pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Daratumumab (Darzalex) for Multiple Myeloma

October 5, 2017

DISCLAIMER

Not a Substitute for Professional Advice

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

Liability

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

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

FUNDING

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

INQUIRIES

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

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

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

TABLE OF CONTENTS

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 in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy. 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 in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy conducted by the Multiple 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 (if any) 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 and multiple myeloma, a summary of submitted Provincial Advisory Group Input on daratumumab and multiple myeloma, and a summary of submitted Registered Clinician Input on daratumumab and multiple myeloma are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

As stated in the Health Canada Product Monograph, daratumumab is an IgG1κ human monoclonal antibody against CD38 antigen.

On April 13, 2017, daratumumab was issued marketing authorization without conditions by Health Canada. Daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone is indicated for the treatment of patients with multiple myeloma who have received at least one prior therapy.[1]

Daratumumab has also been issued marketing authorization with conditions by Health Canada for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or who are refractory to both a PI and an IMiD.[1]

The recommended dose as it appears in the Health Canada Product Monograph[1] is 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule:

Combination therapy with lenalidomide/dexamethasone (4-week cycle regimens)

Weeks	Schedule
Weeks 1 to 8	weekly (total of 8 doses)
Weeks 9 to 24[a]	every two weeks(total of 8 doses)
Week 25 onwards until disease progression[b]	every four weeks
Notes: [a] First dose of the every 2-week-dosing schedule is given at week 9 [b] First dose of the every 4-week-dosing schedule is given at week 25	

Combination therapy with bortezomib/dexamethasone (3-week cycle regimens)

Weeks	Schedule
Weeks 1 to 9	weekly (total of 9 doses)
Weeks 10 to 24[a]	every three weeks (total of 5 doses)
Week 25 onwards until disease progression[b]	every four weeks
Notes: [a] First dose of the every 3-week dosing schedule is given at week 10 [b] First dose of the every 4-week dosing schedule is given at week 25	

Daratumumab is currently available is in 100mg/5mL and 400mg/20mL vials.[1]

The submitter, Janssen Inc. is requesting funding (similar to its Health Canada indication) for daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

The objective of the systematic review is to evaluate the efficacy and safety of daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two ongoing, open-label randomized phase III studies examining the use of daratumumab with bortezomib and dexamethasone versus bortezomib and dexamethasone alone (CASTOR) and daratumumab with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone (POLLUX) in patients with multiple myeloma who had received one or more previous lines of therapy. Patients in both trials were randomized in a 1:1 ratio and stratified by disease stage, number of previous lines of therapy, and whether they were previously treated with bortezomib or lenalidomide. A total of 498 patients were randomized in the CASTOR trial and 569 in the POLLUX trial. Both were trials conducted in multiple international centres but only the POLLUX trial included 10 Canadian centres that spanned 5 provinces. Both trials were superiority trials aimed at demonstrating that the addition of daratumumab can reduce the risk of disease progression or death.[5,10]

Eligibility criteria were similar for both trials: patients must have had documented multiple myeloma, have received at least one previous line of therapy, and have documented evidence of progressive disease. Further, patients must have achieved a partial response or better to at least 1 prior treatment regimen. The median age of patients in the CASTOR trial was 64 years in both treatment arms. The median number of previous lines of therapy was 2, with a range of 1 to 10. Baseline characteristics were well balanced in the both trials. In the POLLUX trial, the median age in both study arms was 65 and the median number of previous lines of therapy for both groups was 1 (range, 1-11).[5,10]

One potential limitation in both the CASTOR and POLLUX trials is the open-label design, where investigators and patients were not blinded to treatment assignment. This introduces a number of biases that can affect the internal validity of the trial and thereby exaggerate the treatment effect. Another concern is that at present, only interim data are available for efficacy and safety considerations and as such, these data should be interpreted with some degree of caution.

The primary outcome for both CASTOR and POLLUX was progression-free survival (PFS), defined as the duration from the date of randomization to either progressive disease or death, whichever occurred first. At the interim analysis for the CASTOR trial, the addition of daratumumab to bortezomib + dexamethasone resulted in a significantly better median PFS compared with bortezomib + dexamethasone alone (not estimable versus 7.16 months; hazard ratio 0.39, $p<0.0001$). The rate of PFS at 12 months was 60.7% in the daratumumab group versus 26.9% in the control group. In the POLLUX trial, the interim analysis demonstrated a 63% reduction in the risk of disease progression in those who received daratumumab + lenalidomide + dexamethasone compared to those who did not receive daratumumab (HR 0.37; 95% CI 0.27 to 0.51, $p<0.001$). The median PFS for the treatment arm has not been reached compared with an estimated PFS of 18.4 months in patients who received lenalidomide + dexamethasone alone.[5,10]

Analyses of the most common Grade 3 or 4 adverse events in the safety population of the CASTOR trial demonstrate that patients in the daratumumab arm experienced a higher rate of such events than the control group (76.1% versus 62.4%, respectively). The most commonly observed events in both groups were thrombocytopenia, anemia, and neutropenia. Similar results were observed in the POLLUX trial, with more patients in the daratumumab arm experiencing Grade 3/4 adverse events than control patients. 45.3% of patients receiving daratumumab in the CASTOR trial and 47.7% of patients receiving daratumumab in the POLLUX trial experienced an infusion-related reaction of any grade, with the majority of reactions occurring during the first infusion. These reactions were

primarily Grade 1 or 2 events, with dyspnea and cough being among the more commonly reported events. Key efficacy and harm data are summarized in Table 1 below.[5,10]

Table 1: Summary of key efficacy outcomes in included trials of daratumumab in combination with bortezomib + dexamethasone or lenalidomide + dexamethasone as subsequent treatment in patients with relapsed or refractory multiple myeloma.

	CASTOR		*POLLUX*	
	DVd Arm (N= 251)	**Vd Arm (N= 247)**	**DRd Arm (N= 286)**	**Rd Arm (N= 283)**
Median follow-up, months	**7.4**		**13.5**	
Treatment Groups	**DVd Arm (n=251)**	**Vd Arm (n=247)**	**DRd Arm (n=286)**	**Rd Arm (n=283)**
Median Follow-up (months)	7.4		13.5	
Primary Outcome – PFS (no. of PFS events, %)	67 (26.7)	122 (49.4)	53 (18.5)	116 (41.0)
Median PFS, months (95% CI)	NE (12.25-NE)	7.16 (6.21-7.85)	NE	18.4 (13.86-NE)
HR (95% CI; p-value)	0.39 (0.28-0.53; p<0.0001)		0.37 (0.27-0.51)	
Secondary Outcome – Overall Response Rate (no. with response)	199	148	261	211
ORR (%, 95% CI) (p value)	82.9 (77.5-87.5)	63.2 (56.7-69.4)	92.9 (89.2-95.6)	76.4 (71.0-81.3)
Difference (95%CI)				
Harms Outcome, %	**DVd Arm (N=243)**	**Vd Arm (N=237)**	**DRd Arm (N=283)**	**Rd Arm (N=281)**
Grade ≥3	76.1%	62.4%		
WDAE	7.4%	9.3%	6.7%	7.8%

Abbreviations: AE = adverse event, **CI =** confidence interval, **HR =** hazard ratio, **NR** = not reported, **ORR** – overall response rate, **TRAE** = treatment-related adverse event, **WDAE** = withdrawal due to adverse event
*HR < 1 favours [arm]

1.2.2 Additional Evidence

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

Patient Advocacy Group

From a patient's perspective, infections, followed by kidney problems, mobility, pain, fatigue, neuropathy, and shortness of breath are important aspects of myeloma to control. The ability to work, followed by the ability to exercise, travel, volunteer, concentrate, conduct household chores, fulfill family obligations, and spend time with family are symptoms associated with myeloma that impact or limit day-to-day activity and quality of life. According to Myeloma Canada, when it comes to treating myeloma, it is important for patients: to maintain quality of life or normal life, manage/minimize side effects, control the disease, have access to effective treatments, control symptoms, achieve or maintain remission, and prolong survival, among others. Patients' expectations for the daratumumab as per the combination under review were as follows: prolonged life, disease control, and remission. Fewer side effects than other treatments was ranked as the last attribute. The same patients indicated that the following expectations were

fulfilled by daratumumab: disease control, remission and fewer side effects than previous treatments.

Of the patients that reported positive and negative outcomes experienced with daratumumab, about half shared it was managing their disease and two indicated the side effects were minimal. Most respondents who had experience with daratumumab as per the combinations under review either had a 'fair quality of life" 27.3% (3/11), "good quality of life" 45.5% (5/11) or "very good quality of life" 27.3% (3/11).

Provincial Advisory Group (PAG)

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

Clinical factors:

- Clarity on patient groups eligible for treatment

Economic factors:

- Drug wastage
- Pre-medication prior to each infusion
- Unknown and variable treatment duration
-

Registered Clinician Input

One clinician input was provided as a joint submission from ten clinicians. The clinicians providing input identified that overall, triplet combination therapy is superior to current therapies as triplet combination therapy provides a marked improvement in progression-free survival and likely improvement in overall survival. They noted that daratumumab triplet combinations have a deeper response, a higher response rate and longer duration of response and thus, would likely replace the current dual combination therapies.

Summary of Supplemental Questions

In addition, one supplemental question was identified during the review as relevant to the pCODR review of daratumumab plus lenalidomide/bortezomib and dexamethasone and is discussed as supporting information:

- Critical appraisal of the network meta-analysis between daratumumab plus lenalidomide or bortezomib plus dexamethasone to carfilzomib plus lenalidomide plus dexamethasone

The objectives of the Submitters' NMA were to compare daratumumab-combination treatments (lenalidomide or bortezomib plus dexamethasone) in patients with multiple myeloma who have received at least one prior therapy to:

- Carfilzomib-combination regimens.

A Bayesian approach was conducted for the NMA. Hazard ratios (HR) were used to measure the relative efficacy for time-to-event endpoints (PFS and OS) in the NMA. To match available daratumumab trial results near the 18-month follow up time point available for POLLUX[2] and 13 months for CASTOR,[6] data from other trials were selected as close as possible to this period. The Manufacturer conducted a systematic literature review to identify eligible studies for the NMA. Four trials were included in the NMA: two for the Rd-based network and two for the Vd-based network. The Rd-based network included the RCTs POLLUX (MMY3003) and ASPIRE. The

Vd-based network included the RCTs CASTOR (MMY3004) and ENDEAVOR.[7] No RCT evidence was available to allow a common comparator to join the two networks.

The Methods team assessed the quality of the evidence NMA according to the recommendations made by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task. The results of the NMA for the Rd-based network indicated that treatment with daratumumab+lenalidomide+dexamethasone was associated with improvement on PFS (HR: 0.54, 95% CrI: 0.37 to 0.78) as compared to carfilzomib+lenalidomide+dexamethasone. However, the results for overall survival were not statistically significant, given that the credible intervals cross one (HR: 0.80, 95% CrI: 0.50 to 1.28). The results of the NMA for the Vd-based network indicated that treatment with daratumumab+bortezomib+dexamethasone was associated with improvement on PFS (HR: 0.62, 95% CrI: 0.45 to 0.86) as compared to carfilzomib +dexamethasone. However, the results for overall survival were not statistically significant, given that the credible intervals cross one (HR: 0.80, 95% CrI: 0.48 to 1.34).

The Bucher method of indirect comparison assumes that the relative effectiveness of a treatment is the same across all trials used in the comparison. In order for this assumption of generalizability to hold, the populations would need to be comparable. For example, the number of lines of prior therapy were not the same for the population and number of lines of prior therapy is a potential effect modifier. This lack of similarity between populations and the failure to adjust for differences makes it difficult to draw conclusions from this NMA.

The overall conclusions of the NMA were limited because of substantial uncertainty in the estimates given differences in patient characteristics among the included studies, notably the number of previous lines of therapy. Further, other treatment effect modifiers such as previous autologous stem-cell transplant were not reported. Given these limitations, and the lack of statistical adjustment to control for these, the comparative efficacy of daratumumab plus lenalidomide plus dexamethasone to carfilzomib-based regimens is uncertain.

See section 7.1 for more information.

Comparison with Other Literature

The Submitter referenced one study, Felix et al, 2013, that reported that an increase of 2.5 months in overall survival (OS) is expected for each additional month spent in PFS, based on analyses of different multiple myeloma trials.[8] The submitter referenced this paper to support PFS as a surrogate for OS to support their base case results of the submitted model. The submitter maintains that truncating the treatment benefit at the *end* of the trial follow-up period is not reflective of clinical reality as they feel that PFS is predictive of OS (i.e., 1 month of additional PFS leads to 2.5 months of additional OS). Therefore, the critical appraisal of the study by Felix et al was included as the study supports assumptions in the Submitter's cost-effectiveness analysis. Overall, the study by Felix et al. demonstrates the potential value of TDEs (TTP, PFS, and EFS) in predicting OS in patients with MM. Relevant to this CGR, while statistically significant correlation between median PFS and median OS was observed, the clinical relevance is questionable given that daratumumab was not included as one of the treatment options. With the separate mechanism of action of daratumumab, and the lack of outcome data for daratumumab being included in the Felix study, an assumption would be needed that the results in Felix et al, based on other treatments other than daratumumab, can be assumed to be the same for daratumumab. This assumption increases the uncertainty in the results. Caution must also be taken when assessing the predictive value of median TDEs on median OS in patients with relapsed/refractory or advanced MM, given that the majority of patients in the study by Felix et al had newly diagnosed MM or were treatment naïve (67.6%). It should also be noted that while Felix et al. report a significant correlation between the TDEs assessed and OS, their analysis was based on aggregate as opposed to individual patient-level data which would be more reliable in predicting OS. Further, including all experimental and observational prospective studies does not allow for comparisons between treatments, which

may have been possible had they conducted an additional analysis limiting to randomized controlled trials that preserved the randomized comparisons within each trial. Felix et al also concede that other assessments of potential surrogate endpoints require a two-step process which is described elsewhere.[9] These factors, combined, leads to uncertainty in the reported claim that there is an increase of 2.5 months in median OS for each additional month in median PFS, even despite the adjustments made for several covariables.

See section 8 for more information.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2.2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for daratumumab for the treatment of patients with multiple myeloma who have received at least one prior therapy.				
Domain	**Factor**	**Evidence**	**Generalizability Question**	**CGP Assessment of Generalizability**
Population	ECOG performance status	Included patients had ECOG PS of 0,1, or 2	Are the results generalizable to patients with an ECOG PS of ≥3? Is there any evidence of a differential effect based on PS?	It would depend on the reason for the poor PS. If the PS was poor as a result of multiple myeloma it might improve with better disease control, whereas patients with poor PS due to other medical conditions may not derive as much benefit. Eligibility should be assessed on a case by case basis.
	Only a small proportion of patients in both trials were ≥75 years	CASTOR: Median age in both arms was 64 (range in DVd arm was 30-88 and in Vd arm was 33-85); 9.2% and 14.2% of pts were ≥75 years, in DVd and Vd arms, respectively POLLUX: Median age in both arms was 65 (range in DRd arm was 34-89 and in Rd arm was 42-87); 10.1% and 12.4% of pts were ≥75 years in DRd and Rd arms, respectively	Are the results of the CASTOR and POLLUX trials generalizable to patients with advanced age (≥75 years)?	Treatment decisions in oncology are complex and should never be based on a single factor such as age. The studies did not specifically exclude patients from treatment on the basis of age and patients over the age of 75 were included in the study populations and so these patients should be eligible to receive daratumumab if their physician feels that is the best treatment for them. Patients in clinical trials are on average younger than the general disease population, which complicates generalizability into older adults.
	Patients with standard risk vs. high risk cytogenetic profile	The majority of patients in both trials had a standard risk cytogenetic profile	Are the results of the trials generalizable to pts with high risk cytogenetic abnormalities?	It is unclear from the results of the identified studies how well patients with high-risk disease respond to daratumumab. It is expected, however, that responses to novel agent-daratumumab combinations will be superior to novel agents alone in high-risk patients. The degree of benefit is uncertain based on the data available.
	Most patients had only one previous line of therapy	The trials did not include newly diagnosed patients	Are the results generalizable to patients with newly diagnosed MM?	No. There are other ongoing trials to assess daratumumab's efficacy in newly diagnosed MM patients.

Intervention	Both CASTOR and POLLUX demonstrated that the intervention arms were superior to the control arms	There is no head-to-head comparison of DVd versus DRd	Do the results of the CASTOR and POLLUX trials provide enough evidence to support the preference of one daratumumab combination regimen over the other (DVd vs. DRd)?	No. The available results do not allow a direct comparison of the two regimens. As both regimens demonstrate efficacy there is no preference for one regimen over the other. In practice, the decision of which combination to use in relapsed/refractory multiple myeloma depends on what treatment the patient has already received, response to prior therapies, expected toxicities, comorbidities and funded options in the patient's province.
	Dose of daratumumab was the same in CASTOR and POLLUX but administration schedules were different	CASTOR: daratumumab administered at 16mg/kg IV weekly (days 1, 8, 15) during cycles 1-3, once q3wks (on day 1) during cycles 4-8, and once q4wks thereafter, until patient withdrawal, disease progression or unacceptable toxicity POLLUX: daratumumab administered at 16mg/kg IV weekly (days 1, 8, 15, 22) for 8 weeks during cycles 1-2, q2wks (on days 1 and 15) for 16wks (cycles 3-6), and q4wks thereafter	Is there evidence to support one dosing schedule over the other? Is one of these dosing schedules more generalizable to the Canadian setting?	Given the long half-life of monoclonal antibody-based therapeutics it is unlikely that scheduling would significantly affect the efficacy. Despite the lack of head to head comparison of the two dosing schedules, the CGP's opinion is that there is no reason to believe that the dosing schedule used in CASTOR would lead to different outcomes (i.e. superior/inferior) as the dosing schedule used in POLLUX.
Comparator	No factors identified			
Outcomes	MRD as an outcome	MRD was an outcome reported in the publication of POLLUX but not in publication of CASTOR.	How useful are MRD results in the Canadian setting?	Most Canadian centres do not have access to MRD measures and therefore the MRD results of the POLLUX trial are not of particular value.
Setting	Details of the study settings were not described	CASTOR and POLLUX were multicenter studies that included several countries in Europe, Asia, and North America. Only the POLLUX trial included centers in Canada (in 8 centers across British Columbia, Alberta, Ontario, Quebec, and Nova Scotia).	What is the generalizability of the CASTOR study findings to the Canadian setting?	While not conducted in Canada, the results of the CASTOR trial are likely generalizable to the Canadian setting.
Abbreviations: CGP – Clinical Guidance Panel; DRd – daratumumab + lenalidomide + dexamethasone; DVd – daratumumab + bortezomib + dexamethasone; MM – multiple myeloma; MRD – minimal residual disease; PS – performance status; q – every; Rd – lenalidomide + dexamethasone; Vd – bortezomib + dexamethasone; vs - versus				

1.2.4 Interpretation

Burden of Illness

Multiple myeloma is a bone marrow-based plasma cell malignancy associated with circulating monoclonal immunoglobulins or free light chains. Multiple myeloma represents 1% of new cancer diagnoses and 10-15% of new hematological malignancies. Patients with myeloma frequently present with fractures or renal impairment, and these complications are increasingly frequent as patients progress from newly-diagnosed to chemotherapy-refractory disease. All patients with myeloma eventually relapse and require retreatment. As multiple myeloma is predominantly a disease of older people, new treatments are required that prolong overall and progression-free survival without increasing treatment toxicity.

Treatment of Multiple Myeloma

Prior to the advent of the so-called novel agents treatment of multiple myeloma was based on melphalan-steroid combination. Young, fit patients were eligible for autologous hematopoietic cell transplant with high-dose melphalan. Retreatment was generally required within 18 months and resistance to therapy developed rapidly. Supportive care with bisphosphonates improved survival by decreasing the frequency of pathological fractures but had limited impact on tumor burden.

The addition of proteasome inhibitors (chiefly bortezomib) and immunomodulatory agents (IMIDs, chiefly lenalidomide) to up-front treatment has resulted in dramatic changes to the life expectancy and quality of life of newly-diagnosed patients with multiple myeloma.[12] These agents show highly potent anti-myeloma activity and are relatively non-toxic, at least in comparison with previously-available treatments. Early experience with bortezomib-based chemotherapy demonstrated improved outcomes for patients receiving bortezomib-doxorubicin-dexamethasone compared with those treated with vincristine-doxorubicin-dexamethasone (PAD vs. VAD): Median progression-free survival (35 vs. 28 months, HR 0.75, 95% CI 0.62-0.90, p=0.002) and overall survival (HR 0.77, 95% CI 0.60-1.00, p=0.049) were better with bortezomib-based treatment.[14] Similar results have been noted with lenalidomide-based regimens in newly-diagnosed patients.[15]

Treatment of Relapsed or Refractory Multiple Myeloma

Progression following first-line therapy is associated with acquisition of mutations leading to treatment resistance. This can often be overcome by switching treatment to the alternate first-generation novel agent (from bortezomib to lenalidomide, for instance) or by changing to a second-generation agent (carfilzomib as a second-line proteasome inhibitor, pomalidomide as a second-line IMID). Clonal tiding within the myeloma cell population allows for the successful retreatment of patients with regimens to which they have previously shown resistance.[20] Despite these numerous options for patients with relapsed myeloma, all patients eventually become resistant to therapy and die as a result. Shortening durations of response to subsequent treatments is a significant cause of stress and anxiety for patients with this disease and options to improve progression-free and overall survival in relapsed or refractory multiple myeloma are needed.

Daratumumab is an IgG1k monoclonal antibody directed against CD38, an antigen over-expressed by myeloma plasma cells. Binding of daratumumab to its antigen triggers apoptosis through antibody-dependent cellular cytotoxicity or complement-mediated killing. The Systematic Review identified two studies, CASTOR and POLLUX, which describe the outcome of the addition of daratumumab to standard therapy for patients with relapsed or refractory multiple myeloma. In the CASTOR trial, 498 subjects were randomly allocated to receive daratumumab, bortezomib and dexamethasone or bortezomib and dexamethasone alone.[6] Patients who received daratumumab experienced improved PFS (12 month PFS 60.7% vs. 26.9%, median PFS at 7.4 months NR vs. 7.2 months, HR 0.39, 95% CI 0.28-0.53, p<0.001) and greater depth of response (ORR 79.3% vs. 59.9% with more VGPR or CR in experimental arm) compared with patients who did not receive daratumumab. In the POLLUX trial 569 subjects with relapsed/refractory multiple myeloma were randomly assigned to receive lenalidomide,

dexamethasone and daratumumab or lenalidomide and dexamethasone alone.[3] Treatment with daratumumab was associated with improved PFS (12-month PFS 83.2% vs. 60.1%, HR 0.37, 95% CI 0.27-0.52, p<0.001) and superior response rates (91.3% vs. 74.6%). More patients who received daratumumab experienced CR and CR without detectable minimal residual disease. In both studies toxicity was described as manageable and consisted of thrombocytopenia, neutropenia and infusion reactions. Overall survival was not analyzed in detail in these studies given the short follow-up; long-term survival results are expected to be reported over the next several years.

As per the International Myeloma Working Group (IMWG) criteria[23]:

- Relapsed and refractory myeloma is defined as disease that is nonresponsive while on salvage therapy, or progresses within 60 days of last therapy in patients who have achieved minimal response (MR) or better at some point previously before progressing in their disease course
- Primary refractory myeloma is defined as disease that is nonresponsive in patients who have never achieved a minimal response or better with any therapy
- Relapsed myeloma is defined as previously treated myeloma that progresses and requires the initiation of salvage therapy but does not meet criteria for either "primary refractory myeloma" or "relapsed-and-refractory myeloma" categories.
- Progression is defined as an increase of 25% from the lowest response value in any of the following: Serum M-component (absolute increase must be $\geq$.5 g/dL) and/or Urine M-component (absolute increase must be $\geq$ 200 mg/24 h); or, only in patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); or, only in patients without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be>10%). Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas or development of hypercalcemia that can be attributed solely to the PC proliferative disorder.

Summary

The treatment of multiple myeloma has changed dramatically over the past two decades. Treatment options have multiplied since novel agents were introduced and refinements to chemotherapy and supportive care have led to a marked improvement in overall survival for patients with this disease. Nonetheless multiple myeloma remains an incurable condition that leads to bone marrow failure, renal failure, pathological fractures and poor quality of life. Improved treatment of relapsed disease is expected to lead to overall better results and reduced symptom burden. The results of the systematic review suggest that daratumumab may play an important role in the management of these patients.

The clinical guidance panel noted that patients who previously had lenalidomide or bortezomib and were relapsed and/or refractory were excluded from the CASTOR and POLLUX trials; however from a clinical practice perspective, patients would be allowed daratumumab if they have progressed after 1 line of therapy. The CGP noted that the effect of daratumumab is independent of lenalidomide, bortezomib, and dexamethasone and in their opinion would suggest that daratumumab could be used even if lenalidomide/bortezomib refractory and/or after progression.

The CGP noted a request from PAG for guidance on the use of daratumumab in combination with lenalidomide or bortezomib and dexamethasone in new patients versus prevalent/heavily pre-treated patients. The CGP's opinion is that patients who have had one previous line of therapy, would be eligible for daratumumab+lendalidomide/bortezomib+dexamethasone. Additionally, for patients who have multiple relapses, it is it reasonable for them to be treated with daratumumab + lenalidomide/bortezomib + dexamethasone. The CGP noted that there can be no consensus on the sequencing of therapy and the choice is dependent on: previous line of therapy, previous response(s) to lines of therapy, duration of response, side effects, patient factors, disease factors (e.g. genetics) and access to medications. The clinical guidance panel also noted that patients on low dose lenalidomide

or bortezomib maintenance therapy would be eligible for daratumumab + lenalidomide/bortezomib + dexamethasone.

The CGP noted that all trials included in the network meta-analysis (ASPIRE, POLLUX and CASTOR), included patients who had to have at least one line of therapy, as long as they were not refractory or relapsed on lenalidomide and dexamethasone or bortezomib and dexamethasone. While it is unknown whether the analysis controlled for effect modifiers, the following may be important effect modifiers: age, EGOG performance status, number of lines of previous therapy, cytogenetic profile, refractory disease to last line of therapy, ISS Disease Staging, previous autologous stem-cell transplantation. The population from POLLUX and CASTOR were not clearly less heavily treated than on ASPIRE; however, the CGP noted that the interventions from independent trials informing the network meta-analysis will never fully be comparable by definition and only indirect conclusions can be drawn. Accepting this methodological caveat raised by the NMA appraisal, the PFS and OS with daratumumab is at least as good as, if not better than carfilzomib.

The CGP noted that myeloma community views daratumumab as "game changing". As such, there is possibility that clinicians might alter their 1st line therapies in order for patients to be able to use daratumumab.

1.3 Conclusions

The clinical guidance panel concluded that there is overall net clinical benefit to be derived from the addition of daratumumab to standard therapy for patients with relapsed or refractory multiple myeloma. The panel based this conclusion on the results of two well-conducted randomized, non-blinded studies demonstrating clinically- and statistically-significant improvements in progression-free survival and overall response rates. In reaching this conclusion the panel considered the following:

- The development of highly-active treatment protocols that do not substantially increase toxicity is a high priority for patients with this disease and their physicians (see Patient Advocacy Group report and registered clinician input).
- The comparators used in the studies identified by the systematic review are relevant in the current environment. Other treatments that could be considered in this setting (carfilzomib and pomalidomide) are likely to remain high-cost drugs and will remain on patent for several more years before generic alternatives become available.
- Given the above it is likely that daratumumab in combination with a novel agent will be favored by Canadian physicians. The novel agent chosen will depend on the patients' prior lines of therapy and provincial funding agreements.
- Although daratumumab may complicate certain laboratory assessments (chiefly red blood cell cross matching and determination of monoclonal immunoglobulin levels) these limitations are manageable in clinical practice and ought not to deter from the use of this agent in this setting.
  The submitter provided a Network Meta-analysis to provide an indirect comparison of a daratumumab-containing regimen with carfilzomib, a second-generation proteasome inhibitor. While this meta-analysis supported the use of daratumumab over the second-generation agent there were methodological concerns raised that appear to limit the conclusions that can be drawn from this study.

2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

Multiple myeloma is an incurable plasma cell neoplasm that represents 1.3-1.5% of all new cancers in Canada with an estimated 2700 new cases annually.[24] The median age of diagnosis is 69 years with a 5 year overall survival estimated at 48.5%.[25]

The morbidity and mortality from myeloma stem from direct and indirect effects of the malignant plasma cells and its monoclonal protein. The diagnosis of symptomatic multiple myeloma (myeloma that necessitates treatment) is made based on the International Myeloma Working Group (IMWG) recommendations.[26] Specifically, one must document clonal bone marrow plasma cells ≥ 10% and any one of the following: 1) Hypercalcemia, 2) Renal insufficiency, 3) Anemia, 4) Bone lesions or 5) One of: clonal bone marrow plasma cells ≥ 60%, involved:uninvolved serum free light chain ratio ≥100 or > 1 focal lesions on MRI studies.

Without effective therapy, the illness results in a significant decrease in quality of life and is universally fatal. The management of symptomatic myeloma is reliant on systemic chemotherapy and supportive measures (pain control, antibiotics, kyphoplasty, radiation therapy, dialysis and psychosocial supports). The median survival of symptomatic myeloma has significantly improved over the last 20 years with concurrent improvements in Health Related Quality of Life (HRQOL).[27-30] Improvements in outcomes, including overall survival have been predominantly attributed to improvements in chemotherapeutics.[28,31]

Based on understanding of myeloma biology and clinical observations, there has been a paradigm shift in the "philosophy" of symptomatic myeloma chemotherapeutic management. Previously, there has been a reluctance to use more effective medications or medication combinations sooner and/or upfront.[32] Rather, clinicians were saving therapeutic options in the relapsed and/or refractory setting. This approach was rationale when the chemotherapeutics "tool-box" was limited, less efficacious and was associated with significant side effect profile. However, with better understanding of biology such as clonal tiding,[20,33-35] emergence of more targeted therapies,[36] indirect data from multiple randomized trials,[37] it is now widely accepted that effective combination novel therapies should be embraced early and continuously while paying attention to side effect profile.

Taken together, a strategy of early continuous therapy result in better outcomes (Overall Survival,[37] Progression Free Survival 1 & 2,[37] HRQOL[38,39] and possibly economics[40]) than a strategy of intermittent therapies based on symptoms.

2.2 Accepted Clinical Practice

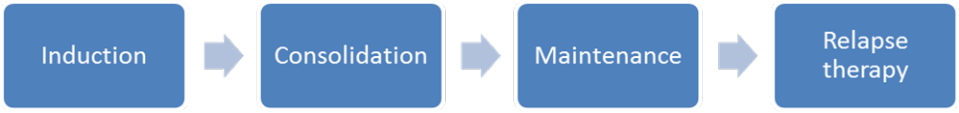
The optimal chemotherapeutic management of symptomatic myeloma remains elusive. Radiation therapy is supportive and reserved for management of pain and localized symptomology from plasmacytomas (localized myeloma). Myeloma is incurable and patients will ultimately receive all possible effective chemotherapeutic options. However, there remains no consensus on the optimal sequencing of effective therapies. It is widely accepted that early combination continuous therapy results in superior outcomes as discussed above.

There are 3 main "currently" available/approved classes of chemotherapeutics in Canada include: 1) Alkylators such as melphalan, cyclophosphamide, liposomal doxorubicin, 2) Immunomodulatory

agents (IMiD) such as thalidomide, lenalidomide and pomolidomide, 3) Proteosome Inhibitors (PI) such as bortezomib and carfilzomib. In principal, an agent from different therapeutic class is used in combination with an agent from another. These combinations are usually employed in conjunction with steroids such as dexamethasone to enhance efficacy. The current chemotherapeutic management can be conceptualized as follows:

Transplant Eligible patients with symptomatic myeloma

Transplant Ineligible patients with symptomatic myeloma



Various combinations of chemotherapeutics are utilized at each stage with the goal of suppressing the malignant clone(s), achieving complete remission and maintaining the remission/suppression, while paying attention to chemotherapeutic side effects.[41]

Relapsed and Refractory Myeloma

Given that patients with myeloma will eventually relapse, further therapy will be required. The choice(s) availed is complex and is dependent on 1) prior therapies and responses, 2) side effects, 3) patient comorbidities/frailty, 4) funding and 5) individual preferences.[42] It remains unclear how the relative contributions of such factors influence eventual choice(s). Historically, it was accepted than prior "failed" chemotherapeutics would not be "reused" again in the management of relapsed myeloma in the belief there would be no value. However coupled with better understanding of myeloma cancer biology and observational studies, it is now widely accepted that re-treatment with prior failed agents or in combination with other active agents may have further utility.

With respect to management of relapsed and refractory myeloma, classic phase 3 studies have supported the use of medications in all the above categories.[7,43-47] Similarly, the above categories of agents have been also evaluated in the newly diagnosed setting demonstrating efficacy and value.[48-53] Taken together, patients with symptomatic myeloma will ultimately receive all possible effective chemotherapeutic options.

The monoclonal antibodies represent a new emerging therapeutic class of chemotherapeutics for the management of myeloma. Daratumumab[54-56] is a human IgG1k monoclonal antibody that binds with affinity to the CD38 molecule, which is highly expressed on the surface of multiple myeloma cells. It is believed to induce rapid tumor cell death through programmed cell death, or apoptosis, and multiple immune-mediated mechanisms, including complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis and antibody-dependent cellular cytotoxicity.

Janssen Canada has submitted a request for funding to CADTH pan-Canadian Oncology Drug Review on 03 March 2017. Specifically, they are requesting review and funding for Daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least 1 prior line of therapy.

2.3 Evidence-Based Considerations for a Funding Population

The population under consideration includes patients with relapsed and/or refractory symptomatic myeloma as defined by the IMWG criteria.[57] Of note, they cannot be considered refractory to either lenalidomide or bortezomib in their respective trials.

There are preclinical,[58] Phase 1[59] and Phase 2[60] studies supporting the potential benefits of Daratumumab as a single agent or in combination with other chemotherapeutics in the management of patients with myeloma.

In May 2013, Daratumumab received Fast Track Designation and Breakthrough Therapy Designation from the US FDA for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteosome inhibitor (PI) and an immunomodulatory agent (IMiD) or who are refractory to both a PI and an immunomodulatory agent. Daratumumab has also received Orphan Drug Designation from the US FDA and the EMA for the treatment of multiple myeloma. In Nov 2015, the US FDA approved Daratumumab injection for intravenous infusion for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy, including a PI and an IMiD , or who are refractory to both a PI and an IMiD.[61]

To our knowledge, there are two (2) Phase 3 studies, as submitted by Janssen examining the use of Daratumumab in combination with other known active anti-myeloma agents in relapsed/refractory setting:

Relapsed and Refractory Multiple Myeloma

1. Addition of Daratumumab to Combination of Bortezomib and Dexamethasone in Participants with Relapsed or Refractory Multiple Myeloma. clinicaltrials.gov registration: NCT02136134[62]
2. A Study Comparing Daratumumab, Lenalidomide, and Dexamethasone with Lenalidomide and Dexamethasone in Relapsed or Refractory Multiple Myeloma. clinicaltrials.gov registration: NCT02076009[63]

Moreover, there are 2 prospective observational studies (Phase 1 /2 and 2) examining the use of single agent Daratumumab in patients with 1) have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD); OR 2) have failed or are intolerant to a PI and who have failed or are intolerant to an IMiD: GEN501[64] and SIRIUS[65] demonstrating efficacy.

Several publications on the economics of management of relapsed and/or refractory multiple myeloma may be illustrative, instructive and assist with benchmarking.[66-72]

2.4 Other Patient Populations in Whom the Drug May Be Used

There are ongoing phase 2/3 trials examining the use of Daratumumab in the listed patient populations:

Newly diagnosed Multiple Myeloma – Transplant Ineligible

1. Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Participants With Previously Untreated Multiple Myeloma. clinicaltrials.gov registration: NCT02252172[73]
2. A Study of Combination of Daratumumab and Velcade (Bortezomib) Melphalan-Prednisone (DVMP) Compared to Velcade Melphalan-Prednisone (VMP) in Participants With Previously Untreated Multiple Myeloma. clinicaltrials.gov registration: NCT02195479[74]

Newly diagnosed Multiple Myeloma – Transplant Eligible

1. A Study to Evaluate Daratumumab in Transplant Eligible Participants With Previously Untreated Multiple Myeloma (Cassiopeia).
   clinicaltrials.gov registration: NCT02541383[75]

High Risk Smoldering Myeloma (Phase 2)

1. A Study to Evaluate 3 Dose Schedules of Daratumumab in Participants With Smoldering Multiple Myeloma.
   clinicaltrials.gov registration: NCT02316106[76]

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Myeloma Canada, provided input on daratumumab in combination with lenalidomide and dexamethasone, or in combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy and their input is summarized below.

Myeloma Canada conducted two online surveys, one for patients and the other for caregivers as well as one-on-one interviews with 5 patients. These surveys were sent to Canadians through Myeloma Canada support group networks and Americans through the International Myeloma Foundation. These surveys were available online from February 21 to March 31 2017. Information on patient and caregiver experience with daratumumab was collected.
Of the total 107 patient respondents to the survey, 9 had experience with daratumumab in combination with lenalidomide and dexamethasone, and 6 had experience with daratumumab in combination with bortezomib and dexamethasone. These 15 patients are referred to as "per the combinations under review" throughout the summary document.

Thirty additional respondents had used daratumumab in other combinations or in one case alone. These combination therapies are as follows: daratumumab with pomalidomide plus dexamethasone; daratumumab with ixazomib; daratumumab with carfilzomib; daratumumab with ixazomib and carfilzomib; and daratumumab with dexamethasone and cyclophosphamide.

Overall, 45 patients respondents had experience with daratumumab. The submitted patient input refers mostly to the 15 "per combinations under review" patients and in some cases these 15 responses are compared to the responses from all 45 patients who have used daratumumab.

In addition, a total of 26 caregiver respondents had experience with daratumumab, of which, one caregiver had experience with daratumumab in combination with lenalidomide and dexamethasone and 3 with daratumumab with bortezomib and dexamethasone.

Myeloma Canada has noted in their input that previous patient and caregiver surveys with related reports to pCODR since December 2015 have reported the patient and caregiver experience with myeloma as well as overall treatment side effects. Therefore, Myeloma Canada has asked pCODR to refer to recent submissions for Kyporlis (September 2016) and Ninlaro (January 2017) for the most recent results as these have not changed since the last disease impact survey for these submissions.

From a patient's perspective, infections, followed by kidney problems, mobility, pain, fatigue, neuropathy, and shortness of breath are important aspects of myeloma to control. The ability to work, followed by the ability to exercise, travel, volunteer, concentrate, conduct household chores, fulfill family obligations, and spend time with family are symptoms associated with myeloma that impact or limit day-to-day activity and quality of life. According to Myeloma Canada, when it comes to treating myeloma, it is important for patients: to maintain quality of life or normal life, manage/minimize side effects, control the disease, have access to effective treatments, control symptoms, achieve or maintain remission, and prolong survival, among others. Patients expectations for the daratumumab as per the combination under review were as follows: prolonged life, disease control, and remission. Fewer side effects than other treatments was ranked as the last attribute. The same patients indicated that the following expectations were fulfilled by daratumumab: disease control, remission and fewer side effects than previous treatments.

Of the patients that reported positive and negative outcomes experienced with daratumumab, about half (5/11) shared it was managing their disease and 2 indicated the side effects were

minimal. Four patients had no comments to share. Negative comments were as follows: Long infusion (2), Lack of appetite (1), weight loss (1), some diarrhea (1), increased blood pressure after first 2 infusions (1). Note some respondents had more than one answer and 7 respondents had no negative outcomes to report. An important consideration for patient is the administration of daratumumab. Patients were asked about their experience with respect to the administration of darartumumab. A total of 10 patients who used daratumumab as ***per the combinations under review*** responded as: Neutral or no impact (3), Long or time consuming (2), No effect (2), Positive impact (2), N/A (1). Most side effects with daratumumab were tolerable and a very small percentage rated "low blood counts" and "Infusion reaction" as completely intolerable. The overall least tolerable were "low blood counts" and "fatigue

These side-effects were managed with the following: Medication (Imodium for diarrhea, meds for high blood pressure) (3), None or no side effects (2), Rested when tired (1), Prunes for constipation (1), Just try to tolerate (1), Worked through (1).

Most respondents who had experience with daratumumab as per the combinations under review either had a 'fair quality of life" 27.3% (3/11), "good quality of life" 45.5% (5/11) or "very good quality of life" 27.3% (3/11).

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

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients Have with Multiple Myeloma (summary from a previous Myeloma Canada submission to pCODR, as per Myeloma Canada's request)

The following information is taken from the patient input summary for ixazomib (Ninlaro). Myeloma Canada had indicated that information from these inputs have not changed with respect to disease impact. A total of 344 patients responded to the patient survey. Among these respondents, 238 were from Canada (representing each province, except New Brunswick and none of the respondents were from the territories), 104 were from the United States and 2 were from Israel. A total of 123 caregivers responded to the caregiver survey. Among these respondents, 82 were from Canada (representing each province, except New Brunswick, Prince-Edward-Island and none of the respondents were from the territories), 40 were from the United States and 1 was from Australia.

When Myeloma Canada asked patient respondents to rate on a scale of 1-5, how important it is to control various aspects of myeloma, patient respondents indicated that infections were the most important, followed by kidney problems, mobility, pain, fatigue, neuropathy and shortness of breath. Based on the responses below, Myeloma Canada expressed that all aspects were important to very important.

	1 - Not important	2	3	4	5 - Very important	N/A	Total
Infections	0.34% 1	1.34% 4	4.36% 13	10.40% 31	83.22% 248	0.34% 1	298

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

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

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

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

- *"Extra care when going out into the public to minimize the potential exposure to disease and germs - easier to get sick, takes longer to get better."*
- *"My emotional well being is significantly impacted due to treatment which includes steroids."*
- *"The impact is cyclical depending on where I am in my disease control, sometimes all of these things (the list above) see(m) very difficult and sometimes not as much."*
- *"Diarrhea limits my day plan - have to plan around it all the time."*
- *"Ability to work n/a as Retired, but often unable to do what I used to enjoy e.g. Woodworking, "outside chores".*
- *Certainly could not have done my job - renovations, building etc."*

3.1.2 Patients' Experiences with Current Therapy for Multiple Myeloma

Similar to Section 3.1.1, the following information is taken from the patient input summary for ixazomib (Ninlaro). Myeloma Canada had indicated that information from these inputs have not changed with respect to disease impact.

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

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

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

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

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

When Myeloma Canada asked Canadian patient respondents in an open-ended question about hardships accessing treatment for myeloma, the responses fell into the following categories: (starting with the most popular) no, not that I'm aware of, not so far and not yet (74%), yes (23%), too soon to tell (1%) and N/A (2%). The "yes" responses included: denied treatment (6%), drug not covered (5%), limited to covered treatments (3%), travel to treatment (2%), cost of drugs (2%), access to physician (1%), access to available bed (1%), treatment not available (1%), and waited for treatment approval(1%). N = 155. Of note, only Canadian responses were included in this question analysis.

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

3.1.3 Impact of Multiple Myeloma on Caregivers

Similar to section 3.1.1, *the following information is taken from the patient input summary for ixazomib (Ninlaro). Myeloma Canada had indicated that information from these inputs have not changed with respect to disease impact.*

When Myeloma Canada asked caregiver respondents in Survey 2 to rate on a scale of 1-5, with 1 = "not at all" and 5 = "significant impact", how much caring for someone with myeloma limits their day-to-day activity and quality of life, caregivers indicated that their ability to travel was most affected, followed by the ability to volunteer, spend time with family and friends, to concentrate, fulfill family obligations, to work, exercise, and to conduct household chores. The total number of caregiver respondents for this answer ranged from 115 to 120.

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

- *"Doesn't seem to have any major side effects the dexamethasone is worse."*
- *"Tired so I give it to him at night."*
- *"My husband developed shortness of breath. Not sure if this is from Ninlaro since it developed after taking Carfilzomib and didn't go away."*
- *"Two to Three days after taking Ninlaro and Dex while taking Revlimid she crashes and is very tired for 2 days."*

Of note, Ninlaro = ixazomib, Dex = dexamethasone, and Revlimid = lenalidomide.

In another open ended question in Survey 4, caregiver respondents were asked if there is anything else about ixazomib that they would like Myeloma Canada to know and include. Two respondents provided the following responses:

- *"great that it can be taken by pill at home"*
- *"it gives us a sense of control, like the cancer is not controlling our life"*

- *"He has an aggressive form of Multiple Myeloma and this drug is being prescribed after three stem cell transplants. It gives us hope because it's keeping his disease in check."*

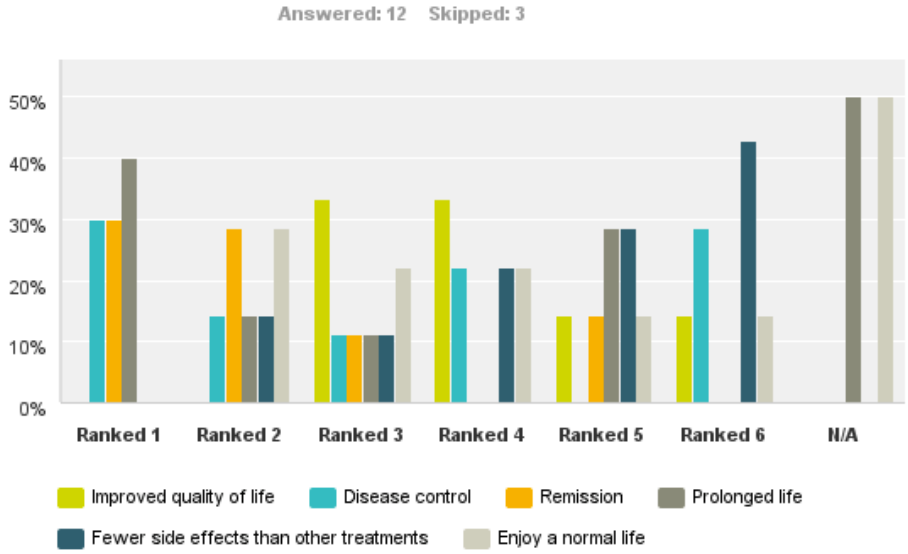
3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences to Date with Daratumumab

Among the 15 respondents who used daratumumab as "per the combinations under review", 8 were on treatment between 1-6 months, 3 between 7-12 months, 1 between 1-2 years, and 3 provided no response.

Myeloma Canada asked patients to rank their expectations of the treatment before taking daratumumab. These expectations are noted below:

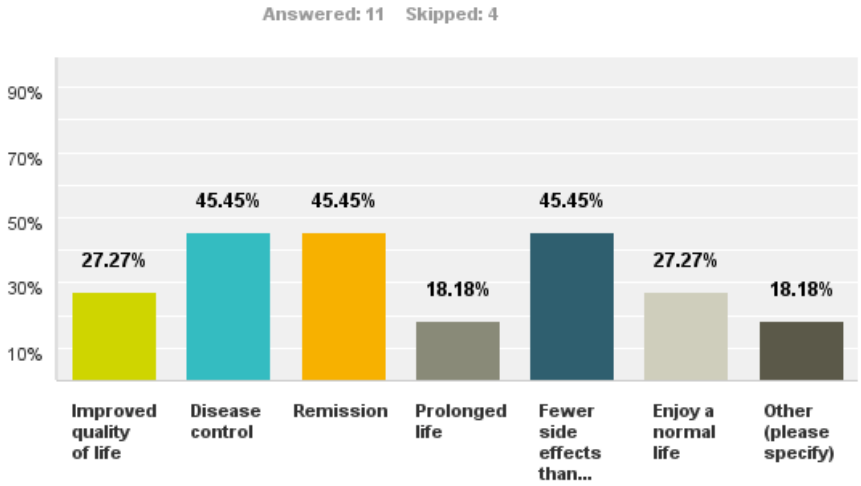
Chart 1 – Expectations of daratumumab before taking the treatment as *per the combinations under review*



Twelve patients who used daratumumab "as per the combination under review" responded to the question above. Forty (40%) expected the treatment to prolonged life as being the first ranked attribute. Disease control (30%) and Remission (30%) were also ranked as first choice. Patients ranked "fewer side effects than other treatments" last by 42% of respondents. Myeloma Canada has attributed this to perhaps be representative of a patient population who has experience a variety of treatments and corresponding side effects.

The same patients who used daratumumab as ***per the combination under review***, were asked what expectations were fulfilled by daratumumab. Their responses are shown in Chart 2.

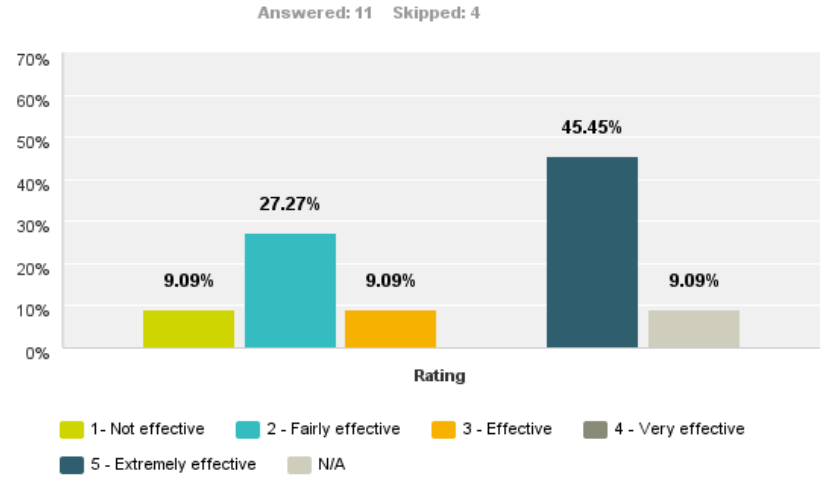
Chart 2 – Expectations fulfilled by daratumumab (as per the combinations under review)



Eleven patients answered the question above of which 45% (5/11) felt the treatments (***daratumumab combinations as per the review***) had the most impact on "Disease Control", "Remission" and "Fewer side effects than previous treatments". As per the noted expectations, the first two attributes fulfilled the patients' expectations. "Fewer side-effects" was also fulfilled, though not listed as an expectation.

Pooled data for all respondents who used daratumumab (38/45), the ranking of attributes was similar to the "as per combinations under review" patients. Remission (33%) and prolonged life (30%) were ranked as most important. Following treatment with daratumumab, patients indicated "disease control" and "fewer side effects than previous treatments" as the most common attributes fulfilled by daratumumab" at 60.5% (23/38) each. Remission had achieved a 34.2 % fulfilment (13/38).

Chart 3: Rating of daratumumab's effectiveness by respondents who used daratumumab *per the combinations under review*.



As per the above graph, a total of 45.5% (5/11) rated their treatment as extremely effective, only 9% (1/11) felt it was not effective. For the entire patient population who used daratumumab, and responded to the question (38 patients), the rating of daratumumab's

effectiveness was noted as similar. A total of 44.7% (17/38) rated it as "extremely effective" and 10.5% (4/38) patients found it "Not effective".

Impression of daratumumab treatment by the respondents who used daratumumab as per combinations under review patient population

Positive outcomes experienced with daratumumab

Patients who responded to the survey were asked to share positive outcomes compared to other myeloma treatments they had received. About half (5/11) shared it was managing their disease and 2 indicated the side effects were minimal. Four patients had no comments to share.

Verbatim response examples: "*Less side effects and no toxicity", "Managing the Myeloma", "It brought my myeloma numbers down very quickly", "Remission in 8 treatments", "It brought down my free light chain count but it has started back up again".*

Negative outcomes experienced with daratumumab

Seven out of 11 patients who responded to this question had no negative outcomes to report. Others responded as follow: Long infusion (2), Lack of appetite (1), weight loss (1), some diarrhea (1), increased blood pressure after first 2 infusions (1). Note some respondents had more than one answer.

Myeloma Canada did not include responses of those respondents who did **not use the treatments as *per the combinations under review*** because their impressions could be influenced by other treatments received in their combination regimen.

Administration

An important consideration for patient is the administration of daratumumab. Patients were asked about their experience with respect to the administration of darartumumab. A total of 10 patients who used daratumumab as ***per the combinations under review*** responded as: Neutral or no impact (3), Long or time consuming (2), No effect (2), Positive impact (2), N/A (1).

Verbatim response examples: "*Wonderful! I get to sit in a comfy chair for a few hours and nap or read etc. and not have to worry about housework! It's ME time!" "The only way to receive this drug. In a bed with easy access to a washroom." "L-O-N-G infusion but tolerable. I had no allergic reaction."*

Among all respondents who used the treatment and responded to the question, (36) 10/36 reported that it was long or time consuming, 17/36 reported that the impact was either neutral or that there was no impact, 5/36 reported a positive impact, 2/36 reported that they found ways to pass the time, and 2 provided answers that were not applicable.

Verbatim response examples: "*Onerous initially with weekly infusions, even maintenance has one tied to location and is a long day*", "*The time turned me off but if was helping me [Darzalex] go for it, I brought things with me to pass the hours*", and "*Infusion time is long, I nap*".

Patient rating of side effects experienced with daratumumab

The majority (45%) of respondents who used the daratumumab as ***per the combinations under review*** felt the side effects they experienced were "extremely tolerable". See Chart 4.

Chart 4 – Tolerability of side effects of daratumumab by respondents who used daratumumab *per the combinations under review*

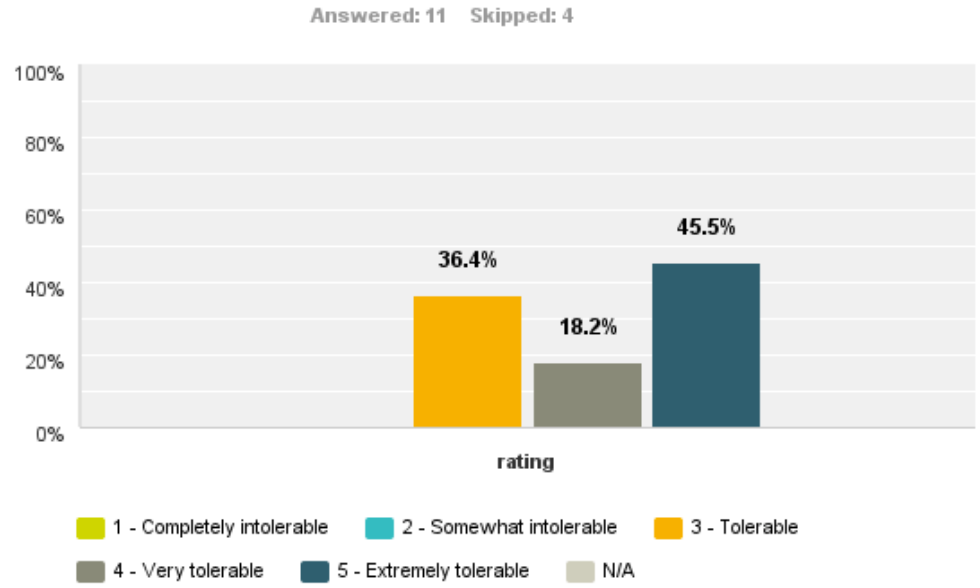
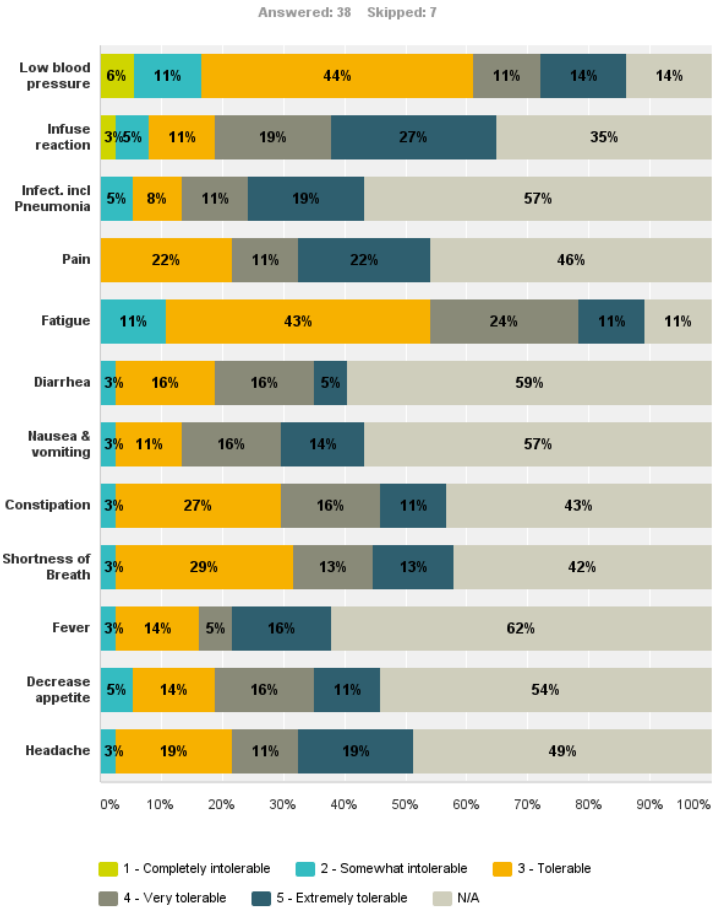


Chart 5 – Rating of the common side effects of daratumumab by respondents who used daratumumab as *per combination under review*



A total of 11 respondents who used daratamumab as ***per the combinations under review***, rated the common side effects of daratumumab on a scale of 1 – 5 as per Chart 5. The chart demonstrates that many of the side effects were not applicable, most were tolerable and a very small percentage rated "low blood counts" and "Infusion reaction" as completely intolerable. The overall least tolerable were "low blood counts" and "fatigue".

A total of 9 respondents who used daratumumab as per the combinations under review provided an answer to the open-ended questions that asked "if you experience side effects with daratumumab, briefly explain how you managed side effects. Their responses were categorized as: Medication (Imodium for diarrhea, meds for high blood pressure) (3), None or no side effects (2), Rested when tired (1), Prunes for constipation (1), Just try to tolerate (1), Worked through (1).

Impact on Quality of life

Chart 6 – Overall impact on patient's quality of life since starting daratumumab by respondents who used daratumumab *per combinations under review*:

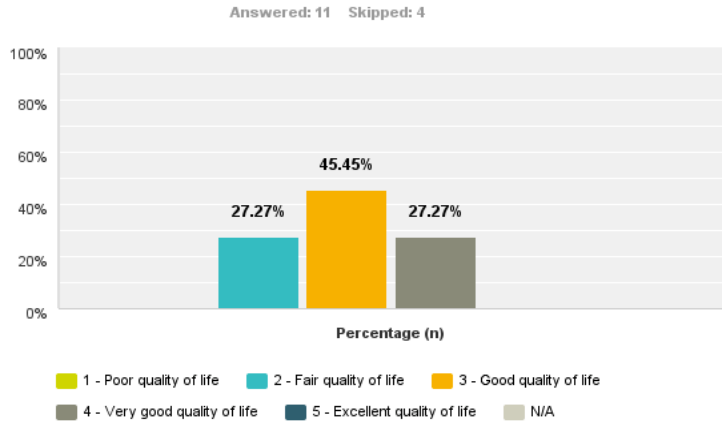
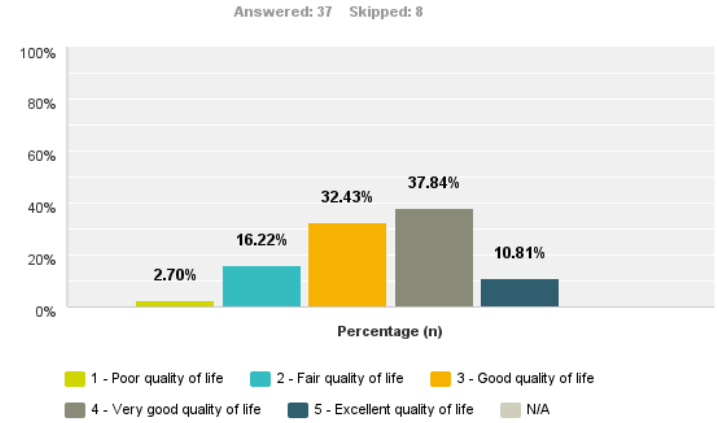


Chart 6 demonstrates that most respondents either had a 'fair quality of life" 27.3% (3/11), "good quality of life" 45.5% (5/11) or "very good quality of life" 27.3% (3/11).

The results were compared to all the respondents who used daratumumab (37) in Chart 7, the rating was somewhat different, more patients (11%) rated daratumumab as providing an excellent quality of life compared to none in the *per combinations under review*. This may be the result of the low number of responses (11).

Chart 7 - Overall impact on patient's quality of life by <u>all</u> respondents who used daratumumab



Patient respondents were asked if daratumumab met their overall expectations?

A total of 11 respondents who used daratumumab in the combinations under review responded as follows: Yes (54.5%, 6), No (18%, 2), Please explain (27%, 3). The responses under please explain:

"*I expected good things and am in stringent complete remission," Don't know yet." "It did not control my disease."*

When we compared these results to **all** the respondents who used daratumumab (38), the percentage who responded "yes" increased to 57.9% (22/38) and the percentage of "no" decreased to 13.1% (5/38).

Patients were asked how has daratumumab changed or expected to change their long-term health and well-being?

A total of 9 respondents who used the treatments ***per the combinations under review*** provided a response to this open-ended question.

The responses were as follows: *"The new thinking is to stay on treatment for life, like having high blood pressure. My problem is lack of sleep on the dex and feeling "jet lagged" all week. I only feel "normal" on Mondays and have to nap every other day." "That is my hope that my health will improve." "Longer survival", "Don't know", "Managed the multiple myeloma.", "I hope this drug continues to keep me in remission.", "Hoping the fatigue will cease after a few months.", "mayo visit in 4 weeks post labs and I can give better response to question then.", "It has not at this point changed my long-term health and well-being."*

When Myeloma Canada reviewed the responses of **all** respondents who used daratumumab, overall the responses were positive where patients felt the drug was working in managing their myeloma, side effects were minimal and most were hopeful that it would start working or would continue to work.

Additional information to know and include.

A total of 6 respondents who used the treatment ***as per the combinations under review*** provided a response to this open-ended question. Their responses: No – 3, *"I only reacted to it on the first 10 HR. drip, but after that there were no problems and I went from weekly to bi-weekly to monthly drips and have gone from 2 Tylenols and Benadryls during treatment to just one of each so I am not so sleepy during drips.", "It only worked when I was on it weekly. When I went to every other week it stopped working.", "$12000 per in fusion. Insurance paying most of it so far."*

Patient one on one interview

In addition to the online survey, respondents were invited to provide their email address if they were interested in discussing their experience with daratumumab by phone. A total of 5 were interviewed.

Patient 1 – On daratumumab in combination with lenalidomide and dexamethasone for 3 months. Patient wasn't sure what to expect in terms of timelines for change. After 3 months, the patient has not had minimal side-effects – some fatigue (not sure it's caused by the daratumumab), a little bit of swelling in the feet and diarrhea which is now under control. The patient has had "tremendous success" and rates it about 85% good and 15% bad.

Patient 2 – On daratumumab in combination with bortezomib and dexamethasone for 2 months. The patient didn't have any side effects. The treatment worked well at first but soon afterwards it stopped working and the patient was switched to another treatment. This

patient is aware of another patient from the support group who is on daratumumab and is having excellent results.

Patient 3 – On daratumumab in combination with lenalidomide and dexamethasone for 10 months. After a few months on treatment, the patient went into "a complete remission". This patient will "be on the treatment for the rest of my life."

Patient 4 – On daratumumab in combination with lenalidomide and dexamethasone for 5 months. The patient was hoping the treatment would get the disease under control. The patient did have some improvement, but after 5 months it no longer worked and patient was taken off the treatment. The treatment didn't have any side-effects. There was a very slight reaction to the initial infusion, but it didn't last long, eyes turned red, but it went away.

Patient 5 – "This medication was the first one that didn't seem to have bad side effects and it seemed to be working well". Patient reported that quality of life was better. This patient found the decrease in frequency of infusions made it better and increased quality of life. Patient was still tired but attributed this to the steroids.

3.3 Additional Information

None.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

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

Clinical factors:

- Clarity on patient groups eligible for treatment

Economic factors:

- Drug wastage
- Pre-medication prior to each infusion
- Unknown and variable treatment duration

Please see below for more details.

4.1 Factors Related to Comparators

Both lenalidomide/dexamethasone (Ld) and bortezomib/dexamethasone (Bd) are funded for patients with previously treated multiple myeloma in all the provinces. PAG noted that pomalidomide is the current treatment of choice for third-line therapy. Other treatments available include cyclophosphamide/bortezomib/dexamethasone, bortezomib/melphalan/prednisone, bortezomib/cyclophosphamide/prednisone, and melphalan plus prednisone.

PAG noted that the comparators used in the CASTOR and POLLUX trials are appropriate, particularly in second-line. Since there will be a large prevalent population of patients with previously treated multiple myeloma, PAG is also seeking information on comparison of daratumumab combination therapy to pomalidomide-dexamethasone, carfilzomib/dexamethasone and carfilzomib/lenalidomide/dexamethasone in later lines of therapy. However, PAG realizes that this is beyond the scope of the funding request.

4.2 Factors Related to Patient Population

There is a large prevalent number of patients with multiple myeloma who have received prior lines of therapy who would be eligible for treatment with daratumumab in combination either with Ld or Bd. PAG is seeking clarity in the patient population who would be eligible for a daratumumab triplet combination. PAG is seeking guidance on the definition of relapsed and refractory disease on previous treatment with Ld and Bd and how biochemical disease progression (not overt clinical disease) fits within this definition.

PAG is also seeking guidance on the appropriateness of

- adding daratumumab for patients currently on Ld or Bd but have not yet progressed or have biochemical progression
- switching patients from daratumumab-Ld to daratumumab-Bd when patients become refractory to lenalidomide
- switching patients from daratumumab-Bd to daratumumab-Ld when patients become refractory to bortezomib

- sequencing other triplet combinations with Ld (e.g. carfilzomib, ixazomib)
- use of daratumumab in patients who are intolerant to lenalidomide or bortezomib

Given the many new treatments recently available and possibly more upcoming new treatments, PAG is seeking information on sequencing of combination treatments and single agent treatments.

Although out of scope of the current review, PAG identified that there may be interest in using daratumumab combination therapy in the first-line setting or in using daratumumab in combination with other agents, such as pomalidomide/dexamethasone or carfilzomib/dexamethasone for later lines of therapy.

PAG indicated that there may be patients who are refractory to both Ld and Bd who may be interested in treatment with daratumumab monotherapy. However, PAG noted that daratumumab monotherapy for third-line and beyond was previously reviewed and pERC recommended not to fund.

4.3 Factors Related to Dosing

The weekly dosing schedule in the first eight or nine weeks, the every two weeks dosing schedule in the next 14 to 15 weeks and the every four weeks thereafter until progression is difficult for many patients, especially those who would have to travel far to and from cancer centres with the resources to administer and monitor daratumumab infusions. In addition, the administration schedule for daratumumab-Ld combination is slightly different than for daratumumab-Bd. PAG noted that processes would need to be in place, prior to implementation of daratumumab, to minimize dosing errors and patient confusion.

PAG noted the dose of bortezomib in the trial is different than the dose in Canadian practice and is seeking guidance on the dose of bortezomib to be used when in combination with daratumumab and the generalizability of the CASTOR trial to Canadian practice.

4.4 Factors Related to Implementation Costs

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

Additional resources will be required for pre-medication, drug preparation, administration time and monitoring for multiple severe adverse effects including infusion reactions.

PAG has concerns for incremental costs due to drug wastage, specifically in centers where vial sharing would be difficult. Although there are two vial sizes available, dosage is based on weight and there will be some drug wastage as any unused portion would be discarded.

4.5 Factors Related to Health System

Affordability and adequate resources (nurses, chemotherapy chairs) will be important factors to consider if and when implementing. PAG noted that access to daratumumab would be limited to cancer treatment centres with the appropriate resources to administer and monitor treatment. 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 need to have RBC phenotyping prior to starting daratumumab.

4.6 Factors Related to Manufacturer

The high cost of daratumumab, as an add-on therapy, is a barrier to implementation.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One clinician input was provided as a joint submission from ten clinicians. The clinicians providing input identified that overall, triplet combination therapy is superior to current therapies as triplet combination therapy provides a marked improvement in progression-free survival and likely improvement in overall survival. They noted that daratumumab triplet combinations have a deeper response, a higher response rate and longer duration of response and thus, would likely replace the current dual combination therapies.

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

5.1 Current Treatment(s) for Multiple Myeloma

The clinicians providing input indicated that the current treatments for relapsed or refractory multiple myeloma include bortezomib, lenalidomide, pomalidomide, cyclophosphamide, and melphalan. They noted that at the time of their input that carfilzomib and ixazomib are available but limited to compassionate supply and are not currently funded by the provinces.

5.2 Eligible Patient Population

The clinicians providing input noted there is potentially a large prevalent population who would be eligible to receive treatment with daratumumab, lenalidomide, and dexamethasone triplet combination therapy. They believe that patients previously treated with bortezomib based therapy would be eligible but that patients previously treated with low dose lenalidomide as maintenance would not be eligible for daratumumab, lenalidomide, and dexamethasone triplet combination.

The opinion of most clinicians was that daratumumab would be added to lenalidomide and dexamethasone based therapy for patients progressing in second line as bortezomib is used most often in first line treatment. Additionally, daratumumab, bortezomib, and dexamethasone triplet combination would be used less often than the lenalidomide triplet combination because of tolerability. However, some clinicians commented that most frontline treated patients will not be refractory to bortezomib per se, and thus, would be eligible for this triplet combination after relapse. It was also noted that in Ontario, bortezomib is only funded for one course of therapy, therefore use of daratumumab, bortezomib, and dexamethasone triplet combination would be limited.

Clinicians providing input identified that daratumumab should not be used in patients with severe respiratory disease, severe cytopenias, or prior life-threatening reaction to daratumumab.

5.3 Identify Key Benefits and Harms with Daratumumab

Benefits of daratumumab, lenalidomide and dexamethasone triplet combination: In summary, the majority of the clinicians felt that this combination is well-tolerated for long-term use and easy to use, provides a marked improvement in progression-free survival over other treatments, and likely improvement in overall survival. In addition, comments were made about the novel mechanism of action in the form of a monoclonal antibody. “Monoclonal antibodies have revolutionized the management of other cancers, and daratumumab is anticipated to do the same for myeloma. The toxicity of this regimen is excellent, and avoids the side effects of other triplet regimens in this setting.”

Benefits of daratumumab, bortezomib and dexamethasone triplet combination: In summary, clinicians felt that this combination was a good option for patients who are contraindicated for lenalidomide. They indicated that there is improved progression-free survival and perhaps overall survival compared to bortezomib and dexamethasone alone. This sentiment was repeated in serval occasions. In addition, comments were made about the combination being well-tolerated, with no GI side effects or fatigue

which extends the duration of response. Again, the mention of the novel mechanism of action was mentioned "the introduction of the highly effective monoclonal antibody to the armamentarium of myeloma care is a big advantage."

Harms of daratumumab, lenalidomide and dexamethasone triplet combination: In summary, the respondents indicated that the harms of this combination are none to very few and most are related to the infusion reaction, which can be mitigated by existing protocols. A few clinicians also commented on other harms such as cytopenias, infections and diarrhea.

Harms of daratumumab, bortezomib and dexamethasone triplet combination: In summary, the harms are none to very few. Most clinicians commented on the possible infusion reaction. A few also identified cytopenias (infections) and diarrhea as possible harms and increased costs to manage.

5.4 Advantages of Daratumumab Over Current Treatments

The clinicians providing input identified that daratumumab, lenalidomide and dexamethasone triplet combination has a longer progression-free survival, more effective for relapsed patients, has better disease control, delay of disease complications, and has higher response rate and depth of response. They noted that improvement in overall survival is expected and may produce extended long term survival in a subset of patients sensitive to immunotherapy. This triplet combination is also easy to use and offers a safe, more convenient triplet regimen for lenalidomide-naïve patients than has ever been available and meets the need of patients for longer duration treatment response.

The clinicians providing input indicated that daratumumab, bortezomib and dexamethasone triplet combination is superior to the approved dosing of bortezomib and dexamethasone, noting that superiority is based on both response and survival endpoints. They noted that data supports corresponding improvements in overall survival and triplet regimens are consistently superior to doublets in all phase 3 studies. In addition, they noted that non-randomized data indicate that the bortezomib + daratumumab regimen is more efficacious than current available regimens. This triplet combination provides another option for patients who have contraindications to lenalidomide and would be the ONLY triplet combination therapy for patients progressing on lenalidomide maintenance.

5.5 Sequencing and Priority of Treatments with Daratumumab

Daratumumab, lenalidomide and dexamethasone triplet combination: In summary, most clinicians providing input felt that this combination should be used as second line (and beyond) treatment for patients who have not had previous exposure to daratumumab but have relapsed following other treatments. The clinicians providing input felt that this triplet combination would replace the lenalidomide plus dexamethasone dual combination.

Daratumumab, bortezomib and dexamethasone triplet combination: In summary, most clinicians providing input felt that this combination should be used as second line (and beyond) treatment for patients who have not had previous exposure to daratumumab but have relapsed following other treatments, including after first or second relapse. One clinician providing input noted that this triplet combination will be used primarily in younger patients "progressing on lenalidomide maintenance after stem cell transplantation, and a small number of younger patients as third line therapy if they were transplanted before the availability of bortezomib-based induction therapy." The clinicians providing input felt that this triplet combination would replace bortezomib/dexamethasone dual combination and other less effective regimens.

5.6 Companion Diagnostic Testing

Although no companion diagnostic test is required to determine eligibility for treatment with daratumumab, the clinicians providing input indicated that red blood cell (RBC) phenotyping would be useful before daratumumab, if not previously performed. Due to daratumumab binding to red blood cells, special precautions are required with regards to blood banking. RBC phenotyping and antibody screening should be considered prior to treatment. Blood banks need to be advised of patient exposure to daratumumab and employ appropriate testing.

5.7 Additional Information

This is an extremely important drug for the myeloma community. It reflects an entirely novel mechanism of action that successfully builds upon existing standards. It has resulted in marked improvements in depth of response and disease control which has translated into clinically meaningful improvements in survival endpoints. It is well tolerated by patients and has a very manageable side-effect profile. It is now widely used in both Europe and the United States. This drug (likely in these combinations) will serve as a new benchmark for future trials.

Daratumumab is an important drug in the treatment of myeloma. The rapid acceptance of daratumumab as a backbone therapy in myeloma trial demonstrate how this drug has impressed the myeloma community with its clinical efficacy and overall tolerability. It is important that Canadian patients with myeloma have the opportunity to receive this drug at some point in their treatment.

Daratumumab has the potential to make significant impacts on the myeloma patient population and should be administered in cancer clinics until the subcutaneous preparation is available, given the rituximab-like infusion reactions.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7 and section 8.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

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

Table 2: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published comparative clinical trials investigating the safety and efficacy of daratumumab should be included	Patients with multiple myeloma who have received at least one prior therapy Subgroups: - ISS Stage III vs. Stage I/II - Cytogenetic profile (high risk vs. standard risk) - # previous lines of therapy (1, 2, 3, >3) - age (<65, 65-74, ≥75)	Daratumumab in combination with lenalidomide + dexamethasone or Daratumumab in combination with bortezomib + dexamethasone	- Dex - Thal + dex - Thal + dex + cyclo - Len + dex - Len + dex + cyclo - Bort + dex - Bort + dex + cyclo - Pom + dex - Pom + dex + cyclo - Carf + len + dex - Elot + len + dex - Ixaz + lena + dex - Pano + bort + dex - pegylated liposomal dox + bort	Primary • Progression Free Survival • Toxicity Secondary • Overall survival • Overall response • Complete response • Partial response • MRD negativity • Health related quality of life • Withdrawal due to adverse event

Abbreviations: bort – bortezomib; carf – carfilzomib; cyclo – cyclophosphamide; dex – dexamethasone; elot – elotuzamab; dox – doxorubicin; ISS – International Staging System; ixaz – ixazomib; len – lenalidomide; MRD – minimal residual disease; pano – panobinostat; pom – pomalidomide; RCT – randomized controlled trial; thal – thalidomide; vs – versus

Notes: Ixazomib and Carfilzomib are not currently available in Canada but are undergoing negotiation or review with pCODR. Both are available via the Special Access Program

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

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7 and section 8.

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

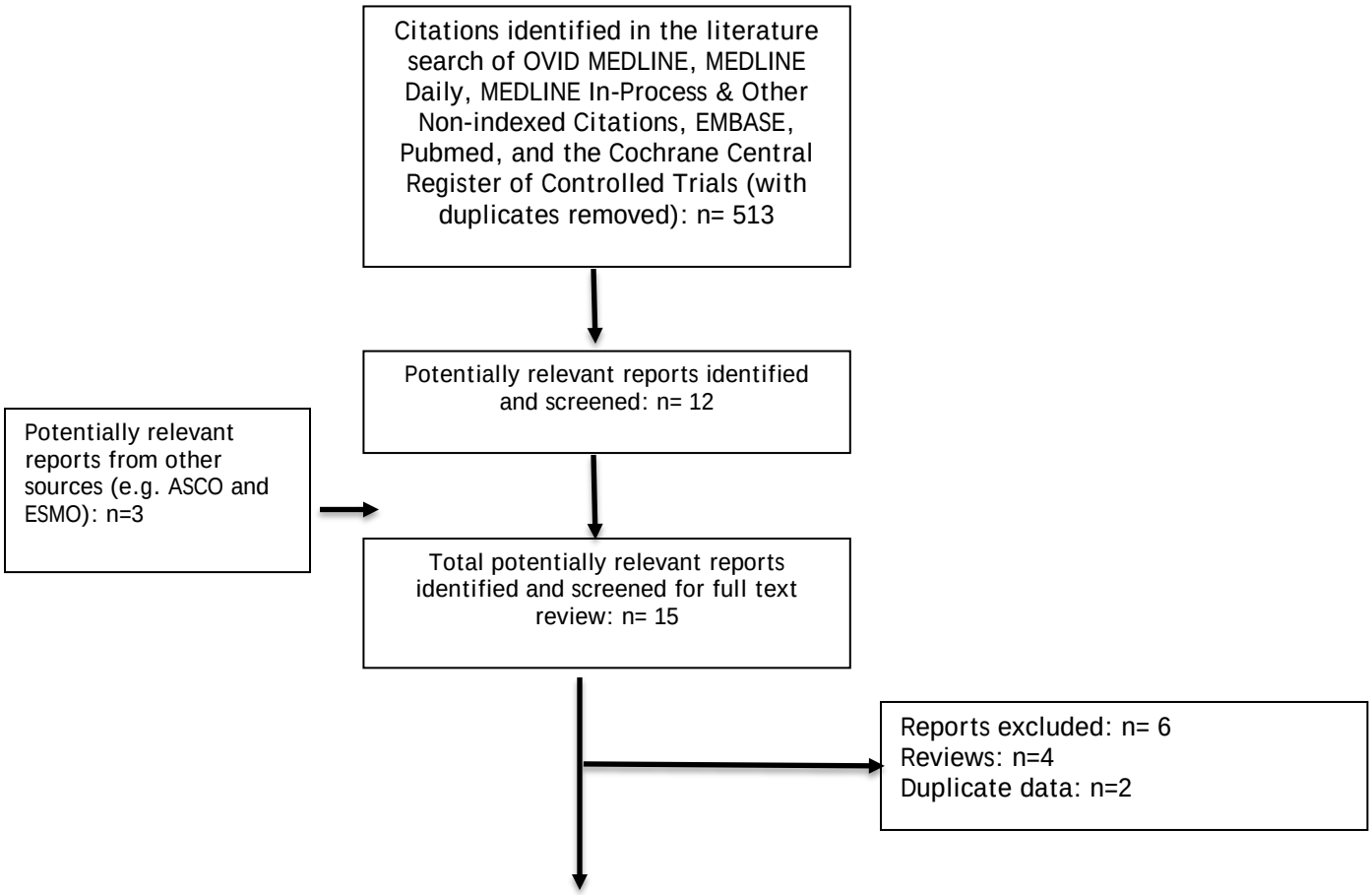
below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

6.3 Results

6.3.1 Literature Search Results

Of the 513 potentially relevant reports identified, 2 studies were included in the pCODR systematic review [5,10] and four studies were excluded. Studies were excluded because they were review articles[42,77-79] or because they reported duplicate data on the included studies.[80,81]

QUOROM Flow Diagram for Inclusion and Exclusion of studies



9 reports presenting data from 2 unique studies

The Pollux trial
Dimopoulos 2016 (primary publication + supplementary appendix)[3,4]
Moreau 2016 (updated analysis of POLLUX)[5]
Usmani 2016 (updated analysis of POLLUX)[2]
The CASTOR trial
Palumbo 2016 (primary publication + supplementary appendix)[6,10]
Mateos 2016 (updated analysis of CASTOR)[11]
Chanan-Khan (updated efficacy analysis of CASTOR)[13]
Reports identified and included from other sources:
POLLUX and CASTOR trial protocols[16,17]
POLLUX and CASTOR trial details on clinicaltrials.gov[18,19]
pCODR Submission[21]
Daratumumab Product Monograph[1]
NCCN Guidelines[22]

Note: Additional data related to the POLLUX and CASTOR studies were also obtained through requests to the Submitter by pCODR[82]

6.3.2 Summary of Included Studies

Two Phase III randomized controlled trials that met the eligibility criteria of this systematic review were identified. Characteristics of the two trials are summarized in Table 3 and specific features of trial quality are summarized in Table 4.

6.3.2.1 Detailed Trial Characteristics

Table 3: Summary of Trial Characteristics of the Included Studies

***CASTOR* Trial**			
Trial Design	**Eligibility Criteria**	**Intervention and Comparator**	**Trial Outcomes**
Clinical Trial NCT02136134 Open-label, active controlled, Phase III RCT Patient enrolment: September 2014-September 2015 Interim analysis data cut-off date: January 11, 2016 N randomized = 498 Multicentre (115 sites in 16 countries) Randomized 1:1 ratio, stratified by: • ISS disease stage at screening (Stage I, II, or III) • N previous lines of therapy (1 vs. 2 or 3 vs. >3) • Previous treatment with bortezomib (no vs. yes) Estimated study completion date: November 11, 2021 Funded by Janssen	Key Inclusion Criteria: • Received at least 1 previous line of therapy for MM • At least a PR to one or more lines of previous therapy • Documented progressive disease by IMWG criteria during or after completion of last regimen • Measurable disease based on serum, urine, or assessment of both, or measurable disease by serum free light-chain assay Key Exclusion Criteria: • Neutrophil count ≤1000 mm^3 • Hemoglobin ≤7.5 g/dL • Platelet count <75,000/mm^3 • Creatinine clearance ≤20mL/min/1.73m^2 body surface area • Alanine-aminotransferase or aspartate aminotransferase level of 2.5 or more times the upper limit of normal • Disease refractory to bortezomib or unacceptable side effects from bortezomib • Disease refractory to another proteasome inhibitor • ≥ Grade 2 peripheral neuropathy or neuropathic pain • Bilirubin level of 1.5 or more times the upper limit of the normal range	**Intervention:** **Dara + Bort + dex** Daratumumab 16 mg/kg IV weekly (days 1, 8, 15) during cycles 1-3, once q3wks (on day 1) during cycles 4-8, and once q4wks thereafter, until patient withdrawal, disease progression, or unacceptable toxicity Bortezomib 1.3 mg/m^2 SC on days 1, 4, 8, 11 of cycles 1-8 Dexamethasone[1] 20mg orally or IV on days 1,2,4,5 8,9,11,12 for a total dose of 160mg/cycle **Comparator:** **Bort + dex** Given at the same dose and schedule as the intervention arm	Primary: • PFS • Response to treatment • Disease progression Secondary: • time to disease progression • overall response rate • proportion of pts achieving VGPR or better • % of pts with results below the threshold for MRD • duration of response • time to response • overall survival • adverse events Exploratory: • time to subsequent antimyeloma treatment
***POLLUX* Trial**			
Trial Design	**Eligibility Criteria**	**Intervention and Comparator**	**Trial Outcomes**
Clinical Trial NCT02076009 Open-label, active controlled, Phase III RCT	Key Inclusion Criteria: • Relapsed or refractory MM and received at least 1 previous line of therapy • Response to one or more lines of previous therapy	**Intervention:** **Dara + Len + dex** Daratumumab	Primary: • PFS Secondary:

Table 3: Summary of Trial Characteristics of the Included Studies			
***CASTOR* Trial**			
Trial Design	**Eligibility Criteria**	**Intervention and Comparator**	**Trial Outcomes**
Patient enrolment: June 2014 – July 2015 Data cut-off date: March 7, 2016 N randomized = 569 Multicentre (135 sites in 18 countries) Randomized 1:1 ratio, by central schedule balanced by randomly permutated blocks, stratified by: • ISS disease stage at screening (Stage I vs. II vs. III) • N previous lines of therapy (1 vs. 2 or 3 vs. >3) • Previous treatment with lenalidomide (no vs. yes) Estimated study completion date: September 2020 Funded by Janssen	• Documented progressive disease by IMWG criteria during or after completion of last regimen • Measurable disease based on serum, urinary M-protein levels, or serum free light-chain levels and abnormal serum immunoglobulin free light-chain ratios <u>Key Exclusion Criteria:</u> • Neutrophil count ≤1.0x10^9/L • Hemoglobin ≤7.5 g/dL • Platelet count <75x10^9/L • Creatinine clearance <30mL/min • Alanine-aminotransferase or aspartate aminotransferase level of 2.5 or more times the upper limit of normal • Alkaline phosphatase level of 2.5 or more times the upper limit of normal • Bilirubin level of 1.5 or more times the upper limit of normal • Disease refractory to lenalidomide or unacceptable side effects from lenalidomide	16 mg/kg IV weekly (days 1, 8, 15, 22) for 8 weeks during cycles 1-2, q2wks (on days 1 and 15) for 16wks (cycles 3-6, and q4wks thereafter <u>Lenalidomide</u> 25mg orally on days 1-21 of each cycle if the creatinine clearance was >60mL/min (or a dose of 10mg daily if the creatinine clearance was 30-60mL/min) <u>Dexamethasone[2]</u> 40mg weekly split dose: 20mg prior to infusion as prophylaxis for IRR and 20mg the next day **<u>Comparator:</u>** **Len + dex** Given at same dose and schedule as intervention arm but dex dose needn't be split in control arm	• time to disease progression • overall response rate • rate of VGPR or better[3] • rate of CR or better[4] • % of pts with results below the threshold for MRD • duration of response • time to response • overall survival • adverse events
Abbreviations: BMI – body-mass index; CR – complete response; IRR – infusion related reactions; IV – intravenous; MM – multiple myeloma; MRD – minimal residual disease; N – number; PFS – progression free survival; PR – partial response; pt -patient; q – every; RCT – randomized controlled trial; SC – subcutaneous; VGPR – very good partial response; wks - weeks			
Notes: [1] Dose of dexamethasone could be reduced to 20mg once weekly for patients >75 years, patients with BMI <18.5, or patients with previous unacceptable side effects from glucocorticoid therapy [2] Dose of dexamethasone could be reduced to 20mg once weekly at the discretion of physician for patients >75 years or whose BMI was <18.5 [3] VGPR or better comprised of: very good partial, complete, and stringent complete responses [4] CR or better comprised of: complete and stringent complete responses			

a) Trials

Two randomized, open-label controlled trials, CASTOR and POLLUX, met the inclusion criteria of this systematic review.

Both CASTOR and POLLUX were Phase III trials that randomized patients in a 1:1 ratio to receive daratumumab and bortezomib + dexamethasone (DVd) versus bortezomib + dexamethasone alone (Vd) (CASTOR) or daratumumab and

lenalidomide + dexamethasone (DRd) versus lenalidomide + dexamethasone alone (Rd) (POLLUX). For inclusion, patients in both trials must have had at least one prior treatment for multiple myeloma.

Randomization in both trials was stratified by International Staging System (Stage I, II, or III), number of previous lines of therapy (1 vs. 2 or 3 vs. >3), and prior treatment with bortezomib (CASTOR) or lenalidomide (POLLUX), (no vs. yes). Within each stratum, patients were randomized using a 1:1 allocation ratio. Blinding strategies were not used in either trial.

Both studies consisted of 3 phases: screening, treatment, and assessment of efficacy. During the screening phase, patient eligibility criteria were reviewed and a complete clinical evaluation was performed within 21 days before the commencement of the first treatment cycle. Clinical and laboratory evaluations continued as clinically necessary during the treatment phase, which continued until disease progression or another reason for treatment discontinuation. An end-of-treatment visit took place 30 days after the last treatment dose and an assessment of tumour response and disease progression was then conducted in accordance with (International Myeloma Working Group) IMWG response criteria.[57,83] Key disease evaluations included serum and urine tests, measurements of myeloma proteins, bone marrow examinations, skeletal surveys, and assessment and measurement of extramedullary plasmacytomas and serum calcium.

CASTOR and POLLUX were both multicentered trials. Both studies were conducted at sites primarily in the United States and Europe, but also included sites in Australia, Asia and South America. Only the POLLUX trial included 10 Canadian study sites spanning 5 provinces.[84]

The primary outcome in both trials was progression-free survival (PFS) defined as the time from randomization to disease progression or death, whichever occurred first. Response to treatment and disease progression were assessed using the IMWG criteria. A computerized algorithm was used to combine and assess all laboratory and imaging results, as assessed by the study investigators, for each patient. Secondary efficacy outcomes for both trials included the time to disease progression, the overall response rate, the proportion of patients who achieved a very good partial response or better, the duration of response, the time to response, and overall survival. Safety evaluations were ongoing and included all patients who were administered at least one treatment dose.

Both CASTOR and POLLUX were superiority trials aimed at rejecting the null hypothesis that there is no difference in progression-free survival (PFS) between the daratumumab-containing combinations and the control groups. The null hypothesis of no difference between the two treatment groups was also evaluated for several secondary objectives including: time to disease progression, rate of very good partial response or better, overall response rate, minimal residual disease rate, and overall survival. The statistical hypothesis for both trials was that the addition of daratumumab can reduce the risk of disease progression or death by 30%, which, in the CASTOR trial assumes PFS can be prolonged from 10 months to 14.3 months.[6] Thus, a total of 295 PFS events were needed to achieve a power of 85% to detect this difference (hazard ratio, 0.70), using a log-rank test and two-sided alpha of 0.05. This translated into an estimated sample size of approximately 480 patients. For the POLLUX trial, the sample size approximation was 560 patients with 295 events, which would give the trial 85% power to detect a 30% lower risk of disease progression or death (hazard ratio, 0.70), with an overall

two-sided significance level of 0.05. Further details on sample size requirements for each trial are summarized in Table 4.

Analyses by subgroups were prespecified in the study protocols for both the CASTOR and POLLUX trials. In both studies, subgroup analyses of the efficacy endpoints including PFS, ORR, and OS, based on pre-specified subgroups were to be conducted and forest plots were to be generated both at the interim and final analyses. The interim subgroup analysis in the CASTOR trial included 11 subgroups all of which confirmed the superiority of daratumumab in combination with bortezomib and dexamethasone over bortezomib and dexamethasone alone based on the intention-to-treat population. This was true for the subgroup of patients who had previously received bortezomib (median PFS was 12.3 months in the daratumumab group versus 6.7 months in the control group), (hazard ratio 0.46, 95% CI 0.32 to 0.66) and for the subgroup who had received one previous line of therapy; not reached in the daratumumab group and 7.5 months in the control group (hazard ratio 0.31, 95% CI 0.18 to 0.52). No significant interaction was observed between treatment groups with regard to any of the subgroups. In the POLLUX trial, 8 subgroups were included in the forest plot comparing median PFS between groups and all confirmed the benefit of daratumumab. This was true regardless of the number of previous lines of therapy and in patients who had previous exposure to lenalidomide compared to those who had no exposure.

b) Populations

A total 498 patients were randomized in the CASTOR trial; 251 to the daratumumab group and 247 to the control group. For inclusion in the trial, patients must have had documented multiple myeloma as defined by specific criteria described elsewhere.[16] Patients must also have received at least 1 prior line of therapy, defined as 1 or more cycles of a planned treatment program and have documented evidence of progressive disease as defined by IMWG criteria. Patients must have achieved a partial response or better to at least 1 prior regimen. The demographic, disease, and clinical characteristics of the two study arms were reportedly balanced at baseline (Table 5). The median age of patients in the CASTOR trial was 64 years in both treatment arms. The median time since the initial diagnosis of multiple myeloma was 3.87 and 3.72 years respectively, in the treatment and control groups. The majority of patients were of standard-risk in terms of cytogenic abnormality, but 23% and 21% of patients in the treatment and control arms, respectively, were of high risk (Del17p, t(4;14), or t(14:16)).[6] The median number of previous lines of therapy for both groups was 2, with a range of 1 to 10. Of note, 23.9% of patients had received at least 3 previous lines of therapy.

In the POLLUX trial, 569 patients were randomized; 286 to the daratumumab group and 283 to the control group. Eligibility criteria were the same as those in the CASTOR trial with the exception of references to bortezomib, since lenalidomide was used in the POLLUX trial. All[16,17] baseline demographic, disease, and clinical characteristics were well balanced between study arms. The median age was 65 years in both groups. The median time since the initial multiple myeloma diagnosis was 3.5 and 4 years, respectively, in the treatment and control groups. There were 35 patients (15% and 17% of DRd and Rd patients, respectively) in each group that had a high risk cytogenetic profile. The median number of previous lines of therapy for both groups was 1 (range, 1-11) and 19.2% of patients had received at

least 3 previous lines of therapy. Additional baseline characteristics are outlined in Table 5.

Table 4: Select quality characteristics of included studies of daratumumab in combination with bortezomib and dexamethasone or lenalidomide and dexamethasone in patients with RRMM.

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
CASTOR	DVd vs. Vd	PFS	480 patients required for 295 events of disease progression or death to provide 85% power to detect a HR=0.70 using a two-sided overall alpha=0.05(stratified log-rank test)[A]	251 vs. 247	Central, computer-generated randomization schedule prepared by the study sponsor. 1:1 randomization balanced by randomly permutated blocks and stratified[B]. The IWRS assigned a unique treatment code dictating the treatment assignment and matching study treatment kit for the subject.	Yes	None	Yes	No	No	Yes
POLLUX	DRd vs. Rd	PFS	560 patients required for 295 events of disease progression or death to provide 85% power to detect a HR=0.70 using a two-sided alpha=0.05 (stratified log-rank test)[C]	286 vs. 283	Central, computer-generated randomization schedule prepared by the study sponsor. 1:1 randomization balanced by randomly permuted blocks and stratified[D]. The IWRS assigned a unique treatment code dictating the treatment assignment and matching study treatment kit for the subject.	Yes	None	Yes	No	No	Yes

Abbreviations: CI – confidence interval; DRd – Daratumumab, lenalidomide, low-dose dexamethasone; DVd – Daratumumab, VELCADE (bortezomib), dexamethasone; HR – hazard ratio; ISS – International Staging System; ITT – intention to treat analysis; IWRS – Interactive Web Response System; PFS – progression-free survival; Rd – lenalidomide, low-dose dexamethasone; RRMM – relapsed or refractory multiple myeloma; Vd – VELCADE (bortezomib), dexamethasone; vs. – versus

Notes: [A] The statistical hypothesis was a 30% reduction in the risk of either progression or death, thereby assuming that the addition of daratumumab could prolong the PFS from 10 months to 14.3 months. With a 16-month accrual period and a 10-month follow-up, the required sample size was 480 subjects (240 per group).[6]

[B] Stratified by ISS disease stage (I, II, or III) at screening, number of prior lines of therapy (1 vs. 2 or 3 vs. >3), and prior treatment with bortezomib (no vs. yes).

[C] The statistical hypothesis was a 30% reduction in the risk of either progression or death, thereby assuming that the addition of daratumumab could prolong PFS from 18 months to 25.7 months. With a 16-month accrual period and an 18-month follow-up, the required sample size was 560 subjects (280 per group).[6]

[D] Stratified by ISS (I, II, or III) at screening, number of prior lines of therapy (1 vs. 2 or 3 vs. >3), and prior lenalidomide treatment (no vs. yes).

c) Interventions

Details of the dosing and administration of the drug regimens used in the treatment and control arms of each trial can be found in Table 3. In both trials, treatment regimens were given until disease progression, unacceptable toxicity, oSr patient withdrawal from the trial.[16,17] The same dose of daratumumab was used in both the CASTOR and POLLUX trials, however, the administration schedules were different and are outlined in detail below. By the interim analysis date (based on a median follow-up for CASTOR of 13.0 months and median follow-up for POLLUX 17.3 months), the median duration of study treatment in the experimental arm of the CASTOR trial was [redacted] months and in the control arm was [redacted] months. For the POLLUX trial, the median duration of treatment was [redacted] months and [redacted] months for the experimental and control arms, respectively.[82] (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed*.)

For patients in the CASTOR trial, cycles 1-8 were 21-day cycles. Cycle 9 and onwards were 28-day cycles. In the experimental arm, daratumumab was administered as an IV infusion at a dose of 16mg/kg weekly for the first 3 cycles, on Day 1 of cycles 4-8, and then every 4 weeks thereafter. Patients received pre- and post-infusion medications as needed to reduce the risk of infusion-related reactions.

For both study arms, bortezomib was administered at a dose of 1.3mg/m^2 subcutaneously on days 1, 4, 8, and 11 of each 21-day cycle. Dexamethasone was also administered in both arms at a dose of 20mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of the first 8 bortezomib treatment cycles. A total of 79.8% of the patients in the daratumumab group and 57.4% in the control group received the maximum of 8 cycles of bortezomib treatment. The median relative dose intensity for bortezomib in the daratumumab and control group was 86.5% and 93.5%, respectively, and 98.2% and 100% for dexamethasone in the daratumumab and control groups, respectively. The median relative dose intensity for daratumumab was 99.2%.[6] In terms of mean *cumulative* doses, the doses of daratumumab, bortezomib, and dexamethasone attained in the experimental group were [redacted]/kg (standard deviation, SD, [redacted]), [redacted]mg/m^2 (SD, [redacted]), and [redacted]mg (SD, [redacted]), respectively. Similar mean cumulative doses were observed in the control group with bortezomib at [redacted]mg/m^2 (SD, [redacted]) and dexamethasone at [redacted]mg (SD, [redacted]).[82] *Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed*.)

In the POLLUX trial, all cycles were approximately 28 days. In the experimental arm, daratumumab was administered as an IV infusion at a dose of 16mg/kg weekly for 8 weeks (on days 1, 8, 15, and 22 for cycles 1 and 2), every 2 weeks for 16 weeks (on days 1 and 15 for cycles 3-6), and then every 4 weeks thereafter. Patients received pre-and post-infusion medications as needed to reduce the risk of infusion-related reactions.

Lenalidomide was administered in both study arms at a dose of 25mg orally each day on days 1-21 of each 28-day cycle, for patients with creatinine clearance 60mL/min. This dose was reduced to 10mg every 24 hours for patients with

creatinine clearance between 30-60mL/min. Dexamethasone was also administered in both study arms at a total dose of 40mg weekly. For the daratumumab group the dose of dexamethasone was split, with a 20mg dose administered before infusion as prophylaxis for infusion-related reactions and 20mg administered the next day. The median relative dose intensity of lenalidomide was 85.2% in the daratumumab group and 95.8% in the control group. The mean dose intensity of lenalidomide in patients who received at least 6 months of treatment was 378mg per cycle in the daratumumab group and 429mg per cycle in the control group.[3] In terms of mean cumulative doses, those for daratumumab, lenalidomide, and dexamethasone in the experimental group were [redacted] mg/kg (SD, [redacted]), [redacted]mg (SD, [redacted]), and [redacted]mg (SD, [redacted]), respectively. Comparative mean cumulative doses were observed in the control group with lenalidomide at [redacted]mg (SD, [redacted]) and dexamethasone at [redacted]mg ([redacted]).[82] (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed*.)

In both CASTOR and POLLUX, dose modifications for daratumumab (increase or decrease) were not permitted. The daratumumab dose was to be held to allow for recovery from toxicity if any of the following criteria were met: Grade 4 hematologic toxicity, Grade 3 or higher non-hematologic toxicities (with some exceptions outlined in the study protocol). Daratumumab treatment was to resume when the toxicity had resolved to ≤ Grade 2. Both trials also modified the dose of dexamethasone to 20mg weekly in both study arms in patients who were >75 years or whose body-mass index was less than 18.5. Neither trial publication provided a statement on concomitant medications and whether or not they were allowed during the trial.

d) Patient Disposition

The disposition of patients at the prespecified interim analysis is outlined in Table 6. In the CASTOR trial, a total of 480 patients received at least one dose of treatment (243 and 237 in the daratumumab and control arms, respectively). Of those that received treatment, there were more treatment discontinuations in the control group compared to the daratumumab group (43.9% vs. 30.5%, respectively). The main reason for treatment discontinuation was disease progression. There were no losses to follow-up in the CASTOR trial and all randomized patients were included in the primary outcome analysis (intention-to-treat, ITT).

In the POLLUX trial, a total of 564 patients received at least one dose of treatment (283 and 281 in the daratumumab and control arms, respectively). There was a greater difference between groups in the POLLUX trial in terms of treatment discontinuations, but there were still fewer patients that discontinued in the control group compared to the daratumumab group (47.0% versus 23.3%, respectively). Disease progression was again the main reason for treatment discontinuation. There was 1 patient in each study arm lost to follow-up.

Table 5: Baseline characteristics in the included trials of daratumumab in combination with bortezomib and dexamethasone or lenalidomide and dexamethasone in patients with RRMM.				
Patient Characteristics	***CASTOR* Trial[6]**		***POLLUX* Trial[3]**	
	Daratumumab + Bortezomib + Dexamethasone (DVd)	**Bortezomib + Dexamethasone (Vd)**	**Daratumumab + Lenalidomide + Dexamethasone (DRd)**	**Lenalidomide + Dexamethasone (Rd)**
N randomized	251	247	286	283
Median age (range) (yr)	64 (30-88)	64 (33-85)	65 (34-89)	65 (42-87)
Distribution no. (%)				
< 65 yr	132 (52.6)	125 (50.6)	133 (46.5)	140 (49.5)
65-74 yr	96 (38.2)	87 (35.2)	124 (43.4)	108 (38.2)
≥75 yr	23 (9.2)	35 (14.2)	29 (10.1)	35 (12.4)
Race no. (%)				
White	216 (86.1)	219 (88.7)	207 (72.4)	186 (65.7)
Black	14 (5.6)	6 (2.4)	5 (1.7)	11 (3.9)
Asian	12 (4.8)	11 (4.5)	54 (18.9)	46 (16.3)
Other or unreported	9 (3.5)	11 (4.5)	20 (7.0)	40 (14.1)
Type of measurable disease				
IgG	125 (49.8)	138 (55.9)	151 (52.8)	158 (55.8)
IgA	56 (22.3)	54 (21.9)	49 (17.1)	51 (18.0)
Other	5 (2.0)	4 (1.6)	5 (1.7)	2 (0.7)
Detected in urine only	40 (15.9)	36 (14.6)	41 (14.3)	37 (13.1)
Detected in serum free light-chains only	25 (10.0)	14 (5.7)	39 (13.6)	33 (11.7)
Not evaluated	0	1 (0.4)	1 (0.3)	0
ECOG performance status score no. (%)				
0	106 (42.4)	116 (47.0)	139 (48.6)	150 (53.0)
1	131 (52.4)	112 (45.3)	136 (47.6)	118 (41.7)
2	13 (5.2)	19 (7.7)	11 (3.8)	15 (5.3)
≥3	0	0	0	0
ISS disease stage no. (%)				
I	98 (39.0)	96 (38.9)	137 (47.9)	140 (49.5)
II	94 (37.5)	100 (40.5)	93 (32.5)	86 (30.4)
III	59 (23.5)	51 (20.6)	56 (19.6)	57 (20.1)
Cytogenic profile no./total (%)				
Standard risk	140/181 (77.3)	137/174 (78.7)	193/228 (84.6)	176/211 (83.4)
High risk	41/181 (22.7)	37/174 (21.3)	35/228 (15.4)	35/211 (16.6)
Del 17p	28/181 (15.5)	21/174 (12.1)	25/228 (11.0)	20/211 (9.5)
t(4;14)	14/181 (7.7)	15/174 (8.6)	10/228 (4.4)	15/211 (7.1)
t (14;16)	4/181 (2.2)	5/174 (2.9)	2/228 (0.9)	6/211 (2.8)
Median time since diagnosis yr (range)	3.87 (0.7-20.7)	3.72 (0.6-18.6)	3.5 (0.4-27.0)	4.0 (0.4-21.7)
No. previous lines of therapy				
1	122 (48.6)	113 (45.7)	149 (52.1)	146 (51.6)
2	70 (27.9)	74 (30.0)	85 (29.7)	80 (28.3)
3	37 (14.7)	32 (13.0)	38 (13.3)	38 (13.4)
>3	22 (8.8)	28 (11.3)	14 (4.9)	19 (6.7)
Median no. of previous lines of therapy (range)	2 (1-9)	2 (1-10)	1 (1-11)	1 (1-8)
Previous therapy no. (%)				
ASCT	156 (62.2)	149 (60.3)	180 (62.9)	180 (63.6)
Proteasome inhibitor (PI)	169 (67.3)	172 (69.6)	245 (85.7)	242 (85.5)
Immunomodulatory drug (IMiD)	179 (71.3)	198 (80.2)	158 (55.2)	156 (55.1)
Glucocorticoid	244 (97.2)	245 (99.2)	280 (97.9)	281 (99.3)
Alkylating agent	240 (95.6)	224 (90.7)	268 (93.7)	270 (95.4)
PI + immunomodulatory drug	112 (44.6)	129 (52.2)	125 (43.7)	125 (44.2)
PI + IMiD + alkylating agent	112 (44.6)	121 (49.0)	118 (41.3)	121 (42.8)

Bortezomib and lenalidomide	75 (29.9)	89 (36.0)	44 (15.4)	43 (15.2)
Refractory disease no. (%)				
To last line of therapy	76 (30.3)	85 (34.4)	80 (28.0)	76 (26.9)
To PI only	3 (1.2)	4 (1.6)	57 (19.9)	46 (16.3)
To IMiD only	74 (29.5)	90 (36.4)	10 (3.5)	11 (3.9)
To PI and IMiD	9 (3.6)	7 (2.8)	7 (2.4)	14 (4.9)
Abbreviations: ASCT – autologous stem-cell transplant; IMiD – immunomodulatory drug; PI – proteasome inhibitor; RRMM – relapsed or refractory multiple myeloma				
Notes:				

Table 6: Patient disposition in the CASTOR and POLLUX trials.

	CASTOR[6]		*POLLUX*[3]	
	DVd	Vd	DRd	Rd
Total patients enrolled (randomized)	597 (498)		702 (569)	
Randomized	251	247	286	283
Received treatment[A]	243	237	283	281
Discontinued treatment, n (%)	74 (30.5)	104 (43.9)	66 (23.3)	132 (47.0)
Reasons for treatment discontinuation:				
Disease progression, n (%)	47 (19.3)	60 (25.3)	40 (14.1)	96 (34.2)
Adverse event, n (%)	19 (7.8)	23 (9.7)	19 (6.7)	23 (8.2)
Non-compliance, n (%)	3 (1.2)	8 (3.4)	1 (0.4)	5 (1.8)
Patient withdrawal, n (%)	1 (0.4)	9 (3.8)	1 (0.4)	5 (1.8)
Physician decision, n (%)	0	0	3 (1.1)	2 (0.7)
Death n (%)	4 (1.6)	4 (1.7)	2 (0.7)	1 (0.4)
Follow-up ongoing, n (%)	169 (69.5)	133 (56.1)	216 (76.3)	148 (52.7)
Lost to follow-up, n (%)	0	0	1 (0.4)	1 (0.4)

Abbreviations: DRd – daratumumab + lenalidomide + dexamethasone; DVd – daratumumab + bortezomib + dexamethasone; Rd – lenalidomide + dexamethasone; Vd – bortezomib + dexamethasone

Notes: [A] – patients who had received at least one treatment, which also comprised the safety population

e) Limitations/Sources of Bias

A summary of key quality indicators for the CASTOR and POLLUX trials is provided in Table 4. The two trials, both sponsored by Janssen to demonstrate the superiority of adding daratumumab to doublet combinations compared with the doublets alone, were conducted in a very similar fashion, the major difference being the agents used with or without daratumumab (i.e., bortezomib + dexamethasone versus lenalidomide + dexamethasone). Overall, both trials were well conducted but the risk of bias was not absent. Both CASTOR and POLLUX used appropriate methods of central randomization and stratified accordingly in 1:1 blocks to successfully ensure that the treatment groups were well balanced in terms of baseline characteristics. Neither trial provided any statement on methods used to ensure allocation concealment, which, if not actually concealed

would introduce selection bias. Formal statistical hypotheses were appropriately noted in both study protocols and sample sizes were based on the determination of sufficient power required to test for the desired difference in treatment effect. All interim efficacy analyses were appropriately performed by assigned treatment according to intention-to-treat. However, the following limitations and biases associated with the trials should be considered when reviewing the results:

- The trials were both open-label, and as such are at risk for a number of different biases that can affect the internal validity of a trial. Investigators and patients were not blinded to treatment assignment and thus, ascertainment bias, when the results of a trial are systematically distorted by knowledge of which intervention each participant is receiving is likely to have been introduced. As a result, patients in the treatment groups may have been more likely to adhere to the experimental therapy and investigators may have been more likely to discontinue treatment in the control therapy arms. This could easily have been overcome by introducing masking at various levels. Masking the investigators responsible for recruiting patients in the trials would also have reduced the chance of sample population bias (a type of selection bias), which can have a major effect on the generalizability of the results. Selection bias can occur if some potentially eligible individuals are selectively excluded from the study, because the investigator knows the group to which they would be allocated if they participated. Given that an exclusion criterion for both trials was "any concurrent medical condition or disease that is likely to interfere with study procedures or results, or that *in the opinion of* the investigator would constitute a hazard for participating in the study", it is possible that certain patients were knowingly or unknowingly excluded from the study, which could exaggerate the treatment effect.
- Both trials were funded by Janssen and sponsor employees were involved in all aspects of their conduct including design, data collection, analyses, and interpretation, as well as writing the final manuscript. While the use of an independent data safety and monitoring committee minimizes bias, and was reportedly used to review unblinded safety data for both trials, other measures such as central review of skeletal surveys and blinding of sponsor staff to treatment assignment were not employed. Further, neither CASTOR nor POLLUX had independent data analysts perform the interim analyses of efficacy and safety. Rather, the study sponsors performed these analyses. Data analysts could have been blinded to reduce the possibility of selective reporting bias. The extent to which the use of blinded independent investigators, outcome assessors, and data analysts would have influenced the results and reporting of the trial is unknown. Of note, in the published CASTOR report it is stated that "On the basis of the results of the interim analysis, the independent data safety and monitoring committee recommended that the trial be unblinded early (and that daratumumab therapy be offered to patients in the control group who had disease progression) because the prespecified statistical boundary for the primary endpoint of PFS had been crossed". This statement may lead one to believe that blinding was indeed used, which, as confirmed by the submitter, it was not. The submitter subsequently clarified that the study sponsor was blinded to *aggregate* safety and efficacy data but that they could review single patient level data and review the treatment assignment.
- While Grade 3/4 hematologic events did occur in both trials, neither trial publication reported on dose reductions or interruptions for any of the drug regimens used; they simply reported the percentage of patients with adverse events leading to the discontinuation of treatment. It is important to report

modifications to the treatment schedules, particularly in combination drug regimens because the ideal administration schedule of daratumumab is still being studied – there is no current standard of care.

- In the POLLUX trial, the proportion of patients randomized that did not receive treatment was very low (≤1%) in both groups. (i.e. 99% of pts who were randomized also received treatment). In the CASTOR trial, slightly more patients (3% and 4% in the treatment and control groups) who were randomized did not actually receive treatment. This has an impact on the intention-to-treat analysis, which requires participants to be included even if they did not fully adhere to the protocol but the overall impact in these trials is minimal.
- With respect to reporting of outcomes, it should be emphasized that the evidence from the CASTOR and POLLUX trials is coming from interim, not final analyses. As such, PFS data are immature and should therefore be interpreted with some degree of caution.
- While not a source of bias, the comparator arms in the CASTOR and POLLUX trials are among several standard of care regimens used to treat patients with relapsed or refractory multiple myeloma in Canada and therefore the generalizability of the trial results should be interpreted within this context. It should also be noted that the same dose of daratumumab was used between trials but different administration schedules were used. While baseline characteristics were similar between trials, cross-trial comparisons should always be made with caution.[85]
- According to the forest plots generated for group comparisons by prespecified subgroups, it would appear that patients with one previous line of therapy had the greatest benefit in terms of median PFS in the CASTOR trial. In the POLLUX trial, patients with two previous lines of therapy had the most significant prolongation of PFS. However, one should not conclude that patients with such treatment histories are the ideal candidates for daratumumab therapy on the basis of these subgroup analyses. These statistics are best reserved for confirmation of benefits rather than treatment decisions, since subgroup analyses are at risk of overstating and misleading results.[86]
- Another limitation relates to the fact that daratumumab is known to cause interference with the determination of complete response.[87] In the CASTOR trial investigators that suspected that a patient's dose of daratumumab had interfered with the quantitation of serum M-protein as determined by either the electrophoresis assay or the immunofixation assay had additional reflex testing done using an antiidiotype antibody to confirm the complete response.[6] Appropriately, it was also reported that no VGPRs were reclassified as either CRs or sCRs as a result of additional immunofixation electrophoresis reflex testing to account for daratumumab. Whether or not any such events were reclassified was not reported by POLLUX investigators.
- The utility of MRD status is gaining greater importance in determining depth of response to therapy and is being used in more trials as a predictor of PFS and OS.[88] While this is promising and meta-analyses have shown a strong association between MRD negativity and improved PFS and OS[77], is important to remember that this is a surrogate outcome, and therefore the effect of the intervention on the surrogate cannot predict the actual effect on the true clinical outcome with 100% accuracy.

Overall, while it is important to point out the various *possible* sources of bias in each trial, it is unlikely that these have a major impact on the treatment

effect. The most notable limitation comes from the fact that these are interim, and not fully mature data.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

The majority of data reported below are from the fully published POLLUX and CASTOR studies at a median follow-up of 13.5 months for POLLUX and a median follow-up of 7.4 months for CASTOR,. The updated efficacy data for the 12 and 18 month Overall Survival (OS) ratesare reported from updated analyses with median follow up of 17.3 months for the POLLUX trial and 13.0 months for the median follow up for CASTOR.

Efficacy Outcomes

Progression-free Survival

Progression-free survival (PFS) was defined as the duration from the date of randomization to either progressive disease (PD) or death, whichever occurred first. The criteria for PD are described elsewhere. A summary of key efficacy outcomes is presented in Table 7. At the prespecified interim analysis, the CASTOR trial demonstrated that the addition of daratumumab to the bortezomib + dexamethasone resulted in a significantly better median PFS compared with bortezomib and dexamethasone alone (not estimable versus 7.16 months; hazard ratio 0.39, p<0.0001). The rate of PFS at 12 months was 60.7% in the daratumumab group versus 26.9% in the control group. In the POLLUX trial, the interim analysis demonstrated a 63% reduction in the risk of disease progression in those who received the combination of daratumumab with lenalidomide and dexamethasone compared to those who did not receive daratumumab (HR 0.37; 95% CI 0.27 to 0.52, p<0.001). The median PFS for the treatment arm has not been reached compared with an estimated PFS of 18.4 months in patients who received lenalidomide + dexamethasone alone. Median PFS at 12 months was not reported.

Time to Disease Progression[82]

Time to disease progression (TTP) was defined as the time from randomization to the date of the first documented evidence of PD. While these data were not reported in the CASTOR and POLLUX journal articles, the clinicaltrials.gov website reported a total of 51 (20.3%) events (at the median follow up of 7.4 months) and a longer median Kaplan-Meier estimate for TTP in the daratumumab group (not estimable, 95% CI 12.25 months to not estimable) compared to the control group (7.29 months, 95% CI, 6.41 to 8.08) for the CASTOR trial (p<0.0001, HR 0.30 (0.21 to 0.43)). A similarly longer TTP was observed in the POLLUX trial for the daratumumab group with the median TTP not estimable due to the short follow-up period in the treatment group compared with a median TTP of 18.43 months (95% CI 14.78 to not estimable) in the control group (p<0.0001, HR 0.34 (0.23 to 0.48)). The total number of events observed at the median follow-up of 13.5 months was 44 (15.4%).

Overall Response

The overall response rate (ORR) was defined as the percentage of patients who achieved a partial response (PR) or better (stringent complete response (sCR), complete response (CR), or very good partial response (VGPR)) according to the

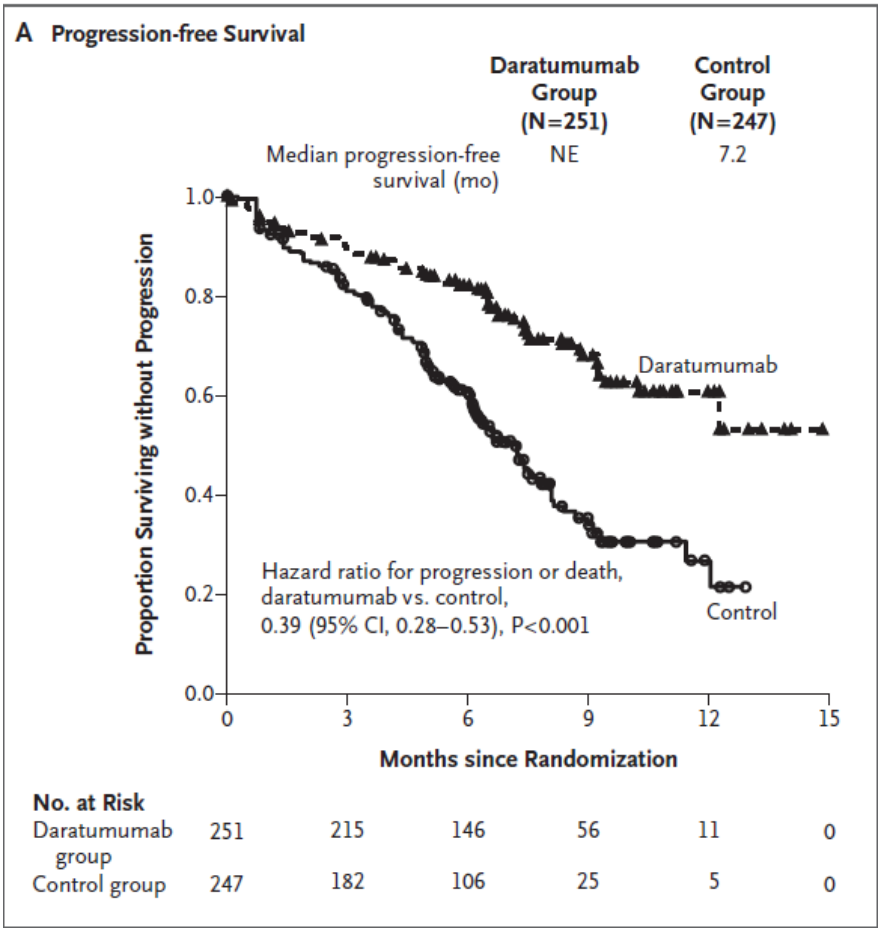
IMWG criteria, during the study or during follow up. These criteria are reported elsewhere[18,19] and the results are presented in Table 7. The response-evaluation population included patients with a confirmed diagnosis of multiple myeloma who had received at least 1 administration of daratumumab and had at least 1 post-baseline disease assessment. In the CASTOR trial, the number of patients analyzed included 240/251 (96%) patients in the daratumumab group in which an ORR of 82.9% (95% CI 77.5 to 87.5) was reported. This was significantly higher (p<0.001) compared with the ORR in the control group of 63.2% (95% CI 56.7 to 69.4) in which 234/247 (95%) patients were analyzed. Results for ORR were similar in the POLLUX trial in that daratumumab conferred a significantly higher ORR (92.9%, 95% CI 89.2 to 95.6) compared to the control group (76.4%, 95% CI 71.0 to 81.3). This outcome was evaluated in 281/286 (98%) patients in the daratumumab group and 276/283 (98%) patients in the control group. Other notable response outcomes that demonstrated significant superiority in the daratumumab group (p<0.001) were the number of patients with a CR or better and the number of patients with a VGPR or better in both the CASTOR and POLLUX trials (p=0.001 for CR response or better in CASTOR) (Table 7).[3,6]

In the CASTOR trial, the median time to the first response (TTR) was 0.9 months in the daratumumab group and 1.6 months in the control group and a longer duration of response (DoR) was observed in the daratumumab group compared to the control group (not reached, 95% CI, 11.5 months to not estimable) versus 7.9 months (95% CI, 6.7 to 11.3 months).[6] These data were not reported in the POLLUX trial.

Overall Survival

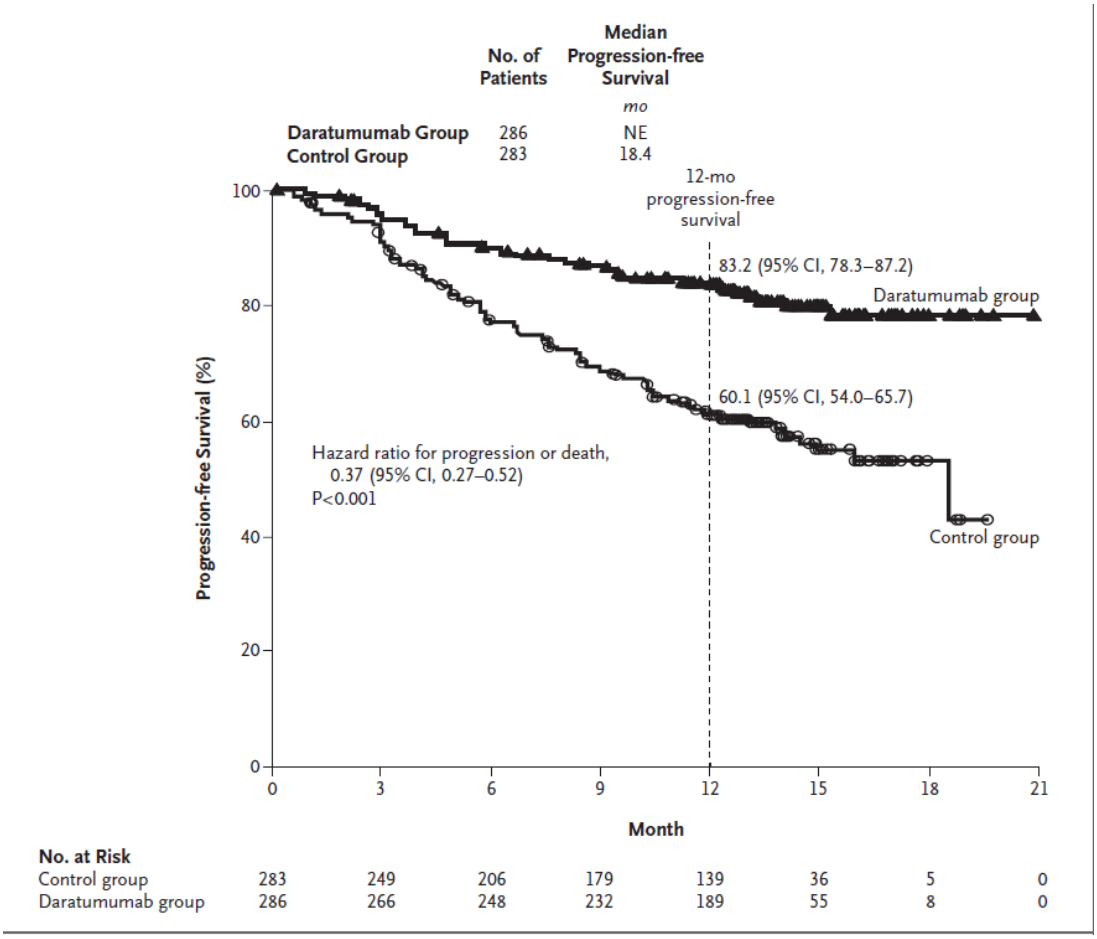
The median overall survival (OS) was measured from the date of randomization to the date of the patient's death, with the anticipated time frame of up to approximately 5 years after the last patient is randomized.[18,19] This outcome is to be calculated based on an ITT analysis but data have not yet been reported due to the short follow-up period up to the interim analysis. However, POLLUX did report 12-month overall survival data (Table 7). At the interim analysis in the CASTOR trial, a total of 65 deaths (29 in the daratumumab group and 36 in the control group; hazard ratio, 0.77; 95% CI 0.47 to 1.26) had been observed. At the interim analysis in the POLLUX trial, a total of 75 deaths had occurred: 30 in the daratumumab arm and 45 in the control arm. Overall survival at 12 months was 92.1% (95%CI, 88.2 to 94.7) in the daratumumab group and 86.8% (95% CI, 82.2 to 90.3) in the control group. At an updated median follow-up of 17.3 months for the POLLUX trial, there were 40 events in the daratumumab arm and 56 events in the control arm. The 12 month survival rate (%) for the POLLUX trial was 92.2 (95%CI, 88.4 – 94.8) in the daratumumab arm and 87.0 (95%CI, 82.4 – 90.4) in the comparator arm. The 18 month survival rate (%) in the POLLUX trial was 85.1 (95% CI 80.1-89.0) and 78.9 (95%CI. 72.9 – 83.7). Similarly, at an updated median follow-up of 13.0 months in the CASTOR arm, there were 37 events in the daratumumab arm and 58 in the control arm. Follow-up for long-term survival is ongoing in both trials. The 12 month survival rate (%) in the CASTOR trial was 85.5 (95%CI, 80.4 – 89.4) in the daratumumab arm and 79.9 (95% CI, 74.1 – 84.5) in the comparator arm. The 18 month survival rate (%) in the CASTOR trial was 83.9 (95%CI, 78.3-88.2) in the daratumumab arm and 68.8 (95% CI 60.4 – 75.8) in the comparator arm.[79]

Figure 1. Kaplan-Meier curve of PFS in CASTOR trial.



From The New England Journal of Medicine, Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma, Volume 375 No. 8, Page 760.

Figure 2. Kaplan-Meier curve of PFS in POLLUX study.



From The New England Journal of Medicine, Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma, Volume 375 No. 14, Page 1324.

Table 7: Summary of key efficacy outcomes in included trials of daratumumab in combination with bortezomib and dexamethasone or lenalidomide and dexamethasone in patients with RRMM.

Treatment Arms (n)	Median Follow-up (mos)	N events of disease progression or death n (%)	PFS		12-mo PFS		ORR	CR or better n (%)	VGPR or better n (%)	Updated Overall Survival at 12 mos
			Median (95% CI)	HR (95% CI)	Rate	HR (95% CI)	n with response Rate (%, 95% CI)			Rate (95% CI)
	***CASTOR* Trial[3,18]**									
DVd (n=251)	*7.4*	67 (26.7%)	NE (12.25-NE)	0.39 (0.28-0.53) *p<0.0001*	60.7		199 82.9 (77.5-87.5) *p<0.001*	46 (19.2%)	142 (59.2%)	85.5 (80.4-89.4) *Median Follow-up of 13.0 months
Vd (n=247)		122 (49.4%)	7.16 (6.21-7.85)		26.9		148 63.2 (56.7-69.4)	21 (9.0%)	68 (29.1%)	79.9 (74.1-84.5) *Median Follow-up of 13.0 months
	***POLLUX* Trial[6,19]**									
DRd (n=286)	13.5	53 (18.5%)	NE	0.37 (0.27-0.52)	NE	83.2 (78.3-87.2) *p<0.0001*	261 92.9 (89.2-95.6)	121 (43.1%)	213 (75.8%)	92.2 (88.4-94.8) *Median Follow-up of 17.3 months
Rd (n=283)		116 (41%)	18.4 (13.86-NE)		18.4	60.1 (54.0-65.7)	211 76.4 (71.0-81.3)	53 (19.2%)	122 (44.2%)	87.0 (82.4-90.4) *Median Follow-up of 17.3 months)

Abbreviations: CI – confidence interval; CR – complete response; DVd – daratumumab + bortezomib + dexamethasone; DRd – daratumumab + lenalidomide + dexamethasone; HR – hazard ratio; mos – months; n – number; NE – not estimable; NR – not reported; ORR – overall response rate; PFS – progression-free survival; Rd – bortezomib + dexamethasone; VD – lenalidomide + dexamethasone; VGPR – very good partial response

Other Key Secondary Outcomes

Minimal Residual Disease (MRD)

The minimal residual disease negativity rate was defined as the percentage of patients who had negative MRD assessment at any timepoint after the first dose of study drugs by evaluation of bone marrow aspirates or whole blood. The percentage of patients who are MRD negative and the percentage with MRD negativity by different thresholds was compared between the two treatment groups. MRD was assessed in patients who achieved complete response (CR) or stringent complete response (sCR) by IMWG criteria. In cases where daratumumab is suspected of interfering with IFE and preventing clinical CR response calls, patients with very good partial response (VGPR) were also evaluated for MRD. This outcome was assessed from the timepoint above up to disease progression. To evaluate the relationship between MRD negativity and clinical outcomes such as progression-free survival, the Kaplan-Meier method was used to estimate the distribution of PFS by MRD status and treatment group for patients.[16,17]

Assessment of MRD negativity included the intention-to-treat population of all randomized patients in the CASTOR (daratumumab n=251, control n=247) and POLLUX (daratumumab n=286, control n=283) trials. In the CASTOR trial, the percentage of patients with negative MRD status was 13.5% in the daratumumab arm and 2.8% in the control arm. In the POLLUX trial, these figures were 29.0% in the daratumumab and 7.8% in the control arms, respectively.[18,19] While not reported in the CASTOR trial, 22.4% of patients in the daratumumab arm in the POLLUX trial had results below the threshold for minimal residual disease (1 tumour cell per 10^5 white cells) as compared to 4.6% of patients in the control group ($p<0.001$). This trend continued in the daratumumab group at all evaluated thresholds (1 tumour cell per 10^4 and 10^6 white cells) No further formal statistical analyses on MRD negativity have been reported. According to the Kaplan-Meier plot for PFS based on a computerized algorithm by MRD status, it is also clear that patients who achieved MRD negativity appeared to have a longer PFS compared with patients who were MRD positive.

Quality of Life

As reported in both study protocols, functional status and well-being was assessed using 2 patient-reported outcome measures, the EORTC-QLQ-C30, which has been widely used among cancer patients and the EQ-5D-5L, which is a generic measure of health status. Key changes from baseline at each time point is to be summarized descriptively by treatment group. A time-to-event analysis (to worsening or improvement) is also to be conducted using Kaplan-Meier methods. To date, results of these outcome measures have not yet been published, however, some preliminary results have been provided by the submitter. In the CASTOR trial, the addition of daratumumab to bortezomib and dexamethasone maintained the quality of life of patients. There were no significant differences in the mean scores over time on the Global Health Status except at Week 24, which favoured the DVd treatment group. In the POLLUX trial, both groups noted an improvement in quality of life over time, with a statistically significant improvement seen at weeks 40 and 48, favouring the DRd treatment group.

Harms Outcomes

Grade 3 or 4 Adverse Events

The most common Grade 3 or 4 (occurring in at least 5% of patients in either treatment group) adverse events in the safety population (daratumumab group n=243; control group n=237) of the CASTOR trial are summarized in Table 8. Patients in the daratumumab experienced a higher rate of Grade 3 or 4 adverse events than those in the control group (76.1% vs. 62.4%, respectively). The most commonly observed events in the treatment and control groups were thrombocytopenia (45.3 and 32.9, respectively), anemia (14.4% and 16.0%, respectively), and neutropenia (12.8% and 4.2%, respectively).

With respect to hematologic and nonhematologic adverse events of *any* grade, higher rates were also observed in the daratumumab group for thrombocytopenia (58.8% vs. 43.9%), neutropenia (17.7% vs. 9.3%), lymphopenia (13.2% vs. 3.8%), peripheral sensory neuropathy (47.3% vs. 37.6%), bleeding events (7.0% vs. 3.8%), and secondary primary cancers (2.5% vs. 0.4%), a rare but important consideration in the treatment of multiple myeloma.[10] Of note, 4 of the 6 cases of secondary primary cancers in the daratumumab group developed within 6 months of the initiation of trial therapy and occurred in patients with previous exposure to immunomodulatory drugs and alkylating agents, which suggests that other etiological risk factors were present.[6,10]

The most common Grade 3 or 4 adverse events in the safety population (daratumumab group n= 283; control group n=281) of the POLLUX trial are presented in Table 8. Again, patients in the daratumumab group experienced more Grade 3/4 adverse events compared to control patients. Common Grade3/4 hematologic events included neutropenia in 51.9% of daratumumab patients and 37.0% of those in the control group, anemia (12.4% and 19.6%, respectively), and thrombocytopenia (12.7% and 13.5%, respectively). Several Grade 3/4 nonhematologic adverse events were also higher in the daratumumab group than the control group including diarrhea (5.3% vs. 3.2%, respectively), fatigue (6.4% vs. 2.5%), nausea (1.4% vs. 0%), and dyspnea (3.2% vs. 0.7%). The rate of Grade 3/4 infection was also higher in the daratumumab group than in the control group (28.3% vs. 22.8%, respectively), with infection being the most common event, which occurred at similar rates in the two groups.[3]

Infusion-related Reactions

Almost half (45.3%) of patients receiving daratumumab in the CASTOR trial experienced an infusion-related reaction of any grade. For most of these patients (98.2%), the reaction occurred during the first infusion. These reactions were primarily limited to Grade 1 or 2 events, but at least one Grade 3 event was reported in 8.6% (21/243) of patients. There were no Grade 4 or 5 infusion-related reactions. The most commonly reported reactions were dyspnea (10.7%), bronchospasm (9.1%), and cough (7.0%). There were two treatment discontinuations due to infusion-related reactions: bronchospasm in one patient and bronchospasm, laryngeal edema, and rash in the other patient.

The rate of infusion-related reactions in the POLLUX trial was similar to CASTOR with 47.7% of patients receiving daratumumab experiencing an event of any grade. Again, most (92%) of these reactions took place during the first infusion. The reactions were mostly Grade 1 or 2 with 15 patients (5.3%) having a Grade 3 reaction. There were no Grade 4 or 5 infusion-related reactions. The most

common reactions were cough (8.5%), dyspnea (8.5%), and vomiting (5.7%). Of note, one patient discontinued daratumumab because of a Grade 3 infusion-related reaction, recovered, and then continued to receive lenalidomide and dexamethasone.[3,6]

Adverse Events Leading to Withdrawals or Death

Adverse events leading to treatment discontinuation in the CASTOR trial occurred in 7.4% and 9.3% of patients in the daratumumab and control groups, respectively. The most common adverse events leading to discontinuation were peripheral sensory neuropathy (0.4% in DVd group, 2.5% in Vd group) and pneumonia (1.2% and 0.4%, respectively). Thirteen (5.3%) daratumumab patients and 14 (5.9%) control patients experienced adverse events leading to death. These events were primarily a general deterioration of the patients' physical health, pneumonia, ischemic stroke, and respiratory failure.

In the POLLUX trial, adverse events leading to treatment discontinuation occurred in 6.7% of patients in the daratumumab and 7.8% of patients in the control group. The most common adverse events that led to discontinuation were pneumonia (1.1% of patients in DRd group, 0.7% of patients in Rd group), pulmonary embolism (<1% in DRd group, 1.1% in Rd group), and deterioration in general physical health (1.1% in DRd group, <1% in Rd group). Eleven (3.9%) daratumumab patients and 15 (5.3%) control patients experienced adverse events leading to death. The most common of these events were acute kidney injury, septic shock, and pneumonia.[3]

Table 8: Number of patients with Grade 3/4 adverse events in the CASTOR and POLLUX trials.

Trial	***CASTOR***		***POLLUX***	
Treatment Arm	**DVd (N=243)**	**Vd (N=237)**	**DRd (N=283)**	**Rd (N=281)**
Hematologic adverse event, N (%)				
Neutropenia	31 (12.8)	10 (4.2)	147 (51.9)	104 (37.0)
Anemia	35 (14.4)	38 (16.0)	35 (12.4)	55 (19.6)
Thrombocytopenia	110 (45.3)	78 (32.9)	36 (12.7)	38 (13.5)
Febrile Neutropenia	4 (1.6)	1 (0.4)	16 (5.7)	7 (2.5)
Lymphopenia	23 (9.5)	6 (2.5)	15 (5.3)	10 (3.6)
Nonhematologic adverse event, N (%)				
Peripheral sensory neuropathy	11 (4.5)	16 (6.8)	1 (0.4)	1 (0.4)
Diarrhea	9 (3.7)	3 (1.3)	15 (5.3)	9 (3.2)
Nausea	1 (0.4)	0	4 (1.4)	0
Vomiting	0	0	3 (1.1)	2 (0.7)
Fatigue	11 (4.5)	8 (3.4)	18 (6.4)	7 (2.5)

Table 8: Number of patients with Grade 3/4 adverse events in the CASTOR and POLLUX trials.				
Trial	***CASTOR***		***POLLUX***	
Treatment Arm	**DVd (N=243)**	**Vd (N=237)**	**DRd (N=283)**	**Rd (N=281)**
URTI	4 (1.6)	2 (0.8)	3 (1.1)	3 (1.1)
Cough	0	0	0	0
Constipation	0	2 (0.8)	3 (1.1)	2 (0.7)
Dyspnea	9 (3.7)	2 (0.8)	9 (3.2)	2 (0.7)
Nasopharyngitis	0	0	0	0
Insomnia	0	3 (1.3)	1 (0.4)	2 (0.7)
Peripheral edema	1 (0.4)	0	2 (0.7)	3 (1.1)
Pneumonia	20 (8.2)	23 (9.7)	22 (7.8)	23 (8.2)
Asthenia	2 (0.8)	5 (2.1)	8 (2.8)	7 (2.5)
Pyrexia	3 (1.2)	3 (1.3)	5 (1.8)	4 (1.4)
Back Pain	3 (1.2)	3 (1.3)	4 (1.4)	4 (1.4)
Muscle spasms	0	0	2 (0.7)	5 (1.8)
Hypertension	16 (6.6)	2 (0.8)	9 (3.2)	1 (0.4)
Abbreviations: DRd – daratumumab + lenalidomide + dexamethasone; DVd – daratumumab + bortezomib + dexamethasone; N – number; Rd – lenalidomide + dexamethasone; URTI – upper respiratory tract infection; Vd – bortezomib + dexamethasone				

6.4 Ongoing Trials[89]

One phase III, randomized, open-label, multicenter study comparing pomalidomide and dexamethasone with or without daratumumab in patients with relapsed or refractory multiple myeloma who received at least one prior line of therapy with both lenalidomide and a proteasome inhibitor is currently active and recruiting patients. The purpose of this study is to evaluate the effects of the addition of daratumumab to pomalidomide and dexamethasone in terms of progression-free survival in subjects with relapsed or refractory multiple myeloma. Details of this trial can be found in Table 9 below.

Table 9. Ongoing trials of daratumumab in patients with relapsed/refractory multiple myeloma.

Trial Design	Inclusion Criteria	Intervention and comparator	Trial Outcomes
NCT03180736 Phase III, multicenter, randomized 1:1, open-label study Previously treated patients with RRMM Estimated Enrolment: N=302 Status: active, currently recruiting Study Location: Greece Estimated Study Completion Date: June 1, 2021 Study Sponsor: European Myeloma Network	**Key Inclusion Criteria:** **Measurable disease of MM by defined criteria** Subjects must have received prior antimyeloma treatment including both a PI- and lenalidomide-containing regimens. The subject must have had a response (ie, PR or better) to prior therapy. Subjects must have documented evidence of PD Subjects who received only 1 line of prior treatment must have demonstrated PD on or within 60 days of completion of the lenalidomide containing regimen. **Key Exclusion Criteria**: Previous therapy with any anti-CD38 monoclonal antibody. Previous exposure to pomalidomide. Subject has received antimyeloma treatment within 2 wks or 5 pharmacokinetic half-lives of the treatment, whichever is longer, before the date of randomization. The only exception is emergency use of a short course of corticosteroids	Experimental Arm 1: Daratumumab+Pomalidomide+Dexamethasone Daratumumab at a dose of 16 mg/kg administered as an IV infusion at weekly intervals for 8 weeks, then every 2 weeks for an additional 16 weeks, then every 4 weeks thereafter. Pomalidomide 4 mg orally (PO) on Days 1 through 21 of each 28-day cycle Dexamethasone 40 mg (20 mg for patients ≥75 years of age) orally, once daily on Days 1, 8, 15, and 22 of each 28-day treatment cycle Active Comparator: Pomalidomide + Dexamethasone Pomalidomide 4 mg orally (PO) on Days 1 through 21 of each 28-day cycle Dexamethasone 40 mg (20 mg for patients ≥75 years of age) orally, once daily on Days 1, 8, 15, and 22 of each 28-day treatment cycle	Primary: Comparison of PFS between treatment arms (assessed monthly from randomization until PD or death Secondary: Overall response rate

	(equivalent of dexamethasone 40 mg/day for a maximum of 4 days) for palliative treatment before Cycle 1, Day 1 (C1D1). Previous allogenic stem cell transplant; or ASCT within 12 wks before C1D1. History of malignancy (other than MM) within 3 years before the date of randomization (some exceptions apply) Clinical signs of meningeal involvement of MM. COPD with a FEV1 <50% of predicted normal. Clinically significant cardiac disease		
Abbreviations: ASCT – autologous stem cell transplantation, COPD – chronic obstructive pulmonary disease, FEV1- forced expiratory volume in 1 second, MM – multiple myeloma, PD – progressive disease, PFS – progression free survival, PR – partial response, RR – relapsed or refractory			

7 SUPPLEMENTAL QUESTIONS

7.1 Critical appraisal of the network meta-analysis between daratumumab plus lenalidomide or bortezomib plus dexamethasone to carfilzomib plus lenalidomide plus dexamethasone

Background

pCODR requested from the submitter an analysis comparing daratumumab-combination regimens to carfilzomib-combination regimens. As there are no randomized control trials (RCT) reporting on the clinical efficacy and safety of daratumumab to carfilzomib, the submitter conducted a network meta-analysis (NMA).

The objective of this section is to summarize and critically appraise the submitted NMA that provides evidence for the efficacy of daratumumab-based regimens versus carfilzomib-based regimens for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Review of manufacturer's NMA

Objectives of manufacturer's NMA

The objectives of the Submitters' NMA were to compare daratumumab-combination treatments (lenalidomide or bortezomib plus dexamethasone) in patients with multiple myeloma who have received at least one prior therapy to:

- Carfilzomib-combination regimens.

Network Meta-analysis Methodology

A Bayesian approach was conducted for the NMA. An NMA combines the direct and indirect estimates of relative treatment effects in a single analysis simultaneously. [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed*). A 95% CrI represents the region where 95% of the time, the point estimate will lie within it. A pairwise probability represents a probability for a treatment to perform better than a comparator. [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed*).

Hazard ratios (HR) were used to measure the relative efficacy for time-to-event endpoints (PFS and OS) in the NMA. [redacted]. (*Non-*

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

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

Study Eligibility and Selection Process

The Manufacturer conducted a systematic literature review to identify eligible studies (criteria in Table 1) for the NMA. The initial search was conducted on March 17, 2016 and was updated on November 3, 2016.

Table 1. Population, interventions, and study design criteria for inclusion of studies

	Inclusion Criteria	Exclusion Criteria
Population	Patients with RRMM	Patients without a primary diagnosis of RRMM
Intervention	[redacted]	[redacted]
Comparison	[redacted]	[redacted]
Outcome	Primary and main secondary outcomes included in the POLLUX (MMY3003[10]) and CASTOR (MMY3004[11]) trials including the following: OS PFS Overall response [redacted]	Data that cannot be extracted
Study Design	RCTs	Abstracts from conferences other than those included in the grey literature search (i.e., ASCO, ASH, EHA, IMWG, and ISPOR).
Timepoint	Publications indexed in the literature databases since 1995; abstracts and other material from conferences held from 2013–2016 (inclusive).	Publications indexed in or before 1994. Conference abstracts presented in or before 2012.

[redacted]

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

Databases searched by the submitter included MEDLINE and MEDLINE In-Process, Embase and Embase In-Process, Cochrane Collaboration Central Register of Clinical Trials (CENTRAL), National Health Services Economic Evaluation Database (NHS-EED), and the Database of Abstracts of Reviews of Effects (DARE). In addition, proceedings from the following key conferences from 2013 to 2106 (inclusive) were reviewed: the American Society of Clinical Oncology (ASCO) Annual Meeting, American Society of Hematology (ASH) Annual Meeting, European Hematology Association (EHA) Annual Meeting, International Myeloma Working Group (IMWG) Bi-annual International Workshop, and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual International European Conference.

Additional selection criteria (as detailed in Table 2) were applied to ensure similarity across studies. The results of applying these additional selection criteria resulted in [redacted] studies being excluded. These are summarized in the below table.

Table 2. Additional criteria added to the NMA

	Inclusion Criteria	Exclusion Criteria
Population	[redacted]	[redacted]
Intervention/Comparators	[redacted]	[redacted]

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

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

Results

Overview of efficacy & safety data availability

[redacted]. (*Non-*

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

Studies were grouped according to the two networks. Four trials were included in the NMA: two for the Rd-based network and two for the Vd-based network. The Rd-based network included the RCTs POLLUX (MMY3003) and ASPIRE. The Vd-based network included the RCTs CASTOR (MMY3004) and ENDEAVOR.[7] No RCT evidence was available to allow a common comparator to join the two networks.

Abbreviations: D = daratumumab; d = dexamethasone; K = carfilzomib; NMA = network meta-analysis; R = lenalidomide
*This diagram has been provided by the Submitter; however, the pCODR review team noted that these are not Rd based regimens and an error in the figure is present.

The availability of the clinical efficacy and safety data across trials included in the network are summarized below.

Table 3. Rd-based Efficacy Outcomes, as taken from pCODR submission

Trial	PFS	OS
Base-case Analyses		
POLLUX (MMY3003)[2]:DRd vs. Rd	HR*^	HR*
ASPIRE: KRd vs. Rd[46]	HR, KM^	HR, KM

* Data not mature yet; ^ Primary outcome
Abbreviations: CR = complete response; D = daratumumab; d = dexamethasone; HR = hazard ratio; K = carfilzomib; KM = Kaplan-Meier; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; sCR = stringent complete response; VGPR = very good partial response

Table 4. Rd-based Safety Outcomes

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

The trial population in the two trials in the Rd-based network are summarized below. Note, one trial was limited to 1 – 3 lines of prior treatment (ASPIRE), whereas in the other trial patients could receive one or more lines of prior treatment (POLLUX). The CGP noted that the number of lines of prior treatment therapy are an important effect modifier and differ between the two trial populations. Other notable differences are the prior treatment criteria (POLLUX does not exclude bortezomib refractory patients), proportion of patients refractory to lenalidomide and the prior treatment at baseline.

Table 5. Trial population – Rd-based

Trial (Intervention vs. Comparator)	Prior LOT (as per Inclusion Criteria; and Median Values at Baseline)	Prior Treatment Criteria	Type of Prior Treatment Patients had Relapsed/were Refractory To	Prior Treatment Exposure at Baseline
POLLUX (MMY3003)[9] (DRd vs. Rd)	[redacted]	[redacted]	[redacted]	[redacted]
ASPIRE[43] (KRd vs. Rd)	[redacted]	[redacted]	[redacted]	[redacted]

* [redacted]

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

The following table highlights the intervention and comparator for the included studies.

Table 6. Intervention and comparators – Rd-based

Trial	Intervention	Lenalidomide Dosing	Dexamethasone Dosing	Treatment Duration
Base-case Analyses				
POLLUX (MMY3003)[9]	DRd	[redacted]	[redacted]	[redacted]
ASPIRE[43]	KRd			

[redacted]

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

The following table highlights the demographics of the patients of the included studies.

Table 7. Patient population – Rd-based

Trial	Intervention vs comparator	Age Median (range)	Gender % male	Cytogenic risk	ECOG performance status	ISS stage
POLLUX (MMY3003)[9]	DRd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Rd					
ASPIRE (KRd vs. Rd)[43]	KRd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Rd					

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

The following table summarizes the direct estimates of PFS and OS from the two included trials in the Rd-based network.

Table 8. The direct effect estimates of PFS and OS from POLLUX and ASPIRE

Outcomes	Study	Comparison	HR	Lower 95% CI	Upper 95% CI	p-value
OS	POLLUX[9]	DRd vs Rd	[redacted]	[redacted]	[redacted]	[redacted]
	ASPIRE[43]	KRd vs Rd	[redacted]	[redacted]	[redacted]	[redacted]
PFS	POLLUX[9]	DRd vs Rd	[redacted]	[redacted]	[redacted]	[redacted]
	ASPIRE	KRd vs Rd	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: **HR** = hazard ratio; **OS** = overall survival; PFS = progression-free survival; **D** = daratumumab; **R** = lenalidomide; **d** = dexamethasone; **K** = carfilzomib

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

Progression-free survival

The Table and Figure below shows that daratumumab compared to other included regimens prolongs PFS among patients with relapsed or refractory multiple myeloma.

Table 9. PFS Efficacy results – Rd-based

Outcome	PFS (HR, 95% CrIs)	Probability of DRd being Better than Comparator
Base-case Analyses		
DRd vs. Rd	[redacted]	[redacted]
DRd vs. KRd	0.54 [0.37, 0.78]	100%
[redacted]		

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

Figure 1. Forest plot of PFS efficacy results – Rd-based

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

Overall survival

The following table highlights that DRd compared to other regimens prolongs overall survival, and in the case of DRd vs Rd, is significantly different.

Table 10. OS Efficacy results – Rd-based network

Outcome	OS (HRs, 95% CrIs)	Probability of DRd Being Better than Comparator
Base-case Analyses		
DRd vs. Rd	[redacted]	[redacted]
DRd vs. KRd	0.80 [0.50, 1.28]	83.1%
[redacted]	[redacted]	

Abbreviations: K = carfilzomib; CrI = credible interval; D = daratumumab; d = dexamethasone; HR = hazard ratio; R = lenalidomide; OS = overall survival

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

The figure below shows that there is a trend towards overall survival benefit for DRd vs KRd, however, the hazard ratio crosses one.

Figure 2. Overall survival forest plot – Rd-based network

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

<u>Network 2: Vd-based</u>

The availability of the clinical efficacy and safety data across trials included in the network are summarized below.

Table 11. Vd-based Efficacy Outcomes, as taken from the pCODR submission

Trial	PFS	OS	ORR	[redacted]	
Base-case Analyses					
CASTOR (MMY3004): DVd vs. Vd[10]	HR*^	HR*	sCR + CR + VGPR + PR	[redacted]	[redacted]

ENDEAVOR[23]: Kd vs. Vd	HR, KM^	HR*	sCR + CR + VGPR + PR	[redacted]	[redacted]

* Data not yet mature; ^ Primary outcome
Abbreviations: CR = complete response; D = daratumumab; d = dexamethasone; HR = hazard ratio K = carfilzomib; KM = Kaplan-Meier; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; sCR = stringent complete response; V = bortezomib; VGPR = very good partial response

Table 12. Vd-based Safety Outcomes

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

The trial population in the two trials in the Vd-based network are summarized below. Note, one trial was limited to 1 – 3 lines of prior treatment (ENDEAVOR), where the other trial patients could receive one or more lines of prior treatment (CASTOR).[6] The CGP noted that the number of lines of prior treatment therapy are an important effect modifier and differ between the two trial populations. Other notable differences are the prior treatment criteria, type of prior treatment patients had relapsed/were refractory to and the prior treatment at baseline.

Table 13. Trial population – Vd-based

Trial	Intervention vs. Comparator	Prior LOT (as per Inclusion Criteria; and Median Values at Baseline)	Prior Treatment Selection Criteria	Type of Prior Treatment Patients had Relapsed/were Refractory To	Prior Treatment Exposure at Baseline
Base-case Analyses					
CASTOR (MMY3004)[10] (DVd vs. Vd)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ENDEAVOR (Kd vs. Vd)[40]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

The following table highlights the intervention and comparator for the included studies.

Table 14. Intervention and comparators – Vd-based

Trial	Intervention	Bortezomib Dosing	Dexamethasone Dosing	Treatment Duration
Base-case Analyses				
CASTOR (MMY3004)[10]	DVd	[redacted]	[redacted]	[redacted]
ENDEAVOR[40]	Kd			[redacted]

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

The following table highlights the demographics of the patients of the included studies.

Table 15. Patient population – Vd-based

Trial	Intervention vs comparator	Age Median (range)	Gender % male	Cytogenic risk	ECOG performance status	ISS stage
CASTOR (MMY3004)[10]	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Vd					
ENDEAVOR[40]	Kd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Vd					

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

The following table summarizes the direct estimates of PFS and OS from the two included trials in the Vd-based network.

Table 16. The direct effect estimates of PFS and OS from POLLUX and ASPIRE

Outcomes	Study	Comparison	HR	Lower 95% CI	Upper 95% CI	p-value
OS	CASTOR[10]	DVd vs Vd	[redacted]	[redacted]	[redacted]	[redacted]
	ENDEAVOR	Kd vs Vd	[redacted]	[redacted]	[redacted]	[redacted]
PFS	CASTOR[10]	DVd vs Vd	[redacted]	[redacted]	[redacted]	[redacted]
	ENDEAVOR	Kd vs Vd	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: **HR** = hazard ratio; **OS** = overall survival; PFS = progression-free survival; **D** = daratumumab; **V** = bortezomib; **d** = dexamethasone; **K** = carfilzomib

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

Progression-free survival

The Table and Figure below shows that daratumumab compared to other included regimens prolongs PFS among patients with relapsed or refractory multiple myeloma.

Table 17. PFS Efficacy results – Vd-based

Outcome	PFS HRs [95% CrIs] (Probability of DVd Being Better than Comparator)	OS
Base-case Analyses		
DVd vs. Vd	[redacted]	[redacted]
DVd vs. Kd	0.62 [0.45, 0.86] (99.8%)	0.80 [0.48, 1.34] (80.5%)

Abbreviations: V = bortezomib; K = carfilzomib; CR = complete response; CrI = credible interval; D = daratumumab; d = dexamethasone; HR = hazard ratio; NMA = network meta-analysis; OR = odds ratio; ORR = overall response rate; OS = overall survival; PFS = progression-free survivalVGPR = very good partial response

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

Figure 4. Progression-free survival forest plot- Vd-based networks

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

Overall survival

The Table and Figure below shows that daratumumab compared to other included regimens (Kd) may improve overall survival, though note that the hazard ratio crosses the value 1.0.

Table 18. OS Efficacy results – Vd-based network

Outcome	OS (HRs, 95% CrIs)	Probability of DVd Being Better than Comparator
Base-case Analyses		
DVd vs. Vd	[redacted]	[redacted]
DVd vs. Kd	0.80 [0.48, 1.34]	80.5%
[redacted]		

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

Figure 3. Overall survival forest plot- Vd-based networks

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

Safety

[redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR*

Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).

Table 19. Discontinuations due to adverse events – Rd and Vd-based networks

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

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

Table 20. Any Grade 3+ adverse events – Rd and Vd-based networks

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

Critical Appraisal of the ITC

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

The Methods team assessed the quality of the evidence NMA according to the recommendations made by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task

Table 21. Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis†

ISPOR Questions	Details and Comments‡
1. Is the population relevant?	**Yes**. The indication for this review was to assess the efficacy and safety of daratumumab, in combination with lenalidomide and dexamethasone, in treatment of adult patients with multiple myeloma who have received at least one prior therapy.
2. Are any critical interventions missing?	**No.** The Manufacturers included all relative interventions for this patient population in the systematic review.
3. Are any relevant outcomes missing?	**Yes.** The Manufacturer did not include any HRQoL outcomes.
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, in part.** The systematic review has not been updated to 2017. A total of [redacted] studies were excluded due to the additional selection criteria for the NMA (as described in Table 2), to ensure similarity across studies. This includes exclusion for

ISPOR Questions	Details and Comments‡
	irrelevant comparator (n=[redacted]), treatment administration (n=[redacted]), lack of common comparator (n=[redacted]) and dose escalation (n=[redacted]).
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**Yes**. The Manufacturer used a Bayesian NMA.
7. Is it apparent that poor quality studies were included thereby leading to bias?	**Yes**. The Manufacturer stated that the quality of evidence of the included studies was [redacted]. Other factors critical to randomized controlled trials such as dropout rates were not specified. It is also not clear if the groups in the trials included were similar at baseline as no significant testing was carried out.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	**Yes, in part**. Though relevant outcomes were reported across studies, the submitter stated that results from other trials included were selected as close as possible to the [redacted]-month follow-up timepoint that was available for POLLUX and [redacted]-months for CASTOR.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	**Yes.** There appears to be differences in important treatment effect modifiers across the different treatment comparison groups, including [redacted], among others. These were not adjusted for.
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?	**N/A.** The Manufacturer did not explore potential effect modifiers.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	**No**.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	**Not applicable**. There was no closed loop.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	**Not applicable**. There was no closed loop.
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?	**No.** According to the Methods Team, there appeared to be imbalances in the distribution of treatment effect modifiers across the different trials. The Manufacturer did not attempt to minimize this bias.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	**Yes**. The Manufacturer stated that [redacted].
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	**Not applicable.**
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**Not applicable.** The submitter stated that [redacted].

ISPOR Questions	Details and Comments‡
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.** The submitter provided the baseline characteristics of the trials used in the NMA is the supplementary data extraction table.
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.** The manufacturer provided the hazard ratio and 95% CrI of PFS and OS.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**Not applicable.** Given the small network, the probability of treatments being the best is not meaningful.
23. Is the impact of important patient characteristics on treatment effects reported?	**No**.
24. Are the conclusions fair and balanced?	**No.** The NMA Report provided by the submitter stated that there are clear efficacy advantages of daratumumab compared with other relevant treatments. However, it is unknown how important treatment effect modifiers were adjusted for.
25. Were there any potential conflicts of interest?	**Not reported.**
26. If yes, were steps taken to address these?	**Not applicable.**
CrI = credible interval; HRQoL = health-related quality of life; ISPOR = International Society For Pharmacoeconomics and Outcomes Research; PFS = progression-free survival.	

Conclusion

The Manufacturer submitted an NMA that compared daratumumab plus lenalidomide plus dexamethasone to carfilzomib-based regimens. The results of the NMA for the Rd-based network indicated that treatment with daratumumab+lenalidomide+dexamethasone was associated with improvement on PFS (HR: 0.54, 95% CrI: 0.37 to 0.78) as compared to carfilzomib+lenalidomide+dexamethasone. However, the results for overall survival were not statistically significant, given that the credible intervals cross one (HR: 0.80, 95% CrI: 0.50 to 1.28). The results of the NMA for the Vd-based network indicated that treatment with daratumumab+bortezomib+dexamethasone was associated with improvement on PFS (HR: 0.62, 95% CrI: 0.45 to 0.86) as compared to carfilzomib +dexamethasone. However, the results for overall survival were not statistically significant, given that the credible intervals cross one (HR: 0.80, 95% CrI: 0.48 to 1.34).

The Bucher method of indirect comparison assumes that the relative effectiveness of a treatment is the same across all trials used in the comparison. In order for this assumption of generalizability to hold, the populations would need to be comparable. For example, the number of lines of prior therapy were not the same for the population and number of lines of prior therapy is a potential effect modifier. This lack of similarity between populations and the failure to adjust for differences makes it difficult to draw conclusions from this NMA.

The overall conclusions of the NMA were limited because of substantial uncertainty in the estimates given differences in patient characteristics among the included studies, notably the number of previous lines of therapy. Further, other treatment effect modifiers such as previous autologous stem-cell transplant were not reported. Given these limitations, and the lack of statistical adjustment to control

for these, the comparative efficacy of daratumumab plus lenalidomide plus dexamethasone to carfilzomib-based regimens is uncertain.

8 COMPARISON WITH OTHER LITERATURE

This section describes how the evidence and results summarized in the pCODR systematic review compare with published literature or other findings.

One study provided by the submitter reported that an increase of 2.5 months in overall survival (OS) is expected for each additional month spent in PFS, based on analyses of different multiple myeloma trials.[8] The submitter referenced this paper to support PFS as a surrogate for OS to support their base case results of the submitted model. The submitter maintains that truncating the treatment benefit at the *end* of the trial follow-up period is not reflective of clinical reality as they feel that PFS is predictive of OS (i.e., 1 month of additional PFS leads to 2.5 months of additional OS). Therefore, the critical appraisal of the study by Felix et al was included as the study supports assumptions in the Submitter's cost-effectiveness analysis.

Given the absence of head-to-head comparative clinical trials, the submitter refers to the 2013 paper by Felix et al. (ref) which attempts to bring some clarity to the controversy surrounding the use of surrogate endpoints as intermediate endpoints for overall survival (OS) in clinical trials. The time-dependent endpoints (TDE) commonly used in clinical oncology trials include: response rate, time to disease progression (TTP), progression-free survival (PFS), and event-free survival (EFS). While Felix et al. report that TTP and PFS are valid and clinically relevant TDEs that can be used to accelerate the drug approval process for multiple myeloma (MM) agents, their predictive value for OS was previouslyunknown[92]. The study objective was therefore to estimate a quantitative relationship between median TDEs and median OS from prospective published MM studies to address the question of what the expected median OS would be given the observed effect in the median TDE.

To answer this question, an appropriate and systematic search for experimental or observational prospective studies that assessed OS in MM using one of the aforementioned TDEs as a primary endpoint was conducted. Retrospective studies were excluded as were studies that lacked surrogate endpoint outcomes or OS data. Variables collected included: authors, publication year, journal, study sample characteristics (period of analysis, percentage of males, median age, type and number of previous therapies), and study results (therapies used, median TDEs, median OS, 12-,24, and 36-month OS). The authors provided a very detailed description of the statistical methods used in the study including the methods used to overcome some of the statistical challenges encountered, such as the endogeneity of the main regressor of interest (TDE), heterogeneity of observations, differences in study designs, patient populations and treatments, and the handling of censored observations. In order to avoid statistical data imputation methods, the association between the median TDE and median OS was quantified using the Spearman rank correlation coefficient in a *subset* of data limited to only those trials with simultaneously observed values for median TDE and median OS, and excluding those trials with unobserved median OS values. Several tests to validate various statistical assumptions were also reported. No a priori hypotheses regarding the correlation between median TDEs and median OS in the included studies were stated nor were any hypotheses stated about what the expected median OS would be given the observed median TDE.

153 studies involving 230 study arms were included, representing a sample of 22,696 MM patients. The majority of study arms, 55.7%, included only patients with newly diagnosed MM (representing 67.6% of a total of 22696 patients in all included study arms), while 29.6% of study arms included patients with relapsed, refractory, or advanced MM (representing 23.2% of the total included patients). The remaining 14.8% of study arms were mixed or not reported. The Spearman's rank correlation coefficient of the aggregated median TDE data on median OS was 0.78 ($p<0.0001$). By TDEs, the correlation coefficient was highly significant, with a moderate correlation 0f 0.51 ($p=0.003$) between median OS and median TTP, and a strong correlation of 0.75 ($p<0.0001$) for median PFS and 0.84 ($p<0.0001$) for median EFS. Using regression analysis (adjusting for all other variables such as surrogate endpoint type and MM treatments included in the model), the authors report an estimated increase of 2.5 months ($p<0.0001$, 95% CI, 1.71-3.20) in the reported median OS for each additional month in the observed median TDE (TTP, PFS, or EFS). Given the reasonably narrow confidence interval, and the fact that all other covariables (eg. age, year of publication) used in the model were nonsig nificant Felix et al conclude that one can be fairly

confident in this estimate. Of note to this clinical guidance report, a near-significant positive association (p=0.06, 95% CI, -0.66-29.14) was reported between trials including patients with relapsed, refractory, or advanced MM, compared with trials including newly diagnosed MM patients. While the authors report that this evidence suggests that other factors not included in the regression model may complement the TDE explanatory power in relapsed, refractory, or advanced MM OS, it must be emphasized that this evidence is weak and the confidence interval for this covariable was very wide. The *type* of surrogate endpoint (TTP, PFS, or EFS) and treatment (thalidomide, bortezomib, lenalidomide) had no significant impact on the explanatory power to median OS, which suggests surrogacy of TTP, PFS, and EFS to OS. Additional modelling techniques were reported but the overall message was that there is consistency in the estimated values for the effect of median TDE on median OS.

With respect to prediction of median OS from the observation of median TDEs, the main observation was that lower predicted median OS values in the study arms using TTP were found. There was a higher proportion of study arms using TTP as the primary endpoint in the relapsed, refractory, or advanced MM population (46%) compared with the study arms evaluating PFS (26%) and EFS (25%). The authors also present several plots to demonstrate the practicality of their regression modeling method in predicting an absolute rather than relative measure for the quantitative relationship between the median OS from and the median TDE. Felix et al. also provide additional practical implications of their model in the Discussion, noting that their model recognizes the influence of subsequent therapies on median OS, which is valuable in trials of newly diagnosed MM patients where median OS may not be reached for several years (ref Felix et al). One note of caution made by Felix et al. concerns the fact that appropriate TDEs *cannot be generalized in oncology* (i.e., to different disease sites), as their validity depends on tumour type.

Information on overall survival is important to this review as it is necessary for accelerated drug approvals and economic considerations (Felix et al). Overall, the study by Felix et al. demonstrates the potential value of TDEs (TTP, PFS, and EFS) in predicting OS in patients with MM. Relevant to this CGR, while statistically significant correlation between median PFS and median OS was observed, the clinical relevance is questionable given that daratumumab was not included as one of the treatment options. With the separate mechanism of action of daratumumab, and the lack of outcome data for daratumumab being included in the Felix study, an assumption would be needed that the results in Felix et al, based on other treatments other than daratumumab, can be assumed to be the same for daratumumab. This assumption increases the uncertainty in the results. Caution must also be taken when assessing the predictive value of median TDEs on median OS in patients with relapsed/refractory or advanced MM, given that the majority of patients in the study by Felix et al had newly diagnosed MM or were treatment naïve (67.6%). It should also be noted that while Felix et al. report a significant correlation between the TDEs assessed and OS, their analysis was based on aggregate as opposed to individual patient-level data which would be more reliable in predicting OS. Further, including all experimental and observational prospective studies does not allow for comparisons *between* treatments, which may have been possible had they conducted an additional analysis limiting to randomized controlled trials that preserved the randomized comparisons within each trial. Felix et al also concede that other assessments of potential surrogate endpoints require a two-step process which is described elsewhere.[9] These factors, combined, leads to uncertainty in the reported claim that there is an increase of 2.5 months in median OS for each additional month in median PFS, even despite the adjustments made for several covariables. How the results of this study affect economic considerations in the current review will be reported by the economic guidance panel (EGP).

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Melanoma 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 the combination of nivolumab plus ipilimumab for melanoma Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

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

This 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 Melanoma 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

See Appendix B for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** February 2017**, Embase** 1974 to 2017 March 08**, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results
1	(daratumumab* or darzalex* or HuMax-CD38 or HuMaxCD38 or JNJ 54767414 or JNJ54767414 or 4Z63YK6E0E or 945721-28-8).ti,ab,kf,kw,rn,nm.	712
2	1 use ppez,cctr	185
3	*daratumumab/	217
4	(daratumumab* or darzalex* or HuMax-CD38 or HuMaxCD38 or JNJ 54767414 or JNJ54767414 or 4Z63YK6E0E or 945721-28-8).ti,ab,kw,hw.	697
5	3 or 4	697
6	5 use oemezd	528
7	2 or 6	713
8	limit 7 to english language	693
9	conference abstract.pt.	2478574
10	8 and 9	176
11	limit 10 to yr="2012-Current"	161
12	8 not 9	517
13	11 or 12	678

14 remove duplicates from 13 525

2. Literature search via PubMed

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

Search	Add to builder	Query	Items found	Time
#3	Add	Search **#1 AND #2**	14	14:34:41
#2	Add	Search **publisher[sb]**	510179	14:34:30
#1	Add	Search **daratumumab*[all fields] OR darzalex*[all fields] OR HuMax-CD38[all fields] OR HuMaxCD38[all fields] OR JNJ 54767414[all fields] OR JNJ54767414[all fields] OR 4Z63YK6E0E[rn] OR 945721-28-8[rn]**		

3. Cochrane Central Register of Controlled Trials (Central)

Searched via Ovid

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

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

Search: daratumumab/darzalex, multiple myeloma

Select international agencies including:

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

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

Search: daratumumab/darzalex, multiple myeloma

Conference abstracts:

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

Search: daratumumab/darzalex, multiple myeloma - last 5 years

ASH

http://www.bloodjournal.org/page/ash-annual-meeting-abstracts

Search: daratumumab/darzalex, multiple myeloma - last 5 years

APPENDIX B: Detailed Methodology of Literature Review

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-2017 March 8) with Epub ahead of print, in-process records & daily updates via Ovid; Embase (1974-2017 March 8) via Ovid; The Cochrane Central Register of Controlled Trials (February 2017) 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 concept was Darzalex (Daratumumab).

No methodological filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents, but not limited by publication year. The search is considered up to date as of June 30, 2017.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and from the American Society of Hematology (ASH) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

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. PrDarzalex® (daratumumab): 20 mg/mL concentrate for solution for infusion [product monograph on Internet]. Toronto: Janssen Inc.; 2017 Apr. [cited 2017 May 5]. Available from: https://pdf.hres.ca/dpd_pm/00038901.PDF

2. Usmani SZ, Dimopoulos MA, Belch A, White D, Benboubker L, Cook G, et al. Efficacy of daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone in relapsed or refractory multiple myeloma patients with 1 to 3 prior lines of therapy: Updated analysis of pollux [abstract]. Blood [Internet]. 2016 [cited 2017 Apr 5];128(22):1151. Available from: http://www.bloodjournal.org/content/128/22/1151 (Presented at 20161203.;- 20161206. 128 (22) (no pagination), 2016. Date of Publication: 02 Dec 2016.).

3. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016 Oct 6;375(14):1319-31.

4. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. Supplementary appendix. N Engl J Med [Internet]. 2016 Oct 6 [cited 2017 Jul 11];375(14). Available from: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1607751/suppl_file/nejmoa1607751_appendix.pdf

5. Moreau P, Kaufman JL, Sutherland HJ, Lalancette M, Magen H, Iida S, et al. Efficacy of daratumumab, lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone for relapsed or refractory multiple myeloma among patients with 1 to 3 prior lines of therapy based on previous treatment exposure: Updated analysis of pollux [abstract]. Blood [Internet]. 2016 [cited 2017 Apr 5];128(22). Available from: http://www.bloodjournal.org/content/128/22/489 (Presented at 20161203.;- 20161206. 128 (22) (no pagination), 2016. Date of Publication: 02 Dec 2016.).

6. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. N Engl J Med [Internet]. 2016 Aug 25 [cited 2017 Apr 5];375(8):754-66. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1606038

7. Dimopoulos MA, Moreau P, Palumbo A, Joshua D, Pour L, Hajek R, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol. 2016 Jan;17(1):27-38.

8. Felix J, Aragao F, Almeida JM, Calado FJ, Ferreira D, Parreira AB, et al. Time-dependent endpoints as predictors of overall survival in multiple myeloma. BMC Cancer. 2013 Mar 16;13:122. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3607860

9. Buyse M, Sargent DJ, Grothey A, Matheson A, de GA. Biomarkers and surrogate end points--the challenge of statistical validation. Nat Rev Clin Oncol. 2010 Jun;7(6):309-17.

10. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma.Supplementary appendix. N Engl J Med [Internet]. 2016 Aug 25 [cited 2017 Jul 11];375(8). Available from: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1606038/suppl_file/nejmoa1606038_appendix.pdf

11. Mateos MV, Estell J, Barreto W, Corradini P, Min CK, Medvedova E, et al. Efficacy of daratumumab, bortezomib, and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory myeloma based on prior lines of therapy: Updated analysis of castor [abstract]. Blood [Internet]. 2016 [cited 2017 Apr 5];128(22):1150. Available from: http://www.bloodjournal.org/content/128/22/1150 (Presented at 20161203.;- 20161206. 128 (22) (no pagination), 2016. Date of Publication: 02 Dec 2016.).

12. Sonneveld P, Verelst SG, Lewis P, Gray-Schopfer V, Hutchings A, Nixon A, et al. Review of health-related quality of life data in multiple myeloma patients treated with novel agents. Leukemia. 2013 Oct;27(10):1959-69. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3806249

13. Chanan-Khan AA, Lentzsch S, Quach H, Horvath N, Capra M, Ovilla R, et al. Daratumumab, bortezomib and dexamethasone versus bortezomib and dexamethasone alone for relapsed or refractory multiple myeloma based on prior treatment exposure: Updated efficacy analysis of castor [abstract]. Blood [Internet]. 2016 [cited 2017 Apr 5];128:3313. Available from: http://www.bloodjournal.org/content/128/22/3313 (Presented at 20161203.;- 20161206. 128 (22) (no pagination), 2016. Date of Publication: 02 Dec 2016.).

14. Sonneveld P, Schmidt-Wolf IG, van der HB, El JL, Bertsch U, Salwender H, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. J Clin Oncol. 2012 Aug 20;30(24):2946-55.

15. Lacy MQ, Gertz MA, Dispenzieri A, Hayman SR, Geyer S, Kabat B, et al. Long-term results of response to therapy, time to progression, and survival with lenalidomide plus dexamethasone in newly diagnosed myeloma. Mayo Clin Proc. 2007 Oct;82(10):1179-84.

16. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. Protocol. N Engl J Med [Internet]. 2016 Aug 25 [cited 2017 Jul 11];375(8). Available from: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1606038/suppl_file/nejmoa1606038_protocol.pdf

17. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. Protocol. N Engl J Med [Internet]. 2016 Oct 6 [cited 2017 Jul 11];375(14). Available from: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1607751/suppl_file/nejmoa1607751_protocol.pdf

18. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine. Identifier NCT02136134, Addition of daratumumab to combination of bortezomib and dexamethasone in participants with relapsed or refractory multiple myeloma; 2016 Dec 20 [cited 2017 Jul 11]. Available from: https://ClinicalTrials.gov/show/NCT02136134

19. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine. Identifier NCT02076009, A Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Relapsed or Refractory Multiple Myeloma; 2016 Dec 20 [cited 2017 Jul 11]. Available from: https://ClinicalTrials.gov/show/NCT02076009

20. Bahlis NJ. Darwinian evolution and tiding clones in multiple myeloma. Blood. 2012 Aug 2;120(5):927-8.

21. pan-Canadian Oncology Drug Review manufacturer submission: Darzalex (daratumumab), 20mg/mL concentrate for solution for infusion. Company: Janssen Inc. Toronto: Janssen Inc.; 2017 Mar 3.

22. Multiple myeloma. Version 3.2017. Fort Washington(PA): National Comprehensive Cancer Network (NCCN); 2016 Nov 28. (NCCN clinical practice guidelines in oncology).

23. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016 Aug;17(8):e328-e346.

24. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian cancer statistics 2015 [Internet]. Toronto: Canadian Cancer Society; 2015. [cited 2017 Apr 27]. Available from: https://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2015-EN.pdf

25. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, et al. SEER Cancer Statistics Review (CSR) 1975-2013 [Internet]. Bethesda (MD): National Cancer Institute; 2016 Apr. [cited 2017 Apr 27]. Available from: http://seer.cancer.gov/csr/1975_2013/ Based on November 2015 SEER data submission.

26. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014 Nov;15(12):e538-e548.

27. Kristinsson SY, Landgren O, Dickman PW, Derolf AR, Bjorkholm M. Patterns of survival in multiple myeloma: a population-based study of patients diagnosed in Sweden from 1973 to 2003. J Clin Oncol. 2007 May 20;25(15):1993-9.

28. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood [Internet]. 2008 Mar 1 [cited 2017 Apr 27];111(5):2516-20. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2254544

29. Pozzi S, Marcheselli L, Bari A, Liardo EV, Marcheselli R, Luminari S, et al. Survival of multiple myeloma patients in the era of novel therapies confirms the improvement in patients younger than 75 years: a population-based analysis. Br J Haematol. 2013 Oct;163(1):40-6.

30. Ahuja A, Attri S, Kamra S, Kalra M. Hrqol and health utility impact on patients with newly diagnosed multiple myeloma in US and Europe: a systematic literature review. Value Health. 2015 Nov;18(7):A468.

31. Warren JL, Harlan LC, Stevens J, Little RF, Abel GA. Multiple myeloma treatment transformed: a population-based study of changes in initial management approaches in the United States. J Clin Oncol [Internet]. 2013 Jun 1 [cited 2017 Apr 27];31(16):1984-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3661935

32. Rajkumar SV, Gahrton G, Bergsagel PL. Approach to the treatment of multiple myeloma: a clash of philosophies. Blood [Internet]. 2011 Sep 22 [cited 2017 Apr 27];118(12):3205-11. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3179390

33. Anderson KC. The 39th David A. Karnofsky Lecture: bench-to-bedside translation of targeted therapies in multiple myeloma. J Clin Oncol [Internet]. 2012 Feb 1 [cited 2017 Apr 27];30(4):445-52. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4800820

34. Corre J, Munshi N, vet-Loiseau H. Genetics of multiple myeloma: another heterogeneity level? Blood [Internet]. 2015 Mar 19 [cited 2017 Apr 27];125(12):1870-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4366624

35. Boise LH, Kaufman JL, Bahlis NJ, Lonial S, Lee KP. The Tao of myeloma. Blood [Internet]. 2014 Sep 18 [cited 2017 Apr 27];124(12):1873-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4468029

36. Blade J, de Larrea CF, Rosinol L. Incorporating monoclonal antibodies into the therapy of multiple myeloma. J Clin Oncol. 2012 Jun 1;30(16):1904-6.

37. Palumbo A, Gay F, Cavallo F, Di Raimondo F, Larocca A, Hardan I, et al. Continuous therapy versus fixed duration of therapy in patients with newly diagnosed multiple myeloma. J Clin Oncol. 2015 Oct 20;33(30):3459-66.

38. Dimopoulos MA, Palumbo A, Hajek R, Kropff M, Petrucci MT, Lewis P, et al. Factors that influence health-related quality of life in newly diagnosed patients with multiple myeloma aged >/= 65 years treated with melphalan, prednisone and lenalidomide followed by lenalidomide maintenance: results of a randomized trial. Leuk Lymphoma [Internet]. 2014 Jul [cited 2017 Apr 27];55(7):1489-97. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4133972

39. Delforge M, Minuk L, Eisenmann JC, Arnulf B, Canepa L, Fragasso A, et al. Health-related quality-of-life in patients with newly diagnosed multiple myeloma in the FIRST trial: lenalidomide plus low-dose dexamethasone versus melphalan, prednisone, thalidomide. Haematologica [Internet]. 2015 Jun [cited 2017 Apr 27];100(6):826-33. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4450629

40. Garrison LP, Jr., Wang ST, Huang H, Ba-Mancini A, Shi H, Chen K, et al. The cost-effectiveness of initial treatment of multiple myeloma in the U.S. with bortezomib plus melphalan and prednisone versus thalidomide plus melphalan and prednisone or lenalidomide plus melphalan and prednisone with continuous lenalidomide maintenance treatment. Oncologist. 2013;18(1):27-36. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3556252

41. Chanan-Khan AA, Giralt S. Importance of achieving a complete response in multiple myeloma, and the impact of novel agents. J Clin Oncol. 2010 May 20;28(15):2612-24.

42. Sonneveld P, Broijl A. Treatment of relapsed and refractory multiple myeloma. Haematologica [Internet]. 2016 [cited 2017 Apr 27];101(4):396-406. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5004403/?report=printable

43. Dimopoulos MA, Chen C, Spencer A, Niesvizky R, Attal M, Stadtmauer EA, et al. Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia. 2009 Nov;23(11):2147-52.

44. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005 Jun 16;352(24):2487-98.

45. San MJ, Weisel K, Moreau P, Lacy M, Song K, Delforge M, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013 Oct;14(11):1055-66.

46. Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Spicka I, Oriol A, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med. 2015 Jan 8;372(2):142-52.

47. Palumbo A, Facon T, Sonneveld P, Blade J, Offidani M, Gay F, et al. Thalidomide for treatment of multiple myeloma: 10 years later. Blood. 2008 Apr 15;111(8):3968-77.

48. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR, Eastern Cooperative Oncology Group. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol. 2006 Jan 20;24(3):431-6.

49. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008 Aug 28;359(9):906-17.

50. Benboubker L, Dimopoulos MA, Dispenzieri A, Catalano J, Belch AR, Cavo M, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014 Sep 4;371(10):906-17.

51. Zweegman S, van der Holt B, Mellqvist UH, Salomo M, Bos GM, Levin MD, et al. Melphalan, prednisone, and lenalidomide versus melphalan, prednisone, and thalidomide in untreated multiple myeloma. Blood. 2016 Mar 3;127(9):1109-16.

52. Harousseau JL, Attal M, vet-Loiseau H, Marit G, Caillot D, Mohty M, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. J Clin Oncol. 2010 Oct 20;28(30):4621-9.

53. Sonneveld P, Goldschmidt H, Rosinol L, Blade J, Lahuerta JJ, Cavo M, et al. Bortezomib-based versus nonbortezomib-based induction treatment before autologous stem-cell transplantation in patients with previously untreated multiple myeloma: a meta-analysis of phase III randomized, controlled trials. J Clin Oncol. 2013 Sep 10;31(26):3279-87.

54. Phipps C, Chen Y, Gopalakrishnan S, Tan D. Daratumumab and its potential in the treatment of multiple myeloma: overview of the preclinical and clinical development. Ther Adv Hematol [Internet]. 2015 Jun [cited 2017 Apr 27];6(3):120-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4480519

55. van de Donk NW, Janmaat ML, Mutis T, Lammerts van Bueren JJ, Ahmadi T, Sasser AK, et al. Monoclonal antibodies targeting CD38 in hematological malignancies and beyond. Immunol Rev. 2016 Mar;270(1):95-112.

56. van de Donk NW, Moreau P, Plesner T, Palumbo A, Gay F, Laubach JP, et al. Clinical efficacy and management of monoclonal antibodies targeting CD38 and SLAMF7 in multiple myeloma. Blood. 2016 Feb 11;127(6):681-95.

57. Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood [Internet]. 2011 May 5 [cited 2017 Apr 27];117(18):4691-5. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3710442

58. Nijhof IS, Groen RW, Noort WA, van Kessel B, de Jong-Korlaar R, Bakker J, et al. Preclinical Evidence for the Therapeutic Potential of CD38-Targeted Immuno-Chemotherapy in Multiple

Myeloma Patients Refractory to Lenalidomide and Bortezomib. Clin Cancer Res. 2015 Jun 15;21(12):2802-10.

59. Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. N Engl J Med [Internet]. 2015 Sep 24 [cited 2017 Apr 5];373(13):1207-19. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1506348

60. Lonial S, Weiss BM, Usmani SZ, Singhal S, Chari A, Bahlis NJ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet. 2016 Apr 9;387(10027):1551-60.

61. FDA approves Darzalex for patients with previously treated multiple myeloma [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2015 Nov 16. [cited 2017 Apr 27]. (FDA news release). Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm472875.htm

62. Janssen Research & Development, LLC. Addition of daratumumab to combination of bortezomib and dexamethasone in participants with relapsed or refractory multiple myeloma. 2014 May 1 [cited 2017 Apr 27]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT02136134 ClinicalTrials.gov Identifier: NCT02136134.

63. Janssen Research & Development, LLC. A study comparing daratumumab, lenalidomide, and dexamethasone with lenalidomide and dexamethasone in relapsed or refractory multiple myeloma. 2014 Feb 27 [cited 2017 Apr 27]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT02076009 ClinicalTrials.gov Identifier: NCT02076009.

64. Janssen Research & Development, LLC. Daratumumab (HuMax®-CD38) safety study in multiple myeloma. 2007 Dec 14 [cited 2017 May 1; Last updated: 2017 Jan 18]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT00574288?term=NCT00574288&rank=1 NLM Identifier: NCT00574288.

65. Janssen Research & Development, LLC. An efficacy and safety study of daratumumab in patients with multiple myeloma who have received at least 3 prior lines of therapy (including a proteasome inhibitor [PI] and immunomodulatory drug [IMiD]) or are double refractory to a PI and an IMiD. 2013 Jul 22 [cited 2017 May 1; Last updated: 2017 Mar 24]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT01985126?term=NCT01985126&rank=1 NLM Identifier: NCT01985126.

66. Gooding S, Lau IJ, Sheikh M, Roberts P, Wong J, Dickens E, et al. Double relapsed and/or refractory multiple myeloma: clinical outcomes and real world healthcare costs. PLoS ONE [Internet]. 2015 [cited 2017 Apr 27];10(9):e0136207. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4569348

67. Borg S, Nahi H, Hansson M, Lee D, Elvidge J, Persson U. Cost effectiveness of pomalidomide in patients with relapsed and refractory multiple myeloma in Sweden. Acta Oncol. 2016 May;55(5):554-60.

68. Roy A, Kish JK, Bloudek L, Siegel DS, Jagannath S, Globe D, et al. Estimating the costs of therapy in patients with relapsed and/or refractory multiple myeloma: a model framework. Am Health

Drug Benefits [Internet]. 2015 Jun [cited 2017 Apr 27];8(4):204-15. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4489189

69. Fragoulakis V, Kastritis E, Psaltopoulou T, Maniadakis N. Economic evaluation of therapies for patients suffering from relapsed-refractory multiple myeloma in Greece. Cancer Manag Res [Internet]. 2013 [cited 2017 Apr 27];5:37-48. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3627436

70. Aguiar PM, Lima TM, Storpirtis S. Systematic review of the economic evaluations of novel therapeutic agents in multiple myeloma: what is the reporting quality? J Clin Pharm Ther. 2016 Apr;41(2):189-97.

71. Gaultney JG, Franken MG, Tan SS, Redekop WK, Huijgens PC, Sonneveld P, et al. Real-world health care costs of relapsed/refractory multiple myeloma during the era of novel cancer agents. J Clin Pharm Ther. 2013 Feb;38(1):41-7.

72. Blommestein HM, Verelst SG, de Groot S, Huijgens PC, Sonneveld P, Uyl-de Groot CA. A cost-effectiveness analysis of real-world treatment for elderly patients with multiple myeloma using a full disease model. Eur J Haematol. 2016 Feb;96(2):198-208.

73. Janssen Research & Development, LLC. Study comparing daratumumab, lenalidomide, and dexamethasone with lenalidomide and dexamethasone in participants with previously untreated multiple myeloma. 2014 Aug 11 [cited 2017 Apr 27]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT02252172 ClinicalTrials.gov Identifier: NCT02252172.

74. Janssen Research & Development, LLC. A study of combination of daratumumab and velcade (bortezomib) melphalan-prednisone (DVMP) compared to velcade melphalan-prednisone (VMP) in participants with previously untreated multiple myeloma. 2014 Jul 18 [cited 2017 Apr 27]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT02195479 ClinicalTrials.gov Identifier: NCT02195479.

75. Intergroupe Francophone du Myelome. A study to evaluate daratumumab in transplant eligible participants with previously untreated multiple myeloma (Cassiopeia). 2015 Jun 24 [cited 2017 Apr 27]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT02541383 ClinicalTrials.gov Identifier: NCT02541383.

76. Janssen Research & Development, LLC. A study to evaluate 3 dose schedules of daratumumab in participants with smoldering multiple myeloma. 2014 Dec 10 [cited 2017 Apr 27]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT02316106 ClinicalTrials.gov Identifier: NCT02316106.

77. Landgren O, Iskander K. Modern multiple myeloma therapy: deep, sustained treatment response and good clinical outcomes. J Intern Med. 2017 Feb 16;281:365-82.

78. Costello C. An update on the role of daratumumab in the treatment of multiple myeloma. Ther Adv Hematol [Internet]. 2017 Jan [cited 2017 Apr 5];8(1):28-37. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5167079/pdf/10.1177_2040620716677523.pdf

79. Agarwal A, Chow E, Bhutani M, Voorhees PM, Friend R, Usmani SZ. Practical Considerations in Managing Relapsed Multiple Myeloma. Clin Lymphoma Myeloma Leuk. 2017 Feb;17(2):69-77.

80. Weisel K, Palumbo A, Chanan-Khan A, Nooka AK, Spicka I, Masszi T, et al. Phase 3 randomised study of daratumumab, bortezomib and dexamethasone (DVd) vs bortezomib and dexamethasone (Vd) in patients (pts) with relapsed or refractory multiple myeloma (RRMM): CASTOR [abstract]. Ann Oncol. 2016;27 Suppl 6:9060. (Presented at 20161007.;- 20161011. 27 (no pagination), 2016. Date of Publication: 2016.).

81. Shah NH, Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, et al. An open-label, randomised, phase 3 study of daratumumab, lenalidomide, and dexamethasone (DRd) versus lenalidomide and dexamethasone (Rd) in relapsed or refractory multiple myeloma (RRMM): POLLUX [abstract]. Indian Journal of Hematology and Blood Transfusion. 2016;32 Suppl:S429. (Presented at 20161110.;- 20161113. 32 ()(pp S429), 2016. Date of Publication: November 2016.).

82. pan-Canadian Oncology Drug Review checkpoint meeting: daratumumab (Darzalex). Janssen Inc. response to pCODR checkpoint meeting clinical questions. Toronto (ON): Janssen Inc; 2017.

83. Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006 Sep;20(9):1467-73.

84. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine. Identifier NCT02076009, A Study comparing daratumumab, lenalidomide, and dexamethasone with lenalidomide and dexamethasone in relapsed or refractory multiple myeloma; 2017 Jun [cited 2017 Jul 11]. Available from: https://clinicaltrials.gov/ct2/show/NCT02076009?term=daratumumab+and+lenalidomide+multiple+myeloma&rank=3

85. Laubach JP, Faber EA, Jr., Voorhees P, Moslehi J, Varga C, Niculescu L, et al. The challenge of cross-trial comparisons using limited data. Haematologica. 2014 Aug;99(8):e145-e146. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4116848

86. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine--reporting of subgroup analyses in clinical trials. N Engl J Med. 2007 Nov 22;357(21):2189-94.

87. PrDARZALEX® (daratumumab): 20mg/mL concentrate for solution for infusion [product monograph]. Toronto (ON): Janssen Inc; 2017 Apr 13.

88. McCudden C, Axel AE, Slaets D, Dejoie T, Clemens PL, Frans S, et al. Monitoring multiple myeloma patients treated with daratumumab: teasing out monoclonal antibody interference. Clin Chem Lab Med [Internet]. 2016 Jun 1 [cited 2017 Apr 5];54(6):1095-104. Available from: https://www.degruyter.com/downloadpdf/j/cclm.2016.54.issue-6/cclm-2015-1031/cclm-2015-1031.pdf

89. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine [cited 2017 Jul 11]. Available from: https://clinicaltrials.gov/

90. Brooks SP, Gelman A. General methods for monitoring convergence of iterative simulations. J Comput Graph Stats. 1998;7(4):434-55.

91. Gelman A. Inference and monitoring convergence. In: Gilks WR, Richardson S, Spiegelhalter DJ, editors. Markov chain Monte Carlo in practice. London: Chapman & Hall; 1998. Chapter 8. p. 131-43.

92. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med. 1998 Dec 30;17(24):2815-34.

93. Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. BMC Med Res Methodol. 2011 Oct 10;11:139. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3198983