pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Daratumumab (Darzalex) for Multiple Myeloma

December 1, 2016

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

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

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

1.1 Introduction

The purpose of this review is to evaluate the safety and efficacy of daratumumab (Darzalex) on patient outcomes for the treatment of patients with multiple myeloma who 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.

Daratumumab is a human monoclonal antibody. Daratumumab has a Health Canada indication 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. Marketing authorization with conditions was based on the primary efficacy endpoint of overall response rate, as well as the observed duration and depth of responses, including stringent complete responses, demonstrated in a single-arm study. The recommended dose of daratumumab is 16 mg/kg body weight administered as an intravenous infusion according to the following schedule:

- Weekly for weeks 1 to 8;
- Every two weeks for weeks 9 to 24;
- Every four weeks for week 25 onwards until disease progression.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two single-arm, open-label studies, phase two (MMY2002) and phase one/two (GEN501) that evaluated daratumumab monotherapy in patients with multiple myeloma.[1,2] As the recommended dose of daratumumab is 16 mg/kg, results are reported for patients who received 16 mg/kg of daratumumab in MMY2002 (n=106) and GEN501 (n=42).

MMY2002

MMY2002 included patients with multiple myeloma who received at least 3 prior lines of therapy (including PIs and IMiDs) or whose disease was refractory to both PIs and IMiDs. Patients received daratumumab intravenously at 16 mg/kg per week for 8 weeks, then every 2 weeks for 16 weeks, and then every 4 weeks thereafter. Patients received therapy until disease progression or until unmanageable level of toxic events occurred. Eligibility criteria in both studies included Eastern Cooperative Oncology Group performance status (ECOG PS) ECOG PS 0-2. Key exclusion criteria include clinically significant cardiovascular and respiratory conditions.

The median age was approximately 64 years. A total of 36 (34%) patients were 65 to 74 years and 12 (11%) were 75 years or older. Most patients were ECOG PS 0 or 1, with 8% of patients of ECOG PS of 2. The median number of prior lines of therapy were 5; most patients had >3 prior lines of therapy (82%).

GEN501

GEN501 is included patients with multiple myeloma that required systemic therapy and whose disease was relapsed or refractory to at least two prior lines of therapy. Patients received daratumumab intravenously at 16 mg/kg once weekly (8 doses; where after the first dose a 3 week washout period occurred and then resumed with weekly doses), then twice monthly (8 doses), and then monthly for up to 24 months. Patients received therapy until disease progression or until unmanageable level of toxic events occurred. Eligibility criteria in both studies included Eastern Cooperative Oncology Group performance status (ECOG PS) ECOG PS 0-2. Key exclusion criteria include clinically significant cardiovascular and respiratory conditions.

The median age was 64 years. A total of 16 (38%) patients were 65 to 74 years and 4 (10%) were 75 years or older. Most patients were ECOG PS 0 or 1, with 5% of patients of ECOG PS of 2. The median number of prior lines of therapy were 4; 62% of patients had >3 prior lines of therapy.

Overall, in MMY2002 and GEN501, the majority of patients received previous PIs (99% with bortezomib, 50% with carfilzomib), IMiDs (99% with lenalidomide, 63% with pomalidomide, and 44% with thalidomide), or allogeneic stem cell transplant (80%). Almost all patients (97%) were refractory to their last line of therapy and (95%) refractory to both a PI and IMiD. A proportion of patients were refractory to bortezomib + lenalidomide + carfilzomib + pomalidomide (31%).[3]

Efficacy

MMY2002

The primary endpoint was overall response rate (ORR) and secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS), and clinical benefit rate (CBR).

Response was seen in 31 patients (29.6%) (see Table 1). The median time to response was 0.9 months. The duration of response was 7.4 months. Responses were noted in pre-specified subgroups, which was irrespective of previous lines of therapy and refractory status. The clinical cut-off date was January 9, 2015, 7.7 months after the last person had received first dose (median follow-up was 9.3 months). The median PFS was 3.7. The 12-month OS rate was 64.8% and at the updated analysis (June 30, 2015 data cut-off), the median OS was 17.5 months.

GEN501

The primary endpoint was safety, which was determined according to the frequencies and severities of adverse events (AEs) and was assessed at each treatment visit; an independent review committee evaluated all serious adverse events (SAEs), non-SAEs of grade ≥3, and events that caused treatment withdrawal. Secondary endpoints included pharmacokinetics, objective response according to the IMWG uniform response criteria for myeloma, time to disease progression, DoR, PFS, and OS.

Response was seen in 15 patients (36%) GEN501 (see Table 1). The median time to response was 1 month. The duration of response was not reached. It is important to note that the primary endpoint in GEN501 was safety and that efficacy outcomes were secondary endpoints. Responses were noted in exploratory subgroups, which was irrespective of previous lines of therapy and refractory status. The median PFS was 5.6 months. The 12-month OS rate was 77%.

Table 1: Efficacy Outcomes of Patients treated at 16 mg/kg in Study MMY2002 and Study GEN501[1,2]

Efficacy Outcomes	MMY2002 (n=106)	GEN501 (n=42)
Duration of follow-up, median (range)	9.3 months (0.5-14.4)	16.9 months (0.4-24.9)
Overall Response Rate, n (%)	n=31 29.6%, 95%CI: 20.8-38.9	n=15 36%, 95%CI: 22-52
TTR, months (range)	1.0 months (0.9-5.6)	0.9 months (0.5-3.2)
DoR, median (95%CI)	7.4 months (5.5-NE)	Not reached
PFS, median (95%CI)	3.7 months (2.8-4.6)	5.6 months (4.2-8.1)
CBR, % (95%CI)	34.0% (95%CI: 25.0-43.8)	NR
OS, median	Not reached (13.7-NE)	NR
12-month OS rate, % (95%CI)	64.8 (51.2-75.5)	77 (58-88)
Updated OS, median (June 30, 2015)	17.5 (13.7-NE)	-
Notes: CBR = clinical benefit rate; CI = confidence interval; DoR = duration of response; IMiD = immunomodulatory drug; NE = not estimable; NR = not reported; OS = overall survival; PFS = progression-free survival; PI = proteasome inhibitor; TTR = time to response		

Safety

MMY2002

The most common treatment emergent adverse events (TEAEs) of any grade (≥20%) were fatigue (40%), anemia (33%), nausea (29%), thrombocytopenia (25%), neutropenia (23%), back pain (22%), and cough (21%). Grade 3 or higher anemia and thrombocytopenia occurred more frequently in responders than non-responders. No patients discontinued daratumumab because of drug-related TEAEs, infusion-related reactions, or death. Thirty percent of patients had a serious TEAE and 23% had grade 3/4 serious TEAE. Infusion-related reactions occurred in 42% of patients (none of grade 4), the most common (≥5%): nasal congestion (12%), throat irritation (7%), and cough, dyspnea, chills, and vomiting (6% each). Five patients (5%) discontinued treatment due to a TEAE; this, however, was not drug-related. A total of 31 (29%) patients died after treatment: 29 (27%) patients died because of progressive disease and two (2%) patients died because of an adverse event.

GEN501

In GEN501, the most common adverse events (≥25%) were fatigue, allergic rhinitis, and pyrexia. A total of 26% of patients had a grade 3/4 adverse event. Serious adverse events were reported in 33% of patients who received 16 mg/kg. Seventy-one percent of patients had an infusion-related reaction.

Overall, in both MMY2002 and GEN501, no patients discontinued treatment with daratumumab due to an infusion-related reaction. Infusion related reactions were managed by administering pre-infusion medications including antihistamines, antipyretics, and corticosteroids. Grade ≥ 3 infusion-related reactions in GEN501/MMY2002 were uncommon, only one patient in both studies experienced grade ≥ 3 dyspnea infusion-related reaction.

1.2.2 Additional Evidence

pCODR received input on daratumumab (Darzalex) for multiple myeloma from one patient advocacy group Myeloma Canada. Provincial Advisory Group (PAG) input was obtained from all nine of the provinces participating in pOCDR. pCODR also received registered clinician input from Dr. Donna Reece, jointly with eight other clinicians, on the behalf of Myeloma Canada Research Network.

One supplemental issue was identified during the development of the review process, a critical appraisal of Propensity Score Matching Analysis used to inform the economic evaluation.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence. An assessment of the limitations and sources of bias can be found in Sections 6.3.2.1.

Table 2: Assessment of generalizability of evidence for daratumumab

Domain	Factor	Evidence[1,2]	Generalizability Question	CGP Assessment of Generalizability
Population	Line of therapy	Study MMY2002 investigated the efficacy and safety of daratumumab in patients with multiple myeloma who have received at least 3 prior lines of therapy (including a PI and IMiD) or are refractory to both a PI and an IMiD. The majority of patients (82%) received greater than 3 prior lines of therapy in study MMY2002.	Do trial results apply to patients who have completed less than three prior lines of therapy?	Only if patients are refractory to both a PI and an IMID.
	Co-morbidities	In Study MMY2002, patients with the following were excluded: Chronic obstructive pulmonary disease; Hepatitis B, hepatitis C, or HIV; Clinically significant cardiac disease; Myocardial infarction within one year; Unstable or uncontrolled angina or heart failure NYHA Class III-IV; Arrhythmias requiring treatment or intervention; Prolonged QT interval at screening (QTcF >470msec). Multiple myeloma is a disease mostly prevalent in older adults who may likely have one of these comorbidities	Do trial results apply to the relapsed/refractory multiple myeloma population based on these exclusion criteria?	The CGP were of the opinion that the exclusion criteria was too restrictive for application to the real-world clinical population. Patients who are physically fit, even those with previous co-morbidities, Hepatitis B, hepatitis C, or HIV, should be offered treatment with daratumumab for their multiple myeloma.
	ECOG PS	In Study MMY2002, inclusion criteria was for patients with an ECOG PS of 0,1 or 2	Do trial results apply to patients with an ECOG PS >2? If so, why?	Patients with ECOG PS of 3 would be treated with best supportive care. The CGP agreed that use of daratumumab in patients with ECOG PS of >2 may be appropriate, particularly when their ECOG PS is related to their multiple myeloma and could be potentially improved with daratumumab. Treatment with daratumumab should be left to physician discretion.
	Refractory patients	Study MMY2002 included patients who were refractory to carfilzomib.	Carfilzomib is currently not funded in Canada. Do trial results apply to the Canadian population of patients with multiple myeloma?	

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Intervention	Dosage	Patients enrolled in Study MMY2002 received daratumumab at a dose of 16 mg/kg.	Do trial results apply to patients on other dose schedules?	Trial results do not apply to other doses such as 8 mg/kg. Response rates by dose were very different.
	Pre-infusion medication	All patients in study MMY2002 were to receive pre-infusion medications one hour prior to each daratumumab dose. For the first and second infusions, methylprednisolone 100 mg IV (or an equivalent intermediate or long acting corticosteroid) was given. For subsequent daratumumab infusions, 60 mg of IV methylprednisolone was given. In addition, one hour prior to all daratumumab infusions, acetaminophen 650 to 1000 mg orally and diphenhydramine 25 to 50 mg (or equivalent) was to be given	Are these pre-infusion medications used in Canadian clinical practise?	Yes.
Outcomes	Endpoint	In Study MMY2002 the primary outcome was ORR.	Is ORR a validated surrogate for overall survival in relapsed refractory multiple myeloma?	As patients in this setting may be in their last line of therapy, HrQoL may be more important.

1.2.4 Interpretation

Burden of Illness and Need

In 2015, the incidence of multiple myeloma was 2,700 with 1,400 Canadians dying of the disease. Multiple myeloma is incurable with the average age of diagnosis being 62.[4] Despite the improvement in clinical outcomes with the use of proteasome inhibitors (PI) and immunomodulatory drugs (IMiDs) patients eventually become resistant to these agents. Given the dismal prognosis of PI and IMiD refractory patients, there is a clear need for novel non-cross-resistant modalities of treatment that overcome the tumor microenviroment-mediated drug resistance and genetic instability of the disease. Daratumumab represents the first therapeutic monoclonal antibody against a unique CD38 epitope of the plasma cell, which when provided to heavily pre-treated myeloma patients, has resulted in improved responses as detailed in this review.[1,2]

Prior to the results of the MMY2002 trial, a randomized control trial comparing daratumumab versus best supportive care would have been possible as the clinical efficacy of the drug was unclear. With the current results of the MMY2002 trial, and its clinical responses published on PI and IMID refractory patients, a trial comparing daratumumab to best supportive care is not feasible. In response to the feedback related to the feasibility of an RCT from the stakeholders, the CGP would like to clarify that a trial comparing daratumumab to best supportive care is not feasible for pragmatic reasons; the CGP recognize that it would be challenging to conduct an RCT of daratumumab versus supportive care given the tacit knowledge of the literature to ask patients to be randomized to daratumumab versus supportive (i.e., there would be difficulties in recruiting patients for an RCT such as this). Moreover, the CGP are aware of two large RCTs (POLLOX and CASTOR) that indirectly evaluate daratumumab combination in the relapsed or refractory multiple myeloma patient population. It is clear that PI and IMiD refractory patients have an accelerated mortality with no successful treatment options, making daratumumab an essential agent in preventing end organ damage from myeloma, improving patient quality of life, and maximizing progression free survival and overall survival.

Effectiveness

The MMY2002 trial is an open-label non-comparative phase 2 trial[2] reporting on the results of 106 patients receiving daratumumab at a dose of 16 mg/kg who had received a median of five previous lines of myeloma therapy (range 2 – 14), with the majority being refractory to PIs and IMIDs (95%). The median time to first response was 1.0 months with a median duration of response of 7.4 months. Overall responses were noted in 31 patients (29.2%, 95% CI 20.8-38.9). Although not powered to assess for progression free survival nor overall survival, the PFS was 3.7 months and 12 month overall survival was 64.8%.

Similar results were identified in a dose finding phase 1/2 trial (GEN501) for heavily pre-treated myeloma patients, with an overall response rate of 36% in 42 patients who received a dose of 16 mg/kg.[1]

Of importance, there was an absence of Health-related Quality of Life (HRQOL) data at time of writing. No HRQOL data were collected for the MMY2002 and GEN501 studies. This is particularly salient given that Daratumumab would likely represent the “last line” of myeloma therapy. Arguably, HRQOL is likely paramount at this point of the illness trajectory and maybe equally as important if not more important than PFS or OS.

Safety

Toxicity:
In the phase 1/2 trial,[1] infusion-related reactions were reported as mild (71% of patients had an event of any grade, and 1% had an event of grade 3). In this dose finding trial 53% (N=30) of patients in the 8mg/kg and 26% in the 16mg/kg cohort (N=42) had a grade 3 or 4 adverse event. The most common adverse events of grade 3 or 4 (in > 5% of patients) were pneumonia and thrombocytopenia.

When looking at specific phase 2 data at a 16mg/kg dose[2] in the MMY2002 trial, infusion reactions occurred in 42% of patients, with only 5% being grade 3 and no grade 4 reported reactions. Such infusion reactions typically occurred with the first infusion and included symptoms such as nasal congestion (13 [12%]), throat irritation (7%), and cough, dyspnea or chills (6%).

Nonresponders to daratumumab had higher rates of grade 3 to 4 anemia and thrombocytopenia (24 [32%] and 18 [24%] of 75 patients respectively). Grade 3 or higher neutropenia was similar in both responders and non-responders (13 and 12% respectively).

Death:
Of the 31 patients in the phase 2 trial[2] who died after treatment with daratumumab, 29 died due to progressive disease and 2 died from adverse events including H1N1 complications and complications post aspiration pneumonia. There is no evidence that daratumumab significantly increases the rate of treatment related death.

Other considerations:
The treatment duration of Daratumumab in this clinical setting is not clearly known. However, as reported by the MMY2002 study, the median duration of response was 7.4 months with a PFS of 3.6 months. Therefore, the Committee speculates that the duration of therapy may be between 3 to 8 months, depending on individual cases.

Another aspect of care may relate to combination therapy that could be used in conjunction with Daratumumab. The Committee is unclear with the likelihood of this occurring at an individual basis or with its incremental associated costs.

Quality of Data:
Our review did not identify any randomized controlled trial data evaluating Daratumumab as a single agent or in combination in patients who have failed 3 prior lines of therapy or are refractory to both PI and IMiD. At the time of writing, the sponsors have no plans to carry out such a study. The Committee acknowledges that such a study would unlikely to be feasible in this clinical setting given the current strong perception of daratumumab's efficacy and usefulness amongst clinicians and patients.

1.3 Conclusions

The Clinical Guidance Panel concluded that there may be a net clinical benefit of daratumumab in patients with heavily treated multiple myeloma. This conclusion was based on the results of a single phase II study of daratumumab in highly-pretreated patients with multiple myeloma, showing clinically meaningful responses with a median duration of response of 7.4 months in MMY2002. The adverse event profiles were manageable at the 16mg/kg dose. The CGP acknowledges a lack of randomized controlled trial evidence supporting an overall progression free and overall survival benefit; however, the CPG concluded that daratumumab may be efficacious in producing acceptable clinical responses in

refractory myeloma patients, a group of patients with limited treatment options and with a poor prognosis.

The Clinical Panel also considered that:

- In the absence of the randomized controlled study data addressing daratumumab versus Best Supportive Care or Therapy (BSC), the Submitter provide a comparative group to the cohort treated with daratumumab within the MMY2002/GEN501 studies. They did so by utilizing a Propensity Score Matching Analysis drawing the control arm population from a retrospective International Myeloma Foundation (IMF) Chart review conducted in 2015. The details, strengths and limitations of this analysis is documented in the report. In brief and taking into account comparability as well as the uncertainty of the estimates, the use of daratumumab may appear to translate into a favorable PFS and OS HR of 0.44 (95% CI: 0.31-0.63) and 0.56 (95%CI: 0.42-0.74) respectively; however, the uncertainty in these estimates may be greater than the confidence intervals indicated due to known prognostic factors that were not included in the propensity score and due to the potential for differences in unknown factors. In their feedback, the submitter commented on the pERC's conclusion related to the propensity score matching analysis. Although the CGP appreciate the opinion of the clinical expert consulted by the submitter (i.e., staging and time since diagnosis may not be as important as other variables in the PSM analysis), the CGP reiterated that staging and time since diagnosis have value and, moreover, staging and time since diagnosis may be more salient given the absence of a RCT.
- It is unclear whether the results of the two studies reviewed, which showed in aggregate clinically meaningful responses and PFS in patients with heavily-pretreated (defined as being double-refractory or who received > 3 prior lines of therapy) multiple myeloma, apply equally to patients who are double-refractory and to patients who are refractory to three or more lines of therapy.
- Specific patient populations were excluded from the phase 2 clinical trial including those with chronic obstructive pulmonary disease, Hepatitis B or C, HIV, unstable angina or heart failure, or unstable cardiac arrhythmia. The exclusion criteria are restrictive to a real world myeloma patient population, and treatment should be offered for patients with optimized and/ or well controlled pulmonic, cardiac or infectious disease.
- The MMY2002 trial investigated the efficacy and safety of daratumumab in patients who received at least 3 prior lines of therapy (including a PI and IMID), or are refractory to both a PI and an IMID. The use of daratumumab should be limited to patients who have received either three or more prior lines of therapy or who have been shown to be refractory to a PI and an IMID.
- Acceptable response rates with less adverse event rates were seen at a 16mg/kg dose, which should be the recommended dose provided to patients.
- Infusion reactions are common with initial dosing daratumumab and decrease with subsequent exposures. Infusion centers will be required to provide appropriate supervision and pre-medication (i.e. corticosteroids) for patients
- ORR was the primary outcome in MMY2002. It is recognized that for many patients in this trial, this was likely their last line of therapy making such an endpoint clinically meaningful. Additional endpoints including quality of life may prove to offer more understanding of value of cancer therapy.
- In the pharmacoeconomic model, daratumumab is compared to treatments often used in third line therapy or beyond including high dose dexamethasone, bortezomib, cyclophosphamide and dexamethasone, and pomalidomide and dexamethasone. Based on surveys of Canadian experts, the manufacturer assumes that the average utilization of such regiments in Canada is 6%, 18% and 76% respectively. Patients transitioned to daratumumab will have failed IMiD and PI therapy, and they typically present with higher rates of end organ damage, immunosuppression, and poor hematopoetic

reserve. Such a treatment refractory patient population along with the necessity of prolonged daratumumab infusions, nursing time, and management of novel toxicities will add to the economic burden of its use. As such, using IMiD or PI based comparators for pharmacoeconomic analysis may underestimate the true economic costs of daratumumab.

- In the pharmacoeconomic model, the effectiveness (OS and PFS) and cost estimates of Daratumumab came from the combined patient sample from GEN501/MMY2002 study. Based on their study designs and patient characteristics, the pooling of study results is appropriate.
- In their feedback to the initial recommendation, PAG commented on the enthusiasm over daratumumab/dexamethasone combination therapy and issues around infusion times. The CGP feel that daratumumab is valuable in this patient group. The CGP would also like to note that a PFS range of 4-6 months is in line with the General Oncology evaluation of meaningful PFS. However, the CGP acknowledge that there has been no significant work on what constitute a meaningful PFS in hematology oncology/myeloma. According to the Institute for Clinician and Economic, additional 3-5 months of OS or PFS was generally recommended as the range for minimum clinically meaningful improvements in breast, lung, pancreatic and colon cancers.[5] Though there are no current specific recommendations for multiple myeloma, it may be reasonable to also consider 3-5 months for multiple myeloma given the consistency of these recommendations across the four different types of cancer noted above.[5] It is worth noting that the feedback from PAG regarding triplet therapy is out of the scope of the review. No formal review of the evidence for triplet therapy was conducted for this report. Lastly, the CGP agree that chair time is a concern from a resource perspective and not necessarily from a patient's perspective.
- Both the registered clinicians and the CGP noted that pERC recognized that additional downstream resources and costs would be incurred due to the interference of daratumumab with blood compatibility testing. In their feedback, registered clinicians comment on their clinical experience related to interference with blood compatibility testing and additional downstream resources. The CGP felt that it is slightly more work from a blood bank perspective, however it is relatively easy to manage. The CGP suspect that the costs would be minimal from a blood bank perspective; as the infrastructure is already set up to do so in other clinical contexts. CGP suggested the possibility of phenotyping all myeloma patients upon diagnosis with the possibility that they may be getting daratumumab, or at minimum, at the time of first red cell transfusion. Alternatively, patients who receive daratumumab could also be red cell genotyped at the time the drug is ordered for them.
- In the Submitter's feedback on pERC's initial recommendation, they state that it is accepted that patients do derive some clinical benefit after they stop taking a drug. According to the CGP, though it is not clearly known, it seems plausible that patients could derive benefit after they stopped receiving the treatment given the published results. Possible assumptions that may explain the amount of clinical benefit derived after progression may be that the drug is not actually stopped on progression, and rather additional agents are added; or, the progression is biochemical and the drug is continued (i.e., in other words, time to progression is not necessarily reflective of the time to next treatment/full palliative care).

2 BACKGROUND CLINICAL INFORMATION

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.[6] The median age of diagnosis is 69 years with a 5 year overall survival estimated at 48.5%.[7]

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

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

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.[14] 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,[15-18] emergence of more targeted therapies,[19] indirect data from multiple randomized trials,[20] 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,[20] Progression Free Survival 1 & 2,[20] HRQOL[21,22] and possibly economics[23]) than a strategy of intermittent therapies based on symptoms.

2.2 Accepted Clinical Practice

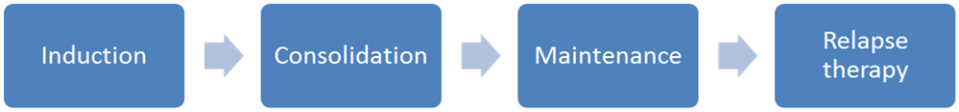
The optimal chemotherapeutic management of symptomatic myeloma remains elusive. Radiation therapy remains supportive and reserved for management of pain and localized symptomology from plasmacytomas (localized myeloma). Given that myeloma is incurable and patients will ultimately receive all possible effective chemotherapeutic options. However, there remains no consensus on the optimal sequencing of effective therapies. However, 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 often

used in combination an agent from another. All these combinations are often 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 chemotherapeutic goal of suppressing the malignant clone(s), achieving complete remission and maintaining the remission/suppression, while paying attention to chemotherapeutic side effects.[24]

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 4) individual preferences.[25] Moreover, 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.[26-31] Similarly, the above categories of agents have been also evaluated in the newly diagnosed setting demonstrating efficacy and value.[32-37] 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. One of the most developed options is Daratumumab,[38-40] 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 21 April 2016. Specifically, they are requesting funding for Daratumumab for the treatment of patients with multiple myeloma who 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.

2.3 Evidence-Based Considerations for a Funding Population

The population under consideration essentially includes patients with relapsed and/or refractory symptomatic myeloma as defined by the IMWG criteria,[41] but more specifically for patients who have previously received therapies with PI and IMiD.

There are preclinical,[42] Phase 1[1] and Phase 2[2] 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 and an immunomodulatory agent 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 proteasome inhibitor (PI) and an immunomodulatory agent, or who are refractory to both a PI and an immunomodulatory agent.[43]

To our knowledge there are several ongoing Phase 3 studies 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[44]
2. A Study Comparing Daratumumab, Lenalidomide, and Dexamethasone with Lenalidomide and Dexamethasone in Relapsed or Refractory Multiple Myeloma. clinicaltrials.gov registration: NCT02076009[45]

Several publications on the economics of management of relapsed and/or refractory multiple myeloma may be illustrative, instructive and assist with benchmarking.[46-52]

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[53]
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[54]

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[55]

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[56]

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Myeloma Canada, provided input on daratumumab for the treatment of patients with multiple myeloma who 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, and their input is summarized below.

Myeloma Canada conducted two online surveys and an interview for this submission. In the case of the surveys, a link was sent by e-mail to myeloma patients and caregivers across Canada. It was also provided to the International Myeloma Foundation who called on the support of their US membership to complete the survey through their online newsletter, and included a link on their website, and through their social media networks.

The first survey was issued from September 16, 2015 to October 8, 2015 (herein referred to as "Survey 1"). This survey was directed to myeloma patients and caregivers about the impact of myeloma on their lives and the effect of treatments on their myeloma. A total of 599 responded completed the survey: 559 respondents were from Canada, 39 respondents were from the United States, and one respondent was from New Zealand. Canadian respondents represented each province and the Yukon; there were no responses from Nunavut or the Northwest Territories. Among the 599 respondents, 463 respondents were individuals living with myeloma and 136 respondents were caregivers.

The second survey (herein referred to as "Survey 2") was conducted more recently in December 2015/January 2016 and again in March 2016. Survey 2 was directed to patients and caregivers with experience with daratumumab and focused specifically on their experience with this treatment. The general questions from the previous survey were not repeated. Myeloma Canada received a total of 38 respondents (29 patient respondents and 8 caregiver respondents), who indicated that they had used daratumumab to treat their myeloma; 14 respondents were from Canada and 24 respondents were from the United States. The treatment experience section of this report reflects the answers from these 38 respondents.

In addition to the online survey, seven patient respondents were interviewed between March 10 and April 8, 2016, who had used daratumumab to treat their myeloma. Among the seven respondents, four respondents had responded to the online survey. These patient respondents were specifically asked whether or not the treatment met their expectations.

From a patient's perspective, the most important aspect of myeloma to control is infection, followed by kidney problems, pain, mobility, neuropathy, fatigue and shortness of breath. Respondents indicated that symptoms associated with myeloma affected their ability to work the most, followed by the ability to travel, exercise, volunteer, conduct household chores, fulfill family obligations, and spend time with their family. Respondents reported using the following current therapies: dexamethasone, bortezomib, lenalidomide, autologous stem cell transplant, melphalan, cyclophosphamide, thalidomide, pomalidomide, and vincristine, doxorubicin and dexamethasone (VAD). Most respondents experienced fatigue with their treatment for myeloma; other treatment side effects included: neuropathy, pain, insomnia, stomach issues, nausea, shortness of breath, confusion, diarrhea, constipation, and skin rashes. Myeloma Canada reported that for respondents to consider taking a new treatment for their myeloma, the majority of respondents indicated that it was important the new treatment bring about improvement in their physical condition and that the expected benefit would be a lack of disease progression. According to Myeloma Canada, of the 38 respondents who have experience with daratumumab, the majority of respondents (58%) rated it as extremely effective, while a minority (11%) rated it

as not effective with controlling their myeloma. The majority of respondents reported the side effects (e.g., fatigue, constipation, diarrhea, dyspnea, low blood counts, infections, pain, decreased appetite, headache, nausea/vomiting, infusion reaction, fever) with using daratumumab as being tolerable. Respondents also commented on the time it takes for the infusion; in particular, some respondents thought this was positive as the infusion frequency is reduced over time. Six out of the seven respondents who were interviewed indicated that daratumumab has met their expectations in that they are responding to the treatment and that it has improved their quality of life.

Please see below for a summary of specific input received from the patient advocacy group. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was 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

When respondents were asked to rate on a scale of 1-5 (where 1=not at all and 5=significant impact), how much symptoms associated with myeloma impact or limit day-to-day activity and quality of life; according to Myeloma Canada, respondents indicated their ability to work was most affected, followed by ability to travel, exercise, volunteer, conduct household chores, fulfill family obligations, and spend time with family. The results from the respondents are reproduced in the table below.

How much symptoms associated with myeloma impact or limit day-to-day activity and quality of life? Respondents rated on a scale of 1-5.							
	1 - Not at all	**2 (%, n)**	**3 (%, n)**	**4 (%, n)**	**5 - Significant impact (%, n)**	**N/A**	**Total**
Ability to work	8.38% 44	12.38% 65	14.29% 75	13.14% 69	39.24% 206	12.57% 66	525
Ability to travel	9.92% 52	15.84% 83	20.61% 108	23.66% 124	28.63% 150	1.34% 7	524
Ability to exercise	7.27% 38	17.59% 92	25.43% 133	24.67% 129	24.28% 127	0.76% 4	523
Ability to volunteer	13.33% 70	16.00% 84	22.67% 119	20.19% 106	20.19% 106	7.62% 40	525
Ability to conduct household chores	11.83% 62	20.61% 108	30.73% 161	19.47% 102	16.22% 85	1.15% 6	524
Ability to fulfill family obligations	15.27% 80	20.23% 106	28.63% 150	19.08% 100	14.50% 76	2.29% 12	524
Ability to spend time with family and friends	18.74% 98	22.94% 120	27.92% 146	16.44% 86	13.00% 68	0.96% 5	523
N/A = not available							

Myeloma Canada indicated the level of impact varies depending on how long a patient has been diagnosed, whether or not he or she has had treatment and whether symptoms are under control. Below were some of the key responses reported to help illustrate the impact on their quality of life:

> "*All of the above, if affected by MM, change the quality of life for both patient and caregiver.*"

"*I am presently in remission so am delighted to be doing as much as possible at his time*."

"*Things are always more significant post chemo*."

Myeloma Canada asked respondents to rate on a scale of 1-5 (where 1=not important and 5=very important), how important it is to control various aspects of myeloma. The results collected from the respondents are reproduced below.

How important it is to control various aspects of myeloma? Respondents rated on a scale of 1-5.							
	1 - Not important	2 (%, n)	3 (%, n)	4 (%, n)	5 - Very important (%, n)	N/A	Total
Infections	1.91% 10	2.49% 13	4.40% 23	6.50% 34	82.60% 432	2.10% 11	523
Kidney problems	2.52% 13	1.94% 10	4.26% 22	10.27% 53	77.33% 399	3.68% 19	516
Pain	1.16% 6	3.09% 16	7.35% 38	18.57% 96	67.50% 349	2.32% 12	517
Mobility	1.54% 8	1.93% 10	7.72% 40	19.88% 103	66.41% 344	2.51% 13	518
Neuropathy	1.37% 7	2.35% 12	7.63% 39	21.72% 111	64.58% 330	2.35% 12	511
Fatigue	0.58% 3	2.53% 13	10.70% 55	25.68% 132	59.14% 304	1.36% 7	514
Shortness of breath	1.95% 10	3.89% 20	11.67% 60	22.76% 117	57.20% 294	2.53% 13	514
N/A = not available							

According to Myeloma Canada, respondents stated that infections were the most important aspect of myeloma to control, followed by kidney problems, pain, mobility, neuropathy, fatigue and shortness of breath. Other aspects of myeloma that respondents would like to control included mood or emotional issues and stomach issues (e.g., diarrhea, nausea, gastrointestinal upset).

3.1.2 Patients' Experiences with Current Therapy for Multiple Myeloma

Of the 506 respondents who responded to Survey 1, the main treatments respondents used included: dexamethasone (n=413); bortezomib (n=370); lenalidomide (n=332); autologous stem cell transplant (n=327); melphalan (n=220); cyclophosphamide (n=207); thalidomide (n=109); pomalidomide (n=89); vincristine, doxorubicin and dexamethasone or VAD (n=54).

Most respondents reported experiencing fatigue with their current treatment for myeloma. Other side effects experienced with their current treatment for myeloma included: neuropathy, pain, insomnia, stomach issues, nausea, shortness of breath, and confusion. Myeloma Canada also stated that an additional 32 respondents reported stomach related issues (e.g., diarrhea, constipation) as a side effect and 12 respondents reported skin rash under 'Other' category. The responses are reproduced in the table below.

What side effects were experienced with treatment for myeloma? Respondents selected all that applied.		
Side Effect	**%**	**# of Respondents**
Fatigue	89	447
Neuropathy	60	304
Pain	43	219
Insomnia	57	287
Stomach Issues	49	248
Nausea	48	240
Shortness of Breath	43	215
Confusion	32	164
Does not apply to me as I have yet to be treated	2	11
I don't know or can't remember	1	4

According to Myeloma Canada, almost all respondents (97% out of 491 respondents) rated access to effective treatment for myeloma as "*very important*." Myeloma Canada also asked respondents to rate on a scale of 1-5 (where 1=not important and 5=very important), how important it is for them and their physician to have choice based on each drug's known side effects. Most respondents (88% out of 509 respondents) rated this as "*5 – very important*."

Myeloma Canada noted that a majority of respondents (81% out of 349 respondents) indicated that they did not experience hardships, were not aware of hardships, or so far are not experiencing hardship in accessing treatment. However, almost 20% of respondents (68 out of 349 respondents) reported hardships which included: delays in treatment, more treatment options needed, cost, and not able to access clinical trials. One respondent also reported side effects and fear of treatment as a hardship (n=1, n=1 respectively).

Most respondents (88% out of 508 respondents) also reported that improvement of quality of life was a "*very important*" consideration with any treatment for myeloma.

3.1.3 Impact of Multiple Myeloma and Current Therapy on Caregivers

Among the 599 respondents, 136 were caregivers. Myeloma Canada noted that more than 136 respondents answered questions directed to caregivers and indicated that these respondents were assumed to be patients.

Myeloma Canada asked caregivers to rate on a scale of 1-5 (where 1=not at all and 5=significant impact), how much symptoms associated with myeloma impact or limit day-to-day activity and quality of life. Myeloma Canada submitted that respondents, some of which were patients, indicated their ability to travel was most affected, followed by ability to work, spend time with family and friends, volunteer, fulfill family obligations, exercise, and conduct household chores.

When asked about challenges caregivers face as a result of the side effect of treatment, respondents, some of which were patients (N=148), indicated having experienced emotional issues such as feelings of helplessness, anxiety/worry, stress and depression (n=55). Other respondents noted having experienced more chores around the home and less time to do their own things (n=22). Some commented on the challenge of dealing with the patient's mood swings (n=14).Other challenges included: tiredness/fatigue, work was affected, food preparation (i.e., patient would not eat, or required different meals, food smells were an issue), and financial burden. A total of 27 respondents indicated experiencing no challenges as a result of the side effect of treatments and 10 respondents replied N/A to the question.

Myeloma Canada included the following comments to help illustrate the caregiver experiences:

> *"I get worn down with all the side effects. It never ends. I have to keep the records, ask the questions, fill the prescriptions, be alert to infections, ask for test results, chart the test results, go to peer group, delay vacations and give my life over to taking care of my spouse. I'm not complaining, but retirement wasn't meant to be like this. My spouse does what he can, and at times that isn't a lot. Our MM peer support groups gets me through and without it I would be less effective and my spouse would not be treated so well."*

> *"Extra burden both financially and not being able to have a family quality of life. the longer the cancer the less support."*

> *"The illness has caused serious damage and my husband is no longer able to help me around the house. The treatments has saved his life but the desease has altered the quality of life for the worst."*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences to Date with Daratumumab

Expectations with Daratumumab

Myeloma Canada asked respondents if they were to consider taking a new treatment for their myeloma, to rate on a scale of 1-5 how important it is to bring about improvement in their physical condition. It was reported that 82% (n= 431) of respondents rated this as "extremely important". Myeloma Canada indicated that 90% (n=436) of respondents also reported that the expected benefit (such as lack of disease progression) from a new treatment was "extremely important".

Myeloma Canada also asked respondents to rate of a scale of 1–5, where 1 was "not important as long as there is a drug" and 5 was "very important to choose which drug would be better suited for me". 87% (n=436) of respondents selected 5 in terms of importance for choice of therapy.

When respondents were asked to rate on a scale of 1 – 5, where 1 was "no side effects" and 5 was "significant side effects", respondents indicated that they were willing to tolerate some side effects. Specifically of the 437 respondents who responded to this question, 10% of respondents selected a rating of 5 (tolerate significant side effects), and 6% of respondents selected a rating of 1 (no side effects).

Experiences with Daratumumab

Myeloma Canada reported that 38 respondents indicated that they had used daratumumab to treat their myeloma. When asked how long they have been on treatment with daratumumab, respondents reported the following:

- 1 to 6 months: n=19 (50%)
- 7 to 12 months: n=7 (18%)
- 1 to 2 years: n=9 (24%)
- 3 to 4 years: n=3 (8%)

A total of 21 respondents who had experience with daratumumab provided a response when asked in an open-ended question on how myeloma affects them. Of these, 13 respondents commented that myeloma is a challenging disease citing pain, low energy and strength, mental and financial

issues, uncertainty about next treatments. One respondent stated: "*It is a very hard sickness. It is very expensive to be treated. Very sensitive disease. Very hard to detect and overall very tricky. And also it is easy to reoccur. I hope that more can be done to fight multiple myeloma*." Two respondents commented on the treatment side effects. Specifically, one respondent stated: "*This is a clinical trial for my wife and the experience has been good. My wife surfers from extreme weight loss and an inability to regain weight, loss of physical strength, hearing problems, pain from her port installation, all side effects from the drugs not the myeloma. The myeloma has caused several spinal fractures, with a loss of 2 inches in height and tolerable back pain w/o use of pain medication. The chemo drugs appear to be worse than the myeloma*." One respondent reported no affect to lifestyle. One respondent was positive about this new treatment and one respondent commented on how the treatments have extended his life.

Respondents were asked in an open-ended question whether daratumumab has changed or is expected to change their long-term health and well-being. Myeloma Canada reported that 23 (72%) respondents provided a positive response. Of the 32 respondents who responded to this question,

- 13 (41%) respondents indicated that they had seen physical benefits,
- four (13%) respondents had experienced mental benefits,
- three (9%) respondents were hopeful for life extension,
- two (6%) respondents reported that they are in remission,
- one (3%) respondent had no change in quality,
- one (3%) respondent was neutral,
- two (6%) respondents indicated that the treatment was not effective,
- one (3%) respondent reported that it was not effective so far,
- four (13%) respondents reported that it was too early to tell,
- one (3%) respondent stated "*more fatigue*"; however, it is uncertain if this was a result of the dexamethasone treatment or daratumumab treatment

Myeloma Canada has incorporated the following quotes to help illustrate the above responses:

> "*My Mprotein number which was on a steep incline has decreased from 27 to 3.5 in over 15 months....not only is it good physically but also mentally. With two teenage girls, I believe I will witness more of their milestones such as graduating from high school/university by living longer.....that is all thanks to dara.....*"
>
> "*Given that I have now failed so many drugs, I have a great deal of optimism about my future and this has improved my health in numerous ways: eating better, exercise, positive thoughts.*"
>
> "*3 months on dara, too early to tell*"
>
> "*I have graduated from wheelchair and bedside commode to independent walking and ability to complete some household chores.*"
>
> "*it helped put mm in remission*"

When respondents were asked to rate their quality of life while taking daratumumab on a scale of 1- 5, with 1 as being "poor quality of life" and 5 as being "excellent quality of life"; of the 37 respondents who answered this question, it was reported that 11 (30%) respondents rated it as 5, 17 (46%) respondents rated it as 4, while one (3%) respondent rated it as 1.

Respondents were asked to rate on a scale of 1 – 5 how convenient they found it to take daratumumab (e.g., does it interfere with their day-to-day activities, does it cause immediate or

intolerable side effects), with 1 as being “not at all convenient” and 5 as being “extremely convenient”. It was reported that, of the 37 respondents who responded, 16 (43%) respondents rated it as 5, nine (24%) respondents rated it as 4. Myeloma Canada indicated that 24 respondents provided additional comments. Of these 24 responses, 18 respondents commented on the time it takes for the infusion; in particular, some thought this was positive as the infusion frequency is reduced over time, and others are retired so they do not mind the time that it takes.

Respondents were asked to rate daratumumab’s effectiveness in controlling their myeloma on a scale of 1 – 5, with 1 as being “not effective” and 5 as being “extremely effective”. According to Myeloma Canada, of the 38 respondents who responded, 22 (58%) respondents rated it as 5 (extremely effective), while four (11%) respondents rated it as 1 “not effective”.

Respondents were also asked to rate daratumumab’s side effects on a scale of 1 – 5, with 1 as being “completely intolerable” and 5 as being “very tolerable”. It was reported that, of the 38 respondents who responded, 28 (74%) respondents rated it as 5 and seven (18%) respondents rated it as 4. The lowest rating was a 3 reported by three (8%) respondents. In addition, respondents were asked to rate specific side effects from 1 – 5, with 1 as being “completely intolerable” and 5 as being “very tolerable”. The results are reproduced in the table below. In many cases the side effect was not applicable, as indicated by the number of respondents in the “N/A” column.

	1 - Completely intolerable -	2 (%, n)	3 (%, n)	4 (%, n)	5 - Very tolerable (%, n)	N/A	Total (n)
Fatigue	0.00% 0	20.00% 7	28.57% 10	31.43% 11	14.29% 5	5.71% 2	35
Constipation	0.00% 0	12.12% 4	18.18% 6	15.15% 5	15.15% 5	39.39% 13	33
Diarrhea	0.00% 0	9.38% 3	31.25% 10	6.25% 2	21.88% 7	31.25% 10	32
Dyspnea (shortness of breath)	0.00% 0	9.38% 3	18.75% 6	25.00% 8	15.63% 5	31.25% 10	32
Low blood counts (low white blood cells, low red blood cells (anemia) and/or low levels of blood platelets	0.00% 0	15.63% 5	15.63% 5	31.25% 10	28.13% 9	9.38% 3	32
Infections including pneumonia	6.25% 2	6.25% 2	6.25% 2	9.38% 3	28.13% 9	43.75% 14	32
Pain	0.00% 0	6.67% 2	10.00% 3	20.00% 6	26.67% 8	36.67% 11	30
Decreased appetite	0.00% 0	3.23% 1	3.23% 1	22.58% 7	35.48% 11	35.48% 11	31
Headache	0.00% 0	6.45% 2	0.00% 0	16.13% 5	38.71% 12	38.71% 12	31
Nausea/vomiting	0.00% 0	0.00% 0	3.13% 1	21.88% 7	31.25% 10	43.75% 14	32
Infusion reaction	0.00% 0	3.03% 1	3.03% 1	18.18% 6	48.48% 16	27.27% 9	33
Fever	0.00% 0	0.00% 0	3.33% 1	16.67% 5	46.67% 14	33.33% 10	30

Nine respondents provided additional comments. Specifically, three respondents stated that they had a reaction following their initial infusion. Three respondents reported that their side effects were caused by other treatments. One respondent reported that blood counts have risen. One respondent reported sweating during and after infusion. One respondent had no effect from the infusion. To help illustrate the respondents' experiences, Myeloma Canada has included the following comments to support the above context.

> "*I believe that Constipation, Pain, and Fatigue can be attributable to pain medication which I started around the same time that I started daratumumab*."
>
> "*I'm taking Dara with Pomalyst and fatigue, etc., may be caused by the Pom, not the Dara*."
>
> "*Initial infusion. Had allergic reaction to drug. Shortness of breath. Skin turned white. Had chest pain. Stop infusion took more Benadryl. Waited 1 hour to continue infusion. No reactions after further infusions. Had 25 infusions to date*."
>
> "*Of all the chemo over 14 years this has been the easiest to take with the fewest side effects*."
>
> "*Although living with daily bowel issues going from one extreme to another, the side effects are very minimal when compared to the ones I experienced prior and shortly after my transplant*."

In addition to the online survey, seven respondents were interviewed who have experience with daratumumab to treat their myeloma. These patients were specifically asked whether or not the treatment met their expectations.

Patient 1 – was on the treatment for 7 weeks, but due to lesions and bone pain, treatment was discontinued – currently not on treatment.

Patient 2 –has been on the treatment for 14 months. When asked about her expectations – respondent stated it had met the respondent's "*expectations and beyond. In every way, I feel normal*". The respondent was expecting a cure. The respondent did have a virus that lasted 5 weeks; following this, the respondent reported that the quality of life has improved.

Patient 3 – has been on treatment for 3 weeks. The respondent believes that daratumumab is a "*wonder drug*". The respondent reported "*The response has been outstanding, more than any other drug taken in the past 10 years*". The drug has exceeded the respondent's expectation, which was to only see results after two months, but the respondent has seen outstanding results after three weeks.

Patient 4 – has been on the treatment for 9 weeks. The respondent stated: "*Compared to chemo it has been a miracle treatment for me. I was reluctant to go back on treatment even though my myeloma was progressing because of my reaction to previous treatments.*" The treatment has "*over exceeded*" the respondent's expectations. The respondent's numbers are responding, and have decreased. "*I know a few other patients who have been on it, and they all say the same thing.*" "*It should get covered, because it is the only treatment that I haven't had side effects, most other chemo treatments have sent me to the ER or hospital*."

Patient 5 – has been on treatment for 18 months. The respondent stated: "*I didn't think the treatment would lead to a complete remission, I thought it would get the levels down to a reasonable level within a few years without having to go through a weekly protocol. Right now I*

go for treatment once a month, this is no big deal. This is so much easier as your whole life revolves around the treatments." The treatment has improved the respondent's quality of life as the respondent doesn't have to worry about the cancer right now and can focus on getting exercise.

Patient 6 – has been on the treatment for 5 months. The treatment has not quite met the respondent's expectations – "*good results with dara, but not as good as expected*." The respondent was expecting to be back in remission. "*Not in a complete remission, but holding on to some good numbers*." Currently, the respondent's quality of life is "great", but the respondent suffered an "*allergic reaction to the first infusion*". The respondent couldn't breathe, but an hour later the respondent was back to normal. The respondent has had constipation, diarrhea, fatigue and depression, but stated "*as you continue with the treatment, they go away*."

Patient 7 – has been on the treatment for 1 year. The respondent's expectation was for the drug to be effective, "*we reach that for at least one year*." The respondent had a "*cough at the first infusion*", which made the respondent nervous that they may not be able to continue with the treatment, but this was not the case as the next infusion had no adverse events. The respondent has been able to travel between treatments.

Respondents were asked in an open-ended question whether there was anything else about daratumumab that they would like us to know and report. A total of 23 respondents answered this question:

- three reported no problems with the treatment,
- two respondents repeated their previous comment that it did not work,
- two indicated that it has the fewest side effects,
- two noted the side effects are minimal,
- two noted that the side effects will reduce following first treatment,
- two reported that the treatment is working,
- one didn't understand why all myeloma patients did not have access,
- one indicated that it was effective for 2 years and then had to switch treatment,
- two reported that they are taking the drug in combination,
- one "loved" it,
- one suggested making the drug more "*tolerable for people to digest. It brings down the white blood cell count by way too much*",
- one had nothing more to add,
- two answered "*not at this time*",
- one did not understand the question.

3.3 Additional Information

Not applicable.

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 plus dexamethasone and bortezomib plus dexamethasone are funded in all the provinces for previously treated multiple myeloma. 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 trial submitted for review is a phase 2, non-comparative study. Given the current treatment options available, PAG is seeking data on the long term benefits and safety of daratumumab compared to currently available treatments.

4.2 Factors Related to Patient Population

PAG noted that the prevalent number of patients with multiple myeloma who have received three prior lines of therapy and would be eligible for treatment with daratumumab is unknown.

PAG is seeking clarity in the patient population who would be eligible for daratumumab.

PAG noted that if and when data becomes available to use daratumumab in earlier lines therapy or in combination with chemotherapy, there may be pressure from clinicians and patients to use daratumumab outside of the current funding request and review scope.

Given the many new treatments recently available and possibly more upcoming new treatments, PAG is seeking guidance from tumour groups for a national treatment algorithm for multiple myeloma and sequencing of treatments.

4.3 Factors Related to Dosing

The weekly dosing schedule in the first eight weeks, the every two weeks dosing schedule in weeks 9 to 24 and the every four weeks thereafter until progression are inconvenient for patients, especially those who would have to travel far to and from cancer centres with the resources to administer and monitor daratumumab infusions.

4.4 Factors Related to Implementation Costs

PAG noted that there may be a large prevalent population who would be eligible for treatment with daratumumab. As treatment is continued until progression, the unknown duration of treatment is a barrier to implementation.

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

PAG noted that access to daratumumab would be limited to cancer treatment centres with the appropriate resources to administer and monitor treatment.

The weekly dosing schedule for the first eight weeks is challenging for managing of chemotherapy chair time and pharmacy preparation time, in addition to being inconvenient for patients coming in weekly for the infusions. After eight weeks of weekly infusions, daratumumab will be given every two weeks for another sixteen weeks and then every four weeks until progression, which will also strain chemotherapy chair time, clinic time, human resources and patient access. PAG also noted that long infusion time would have impact on chemotherapy chair time and the frequent adjustment to infusion rates require nursing resources.

Daratumumab, being an intravenous drug, would be administered in an outpatient chemotherapy centre or inpatient hospital for appropriate administration and monitoring of toxicities. If recommended for funding, intravenous chemotherapy drugs would be fully funded in all jurisdictions for eligible patients.

4.6 Factors Related to Manufacturer

PAG identified the lack of comparative data and long term data are barriers to implementation.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One clinician input was received in a joint submission from nine clinicians, on the behalf of Myeloma Canada Research Network.

Overall, the clinicians providing input cited that daratumumab provides another therapeutic option with a different mechanism of action than current treatments for patients who are refractory to PI and IMiD. They identified that daratumumab demonstrates better activity in the heavily pretreated and refractory patients and noted that there are currently no approved therapy that provides such response with such favourable toxicity profile.

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

5.1 Current Treatment(s)

The clinicians providing input identified that the current treatments include pomalidomide, cyclophosphamide, dexamethasone, carfilzomib, bortezomib and melphalan. It was also noted that some patients enter clinical trials or may receive combination chemotherapy.

5.2 Eligible Patient Population

Some of the clinicians indicated that the eligible patient population will depend how "failed PI and IMiDs" is defined. They noted that the current survival for myeloma patients is about 5-7 years and since about 15% of myeloma patients will die of their disease yearly, a proportion of patients will die prior to reaching the refractory state described in the funding proposal. They indicated that all patients who reach fourth-line treatment may be eligible for treatment with daratumumab but identified that a number of patients (e.g. the very sick, poor performance status, those on dialysis, the very old and those with severe comorbidities) should not be prescribed daratumumab and a number of patients decline further treatment or cannot travel to chemotherapy clinics for intravenous infusions.

5.3 Identify Key Benefits and Harms

The clinicians providing input cited high response rate (progression-free survival and complete response) of daratumumab as the most important benefit of this drug leading to improved quality and length of life. Lack of side effects and monotherapy were also seen as strong benefits.

The most common side effect noted by the clinicians providing input was infusion reactions associated with the first cycle; however, they noted that these can be controlled easily with pre-medications and without long-term harm.

5.4 Advantages Over Current Treatments

The clinicians providing input identified that for patients refractory to a PI and IMiD current therapies are of limited value and options for patients who have failed pomalidomide are very poor. In the majority of patients not responding to pomalidomide, having access to another agent with significant activity will provide benefit and extend the life of these patients. The clinicians providing input stated that daratumumab, a monoclonal antibody with a different mechanism of action than pomalidomide, provides another line of therapy for these patients and can improve survival and quality of life for those patients who respond to treatment. They noted that the overall results are better than those for pomalidomide in a more refractory population and appears to be superior to carfilzomib.

5.5 Sequencing and Priority of Treatments

The clinicians providing input indicated that daratumumab should be used after at least three prior regimens or when patients are refractory/intolerant to PI and IMiD, as a last line of therapy following failure of PI and IMiD combination, or as per the SIRIUS trial.

Some of the clinicians providing input believe that daratumumab could be used as monotherapy or combined with other current treatments. They also indicated that it may possibly replace pomalidomide or reduce the use of pomalidomide, which currently may be continued in non-responding patients due to the lack of any other option for therapy.

5.6 Companion Diagnostic Testing

The clinicians providing input indicated that there is no companion diagnostic test required for the use of daratumumab. However, it was noted that erythroid phenotype has to be done before use of daratumumab in case the patients require red blood cell transfusion.

5.7 Additional Information

One of the physicians indicated that daratumumab is the first monoclonal antibody to demonstrate single agent activity in relapsed and refractory disease. The physician noted that it has demonstrated “incredible activity” in very advanced and heavily pre-treated patients. The clinicians providing input noted that there are currently no approved therapies that provides such response and with such favourable toxicity profile to this population of myeloma patients.

6 SYSTEMATIC REVIEW

6.1 Objectives

The objective of this review is to evaluate the safety and efficacy of daratumumab (Darzalex) 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.

Note: A Supplemental Question relevant to the PCODR review for the economic evaluation was identified:

Critical appraisal of the Propensity Score Matching Analysis of MMY2002/GEN501 Data and International Myeloma Foundation Medical Chart Review: Daratumumab versus Standard Care Therapy for Heavily Pre-Treated and Highly Refractory Multiple Myeloma[57]

6.2 Methods

Review Protocol and Study Selection Criteria

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

Table 3: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs or non RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of daratumumab should be included.	Adult 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.	daratumumab	All appropriate multi-agent chemotherapy regimens including but not limited to: IMiDs: • Pomalidomide • Lenalidomide PIs: • Bortezomib • carfilzomib • Other later generation PI and IMiDs • BSC	• OS • PFS • ORR • **HRQoL** • **AEs** • **SAEs** • WDAE • **Renal dysfunction** • **Infusion reactions**
[Abbreviations] **OS**= overall survival; **PFS**= progression-free survival; **ORR**= overall response rate; **HRQoL**= health-related quality of life; **RCT**=randomized controlled trial; **SAE**=serious adverse events; **AE**=adverse events; **WDAE**=withdrawals due to adverse events				

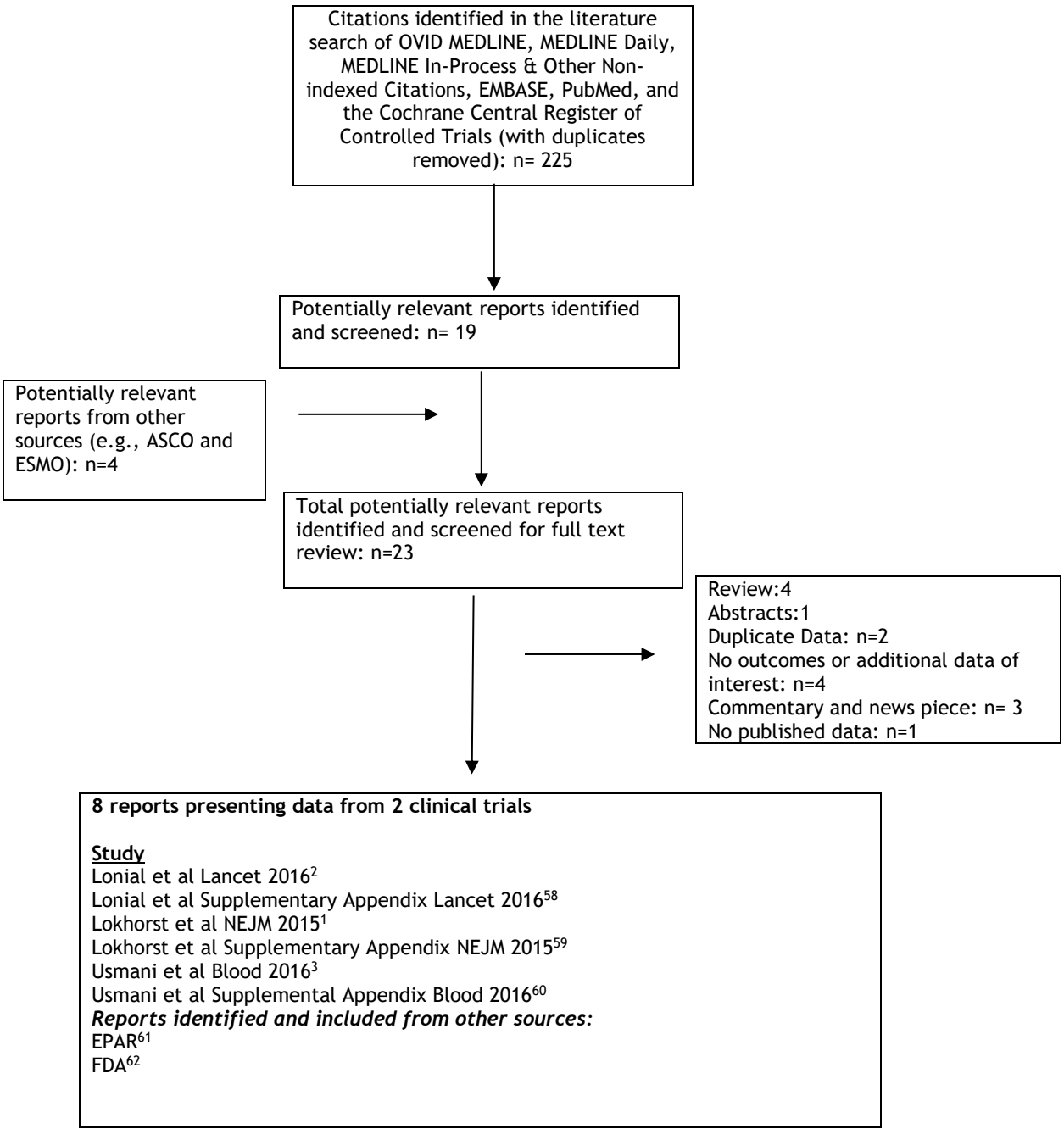
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

Literature Search Results

Of the 23 potentially relevant reports identified and screened for full text, 8 studies were included in the pCODR systematic review and 14 studies were excluded. Reasons for exclusion are provided in the diagram below.

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



Note: Additional data related to Study MMY2002 and GEN501 was also obtained through requests to the Submitter by pCODR[57]

Summary of Included Studies[1-3,58-62]

a) Trials[1,2,61,62]

Two clinical trials were identified that met the eligibility criteria of this review and were selected for inclusion (please see Table 4). The key inclusion and exclusion criteria of both trials were similar.

Detailed Trial Characteristics

MMY2002

Study MMY2002 was a phase II randomized, open-label, multi-centre study that assessed the efficacy and safety of daratumumab in the treatment of patients with multiple myeloma who received at least 3 prior lines of therapy including a PI and an IMiD or whose disease was refractory to both a PI and an IMiD. The trial included dose randomization and expansion cohorts using the early and final drug products. The planned study design for study MMY2002 centrally randomized patients in part 1 to either group A or group B. Patients in group A, received the dose regimen of 16 mg/kg per week for 8 weeks, then every 2 weeks for 16 weeks, and then every 4 weeks thereafter. Patients in group B received 8 mg/kg every 4 weeks.

The purpose of part 1 was to select the optimal dose and schedule with a higher overall response rate (ORR). Within each randomized treatment group in part 1, a 2-stage design was used in order to allow an inefficacious dose schedule to be terminated early for futility (REF-EPAR). The purpose of part 2 was to evaluate the efficacy of the selected dose regimen identified in part 1.

The primary endpoint in MMY2002 was overall response rate (ORR), secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS), and clinical benefit rate (CBR). Response was confirmed on two consecutive measurements, and data were assessed by an independent review committee. With a one-sided α of 2.5% and a power of 85%, the total sample size within each randomized treatment group in part 1 was 36 response-evaluable subjects. If it was determined at the end of part 1 that another treatment group was to be evaluate din part 2, an additional 60 subjects were to be enrolled to bring a total number of subjects treated during the study to approximately 100 subjects. Central randomization was used in part 1 stage 1 using an interactive web response system. Patients were randomly assigned to either daratumumab at 8 mg/kg or 16 mg/kg; randomization was stratified by International Staging System (I, II, or III) and refractory status (none, refractory to either a PI or IMiD, or refractory to both a PI and IMiD). No formal statistical hypothesis testing or statistical comparisons were planned or performed.

GEN501

Study GEN501 was a phase 1/2, open-label, multicentre, safety study in patients with multiple myeloma whose disease as relapsed or refractory to at least 2 prior lines of therapies. There were two parts to GEN501, part 1 consisted of a dose-escalation phase and part 2 was a single-arm phase with multiple cohorts. In part 1, the dose-escalation study, patients receive doses of 0.005 to 24 mg of daratumumab per kg of body weight in 10 cohorts. All patients in part 1 received a pre-dose before the first full dose, after the first full dose, there was a 3-week washout period of time for assessment of safety and pharmacokinetics. Patients in part 2 received doses of daratumumab of 8 mg per kg and 16 mg per kg with different schedules. Patients treated with 16 mg/kg of daratumumab received weekly a dose for 7 weeks, then twice monthly, and then monthly for up to 24 months. Patients received treatment until disease progression or until unmanageable toxicity.

The primary endpoint in GEN501 was safety, which was determined according to the frequencies and severities of adverse events (AEs) and was assessed at each treatment visit; an independent review committee evaluated all serious adverse events (SAEs), non-SAEs of grade ≥3, and events that caused treatment withdrawal. Secondary endpoints included pharmacokinetics, objective response according to the IMWG uniform response criteria for myeloma, time to disease progression, DoR, PFS, and OS. In part 2, up to 80 subjects could be enrolled for a maximum of 112 subjects across both parts. Formal statistical hypotheses were not formulated or tested as well as no power calculations.

The definition of 'line of therapy' used in both GEN501 and MMY2002 was based on the International Myeloma Working Group (IMWG) Criteria. From the MMY2002 Protocol, a single line of therapy may consist of 1 or more agents, and may include induction, hematopoietic stem cell transplantation, and maintenance therapy (refer to Attachment 1). Radiotherapy, bisphosphonate, or a single short course of steroids (i.e., less than or equal to the equivalent of dexamethasone 40 mg/day for 4 days) would not be considered prior lines of therapy.[57]

Prior Cancer Therapy for Multiple Myeloma

A line of therapy is defined as one or more cycles of a planned treatment program. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered one line of therapy. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.[57]

Table 4: Summary of Trial Characteristics of the Included Studies[1,2]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
N**CT01985126** **Other Study ID numbers:** CR102651, 54767414 MMY2002, 2013-000752-18, SIRUS Randomized, open-label, multicentre, phase 2 study **Enrollment:** 124 **Start date:** September 2013 **Estimated Primary Completion date:** October 2016 **Study Sponsor:** Janssen Research & Development, LLC **26 sites in 3 countries:** United States, Canada and Spain, (72%) were	**Key Inclusion Criteria:** • Documented multiple myeloma and evidence of disease progression on the most recent prior treatment regimen based on IMWG criteria • Laboratory values and electrocardiogram within protocol-defined parameters at screening • Disease was refractory to both a PI and an IMiD. For patients who received more than 1 type of PI or IMID, their disease was to be refractory to the most recent one of them, or at least 3 lines of prior therapy including PI and IMiD in any order. • ECOG performance status score of 0, 1, or 2 **Key Exclusion Criteria:** • Previously received daratumumab or other anti-CD38 therapies. • Received anti-myeloma treatment within 2 weeks before Cycle 1, Day 1. • Nonsecretory multiple myeloma based upon standard M-component criteria (i.e., measurable serum/urine M-component) unless the baseline serum FLC level was elevated.	**Intervention:** Daratumumab was administered as an IV infusion in 28-day cycles until disease progression or unacceptable toxicity In Part 1, patients received 1 of the following 2 treatment regimens: Group A: daratumumab 16 mg/kg: Cycles 1 and 2: Days 1, 8, 15, and 22 (weekly), Cycle 3 to 6: Days 1 and 15 (every other week), and Cycles 7+: Day 1 (every 4 weeks) Group B: daratumumab 8 mg/kg: Cycle 1+: Day 1 (every 4 weeks) Patients enrolled in Part 2 of the study received a dose of 16 mg/kg	**Primary:** ORR **Secondary:** • OS • PFS • DOR • Clinical benefit rate (including PR, very good partial response, CR, and sCR) • Time to response • Time to disease progression (TTP)

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
enrolled at sites in the United States.	• Previously received an allogeneic stem cell transplant or ASCT within 12 weeks before Cycle 1, Day 1. • Received a cumulative dose of corticosteroids more than the equivalent of ≥ 140 mg of prednisone within the 2-week period before Cycle 1, Day 1. • History of malignancy (other than multiple myeloma) within 5 years before Cycle 1, Day 1	**Comparator:** N/A	
NCT00574288 **Other Study ID numbers:** CR101876, GEN501, DARA-GEN501 Non-randomized, open-label, phase 2 safety study **Enrollment:** 104 **Estimated Primary Completion date:** December 2016 **Estimated Completion date:** August 2017 **Study Sponsor:** Janssen Research & Development, LLC	**Key Inclusion Criteria:** • Diagnosis of multiple myeloma (MM) requiring systemic therapy • Age greater than or equal to (>=) 18 years • Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 • Life expectancy greater than (>) 3 months • Relapsed from or refractory to two or more different prior therapies • Signed Informed consent **Key Exclusion Criteria:** • Plasma cell leukemia defined as a plasma cell count > 2000/millimeter^3 (mm^3) • Known amyloidosis • Participants who previously have received an allogeneic stem cell transplant • Sensory or motor neuropathy of >= grade 3 • Past or current malignancy • Chronic or ongoing active infectious disease • Clinically significant cardiac disease • Significant concurrent, uncontrolled medical condition including, but not limited to, renal (except related to MM), hepatic, hematological except MM, gastrointestinal, endocrine, pulmonary, neurological, cerebral or psychiatric disease • Significant concurrent, uncontrolled medical condition including, but not limited to, renal (except related to MM), hepatic, hematological except MM, gastrointestinal, endocrine, pulmonary, neurological, cerebral or psychiatric disease • Other chemotherapy that is or may be active against myeloma within 3 weeks prior to Visit 2 (Part 1) or the first dose of daratumumab (Part 2).	**Intervention:** In Part 1, patients received daratumumab in 10 cohorts, doses of 0.005 to 24 mg of daratumumab per kg of body weight (0.005, 0.05, 0.1, 0.5, 1, 2, 4, 8, 16, and 24 mg per kilogram). The two lowest-dose cohorts (0.005 and 0.05 mg per kilogram) had a 1+3 design, and the other eight cohorts (0.1, 0.5, 1, 2, 4, 8, 16, and 24 mg per kilogram) had a 3+3 design. In part 2, patients received daratumumab in 5 schedules: Patients who received the schedule A, B, or C regimen received 8 mg per kilogram, and those who received the schedule D or E regimen received 16 mg per kilogram. The duration (3.25 to 6 hours) and infusion (500 to 1000 mL) varied by schedule. **Comparator:** N/A	**Primary:** Part 1 and 2: Adverse Events **Secondary:** • Part 1 and 2: Pharmacokinetic parameters based on serum/plasma concentrations of daratumumab • Part 1 and 2: ORR • Time to progression • DOR • PFS • OS • AEs

b) Populations[1-3,61,62]

Details of baseline characteristics for MMY2002 and GEN501 are listed in Table 5. In MMY2002 106 patients and in GEN501 42 patients were treated with daratumumab at a dose of 16 mg/kg. The

median age in both studies was approximately 64 years of age. In MMY2002, 36 (34%) patients were 65 to 74 years and 12 (11%) were 75 years or older. In GEN501, 16 (38%) patients were 65 to 74 years and 4 (10%) were 75 years or older. In both studies, most patients were ECOG PS 0 or 1, with 8% and 5% of patients who had an ECOG PS of 2 in MMY2002 and GEN501, respectively.

The median number of prior lines of therapy were 5 and 4 in MMY2002 and GEN501, respectively; many patients had >3 prior lines of therapy (82% and 62%). Most patients had prior treatment with a PI and an IMiD. In MMY2002, the majority of patients received previous PIs (99% with bortezomib, 50% with carfilzomib), IMiDs (99% with lenalidomide, 63% with pomalidomide, and 44% with thalidomide), or allogeneic stem cell transplant (80%). Almost all patients (97%) were refractory to their last line of therapy and (95%) refractory to both a PI and IMiD. A proportion of patients were refractory to bortezomib + lenalidomide + carfilzomib + pomalidomide (31%). In GEN501, refractory disease was noted in a smaller proportion of patients than MMY2002, 64% of patients were refractory to both a PI and an IMiD. Prior therapies to which patients had refractory disease carfilzomib (17% of patients) and lenalidomide (74%). Pooled data on types of prior therapies in GEN501 and MMY2002 are reported in Table 6.

The baseline characteristics of patients in MMY2002 and GEN501 appeared similar, however, more patients in MMY2002 were heavily pre-treated with PIs and IMIDs and the number of prior lines of therapies. Key inclusion and exclusion criteria of both studies are presented in Table 4. Eligibility criteria in both studies included ECOG PS 0-2. Key exclusion criteria include clinically significant cardiovascular and respiratory conditions.

Table 5: Baseline Characteristics of Study MMY2002 and Study GEN501

Patient Characteristics	MMY2002 (n=106)	GEN501 (n=42)	Combined (n=148)
Age, median in years (range)	63.5 (31-84)	64 (44-76)	64 (31-84)
65 to <75, n (%)	36 (34)	16 (38)	52 (35)
≥75, n (%)	12 (11)	4 (10)	16 (11)
Male, n (%)	52 (49)	27 (64)	79 (53)
ECOG PS, n (%)			
0	29 (27)	12 (29)	41 (28)
1	69 (65)	28 (67)	97 (66)
2	8 (8)	2 (5)	10 (7)
Lines of Therapy, median (range)	5 (2-14)	4 (2-12)	5 (2-14)
>3, n (%)	87 (82)	26 (62)	113 (76)
Prior therapy disease refractory to			
PI			
Bortezomib	95 (90)	30 (71)	125 (85)
Carfilzomib	51 (48)	7 (17)	58 (39)
IMiD			
Lenalidomide	93 (88)	31 (74)	124 (84)
Pomalidomide	67 (63)	15 (36)	82 (55)
Thalidomide	29 (27)	12 (29)	41 (28)
Alkylating Agent	82 (77)	25 (60)	107 (72)
Both PI and IMiD	101 (95)	27 (64)	128 (87)
Bortezomib + lenalidomide	87 (82)	27 (64)	114 (77)

Notes: CI = confidence interval; IMiD = immunomodulatory drug; NE = not estimable; NR = not reported; PI = proteasome inhibitor

Table 6: Types of prior therapies in MMY2002 and GEN051

Prior Line of Therapy, n (%)	GEN501 and MMY2002 Studies (N=148)
Prior ASCT	116 (78)
Prior PI	148 (100)
Bortezomib	147 (99)
Carfilzomib	61 (41)
Prior IMiD	146 (99)
Lenalidomide	145 (98)
Pomalidomide	82 (55)
Thalidomide	66 (45)

Table 7: Number and Proportion of Patients by the Number of Prior Lines of Therapy[57]

Number of Prior Lines of Therapy Received in GEN501 and MMY2002	Number and Proportion of Patients (N=148) n, (%)
2	11 (7%)
3	24 (16%)
4	30 (20%)
5	24 (16%)
≥ 6	59 (40%)

c) Interventions[1-3,61]

MMY2002

Daratumumab was administered as an intravenous infusion until disease progression, unacceptable toxicity, or other reasons according to the Clinical Summary report. There were no dose modifications allowed either to increase or decrease to the 16 mg/kg dose.

For part 1, patients received one of two regimens:

Group A: daratumumab 16 mg/kg: Cycles 1 and 2: Days 1, 8, 15, and 22 (weekly), Cycle 3 to 6: Days 1 and 15 (every other week), and Cycles 7+: Day 1 (every 4 weeks)
Group B: daratumumab 8 mg/kg: Cycle 1+: Day 1 (every 4 weeks)

An amendment in the study protocol allowed patients in group B the option to cross over to group A. Patients who crossed over to group A could begin receiving daratumumab at 16 mg/kg after consultation between the investigator and the sponsor's medical monitor. Patients who crossed over from group B and those enrolled in part 2 of the study received a dose of 16 mg/kg (Ref-EPAR).

All patients were to receive pre-infusion medications one hour prior to each daratumumab dose. For the first and second infusions, methylprednisolone 100 mg IV (or an equivalent intermediate or long acting corticosteroid) was given. For subsequent daratumumab infusions, 60 mg of IV methylprednisolone was given. In addition, one hour prior to all daratumumab infusions, acetaminophen 650 to 1000 mg orally and diphenhydramine 25 to 50 mg (or equivalent) was to be given (Ref – FDA medical review). In order to prevent delayed infusion reactions, all patients in study MMY2002 were to receive an oral corticosteroid equivalent to 20 mg methylprednisolone once daily for the 2 days following all daratumumab infusions.

GEN501

In Part 1, patients received daratumumab in 10 cohorts, doses of 0.005 to 24 mg of daratumumab per kg of body weight (0.005, 0.05, 0.1, 0.5, 1, 2, 4, 8, 16, and 24 mg per kilogram). The two

lowest-dose cohorts (0.005 and 0.05 mg per kilogram) had a 1+3 design, and the other eight cohorts (0.1, 0.5, 1, 2, 4, 8, 16, and 24 mg per kilogram) had a 3+3 design. In part 2, patients received daratumumab in 5 schedules: Patients who received the schedule A, B, or C regimen received 8 mg per kilogram, and those who received the schedule D or E regimen received 16 mg per kilogram.

All patients in part 1 received a pre-dose (10% of the full dose but not more than 10 mg in total) before the first full dose, then after the first full dose there was a 3-week washout period. A second pre-dose was then administered which was then followed by six full infusions weekly. Pre-dosing was done before the first two full infusions to minimize the risk of infusion-related reactions. Pre-medications included antihistamines, acetaminophen, and glucocorticoids.

In part 2, doses of daratumumab of 8 mg/kg and 16 mg/kg were administered with different schedules. Patients received daratumumab until disease progression or until unmanageably toxicity. Patients received a single pre-dose of daratumumab (10mg) before the first full infusion in schedules A and B.

In MMY2002 and GEN501, treatment with daratumumab ended with disease relapse/progression. Upon request from the pCODR Methods Team, the submitter reported that of the 107 patients in both studies for whom data on subsequent therapies were available, the most common included dexamethasone (58%), pomalidomide (34%), cyclophosphamide (32%), carfilzomib (28%), bortezomib (24%), and lenalidomide (16%).[57]

d) Patient Disposition[61]

Details of the patient disposition for both studies can be found in Table 8.

A total of 157 patients were screened for enrollment into study MMY2002. Of these patients, 124 were enrolled and treated. In MMY2002, the clinical cut-off date was January 9, 2015, 7.7 months after the last person had received first dose (median follow-up was 9.3 months). At the clinical data cut-off date of January 9, 2015, 85% of patients treated at a dose of 16 mg/kg had discontinued treatment. The majority of patients discontinued treatment due to disease progression, whereas 5% of patients discontinued due to an adverse event, and 3% discontinued due to withdrawal of consent. Three patients were lost to follow-up with the reason unknown.

A total of 93 patients were screened for enrollment into study GEN501. Of these 93 patients, 72 patients were enrolled and treated. For 16 mg/kg, 42 patients were allocated and received daratumumab. At the clinical data cut-off date of January 9, 2015, 67% of patients treated at a dose of 16 mg/kg had discontinued treatment. The majority of patients discontinued due to disease progression, whereas 2% discontinued due to an adverse event, and 10% discontinued due to physician decision. No patients were lost to follow-up.

Table 8: Patient Disposition for study MMY2002 and study GEN501

	MMY2002	GEN501
Treated with 16 mg/kg, n (%)	**106 (100)**	**42 (100)**
Discontinuation	**90 (84.9)**	**28 (66.7)**
Due to Progressive disease	82 (77.4)	23 (54.8)
Due to Adverse Events	5 (4.7)	1 (2.4)
Due to Physician Decision/Withdrew consent	3 (2.8)	4 (9.5)

e) Limitations/Sources of Bias

The main limitations of MMY2002 and GEN501 were their non-comparative study designs (phase 1/2, single-arm, open-label, non-randomized). Both studies are at risk for a number of different biases that can affect the internal validity of a trial. No one was masked to treatment assignment. Examples of such biases are patient selection as part of inclusion criteria for eligibility and

performance bias due to knowledge of the study treatment. In open-label trials, the reporting of adverse events are also likely to be subjectively biased.

In addition the following limitations/sources of bias exist:

- Formal statistical hypotheses were not formulated or tested and no power calculations were performed. Subgroup analyses were performed; however, results should be interpreted with caution owing to small sample sizes.
- No health-related quality of life data were collected for MMY2001 and GEN501.
- Patients with select co-morbidities were excluded. Multiple myeloma is a disease mostly prevalent in older adults who may likely have one of these comorbidities. Consequently, excluding these adults from the trial population limits the applicability of results to the overall multiple myeloma population.
- In both studies, patients were previously treated with carfilzomib and thalidomide, both agents which are not currently funded in Canada for multiple myeloma.
- The MMY2002 protocol was amended three times. Major protocol violations occurred in nine (8.5%) patients who received daratumumab treatment at 16 mg/kg. Five of these patients entered the trial but did not satisfy the inclusion criteria and three received the wrong treatment or incorrect dose.[61] The GEN501 protocol was amended fourteen times. Key amendments included changes to the dosing period and treatment duration. For patients who received 16 mg/kg in GEN501, nine patients received the wrong treatment or incorrect dose and one patient entered the trial but did not satisfy the inclusion criteria.
- Study MMY2002 is an ongoing trial, and there is a lack of long-term efficacy and safety data.
- The primary endpoint of GEN501 was safety.

Detailed Outcome Data and Summary of Outcomes

The main efficacy outcomes for MMY2002 and GEN501 for patients treated with daratumumab at a dose of 16 mg/kg are presented in Table 9.[1,2,61]

The efficacy results for patients who have received at least three prior lines of therapy or who are refractory to a PI and an IMiD, are consistent with the results of the overall patient population from GEN501 and MMY2002.[57]

Table 9: Efficacy Outcomes of Study MMY2002 and Study GEN501

Efficacy Outcomes	MMY2002 (n=106)	GEN501 (n=42)
Duration of follow-up, median (range)	9.3 months (0.5-14.4)	16.9 months (0.4-24.9)
Overall Response Rate, n (%)	n=31 29.6%, 95%CI: 20.8-38.9	n=15 36%, 95%CI: 22-52
TTR, months (range)	1.0 months (0.9-5.6)	0.9 months (0.5-3.2)
DoR, median (95%CI)	7.4 months (5.5-NE)	Not reached
PFS, median (95%CI)	3.7 months (2.8-4.6)	5.6 months (4.2-8.1)
CBR, % (95%CI)	34.0% (95%CI: 25.0-43.8)	45.2% (29.8%-61.3%)
OS, median	Not reached (13.7-NE)	NR
12-month OS rate, % (95%CI)	64.8 (51.2-75.5)	77 (58-88)
Updated OS, median (June 30, 2015)	17.5 (13.7-NE)	-

Notes: CBR = clinical benefit rate; CI = confidence interval; DoR = duration of response; IMiD = immunomodulatory drug; NE = not estimable; NR = not reported; OS = overall survival; PFS = progression-free survival; PI = proteasome inhibitor; TTR = time to response

Response

The primary endpoint of study MMY2002 was objective response rate (ORR), defined as the proportion of patients who achieve a partial response (PR), very good partial response (VGPR), complete response (CR), and stringent complete response (sCR) based on the International Myeloma Workshop Consensus Panel 1 criteria using results from a central laboratory. An independent review committee (IRC) was established to review data and assess response of all patents on the trial.

Response was seen in 31 patients (29.6%) and 15 patients (36%) in MMY2002 and GEN501 (Table 9). The median time to response was approximately 1 month. In MMY2002, three patients had a stringent complete response, no patients had a complete response, 10 had a very good partial response, and 18 had a partial response. In GEN501, two patients had a complete response, 2 had a very good partial response, and 11 had a partial response. The combined (n=148) overall response rate was 31% (95%CI: 23.7-39.2). The duration of response was 7.4 months in MMY2002 and was not reached in GEN501. It is important to note that the primary endpoint in GEN501 was safety and efficacy outcomes were secondary endpoints. In both studies, responses were noted in subgroups (pre-specified in MMY2002 and exploratory in GEN501), which was irrespective of previous lines of therapy and refractory status (presented in Figure 2 and 3).

Progression-free Survival

In MMY2002, the clinical cut-off date was January 9, 2015, 7.7 months after the last person had received first dose (median follow-up was 9.3 months). Of patients treated with 16 mg/kg of daratumumab in MMY2002, 75 (70.8%) patients experienced progression. For these patients, the 3-month, 6-month, and 12-month progression-free survival (PFS) rate was 50.2%, 36.7%, 18.3%, respectively. Overall for patients treated with 16 mg/kg of daratumumab, the median PFS was 3.7 and 5.6 months in MMY2002 and GEN501, respectively.

Overall Survival

Of patients treated with 16 mg/kg of daratumumab, 47 (44.3%) patients in MMY2002 and 11 (26.2%) patients in GEN501 experienced death. The 12-month OS rate was 64.8% and 77% in MMY2002 and GEN501, respectively. At the updated analysis of June 30, 2015, the median OS was 17.5 months in MMY2002. The median OS was not reached in GEN501.

Health-related Quality of Life

Studies MMY2002 and GEN501 did not collect quality of life data.

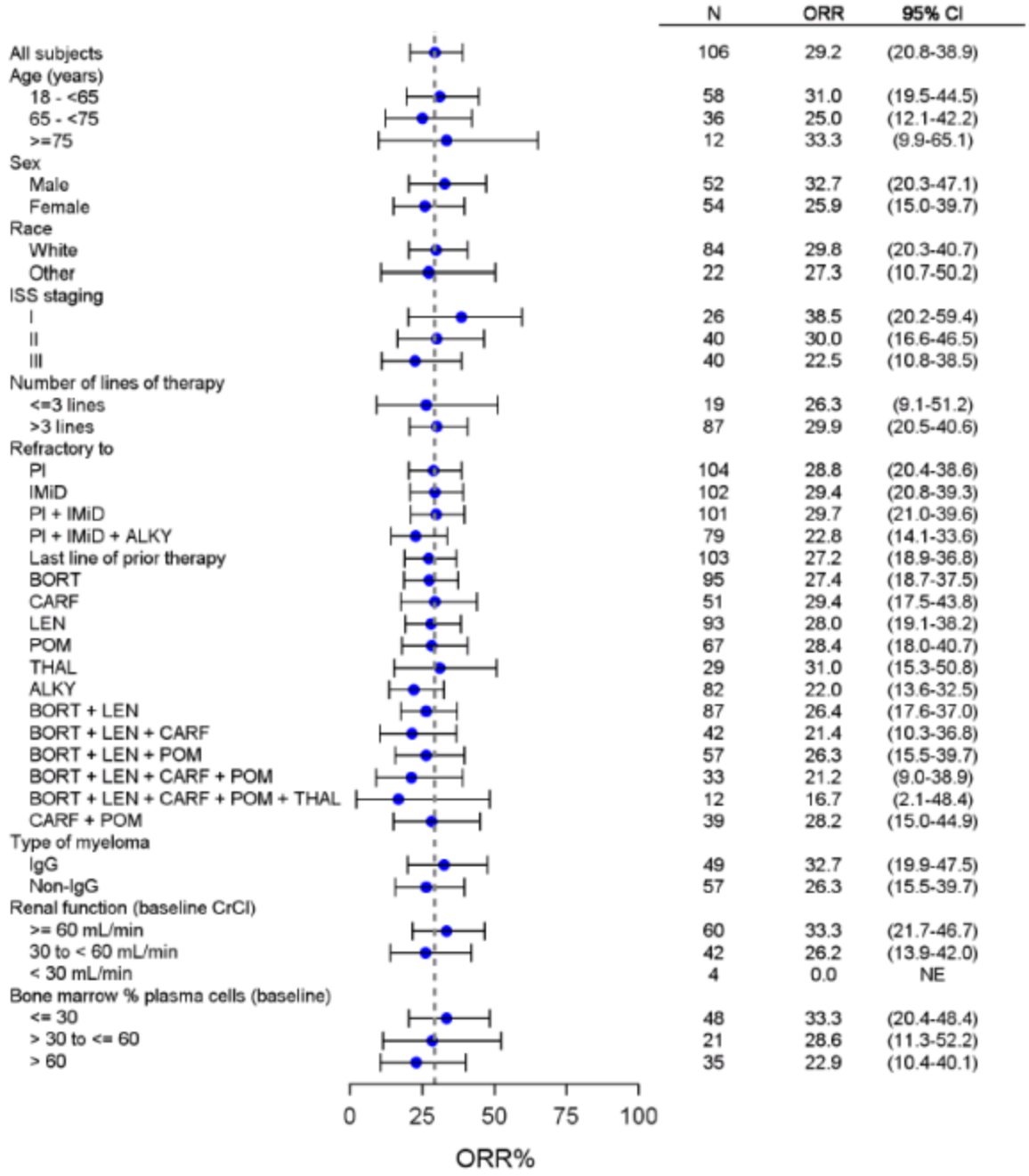


Figure 2. Forest Plot of Subgroup Analysis on Overall Best response on IRC Assessment of all treated patients in MMY2002 (16 mg/kg)[61]

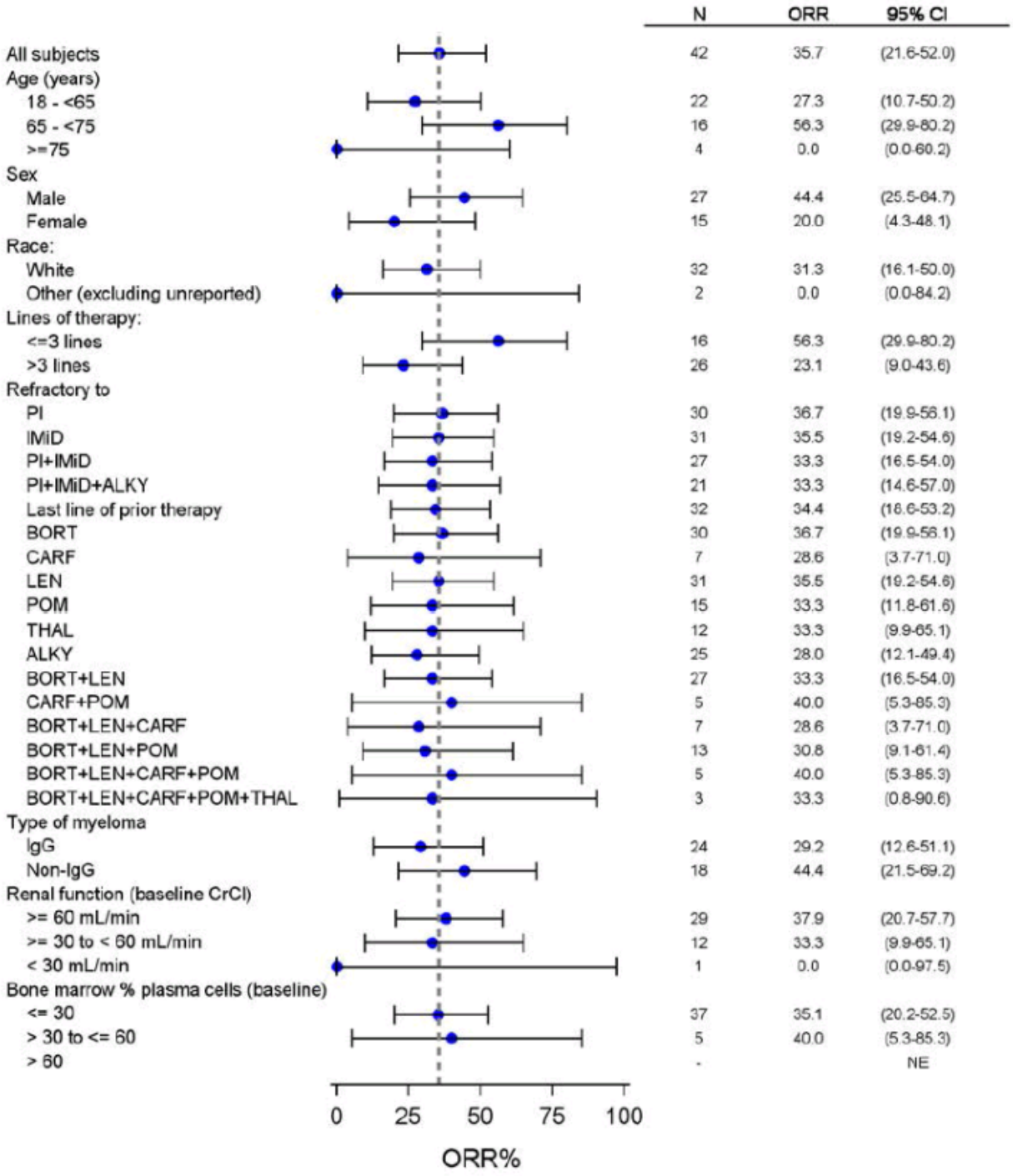


Figure 3. Forest Plot of Subgroup Analysis on Overall Best response of all treated patients in GEN501 Part 2 (16 mg/kg)[61]

Adverse Events and Safety[61]

Adverse Events

In MMY2002, the most common TEAEs of any grade (≥20%) were fatigue (40%), anemia (33%), nausea (29%), thrombocytopenia (25%), neutropenia (23%), back pain (22%), and cough (21%). In GEN501, the most common adverse events (≥25%) were fatigue, allergic rhinitis, and pyrexia. In MMY2002, grade 3 or higher anemia and thrombocytopenia occurred more frequently in responders than non-responders. In GEN501, 26% of patients had a grade 3/4 adverse event.

Serious Adverse Events

Thirty percent of patients had a serious TEAE and 23% had grade 3/4 serious TEAE in MMY2002. Serious adverse events were reported in 33% of patients who received 16 mg/kg in GEN501.

Withdrawals Due to Adverse Events

In MMY2002, no patients discontinued daratumumab because of drug-related treatment-emergent adverse events (TEAEs), infusion-related reactions, or death. There were no discontinuations in GEN501 and MMY2002 that were deemed related to the study medication.

Renal Dysfunction

In MMY2002 and GEN501, there were no renal adverse events that were deemed related to the study drug.

Infusion Reactions

Infusion-related reactions occurred in 42% of patients in MMY2002 (none of grade 4), the most common (≥5%): nasal congestion (12%), throat irritation (7%), and cough, dyspnea, chills, and vomiting (6% each). In GEN501, 71% of patients had an infusion-related reaction and were of grade 1 or 2 except one who had a grade 3 reaction. In both MMY2002 and GEN501, no patients discontinued treatment with daratumumab due to an infusion-related reaction. Infusion related reactions were managed by administering pre-infusion medications including antihistamines, antipyretics, and corticosteroids. Grade ≥ 3 infusion-related reactions in GEN501/MMY2002 were uncommon, only one patient in both studies experienced grade ≥ 3 dyspnea infusion-related reaction (see Table 10).

Table 10: Most Common (≥5%) infusion-related reactions in MMY2002/GEN501[60]

	Daratumumab 16 mg/kg (n=148)	
Event, n (%)	All grade	Grade ≥3
Nasal Congestion	17 (11.5)	0
Cough	12 (8.1)	0
Rhinitis allergic	10 (6.8)	0
Chills	10 (6.8)	0
Throat irritation	9 (6.1)	0
Dyspnea	8 (5.4)	1 (0.7)
Nausea	8 (5.4)	0

Treatment-related adverse events and deaths

Details on treatment-emergent adverse events (TEAEs) for MMY2002, GEN501, and MMY1002 are reported in Figure 4. Of note, MMY1002 is a phase one study in Japan with two sites, five patients

were treated with 16 mg/kg and four patients with 8 mg/kg of daratumumab. The pCODR review did not include this study in its review of daratumumab for multiple myeloma because it is not meet the systematic review inclusion criteria. For patients treated with 16 mg/kg, 77% of TEAEs were drug-related and the maximum severity of any TEAE were mostly grade 2 or 3. No deaths were considered to be due to a treatment-related adverse event in the GEN501 and MMY2002 studies.

	<=4 mg/kg	8 mg/kg	16 mg/kg	24 mg/kg	Total
Analysis set: all treated	23	55	156	3	237
Any TEAE	22 (95.7%)	55 (100.0%)	154 (98.7%)	3 (100.0%)	234 (98.7%)
Drug-related	21 (91.3%)	48 (87.3%)	120 (76.9%)	3 (100.0%)	192 (81.0%)
Any serious TEAE	7 (30.4%)	20 (36.4%)	50 (32.1%)	2 (66.7%)	79 (33.3%)
Drug-related	4 (17.4%)	0	15 (9.6%)	1 (33.3%)	20 (8.4%)
Maximum severity of any TEAE					
Grade 1	1 (4.3%)	3 (5.5%)	10 (6.4%)	0	14 (5.9%)
Grade 2	12 (52.2%)	21 (38.2%)	56 (35.9%)	2 (66.7%)	91 (38.4%)
Grade 3	7 (30.4%)	21 (38.2%)	59 (37.8%)	1 (33.3%)	88 (37.1%)
Grade 4	1 (4.3%)	10 (18.2%)	19 (12.2%)	0	30 (12.7%)
Grade 5	1 (4.3%)	0	10 (6.4%)	0	11 (4.6%)
Treatment discontinuation due to TEAE[a]	4 (17.4%)	0	6 (3.8%)	1 (33.3%)	11 (4.6%)
Drug-related	4 (17.4%)	0	0	1 (33.3%)	5 (2.1%)
Death due to TEAE[b]	0	0	3 (1.9%)	0	3 (1.3%)
Drug-related	0	0	0	0	0

Keys: TEAE = treatment-emergent adverse event.
[a]Treatment discontinuation due to adverse event on the end of treatment CRF page.
[b]Death due to adverse event on the death CRF page.
Percentages are calculated with the number of subjects in each group as denominator.

Figure 4: Overview of treatment-emergent adverse events (all treated analysis set of MMY2002, GEN501, and MMY1002).[61]

6.4 Ongoing Trials

None identified.

7 SUPPLEMENTAL QUESTION

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of daratumumab (Darzalex) 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. Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Critical Appraisal of Propensity Score Matching Analysis of MMY2002/GEN501 Data and International Myeloma Foundation Medical Chart Review: Daratumumab versus Standard Care Therapy for Heavily Pre-Treated and Highly Refractory Multiple Myeloma[57]

7.1.1 Objective

The two pivotal studies included in the pCODR systematic review to assess the efficacy and safety of daratumumab in the specified patient population were non-comparative studies. To inform the comparator of standard care, propensity score matching techniques were used to form a cohort of patients with multiple myeloma who were highly pre-treated and highly refractory to available treatment. Effectiveness outcomes included overall survival and progression-free survival.

Methodology

The retrospective IMF Chart review was conducted in 2015. The review enrolled patients with relapsed MM who had received at least three prior lines of therapy, were refractory to both an IMiD and a PI, and were diagnosed on or after January 1, 2006.

Propensity score calculation was performed using a multivariable logistic regression where patients' treatment was the dependent variable and the modeled covariates were age, gender, prior lines of therapy, proportion of patients who were refractory to bortezomib, carfilzomib, lenalidomide, and pomalidomide, and albumin at multiple myeloma diagnosis.

Overall, 148 daratumumab patients and 543 standard of care patients were available for this study.

At baseline eligibility, only 5.5% of IMF patients were refractory to pomalidomide, compared to 55% of the patients in the MMY2002 and GEN501 studies. This was one of the discrepancies that posed a challenge for matching across data sources. In order to address this, a secondary analysis of the IMF chart review was conducted to increase the proportion of patients in the IMF study who were refractory to pomalidomide at baseline to match the MMY2002/GEN501 patient populations. For this purpose, first they identified patients in the sample that were treated with pomalidomide after inclusion into the cohort (Time $_0$). These patients were then followed up prospectively until they became refractory to it, thus creating a new Time$_0$ for them (excluding patients whose date of death or last contact was the same as the date of refractory status). The remaining patients were included into the IMF propensity score sample from the time point they were identified to be exposed to three or more prior lines and be refractory to a PI and LEN. This approach increased the proportion of pomalidomide refractory patients to 39% but decreased the number of eligible IMF patients for propensity score matching to 400.

Propensity scores

Propensity scores are a statistical method of adjusting for bias from confounding by indication. Through the use of a prediction model the likelihood or propensity of treatment based on a specified set of patient characteristics is predicted. By applying the propensity score to two non-equivalent groups, one is able to balance differences in observed characteristics and potentially

obtain less biased estimates of treatment effects. Essentially, propensity scoring attempts to simulate randomization of subjects as would occur in a randomized controlled trial.

Propensity scores are calculated by selecting all covariates that are expected to have an impact on the expected results (e.g. patient characteristics, disease severity, and characteristics of the treatment). The eventual utility of the propensity score therefore greatly depends on the ability to identify all potential confounding factors and including them into the propensity score calculation. Additionally, the exclusion of potential confounders or the presence of unknown confounders, which would be accounted for during randomization, remains a source of potential bias when using propensity score. Once calculated, the score is applied to the data under question through 1 of 4 methodologies.

Findings

Prior to the propensity score matching analyses, there were imbalances which existed between the daratumumab and standard care groups for the mean number of prior lines of therapy, proportion of male patients, and proportion of patients refractory to pomalidomide, carfilzomib, and lenalidomide, and serum albumin (standardized differences >0.1). A greedy matching was performed with a caliper of 25% of the standard deviation of the logit-transformed propensity scores, without replacement.

After propensity score matching analyses was performed, a total of 126/148 (85.1%) of the daratumumab patients were successfully matched with a control patient from the standard care group.

Please see Table 12 for further details of the primary analysis and summary of patient characteristics prior to and following propensity score matching.

Table 12: Summary of Patient Characteristics prior to and following PSM

	Prior to PSM (all patients)				After PSM (matched groups)			
Characteristic	Daratumumab 16 mg (n=148)	Standard care (n = 380)	Standardized difference	p-value	Daratumumab 16 mg (n=126)	Standard care (n=126)	Standardized difference	p-value
# of patients	**148**	**380**			126	126		
Mean age in years	63.17	62.52	0.07	0.48	63.23	62.17	**0.11**	0.36
% male	53.38	61.58	-0.17	0.09	52.38	54.76	-0.05	0.71
Albumin	35.78	34.60	0.18	0.07	35.46	35.47	-0.002	0.81
Mean # prior lines of therapy	5.38	4.91	0.21	0.04	5.44	5.42	0.01	0.99
% POM refractory	55.41	37.63	0.36	<0.01	57.14	56.35	0.02	0.90
% CAR refractory	39.19	15.26	0.56	<0.01	40.48	40.48	0.02	0.90
% BOR refractory	84.46	94.21	-0.30	<0.01	88.10	84.13	**0.11**	0.36
% LEN refractory	83.78	98.42	-0.53	<0.01	95.24	95.24	0.0	1.00

Two variables were not well balanced after matching (mean age and % BOR refractory) but the differences were considered not clinically important by the clinical expert's. After checkpoint meeting, it was also reported that in terms of the double refractory status to PI/IMiD, 86.5% versus 100% of patients met the criteria in DARA versus IMF sample, pre-match (see Table 13). After matching, percent double refractory was 92.9% in DARA group compared to 100% in IMF

sample (standardized difference = -0.39). Overall, DARA sample seemed to be more heavily treated in the past than the IMF sample.

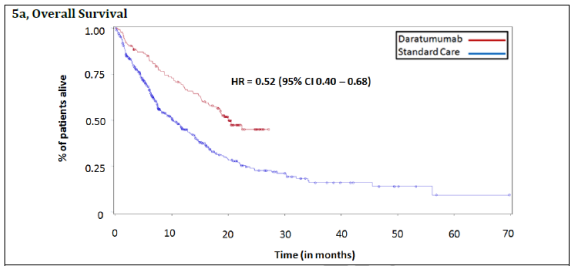
Table 13: Summary of Refractory Status Characteristics Post-Match, by Intervention Group[57]

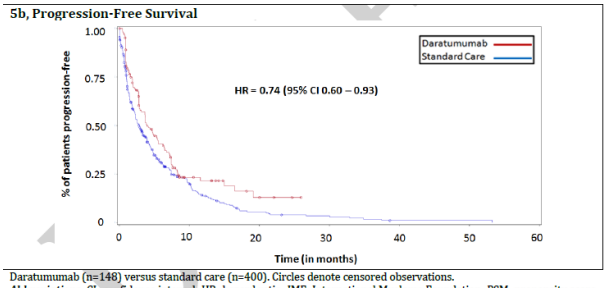
Refractory Status	DARA Post-Match (n=126)		IMF Post-Match (n=126)		Standardized Difference Post-Match	P-Value for Difference between Groups
Refractory to PI/IMiD	117	(92.9%)	126	(100.0%)	-0.39	**<0.01**
Refractory to						
BOR	111	(88.1%)	106	(84.1%)	0.11	0.36
CAR	51	(40.5%)	52	(41.3%)	-0.02	0.90
LEN	120	(95.2%)	120	(95.2%)	0	1
POM	72	(57.1%)	71	(56.3%)	0.02	0.90
Refractory to						
BOR+LEN	110	(87.3%)	100	(79.4%)	0.21	0.09
CAR+POM	37	(29.4%)	37	(29.4%)	0	1
BOR+LEN+CAR	45	(35.7%)	30	(23.8%)	0.26	**0.04**
BOR+LEN+POM	66	(52.4%)	55	(43.7%)	0.18	0.17
BOR+LEN+CAR+POM	34	(27.0%)	25	(19.8%)	0.17	0.18

Next, Cox proportional models with robust variance structure was applied to obtain relative effectiveness estimates for OS and PFS.

Figures of Kaplan-Meier Curves from Submission[57]

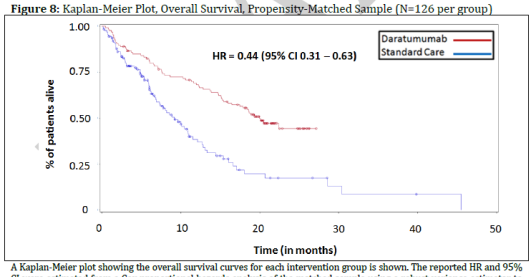
Figures 5a and 5b: Kaplan Meier Curves, Overall Survival and Progression-Free Survival in Daratumumab and Standard Care Groups (Prior to PSM)





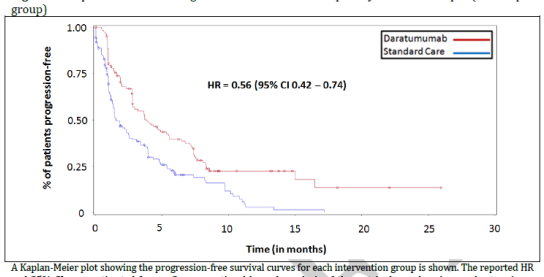
Daratumumab (n=148) versus standard care (n=400). Circles denote censored observations.
Abbreviations: CI=confidence interval; HR=hazard ratio; IMF=International Myeloma Foundation; PSM=propensity score matching.

Figure 8: Kaplan-Meier Plot, Overall Survival, Propensity-Matched Sample (N=126 per group)



A Kaplan-Meier plot showing the overall survival curves for each intervention group is shown. The reported HR and 95% CI were estimated from a Cox proportional hazards analysis of the matched sample using a robust variance estimator to account for the presence of matching.
Abbreviations. CI=confidence interval; HR=hazard ratio.

Figure 9: Kaplan-Meier Plot, Progression-Free Survival, Propensity-Matched Sample (N=126 per group)



A Kaplan-Meier plot showing the progression-free survival curves for each intervention group is shown. The reported HR and 95% CI were estimated from a Cox proportional hazards analysis of the matched sample using a robust variance estimator to account for the presence of matching.
Abbreviations. CI=confidence interval; HR=hazard ratio.

Based on the primary analysis, median (IQR) and mean (SD) overall survival with daratumumab 16 mg/kg were 19.92 months (7.59-NR) and 15.70 (0.72). In the standard care group the corresponding values were 9.17 months (4.83-16.64) and 10.3 (0.70). This translated into an OS HR of 0.44 (95% CI: 0.31-0.63), statistically significant in favour of daratumumab 16 mg/kg. The results were in the same direction for PFS as well with an HR of 0.56 (95%CI: 0.42-0.74)

The submitter conducted sensitivity analysis for propensity score matching approaches using i) matching with replacement of the control cohort, ii) using caliper of 20%, and iii) using optimal rather than greedy matching checking both the balance of baseline characteristics and resulting OS HR. The results from the sensitivity analysis scenarios were close to the base case results.

Limitations

- As noted by submitter, some prognostically important variables were not available in IMF data because they were not measured or had high % missing; and were not included in the analysis including beta-2 microglubluin (precluding from obtaining International Staging System for multiple myeloma), performance status, cytogenetics, and immunoglobulin subtype. The submitter did not have permission to share the IMF chart review protocol with the CGP to obtain more details.
- In addition, the variable on time since diagnosis was not used in the matching since it would have limited the matched sample since IMF chart abstraction included only patients who have been diagnosed after 2006. The average time since the diagnosis of multiple myeloma was 6.3 years in the daratumumab group and 3.5 years in the IMF sample.

Strengths

- Use of sensitivity analyses and report of matching diagnostics (propensity score distribution plots, patient characteristics before and after matching with standardized differences).

Conclusions

Some prognostically important variables were missing from matching including staging and time since diagnosis, and the groups were not balanced in double refractory status. The effect of these limitations on outcomes in terms of over- or underestimation of true difference is uncertain.

8 COMPARISON WITH OTHER LITERATURE

MMY3010 is a multicenter (not including Canada), open-label, early access treatment protocol of single-agent daratumumab in patients with multiple myeloma who have received at least 3 prior lines of therapy including a PI and an IMiD or whose disease is double refractory to both a PI and an IMiD, who reside in areas where daratumumab is not commercially available or available through another protocol, who have not been enrolled in another daratumumab study, and who are not eligible for or who do not have access to enrollment in another ongoing clinical study of daratumumab.[63] Patients received daratumumab (16 mg/kg) as intravenous infusion on Day 1, 8, 15, and 22 of Cycles 1 and 2 (weekly dosing), on Day 1 and 15 of Cycles 3 to 6 (every 2 weeks dosing), and on Day 1 of Cycle 7 and subsequent cycles (every 4 weeks dosing) until documented progression, unacceptable toxicity, or study end. Each cycle was 28 days.[63]

Key inclusion criteria included:

- 18 years of age
- Documented multiple myeloma and have evidence of disease progression on or after the most recent prior treatment regimen as defined by IMWG criteria
- ECOG performance status score of 0, 1, or 2[63]

Exclusion Criteria:

- Ever enrolled in another daratumumab study or eligible for enrollment in another ongoing clinical study of daratumumab
- Received any other anti-myeloma therapy while receiving daratumumab
- Enrolled in another interventional clinical study with therapeutic intent
- Known chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) less than 50% of predicted normal
- Known moderate or severe persistent asthma within the past 2 years, or currently has uncontrolled asthma of any classification
- Prior exposure to any anti-CD38 monoclonal antibody[63]

The primary outcome was safety.[63] Overall response rates were collected.[63] According to the submitter, patient reported outcomes (EQ-5D-5L and the EORTC QLQ-C30) were also collected.[64] The estimated enrollment is 400 patients, with an estimated completion of July 2020.[63]

Outcomes were not publicly available. However, according to the submitter, in general patients maintained their QOL scores while on daratumumab treatment.[64]

Given the expanded access design of the study and the lack of peer-reviewed, publicly available results, the quality life data described by the Submitter should be interpreted with caution.

9 ABOUT THIS DOCUMENT

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

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

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

The Lymphoma & Myeloma Clinical Guidance Panel is comprised of three hematologists. 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 & DETAILED METHODOLOGY OF LITERATURE REVIEW

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** March 2016**, Embase** 1974 to 2016 April 28**, 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,ot,ab,rn,hw,nm,kf.	383
2	1 use ppez,cctr	86
3	*daratumumab/	105
4	(daratumumab* or darzalex* or HuMax-CD38 or HuMaxCD38 or JNJ 54767414 or JNJ54767414 or 4Z63YK6E0E or 945721-28-8).ti,ot,ab,kw.	255
5	or/3-4	263
6	5 use oemezd	186
7	2 or 6	272
8	limit 7 to english language	258
9	remove duplicates from 8	194

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
#3	Add	Search **(#1 AND publisher[sb])**	9
#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])**	66

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 terms: daratumumab

Select international agencies including:

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

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

Search terms: daratumumab

Conference abstracts:

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

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

Search terms: daratumumab
last 5 years

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-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (March 2016) 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 daratumumab.

No filters were applied to limit the retrieval by study type. The search was also limited to English-language documents, but not limited by publication year. The search is considered up to date as of September 1, 2016.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies, clinical trial registries and relevant conference abstracts. Searches of conference abstracts were limited to the last five years. 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 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. 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. 2015 Sep 24;373(13):1207-19.

2. 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;387(10027):1551-160.

3. Usmani SZ, Weiss BM, Plesner T, Bahlis NJ, Belch A, Lonial S, et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma [manuscript submitted to Blood].2016.

4. Canadian Cancer Society. Multiple myeloma [Internet]. Toronto: Canadian Cancer Society; c2016. Multiple myeloma statistics; 2015 [cited 2016 Jul 24]. Available from: http://www.cancer.ca/en/cancer-information/cancer-type/multiple-myeloma/statistics/?region=on

5. Ollendorf DA, Chapman R, Khan S, Russo ET, Synnott PG, Pearson SD, et al. Treatment options for relapsed or refractory multiple myeloma: effectiveness and value [Internet]. Draft report. Boston: Institute for Clinical and Economic Review; 2016 Apr 7. [cited 2016 Nov 4]. Available from: https://icer-review.org/wp-content/uploads/2016/04/MWCEPAC_MM_Draft_Evidence_Report_040716.pdf

6. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian cancer statistics 2015 [Internet]. Toronto: Canadian Cancer Society; 2015. [cited 2016 Jun 7]. Available from: https://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2015-EN.pdf

7. 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 2016 Jun 7]. Available from: http://seer.cancer.gov/csr/1975_2013/ Based on November 2015 SEER data submission.

8. 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.

9. 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.

10. 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 2016 Jun 7];111(5):2516-20. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2254544

11. 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.

12. 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.

13. 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 2016 Jun 7];31(16):1984-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3661935

14. Rajkumar SV, Gahrton G, Bergsagel PL. Approach to the treatment of multiple myeloma: a clash of philosophies. Blood [Internet]. 2011 Sep 22 [cited 2016 Jun 7];118(12):3205-11. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3179390

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

16. 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 2016 Jun 7];30(4):445-52. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4800820

17. Corre J, Munshi N, Avet-Loiseau H. Genetics of multiple myeloma: another heterogeneity level? Blood [Internet]. 2015 Mar 19 [cited 2016 Jun 7];125(12):1870-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4366624

18. Boise LH, Kaufman JL, Bahlis NJ, Lonial S, Lee KP. The Tao of myeloma. Blood [Internet]. 2014 Sep 18 [cited 2016 Jun 7];124(12):1873-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4468029

19. 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.

20. 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.

21. 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 2016 Jun 17];55(7):1489-97. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4133972

22. 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 2016 Jun 17];100(6):826-33. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4450629

23. 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 [Internet]. 2013 [cited 2016 Jun 17];18(1):27-36. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3556252

24. 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.

25. Sonneveld P, Broijl A. Treatment of relapsed and refractory multiple myeloma. Haematologica. 2016 Apr;101(4):396-406.

26. 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.

27. 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.

28. 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.

29. San Miguel J, 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.

30. 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.

31. 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.

32. 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.

33. 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.

34. 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.

35. 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.

36. Harousseau JL, Attal M, Avet-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.

37. 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.

38. 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 2016 Jun 24];6(3):120-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4480519

39. 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.

40. 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.

41. 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 2016 Jun 23];117(18):4691-5. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3710442

42. 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.

43. FDA approves Darzalex for patients with previously treated multiple myeloma [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2015 Nov 16. [cited

2016 May 12]. (FDA news release). Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm472875.htm

44. 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 2016 Sep 2; last updated 2016 Aug 8]. 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.

45. 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 2016 Sep 2; last updated 2016 Jun 23]. 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.

46. 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 2016 Jun 24];10(9):e0136207. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4569348

47. 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.

48. 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 2016 Jun 24];8(4):204-15. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4489189

49. 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 2016 Jun 23];5:37-48. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3627436

50. 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.

51. 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.

52. 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.

53. 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 2016 Sep 2; last updated

2016 Aug 16]. 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.

54. 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 2016 Sep 2; last updated 2016 Jun 14]. 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.

55. Intergroupe Francophone du Myelome. A study to evaluate daratumumab in transplant eligible participants with previously untreated multiple myeloma (Cassiopeia). 2015 Jun 24 [cited 2016 Sep 2; last updated 2016 May 31]. 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.

56. Janssen Research & Development, LLC. A study to evaluate 3 dose schedules of daratumumab in participants with smoldering multiple myeloma. 2014 Dec 10 [cited 2016 Sep 2; last updated 2016 Aug 24]. 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.

57. pan-Canadian Oncology Drug Review manufacturer submission: Darzalex™ (daratumumab) 20 mg/mL concentrate for solution for infusion. Company: Janssen Inc. Toronto (ON): Janssen Inc; 2016 Apr 21.

58. 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 [supplementary material]. Lancet. 2016.

59. Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, et al. Supplementary appendix.Targeting CD38 with daratumumab monotherapy in multiple myeloma. N Engl J Med [Internet]. 2016 Sep 24 [cited 2016 Apr 25];373(13):1207-19. Available from: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1506348/suppl_file/nejmoa1506348_appendix.pdf

60. Supplementary material for: Usmani SZ, Weiss BM, Plesner T, Bahlis NJ, Belch A, Lonial S, et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma [manuscript submitted to Blood].2016.

61. Committee for Medicinal Products for Human Use (CHMP). Assessment report: Darzalex [Internet]. London: European Medicines Agency; 2016 Apr 1. [cited 2016 Aug 23]. (EPAR - Public assessment report). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004077/WC500207295.pdf

62. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical/statistical review(s). In: Darzalex (daratumumab) injection. Company: Janssen Biotech, Inc. Application no.: 761036. Approval date: 11/16/2015 [Internet]. Rockville (MD): FDA; 2016 Nov [cited 2016 Apr 25]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/761036Orig1s000TOC.cfm

63. Janssen Research & Development, LLC. Early access treatment with daratumumab for (relapsed or refractory) multiple myeloma. 2015 Jun 15 [cited 2016 Sep 14; last updated 2016 Aug 24]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/study/NCT02477891 ClinicalTrials.gov Identifier: NCT02477891.

64. pan-Canadian Oncology Drug Review checkpoint meeting: daratumumab (Darzalex). Janssen Inc. response to pCODR checkpoint meeting clinical questions. Toronto (ON): Janssen Inc; 2016 Jun 23.