search **#16 AND #17** |
| #17 | Search **publisher[sb]** |
| #16 | Search **#12 OR #15** |
| #15 | Search **#13 OR #14** |
| #14 | Search **(daratumumab*[tiab] OR darzalex*[tiab] OR DARA[tiab] OR RD[tiab]) AND (revlimid-dexamethasone[tiab] OR lenalidomide-dexamethasone[tiab] OR len-dex[tiab] OR rev-dex[tiab])** |
| #13 | Search **DARADEXALENA[tiab] OR Rev/Dex[tiab]** |
| #12 | Search **#1 AND #2 AND #11** |
| #11 | Search **#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10** |
| #10 | 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 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]** |
| #9 | 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]** |
| #8 | 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]** |

| Search | Query |
|---|---|
| | **OR fortecortin* OR gammacorten* OR grosodexon*[tiab] OR hexadecadiol*[tiab] OR hexadecadrol*[tiab] OR hexadiol*[tiab]** |
| #7 | 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]** |
| #6 | 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]** |
| #5 | Search **"de-sone Ia"[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]** |
| #4 | 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]** |
| #3 | Search **Dexamethasone[mh] OR 7S5I7G3JQL[rn]** |
| #2 | Search **Lenalidomide[mh] OR F0P408N6V4[rn] OR Revlimid*[tiab] OR Revimid*[tiab] OR lenalidomid*[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]** |
| #1 | Search **daratumumab*[tiab] OR darzalex*[tiab] OR HuMax-CD38[tiab] OR HuMaxCD38[tiab] OR JNJ 54767414[tiab] OR JNJ54767414[tiab] OR 4Z63YK6E0E[rn]** |

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

**4.** Grey literature search via**:**

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

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

Search: darzalex (daratumumab)/ lenalidomide / dexamethasone (DRd), multiple myeloma

Select international agencies including:

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

European Medicines Agency (EMA)
https://www.ema.europa.eu/
Search: darzalex (daratumumab)/ lenalidomide / dexamethasone (DRd), multiple myeloma

Conference abstracts:

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

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

Search: darzalex (daratumumab)/ lenalidomide / dexamethasone (DRd), multiple myeloma

**Detailed Methodology**

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[34]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946– ) via Ovid, Embase (1974– ) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were darzalex (daratumumab), lenalidomide and dexamethasone.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of November 28, 2019.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[35] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov and Canadian Partnership Against Cancer Corporation's 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) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

## Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. 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.

### Quality Assessment

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

### Data Analysis

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

### Writing of the Review Report

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

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

## REFERENCES


1. Darzalex (daratumumab): 20mg/mL concentrate for solution for infusion [product monograph]. Toronto (ON): Janssen Inc.; 2019 Oct 25.
2. Facon T, Kumar S, Plesner T, et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N Engl J Med*. 2019;380(22):2104-2115.
3. pan-Canadian Oncology Drug Review sponsor submission: darzalex (daratumumab) 20mg/mL concentrate for solution for infusion. Janssen Inc. Toronto (ON): Janssen Inc.; 2019 Jul 17.
4. Janssen Inc. response to pCODR checkpoint meeting questions on darzalex (daratumumab) for newly diagnosed multiple myeloma. Toronto (ON): Janssen Inc.; 2019 Sep 30.
5. Perrot A, Facon T, Plesner T, Usmani SZ, Kumar S, Bahlis NJ. Faster and sustained improvement in health-related quality of life for newly diagnosed multiple myeloma (NDMM) patients ineligible for transplant treated with daratumumab, lenalidomide, and dexamethasone (D-Rd) vs Rd alone: MAIA. Paper presented at: ASCO2019; Chicago.
6. Jansen J, Trikalinos T, Cappelleri J, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health*. 2014;17(2):157-173.
7. Jimenez-Zepeda VH, Duggan P, Neri P, Tay J, Bahlis NJ. Bortezomib-containing regimens (BCR) for the treatment of non-transplant eligible multiple myeloma. *Ann Hematol*. 2017;96(3):431-439.
8. Munshi NC, Avet-Loiseau H, Rawstron AC, et al. Association of minimal residual disease with superior survival outcomes in patients with multiple myeloma: a meta-analysis. *JAMA Oncol*. 2017;3(1):28-35.
9. Barr H, Dempsey J, Waller A, et al. Ninety-minute daratumumab infusion is safe in multiple myeloma. *Leukemia*. 2018;32(11):2495-2518.
10. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15(12):e538-548.
11. Durie BG, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet (london, england)*. 2017;389(10068):519-527.
12. Goldschmidt H, Lokhorst HM, Mai EK, et al. Bortezomib before and after high-dose therapy in myeloma: long-term results from the phase III HOVON-65/GMMG-HD4 trial. *Leukemia*. 2018;32(2):383-390.
13. Canadian Cancer Statistics Advisory Committee. Canadian cancer statistics: a 2018 special report on cancer incidence by stage. Toronto (ON): Canadian Cancer Society; 2018: http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2018-EN.pdf?la=en. Accessed 2019 June 12.
14. Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. *J Clin Oncol*. 2005;23(15):3412-3420.
15. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. *J Clin Oncol*. 2015;33(26):2863-2869.
16. Cejalvo MJ, de la Rubia J. Clinical treatment of newly diagnosed multiple myeloma. *Expert Rev Hematol*. 2015;8(5):595-611.
17. McCarthy PL, Holstein SA, Petrucci MT, et al. Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: a meta-analysis. *J Clin Oncol*. 2017;35(29):3279-3289.
18. Rosen LS, Gordon D, Kaminski M, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer*. 2003;98(8):1735-1744.

19. Areethamsirikul N, Masih-Khan E, Chu CM, et al. CyBorD induction therapy in clinical practice. *Bone Marrow Transplant*. 2015;50(3):375-379.
20. Fayers PM, Palumbo A, Hulin C, et al. Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials. *Blood*. 2011;118(5):1239-1247.
21. San Miguel JF, Schlag R, Khuageva NK, et al. Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma. *J Clin Oncol*. 2013;31(4):448-455.
22. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med*. 2008;359(9):906-917.
23. Jimenez-Zepeda V, Reece DE, Arleigh MR, et al. 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. *Blood*. 2018;132(Supplement 1):2008-2008.
24. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. *N Engl J Med*. 2014;371(10):906-917.
25. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;375(14):1319-1331.
26. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *The New England journal of medicine*. 2016;375(8):754-766.
27. Mateos M-V, Dimopoulos MA, Cavo M, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. *N Engl J Med*. 2017;378(6):518-528.
28. Usmani SZ, Facon T, Kumar S, et al. Impact of age on efficacy and safety of daratumumab in combination with lenalidomide and dexamethasone (D-Rd) in patients (pts) with transplant-ineligible newly diagnosed multiple myeloma (NDMM): MAIA. *J Clin Oncol*. 2019;37.
29. Facon T, Kumar SK, Plesner T, et al. Phase 3 randomized study of daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) in patients with newly diagnosed multiple myeloma (NDMM) ineligible for transplant (MAIA). *Blood Conference: 60th Annual Meeting of the American Society of Hematology, ASH*. 2018;132(Suppl. 1).
30. Facon T, Cavo M, Jakubowiak A, et al. Two randomized open-label studies of daratumumab (DARA) plus standard of care treatment versus standard of care alone in patients with previously untreated multiple myeloma (MM) ineligible for high-dose therapy: 54767414MMY3007 (Alcyone) and 54767414MMY3008 (Maia). *Clin Lymphoma Myeloma Leuk*. 2015;15:e294-e295.
31. Janssen Research & Development. NCT02252172: Study comparing daratumumab, lenalidomide, and dexamethasone with lenalidomide and dexamethasone in participants with previously untreated multiple myeloma. *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2014: https://clinicaltrials.gov/ct2/show/NCT02252172. Accessed 2019 Dec 3.
32. Usmani SZ MM, Hungria V, et al. . Greater treatment satisfaction in patients receiving subcutaneous versus intravenous daratumumab for relapse or refractory multiple myeloma: COLUMBA. Paper presented at: 17th International Myeloma Workshop2019; Boston, MA.
33. Daratumumab combination treatement to treat patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation: a network meta-analysis. In: pan-Canadian Oncology Drug Review sponsor submission: darzalex (daratumumab) 20mg/mL concentrate for solution for infusion. Toronto (ON): Janssen Inc.; 2019 Jul 17.
34. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. *J Clin Epidemiol*. 2016;75:40-46.
35. Grey matters: a practical tool for searching health-related grey literature. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/grey-matters. Accessed 2019 Dec 3.