Canadian Journal of Health Technologies
April 2024 Volume 4 Issue 4

CADTH Reimbursement Review

Optimal Pharmacotherapy for Transplant-Ineligible Multiple Myeloma

PROSPERO Registration Number: CRD42021255578

Clinical Review
Pharmacoeconomic Review

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Clinical Review

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Abbreviations

CI	confidence interval
CrI	credible interval
ECOG	Eastern Cooperative Oncology Group
ESHPM	Erasmus School of Health Policy & Management
HR	hazard ratio
IMiD	immunomodulatory drug
MESH	Medical Subject Headings
MM	multiple myeloma
NCT	national clinical trial
NDMM	newly diagnosed multiple myeloma
NMA	network meta-analysis
PAG	Provincial Advisory Group
pCODR	pan-Canadian Oncology Drug Review
pERC	pCODR Expert Review Committee
PFS	progression-free survival
PICOS	population(s), intervention(s), comparator(s), outcome(s), and study design(s)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
r/r	relapsed and/or refractory
RCT	randomized controlled trial
RoB 2	second version of the Cochrane risk-of-bias tool for randomized trials
SLR	systematic literature review
TTP	time to progression

Executive Summary

Rationale and Policy Issues

Multiple myeloma (MM) is an incurable plasma cell neoplasm where the first-line therapy often involves high-dose chemotherapy followed by autologous stem cell transplant. For patients who are not eligible for this treatment strategy with transplant due to health risks or other issues, other treatment regimens are available for consideration based on patient characteristics, personal preference, experience with previous therapies and funding by regional cancer centres.

Despite an abundance of clinical literature on treatment regimens in MM, there is a general lack of high-quality evidence from head-to-head comparisons to inform the optimal sequencing of therapies in this specific population, transplant-ineligible patients with MM.

As such, the following policy question needs to be addressed: In what sequences should drugs for transplant-ineligible MM be reimbursed to maximize clinical and cost-effectiveness while considering patient safety, characteristics, experience, and preferences?

Objectives and Research Questions

To address the policy question, a clinical review, an economic analysis, and a perspectives and experiences review have been conducted.

The research questions for the clinical review include the following:

- Research Question 1: What is the comparative efficacy and safety of drug combinations for newly diagnosed, previously untreated MM in patients who are not eligible for autologous stem cell transplant?
- Research Question 2: What is the comparative efficacy and safety of drug combinations for MM in patients who have relapsed or are refractory to first-line drugs?

The research questions for the perspectives and experiences review include the following:

- What are the perspectives and experiences of patients with newly diagnosed and transplant-ineligible or relapsed and/or refractory (r/r) MM on expectations of treatment, treatment decision-making, experiences of treatment, and barriers to accessing or receiving treatment across the course of their cancer?

Methods

Clinical Review

For the clinical review, a systematic literature review and network meta-analysis were conducted to answer the research questions on the comparative efficacy and safety of drug combinations in newly diagnosed transplant-ineligible MM and r/r MM.

For both categories of patients with newly diagnosed MM (NDMM) and r/r MM, the subgroups of interest included: age groups (< 75 years and ≥ 75 years), patients with high-risk cytogenetics and Eastern Cooperative Oncology Group (ECOG) performance status.

Studies were deemed eligible for inclusion if they included drug regimens that were used in Canada for the treatment of MM (refer to Table 3 and Table 4 for more details). In response to stakeholder feedback on the project scope, CADTH also included ixazomib, melphalan, and thalidomide to strengthen the network, although they are not as widely used in Canada. The comparators could be placebo or any other drugs used in the identified studies. For NDMM, the regimens of interest were bortezomib, carfilzomib, cyclophosphamide, daratumumab, dexamethasone, ixazomib, lenalidomide, melphalan, prednisone, and thalidomide. For r/r MM, the regimens of interest were bortezomib, carfilzomib, daratumumab, dexamethasone, elotuzumab, idecabtagene, vicleucel, isatuximab, ixazomib, lenalidomide, pomalidomide, prednisone and thalidomide.

The primary outcome was progression-free survival (PFS). The secondary outcomes included time to progression (TTP), health-related quality of life and severe adverse events defined as at least grade 3. Only published phase III RCTs (randomized control trials) were included in the review. Based on consultation with clinical experts, the base case for comparison was determined to be lenalidomide-dexamethasone (RD).

Health-Related Quality of Life Outcome

Given that data related to health-related quality of life outcomes were not expected to be extracted from the included studies, this outcome was evaluated separately through a review of previous CADTH reimbursement reviews of MM therapeutics.

Perspectives and Experiences Review

For the perspectives and experiences review, patient input was collected through engagement with Myeloma Canada. Results of patient experiences living with MM and patient expectations and preferences with treatment were collated.

To explore the question of what the perspectives and experiences of patients with newly diagnosed and transplant-ineligible MM or r/r MM have on treatment considerations, a rapid qualitative evidence synthesis was conducted. The inclusion criteria were on people living with newly diagnosed transplant-ineligible or r/r MM with treatment, with the aim to evaluate treatment expectations, decision-making around treatment, experience, and barriers to accessing or receiving treatment. Primary qualitative studies were synthesized using a framework approach.

Summary of Evidence

Clinical Review

Research Question 1: Comparative Efficacy and Safety of Drug Combinations in Patients With Newly Diagnosed and Transplant-Ineligible MM

The network for NDMM compared 31 RCTs, which incorporated 27 regimens. Data on the efficacy outcome of PFS were available for 30 of the 31 RCTs; 1 RCT (3%) only reported event-free survival (EFS; defined as the

time between the start of therapy and disease progression, relapse, death, or last follow-up), which was used as a proxy for PFS.

Due to variations in data reporting and missing data, NMA (network meta-analysis) for the subgroups of interest could not be conducted. Likewise, the NMA for the outcome of at least grade 3 AEs could not be conducted because of inconsistency in data reporting.

The risk-of-bias assessment was conducted for all included studies and judged to be low overall. In addition, sensitivity analyses have been conducted using 6 different scenarios where RCTs were excluded for potential concerns from clinical experts, risk of bias or other potential methodological flaws (e.g., using different definitions of PFS); 5 scenarios yielded little impact on the overall NMA results. In scenario 1 where indirect evidence was excluded based on expert opinion, the NMA results had a substantial impact. This scenario was used in the economic analysis based on feedback from the clinical experts.

Research Question 2: Comparative Efficacy and Safety of Drug Combinations in Patients With r/r MM

The network for r/r MM compared 31 RCTS, which incorporated 32 regimens. Two separate networks were identified. One network (network A) consisted of 13 treatments informed by 13 studies, while the other (network B) consisted of 18 treatments informed by 18 studies. Data on the efficacy outcome of PFS were available for 25 of the 31 RCTs. Similar to the reasons specified for research question 1, NMA could not be conducted for subgroups of interest and outcome for at least grade 3 AEs.

The risk-of-bias assessment was conducted for all included studies and judged to be low overall. In addition, sensitivity analyses have been conducted using 3 different scenarios, all of which had little impact on the overall NMA results.

Perspectives and Experiences Review

Ten primary qualitative studies met the inclusion criteria. Overall, the set of included primary studies was judged to be low to moderate in terms of trustworthiness.

Limitations

In the clinical review, the results from the NMA were only able to inform the comparative efficacy with PFS of different regimens used in NDMM and r/r MM. The data available were unable to inform on the comparative safety of these regimens. Analysis of subgroups of interest was also not feasible. In addition, the data were also heterogeneous across studies, especially for NDMM. A proportional hazard assessment was not performed to validate the NMA results.

The small number of included studies in the perspectives and experiences review affected the ability to describe patients' perspectives and experiences, particularly around treatment expectations and decision-making.

Results

Clinical Review

Research Question 1: Comparative Efficacy and Safety of Drug Combinations in Patients With Newly Diagnosed and Transplant-Ineligible MM

For NDMM, 12 regimens were shown to have a favourable PFS when compared with RD (lenalidomide-dexamethasone), with HRs ranging from 0.38 to 0.99. Two regimens (i.e., DaraVMP and DaraRD) were statistically significantly different from RD:

- daratumumab-bortezomib-melphalan-prednisone (DaraVMP; HR of 0.38; 95% (credible interval), 0.14 to 0.97)
- daratumumab-lenalidomide-dexamethasone (DaraRD; HR: 0.53; 95%, 0.30 to 0.95).

The included studies provided insufficient data to inform NMAs to estimate health-related quality of life (HRQoL) outcomes and the comparative safety of the identified drug regimens in patients with NDMM.

Research Question 2: Comparative Efficacy and Safety of Drug Combinations in Patients With r/r MM

For r/r MM, 15 regimens were shown to have a favourable PFS compared to RD, with HRs ranging from 0.44 to 0.99. One regimen (i.e., DaraRD) was statistically significantly different from RD:

- daratumumab-lenalidomide-dexamethasone (DaraRD; HR: 0.44; 95%, 0.28 to 0.70).

The included studies provided insufficient data to inform NMAs to estimate HRQoL outcomes and the comparative safety of the identified drug regimens in patients with r/r MM.

Health-Related Quality of Life

It was found that for patients with both NDMM and r/r MM, the most commonly used HRQoL measure was the EORTC QLQ-C30. Overall, CADTH reviews of treatments for newly diagnosed MM generally showed favourable HRQoL outcomes at earlier times of assessment compared to later times of assessment. For r/r MM, the measure of this outcome varied in the method of reporting; in addition, the HRQoL outcomes were exploratory and subject to uncertainty due to low completion and compliance rates at later time points. There were generally no clinically meaningful between-group differences in HRQoL for any measures evaluated.

Perspectives and Experiences Review

In both the identified literature and patient input submitted to CADTH, physical fatigue, peripheral neuropathy, risk of infection, diarrhea, and pain were described as affecting patients' ability to move and this could make it difficult to leave their homes, to do activities that gave them meaning or pleasure, or even complete routine activities of daily living.

Patients' experiences of and views on treatment could change over time, with each new relapse bringing worries about narrowing treatment options and debilitating or worsening symptoms. When thinking about treatment, patients considered the physical, emotional, and social impact of the disease and its treatment and wanted a holistic approach that considered their whole being and not just their physical condition.

Patients identified challenges they faced in accessing treatment, including the need to travel to health care facilities or temporarily locate near them, and the chronic financial strain that living with constant treatment caused.

Conclusions

Based on the NMA results from the clinical review, several treatment regimens are found to be more favourable than the base comparator with RD (lenalidomide-dexamethasone) in transplant-ineligible MM. In NDMM, DaraVMP (daratumumab-bortezomib-melphalan-prednisone) and DaraRD (daratumumab-lenalidomide-dexamethasone) showed statistically significant difference of PFS when compared to RD. In r/r MM, DaraRD (daratumumab-lenalidomide-dexamethasone) was statistically significant different in PFS when compared to RD. These results suggest that adding a new treatment with a different mechanism of action (e.g., daratumumab as an anti-CD38 therapy) for MM may offer PFS benefits in MM. Due to various limitations of the analysis, such evidence should be interpreted with caution and further studies would be needed to validate the results.

Based on the perspectives and experiences review, patients have described various symptoms such as physical fatigue and risk of infection that have affected their abilities to engage in routine activities of daily living. They also prefer a holistic approach to disease management and to consider the physical, emotional and social impact of the disease and its treatment.

These highlights will be discussed again along with the results of the economic analysis in the second part of this report. Together, they can provide insights on implications for decision- or policy-making.

Introduction and Rationale

Background and Rationale

Symptomatic MM is an incurable plasma cell neoplasm characterized by an uncontrolled growth of plasma cells in the bone marrow. It represents 1.5% of all new cancers in Canada, with an estimated 3,400 new cases annually.[1] MM accounts for approximately 10% of all hematologic malignancies.[2] Symptomatic myeloma affects older adults, with the average age at diagnosis being 62 years for men and 61 years for women, and only 4% of cases are diagnosed in individuals younger than 45 years of age.[3] In Canada, the 5-year net survival rate for MM is 44%, with a higher incidence in males.[2] MM had the second-largest increase in male cancer incidence in 2019, with an annual percentage change of 2.6%.[4]

The preferred first-line therapy for NDMM patients is high-dose chemotherapy followed by autologous stem cell transplant.[5] However, over 50% of patients may not be eligible for this procedure because of health risks or other issues.[5,6] MM is often diagnosed over the age of 65,[7] and these patients are more likely to have pre-existing comorbidities, potentially rendering them ineligible for transplant. However, the clinical experts consulted by CADTH noted that age is often not a simple predictor of transplant eligibility. As such, recent discussions have begun to focus on frailty assessment as well as treatment tolerability as potential signals

for whether a patient is eligible for a transplant.[8] When transplant is not deemed an option, several multidrug regimens can be offered to these patients as first- or subsequent-line of therapy. The choice of drug therapy may depend on patient characteristics, personal preferences, experience with previous therapies, and funding by regional cancer centres.[9] Table 1 and Table 2 list all regimens for the first- and subsequent lines of MM treatment that are in use or being considered for public reimbursement in Canada.

By hitting multiple molecular targets simultaneously, these drug combinations can often control disease and delay its progression. For example, lenalidomide and other members of the immunomodulatory drugs (IMiDs) have immune-modulating and proapoptotic activities on blood cancer cells. Bortezomib is a proteasome inhibitor that inhibits cell survival pathways and modulates the tumour microenvironment and marrow niche. Melphalan is an alkylating chemotherapeutic drug. Corticosteroids like prednisone and dexamethasone dampen the activity of immune cells, including myeloma cells. Finally, daratumumab and isatuximab are monoclonal antibodies directed against cluster of differentiation 38, or CD38, which is expressed on plasma cells. Additional members of these classes such as pomalidomide (an analogue of lenalidomide), carfilzomib, and ixazomib (analogues of bortezomib) can be given to patients with r/r MM after the failure of primary drugs. Many drugs are in development for MM, including venetoclax, selinexor, various bispecific T-cell engagers, and chimeric antigen receptor T-cell therapies directed against the B-cell maturation antigen marker and other plasma cell-specific targets.[10]

Table 1: Treatment Regimens for Newly Diagnosed Transplant-Ineligible MM

Treatment regimen	Reviewed[a] by CADTH pERC
Bortezomib + melphalan + prednisone	No
Cyclophosphamide + bortezomib + dexamethasone	No
Cyclophosphamide + bortezomib + prednisone	No
Daratumumab + bortezomib + melphalan + prednisone	Yes
Daratumumab + cyclophosphamide + bortezomib + dexamethasone	No
Daratumumab + lenalidomide + dexamethasone	Yes
Lenalidomide + bortezomib + dexamethasone	Yes
Lenalidomide + dexamethasone	Yes
Bortezomib + melphalan + prednisone	No

MM = multiple myeloma; pCODR = pan-Canadian Oncology Drug Review. pERC = pCODR Expert Review Committee.

Note: These regimens for newly diagnosed transplant-ineligible MM are as per the indication reviewed by CADTH pERC or are according to the provincial funding status.

[a]The information in this column is indicative of completed CADTH reviews with positive reimbursement recommendations at the time of protocol development.

Table 2: Treatment Regimens for r/r MM

Treatment regimen	Reviewed[a] by CADTH pERC
Bortezomib + dexamethasone	No
Carfilzomib + dexamethasone ± cyclophosphamide[b]	Yes
Carfilzomib + lenalidomide + dexamethasone	Yes
Carfilzomib + pomalidomide + dexamethasone	No
Cyclophosphamide + bortezomib + dexamethasone	No
Daratumumab + bortezomib + dexamethasone	Yes
Daratumumab + lenalidomide + dexamethasone	Yes
Daratumumab + pomalidomide + dexamethasone	No
Lenalidomide + dexamethasone ± cyclophosphamide[b]	No
Isatuximab + carfilzomib + dexamethasone	Yes
Isatuximab + pomalidomide + dexamethasone	Yes
Pomalidomide + bortezomib + dexamethasone	Yes
Pomalidomide + dexamethasone ± cyclophosphamide[b]	Yes

MM = multiple myeloma; pCODR = pan-Canadian Oncology Drug Review; pERC = pCODR Expert Review Committee; r/r = relapsed and/or refractory.
Note: These regimens for r/r MM are as per the indication reviewed by CADTH pCODR Expert Review Committee or are according to the provincial funding status.
[a]The information in this column is indicative of completed CADTH reviews with positive reimbursement recommendations at the time of protocol development.
[b]The addition of cyclophosphamide was not reviewed by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.

Despite an abundance of clinical literature on drugs for MM, head-to-head comparisons of first-line drug regimens for transplant-ineligible patients are few and, as a result, uncertainty remains regarding their relative effectiveness, safety and optimal sequence. As a result, it is difficult to predict the fate of MM patients initiating therapy and the optimal sequencing of MM treatments is clouded with uncertainty.

NMAs enable a comparison of all treatments based on direct and indirect evidence from previously published clinical trials in MM. Several NMAs have been performed to date (e.g., Blommestein et al.[11] and Van Beurden-Tan et al.[12]); however, since the time of their publication, additional (long-term) results of trials such as the ALCYONE,[13] OPTIMISMM,[14] and MAIA[15] have become available, necessitating an update of these NMAs.

Following a topic prioritization process, the Provincial Advisory Group (PAG) which provides CADTH Pharmaceutical Advisory Committee with advice and strategic or policy directions, selected MM first-line drugs for patients ineligible for stem cell transplant as the preferred topic for the development of a CADTH Optimal Use project. Note that a CADTH Optimal Use project consists of a systematic review of the clinical evidence; a cost-effectiveness analysis; a review of the legal, social, and ethical issues; and the development of recommendations, guidance, and tools. An optimal use project aims to define the effective and efficient use of health technology to inform policy and practice decisions and to encourage the appropriate use of health technologies by health care providers, policy-makers and consumers, PAG members also mentioned that any CADTH work on subsequent treatments and sequencing would be of high value. PAG members noted the considerable amount of resources consumed for MM treatment in cancer centres and highlighted

the complex array of therapeutic options. Evidence on the relative clinical- and cost-effectiveness of multidrug regimens and their sequencing across the treatment pathway is generally not included in CADTH reimbursement reviews, thus preventing recommendations on sequencing — an issue that is consistently acknowledged by the CADTH pCODR Expert Review Committee (pERC).

To fill this gap in sequencing, CADTH initiated the current project. The project consists of 3 parts: a clinical review, an economic analysis and a perspectives and experiences review.

Policy Question

The policy question defined for this project is: **In what sequences should drugs for transplant-ineligible MM be reimbursed to maximize clinical and cost-effectiveness while considering patient safety, characteristics, experience, and preferences?**

Research Questions

This project will address the above-cited policy question by exploring the following research questions:

Clinical Review

Research Question 1: What is the comparative efficacy and safety of drug combinations for newly diagnosed, previously untreated MM in patients who are not eligible for autologous stem cell transplant?

Research Question 2: What is the comparative efficacy and safety of drug combinations for MM in patients who have relapsed or are refractory to first-line drugs?

Economic Analysis

What is the cost-effectiveness of various treatment sequences for transplant-ineligible MM patients?

Perspectives and Experiences Review

What are the perspectives and experiences of patients with newly diagnosed and transplant-ineligible or r/r MM on expectations of treatment, treatment decision-making, experiences of treatment, and barriers to accessing or receiving treatment across the course of their cancer?

Stakeholder Engagement

Overview

CADTH involves clinicians, patients, associations, and industry to improve the quality and significance of our work. It also allows those affected by our reviews to have an opportunity to learn about and contribute to them. Within the International Association for Public Participation Spectrum, our engagement activities can be described as “involve” as we interact with stakeholders multiple times during our process to ensure concerns and aspirations are consistently understood and considered. We aim for all stakeholders to find engaging with CADTH to be a productive and worthwhile experience.

Methods

Clinicians: Two oncologists are involved as specialist members for this therapeutic review, in addition to the pharmacist, endocrinologist, gerontologist, and 2 oncologists who are core members of the CADTH Formulary Management Expert Committee. Specialist members are selected by CADTH and have clinical experience with the drugs in the review, in addition to expertise in health research or health policy. Specialist members work directly with the CADTH team and expert committee to evaluate the therapeutic value and cost of the drugs under review; answer clinical questions related to their practical experience in diagnosing and managing treatment for MM; actively involved in committee deliberations; and vote on the recommendations. The names and backgrounds of the 2 specialist members will be shared at the conclusion of the review to discourage attempts to directly lobby the specialists.

Associations: CADTH attended the Myeloma Canada Scientific Roundtable, before publishing the proposed project scope in December 2019. CADTH provided updates to Myeloma Canada as the project progressed and worked with Myeloma Canada to collate past patient input on MM and run a 2021 survey to generate patient input specific for this therapeutic review. CADTH also worked closely with the CMRG in benefit from their comprehensive MM database of patient level data collected from multiple centres across Canada. These real-world data are used in CADTH's economic analysis. The approach and preliminary results of the network meta-analyses were presented to clinicians from CMRG and Myeloma Canada.

Industry: Amgen Canada, Janssen, Takeda Canada, and Celgene provided feedback on the proposed project scope in December 2019.

Patients: In addition to a patient member on the CADTH Formulary Management Expert Committee, there is an opportunity for a person living with transplant-ineligible MM to interact with the expert committee. The aim is to enable a deeper understanding by committee members of the lived experience of receiving treatment in Canada. An opportunity for patients and caregivers to present to expert committee making reimbursement recommendations has long been requested from CADTH. However, sharing difficult stories can feel sided, and triggering, if the person is not appropriately supported. The person with lived experience will be acknowledged by name for their insights. An emotional support person is available for debrief and the associations who helped identify the person with lived experience will also attend the committee meeting in a supporting role. CADTH staff will brief and de-brief with the person with lived experience and the patient and clinician associations.

All stakeholders: CADTH provides 10 business days for stakeholders to provide feedback at the following stages: proposed project scope (December 2019); draft clinical report and experience and perspective report (available August 31, 2023); draft economic report (available in September) and draft recommendations (available November 2023). Feedback opportunities were communicated through the CADTH Weekly Summary emails to subscribers. Any interested stakeholders are welcome to contact CADTH, to learn more about this review. Reach us at Requests@cadth.ca.

Results

CADTH received feedback on project scope from Myeloma Canada; clinicians from Hamilton, Ontario; Toronto, Ontario; Vancouver, British Columbia; and St John, New Brunswick; and Amgen Canada, Janssen, Takeda Canada, and Celgene.

Stakeholders welcomed the project, but expressed caution given the complexity of the disease, the heterogeneity of MM patients, and the constantly evolving treatment landscape. Patients asked, "Which treatment is going to help me live the longest?" "How can I get access to that therapy?"

With a recognition that some drug regimens are being used in Canada based on phase II data, would the analysis using phase III and IV data, offer relevant guidance? As phase II trials are considered hypothesis-generating and are generally superseded by phase III studies, for simplicity of the NMA and economic modelling, phase II trial data were not included.

Stakeholders highlighted a need for real-world data from the Myeloma Canada Research Network Canadian MM Database and similar administrative databases, rather than a reliance on published trial data alone, especially for transplant-ineligible patients. Clinicians asked for an exploration of frail or high-risk patients as a specific subpopulation in the analysis.

In response, CADTH is using real-world data from sources in Canada in our economic analysis to complement phase III data used in the network meta-analyses. CADTH initially explored gaining data from the Myeloma Canada Research Network database, although the CMRG provided real-world data to CADTH from their disease registries.

Stakeholders asked that the review include patient reported outcomes and/or patient preferences, for example, on how the therapy be administered. CADTH discovered that few of the clinical trials included patient reported outcomes. Instead, CADTH added HRQoL as an outcome of interest. Data on HRQoL was gathered from previous CADTH Reimbursement Review. CADTH also conducted a rapid qualitative evidence synthesis to explore perspectives and experiences of patients with transplant-ineligible and/or r/r MM. This was bolstered by patient input, and continued engagement, with Myeloma Canada.

The absence of ixazomib from the treatments used in MM was noted by several stakeholders. In response, CADTH included ixazomib, melphalan, and thalidomide to strengthen the network, although they are not as widely used in Canada.

Ongoing dialogue, between CADTH, Myeloma Canada, Myeloma Canada Research Network, and CMRG helped build trust and greater understanding of each other's goals.

Clinical Review

The clinical review was designed as an SLR (systematic literature review) and NMA to answer the clinical research questions. The SLR was performed to identify all published phase III RCTs involving patients with transplant-ineligible NDMM or r/r MM. Data from the studies of NDMM (research question 1) and those from

the studies of r/r MM (research question 2) were separately analyzed. In addition, there was an absence of usable data related HRQoL outcomes from the included RCTs. As such, this outcome was evaluated using data collected from a review of previous CADTH reimbursement reviews.

Literature Search Methods

The literature search was performed by a biomedical information specialist using a peer-reviewed search strategy. The search strategy is presented in Appendix 1. Published literature was identified by searching the following bibliographic databases: Embase, Ovid MEDLINE, and the Cochrane Central Register of Controlled Trials. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings, and keywords. The main search concepts were MM and RCTs. In addition, the following clinical trial registry was searched: the US National Institutes of Health's clinicaltrials.gov. Methodological filters were applied to limit retrieval to RCTs. Retrieval was further limited to publications published from January 1996 onward, the human population, and English-language results. Conference abstracts were excluded from the search results. The search was completed on February 28, 2023.

Eligibility Criteria

Studies were included if they met the eligibility criteria, i.e., the population, interventions, comparators, outcomes, and study design (PICOS). The eligibility criteria for NDMM and r/r MM are summarized in Table 3 and Table 4, respectively.

Population and Subgroups

For NDMM, the population of interest was adult patients who were not eligible for stem cell transplant. The subgroups of interest for this population were patients aged at least 75 years, patients with high-risk cytogenetics, and patients with an ECOG performance status of at least 2. For r/r MM, the population of interest was patients who had relapsed following response, or who were refractory to at least 1 regimen. The subgroups of interest for this population were the same subgroups as those defined for NDMM. In addition, a subgroup based on the number of prior lines of therapy received was of interest.

Table 3: Eligibility Criteria for NDMM

Criteria	Description
Population and subgroups	Adult patients with transplant-ineligible NDMM Subgroups of interest: • Patients aged ≥ 75 years • Patients with high-risk cytogenetics • Patients with an ECOG performance status of ≥ 2
Interventions	Regimens with at least one of the following drugs: • Bortezomib • Carfilzomib • Cyclophosphamide • Daratumumab

Criteria	Description
	• Dexamethasone • Elotuzumab • Ixazomib[a] • Lenalidomide • Melphalan[a] • Prednisone • Thalidomide[a]
Comparators	Any other drug/regimen Placebo
Outcomes	PFS[b] TTP (as proxy for PFS) Grade ≥ 3 AEs HRQoL
Study design	Published phase III RCTs (from 1996 onwards)

AE = adverse events; ECOG = Eastern Cooperative Oncology Group; HRQoL = health-related quality of life; NDMM = newly diagnosed multiple myeloma; PFS = progression-free survival; RCTs = randomized controlled trials; TTP = time to progression.

[a]Although these regimens are not used in Canada; they were included to strengthen the network. Refer to Table 1 for the list of regimens that are relevant for the Canadian setting. [b] Although not prespecified, EFS was used as a proxy for PFS (from 1 study) in the NMA.

Table 4: Eligibility Criteria for r/r MM

Criteria	Description
Population	Adult patients with r/r MM Subgroups of interest: • Patients aged ≥ 75 years • Patients with high-risk cytogenetics • Patients with an ECOG performance status of ≥ 2 • Number of prior lines of therapy
Interventions	Regimens with at least one of the following drugs: • Bortezomib • Carfilzomib • Cyclophosphamide • Daratumumab • Dexamethasone • Elotuzumab • Idecabtagene vicleucel • Isatuximab • Ixazomib[a] • Lenalidomide • Pomalidomide • Prednisone • Thalidomide[a]

Criteria	Description
Comparators	Any other drug or regimen Placebo
Outcomes	PFS TTP (as proxy for PFS) Grade ≥ 3 AEs HRQoL
Study design	Published phase III RCTs[b] (from 1996 onward)

AEs = adverse events; ECOG = Eastern Cooperative Oncology Group; HRQoL = health-related quality of life; PFS = progression-free survival; RCTs = randomized controlled trials; r/r MM = relapsed and/or refractory multiple myeloma; TTP = time to progression.

[a]Although these regimens are not used in Canada; they were included to strengthen the network. Refer to Table 2 for the list of regimens that are relevant for the Canadian setting.

[b]Phase III RCTs that only included patients who had previously undergone stem cell transplant were excluded.

Intervention and Comparators

For NDMM, the regimens of interest were bortezomib, carfilzomib, cyclophosphamide, daratumumab, dexamethasone, elotuzumab, ixazomib, lenalidomide, melphalan, prednisone, and thalidomide. For r/r MM, the regimens of interest were bortezomib, carfilzomib, cyclophosphamide, daratumumab, dexamethasone, elotuzumab, idecabtagene vicleucel, isatuximab, ixazomib, lenalidomide, pomalidomide, prednisone, and thalidomide. Although ixazomib, melphalan, and thalidomide are not used in Canada, they were included to strengthen the network. Lists of regimens that are relevant for settings in Canada are presented in Table 1 and Table 2.

Outcomes Definitions

For both populations, the outcomes of interest were PFS, (TTP as proxy for PFS), at least grade 3 adverse events (AEs), and HRQoL. PFS was defined as the time from randomization to either disease progression or death; whereas TTP was defined as the time from randomization to disease progression. In case an RCT defined (1 of) these outcomes differently, this was explicitly mentioned.

Study Designs

For both populations, published phase III RCTs that met the previously described interventions, comparators, and outcomes were eligible for inclusion.

Study Selection Process

Two independent reviewers applied the eligibility criteria to each title and abstract identified by the literature search. All records deemed potentially relevant by at least 1 reviewer were obtained in full-text format. The eligibility criteria were applied to the full-text publications by both reviewers independently, and a final decision about inclusion was made. If multiple publications for a unique RCT were eligible, all publications were included. Discrepancies were resolved by discussion, through involvement of a third reviewer, or by consultation with clinical experts. The study selection process was documented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (refer to Figure 1).

Data Extraction

Data were extracted by 1 reviewer by use of prespecified data extraction forms, and the extracted data were checked for accuracy by a second reviewer. Discrepancies were resolved by discussion or through involvement of a third reviewer. The following data were extracted: publication details, study characteristics, patient characteristics, and clinical outcomes. Refer to Table 10, Table 11, Table 12, and Table 13. Data were extracted for all outcomes at any duration of follow-up. For PFS and TTP, hazard ratios (HRs) and 95% confidence intervals (CIs) were extracted. In case HRs and/or 95% CIs were not reported, they were obtained from previous (network) meta-analyses[11,12,16] or estimated from published Kaplan-Meier curves following the methodology as described by Guyot et al.[17] Data on subgroups of interest (refer to Table 3 and Table 4) were extracted when available. The most recently published HR for PFS for a RCT was used for data extraction in case multiple publications for a unique RCT were included.

Quality Assessment

The risk of bias of the RCTs included in the NMA was assessed using the method described in the second version of the Cochrane risk-of-bias tool for randomized trials (RoB 2).[18] This tool addresses 5 domains through which bias might be introduced: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported results. Within each domain, a series of questions (i.e., signalling questions) should be answered with yes, probably yes, probably no, no, or no information. Based on these answers, a judgment about the risk of bias arising from each domain is generated by an algorithm. The risk-of-bias judgments can be low risk of bias, some concerns, or high risk of bias. Risk-of-bias assessments were performed by 1 reviewer and verified by a second reviewer. Discrepancies were resolved by consensus or through involvement of a third reviewer. The risk-of-bias assessments were not used to exclude RCTs from the NMA.

Data Analyses and Synthesis

Two networks of comparisons (one for NDMM and 1 for r/r MM) were created from the regimens that were compared, head-to-head, in the identified RCTs. The majority of comparisons in both networks were informed by single RCTs. The NMAs were conducted in R (version 4.0.5) using the rjags package (version 4 to 10). For both populations, a Bayesian random-effect model was used to estimate HRs for PFS including the corresponding 95% CrIs. The analyses were conducted with noninformative priors, burn-in of 500,000 iterations, collection over a further 500,000 iterations, and selection of every 10th run for analysis. When the burn-in was set to below 100,000 runs, a few parameters had not yet converged. Convergence, which was assessed using the Gelman-Rubin diagnostic, was achieved before 200,000 runs in all cases. A random-effect model was deemed more appropriate than a fixed-effect model as random-effect models allow for between-study heterogeneity. Based on feedback from the clinical experts, lenalidomide/dexamethasone (RD) was selected as the reference regimen for both populations. An HR below 1 indicates that the specific regimen is more efficacious than the reference regimen, whereas an HR above 1 indicates that the specific regimen is less efficacious than the reference regimen. Face validity was checked by comparing the HRs computed by the NMA with the HRs published in the included RCTs.

All identified RCTs were included in the base-case analyses except for RCTs that had no connection in the network or that terminated early because of poor accrual. To assess the sensitivity of the results, the following scenario analyses were conducted:

Scenario 1: Exclusion of some indirect evidence based on expert opinion (for NDMM only): The rationale for this scenario is that, based on feedback from the clinical experts, it was assumed that the relative effectiveness of bortezomib-melphalan-prednisone (VMP) versus lenalidomide-dexamethasone (RD) can best be informed by the comparison bortezomib-melphalan-prednisone (VMP) versus melphalan-prednisone (MP) versus melphalan-prednisone-thalidomide (MPT) versus lenalidomide-dexamethasone (RD) where MPT versus lenalidomide-dexamethasone (RD) is best informed by the FIRST trial.[19] Therefore, indirect evidence as obtained from E1A06, EMN01, HOVON 87, IFM 95 to 01, MM-015, MM-PETHEMA 96, MRC Myeloma IX, MY.7, Myeloma XI, S0232, THAL-MM-03, and NCT00205751 was excluded.

Scenario 2: Exclusion of RCTs that were judged to be at a high risk of bias.

Scenario 3: Exclusion of RCTs that were judged to be at a high risk of bias or that were judged to raise some concerns in at least 1 domain.

Scenario 4: Exclusion of RCTs that included relapse as PFS event, excluded death as PFS event, and/or did not report, which events were incorporated in the definition of PFS.

Scenario 5: Exclusion of RCTs that included relapse as PFS event and/or excluded death as PFS event.

Consistency and Heterogeneity

NMAs are based on the assumption of consistency, which means that direct and indirect evidence should agree for each treatment comparison. To verify this assumption, we compared HRs derived only from direct evidence against those derived only from indirect evidence. Furthermore, the presence of between-study heterogeneity was tested using the I^2 statistic. This statistic represents the proportion of variation between studies that is due to heterogeneity rather than sampling error (i.e., chance).

HRQoL

As data for HRQoL were not expected to be found through the included studies, a review of previous CADTH reimbursement reviews of MM therapeutics was conducted to extract information related to HRQoL.

A search of the CADTH Reimbursement Review Reports database was conducted for treatments reviewed for MM. A total of 17 reviews were conducted by CADTH for the indication of multiple myeloma between January 2013 and December 2021.[20-36] At the time of the initial search, a total of 6 reviews were conducted for the NDMM population,[22,23,30-32,34] while 9 reviews were conducted for the r/r MM population.[20,21,24-29,33] An updated search was performed in June 2023 to identify reviews conducted between January 2022 and June 2023. As of the updated search, CADTH had reviewed 4 additional drugs in MM, all for the r/r MM population.[37-40]

Results of Clinical Review

Included Studies

The literature search identified 14,194 records. After removing duplicates, 8,225 records were screened on title and abstract. Following the title and abstract screening, 7,655 records were excluded, and 570 reports were retrieved for full-text screening. Of the 570 potentially relevant reports, 468 reports were excluded for various reasons (including wrong population, wrong study design, and wrong publication type) and 101 publications describing 70 RCTs were included. The PRISMA flow chart is presented in Figure 1.

Study Characteristics, Patient Characteristics, and Outcomes

Research Question 1: Newly Diagnosed Multiple Myeloma

Study Characteristics and Patient Characteristics

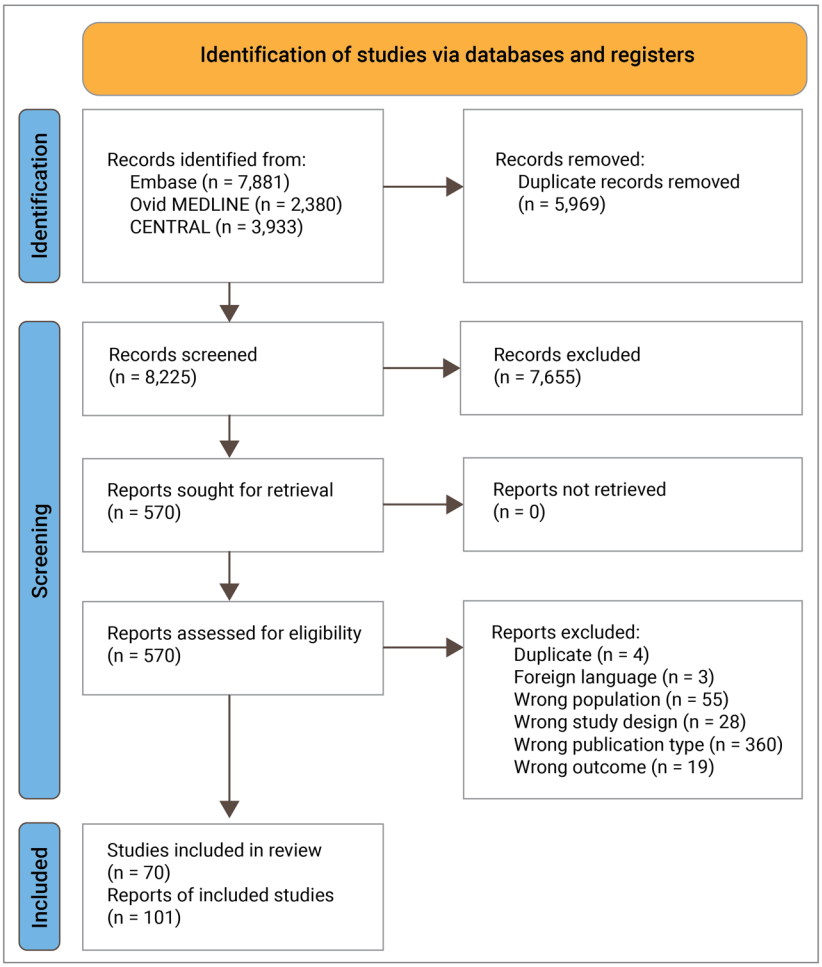
A summary of the extracted data for NDMM are presented in Appendix 6. The 31 RCTs (included in the NMA) incorporated 27 regimens. More than three-quarters of the RCTs (77%) were open label. Twenty-six RCTs (84%) were two-armed, 4 RCTs[49-52](13%) were three-armed, and 1 RCT[53] (3%) was four-armed. PFS was the primary outcome in approximately two-thirds of the RCTs (68%). The smallest RCT[54] had a sample size of 115 patients, while the largest RCT[55] had a sample size of 1,852 patients. The median age ranged from 63 to 79 years, and the median length of follow-up from 6.6 to 84 months.

Outcomes

Data on PFS was available for 30 of the 31 RCTs; 1 RCT[56] (3%) only reported EFS; defined as the time between the start of therapy and disease progression, relapse, death, or last follow-up), which was used as proxy for PFS. Of the 30 RCTs for which data on PFS was available, 19 RCTs (63%) defined PFS conforming our definition, 6 RCTs[49,52,57-60] (20%) included relapse as PFS event, 1 RCT[61] (3%) excluded death as PFS event, and 4 RCTs[54,62-64] (13%) did not report which events were incorporated in the definition of PFS. HRs for PFS (or EFS) were obtained from the published RCTs (n = 20), from previous (network) meta-analyses[11,16] (n = 7), or estimated following the methodology as described by Guyot et al.[17] (n = 4).

For the subgroups of interest (i.e., patients aged ≥ 75 years, patients with high-risk cytogenetics, and patients with an ECOG performance status of ≥ 2), there was a considerable variation in reporting and a large amount of missing data. For example, 8 RCTs (26%) reported the proportion of patients aged at least 76 years instead of at least 75 years, more than half of RCTs (55%) did not report the proportion of patients with high-risk cytogenetics, and most RCTs did not report HRs (for PFS) for the subgroups. The same was observed for AEs. Only 12 RCTs (39%) reported the proportion of patients with at least grade 3 AEs. Two RCTs (6%) reported the proportion of patients with grade ≥ 3 treatment-emergent AEs (TEAEs) and 1 RCT (3%) reported the proportion of patients with at least grade 3 serious AEs (SAEs). Fifteen RCTs (48%) did not report the proportion of patients with at least grade 3 AEs (or TEAEs/SAEs). They only reported the proportion of patients with particular AEs. Due to the aforementioned factors, it was not feasible to conduct NMAs for the subgroups of interest and for at least grade 3 AEs.

Figure 1: PRISMA Flow Chart of Selected Reports



Note: Thirty-six RCTs in 50 publications were relevant to NDMM and 34 RCTs in 51 publications were relevant to r/r MM. Lists of included RCTs are presented in Appendix 2. Ongoing RCTs that met the selection criteria whose results were not yet published in a peer-reviewed journal (before the completion of the NMA) are listed in Appendix 3. Of the 36 RCTs that were relevant to NDMM, 5 RCTs[41-45] were excluded from the NMA. Four RCTs[41,42,44,45] had no connection in the network and one RCT[43] terminated early because of poor accrual. Of the 34 RCTs that were relevant to r/r MM, 3 RCTs[46-48] were excluded. Two RCTs[46,47] had no connection in the network and one RCT[48] terminated early because of poor accrual.

Research Question 2: Relapsed and/or Refractory Multiple Myeloma

Study Characteristics and Patient Characteristics

A summary of the extracted data for r/r MM is presented in Appendix 6. The 31 RCTs (included in the NMA) incorporated 32 regimens. More than three-quarters of the RCTs (77%) were open label. Thirty RCTs (97%) were two-armed and 1 RCT[65](3%) was four-armed. PFS was the primary outcome in approximately three-quarters of the RCTs (74%). The smallest RCT[66]had a sample size of 93 patients, while the largest RCT[67] had a sample size of 929 patients. The median age ranged from 59 to 71 years. In 2/3 of the RCTs (68%), more than half of the patients had previously undergone a stem cell transplant. The median length of follow-up ranged from 5.6 to 85.1 months.

Outcomes

Data on PFS were available for 25 of the 31 RCTs; 6 RCTs[65,66,68-71] (19%) only reported TTP (for all regimens compared within the RCT), which was used as proxy for PFS. Of the 25 RCTs for which data on PFS were available, 24 RCTs (96%) defined PFS conforming our definition and 1 RCT[72] (4%) included relapse as PFS event. Of the 6 RCTs that (only) reported TTP, 4 RCTs (67%) defined TTP conforming our definition, 1 RCT[66](17%) included death as TTP event, and 1 RCT[68](17%) did not report which events were incorporated in the definition of TTP. HRs for PFS (or TTP) were obtained from the published RCTs (n = 26), from a previous NMA[12](n = 3), or estimated following the methodology as described by Guyot et al.[17] (n = 2).

For the subgroups of interest (i.e., patients aged ≥ 75 years, patients with high-risk cytogenetics, patients with an ECOG performance status of ≥ 2, and number of prior lines of therapy), there was a considerable variation in reporting and a large amount of missing data. For example, some RCTs reported the proportion of patients with 1 or at least 2 prior lines of therapy, while other RCTs reported the proportion of patients with 1, 2, or 3 prior lines of therapy. Eleven RCTs (35%) did not report the proportion of patients with high-risk cytogenetics, and most RCTs did not report HRs (for PFS) for the subgroups. The same was observed for AEs. Only 12 RCTs (39%) reported the proportion of patients with at least grade 3 AEs, and 8 RCTs (26%) reported the proportion of patients with grade ≥ 3 TEAEs. Eleven RCTs (35%) did not report the proportion of patients with at least grade 3 AEs (or TEAEs). They only reported the proportion of patients with particular AEs. Due to the aforementioned factors, it was not feasible to conduct NMAs for the subgroups of interest and for at least grade 3 AEs.

Risk-of-Bias Assessment

The risk-of-bias assessment consists of 5 domains. The first domain relates to the randomization process. The second domain looks at deviations from the intended interventions. The third domain looks for missing outcome data. The fourth domain relates to the measurement of the outcome. Finally, the first domain looks at the selection of the reported result.

Research Question 1: Newly Diagnosed Multiple Myeloma

Of the 31 RCTs, 23 RCTs were judged to be at a low risk of bias for all domains (refer to Table 5). Seven RCTs[54,55,61,73-75] were judged to raise some concerns in the second domain (deviations from the intended interventions) or fifth domain (selection of the reported result). One RCT[56] was judged to be at a high risk of bias in the third domain (missing outcome data). The impact of the RCTs that were judged to be at a high risk of bias or that were judged to raise some concerns in at least 1 domain was evaluated in scenario analyses (refer to the Network Meta-Analysis).

Table 5: Risk-of-Bias Assessment for PFS in NDMM

Trial name	D1 Randomization process	D2 Deviation from the intended interventions	D3 Missing data outcome	D4 Measurement of the outcome	D5 Selection of the reported results	Overall
ALCYONE	Low	Low	Low	Low	Low	Low
CLARION	Low	Low	Low	Low	Low	Low
E1A06	Low	Low	Low	Low	Some	Some
ELOQUENT-1	Low	Low	Low	Low	Low	Low
EMN01	Low	Low	Low	Low	Low	Low
ENDURANCE (E1A11)	Low	Low	Low	Low	Some	Some
FIRST (MM-02)	Low	Low	Low	Low	Low	Low
GEM2005	Low	Low	Low	Low	Low	Low
GEM-CLARIDEX	Low	Low	Low	Low	Low	Low
GIMEMA MM-03 to 05	Low	Low	Low	Low	Low	Low
GISMM2001-A	Low	Low	Low	Low	Low	Low
HOVON 49	Low	Low	Low	Low	Low	Low
HOVON 87	Low	Low	Low	Low	Low	Low
IFM 01/01	Low	Low	Low	Low	Low	Low
IFM 95 to 01	Low	Low	Low	Low	Low	Low
KEYNOTE-185	Low	Low	Low	Low	Some	Some
MAIA (MMY3008)	Low	Low	Low	Low	Low	Low
MM-015	Low	Low	Low	Low	Low	Low
MM-PETHEMA 96	Low	Low	High	Low	Some	High
MRC Myeloma IX	Low	Low	Low	Low	Low	Low
MY.7	Low	Low	Low	Low	Some	Some
Myeloma XI	Low	Some	Low	Low	Low	Some
NMSG 12	Low	Low	Low	Low	Low	Low
S0232	Low	Low	Low	Low	Low	Low
S0777	Low	Low	Low	Low	Low	Low
THAL-MM-03	Low	Low	Low	Low	Low	Low
TMSG-2005 to 001	Low	Some	Low	Low	Low	Some
TOURMALINE-MM2	Low	Low	Low	Low	Low	Low

Trial name	D1 Randomization process	D2 Deviation from the intended interventions	D3 Missing data outcome	D4 Measurement of the outcome	D5 Selection of the reported results	Overall
UPFRONT	Low	Low	Low	Low	Low	Low
VISTA	Low	Low	Low	Low	Low	Low
NCT00205751	Low	Some	Low	Low	Low	Some

NDMM = newly diagnosed multiple myeloma; PFS = progression-free survival.

Research Question 2: Relapsed and/or Refractory Multiple Myeloma

Of the 31 RCTs, 24 RCTs were judged to be at a low risk of bias for all domains (refer to Table 6). Five RCTs[68,71,76-78] were judged to raise some concerns in the first domain (randomization process), second domain (deviations from the intended interventions), or fifth domain (selection of the reported result). Two RCTs[66,79] were judged to be at a high risk of bias in the second domain (deviation from the intended interventions) or third domain (i.e., missing outcome data). The impact of the RCTs that were judged to be at a high risk of bias or that were judged to raise some concerns in at least 1 domain was evaluated in scenario analyses (refer to the Network Meta-Analysis).

Table 6: Risk-of-Bias Assessment for PFS in r/r MM

Trial name	D1 Randomization process	D2 Deviation from the intended interventions	D3 Missing data outcome	D4 Measurement of the outcome	D5 Selection of the reported results	Overall
ADMYRE	Low	Low	Low	Low	Low	Low
APEX	Low	Some	Low	Low	Low	Some
APOLLO	Low	Low	Low	Low	Low	Low
ASPIRE	Low	Low	Low	Low	Low	Low
BELLINI	Low	Low	Low	Low	Low	Low
BOSTON	Low	Low	Low	Low	Low	Low
CANDOR	Low	Low	Low	Low	Low	Low
CASTOR	Low	Low	Low	Low	Low	Low
CC-5013-MM-009	Low	Low	Low	Low	Low	Low
CC-5013-MM-010	Low	Low	Low	Low	Low	Low
ELOQUENT-2	Low	Low	Low	Low	Low	Low
ENDEAVOUR	Low	Low	Low	Low	Low	Low
ICARIA-MM	Low	Low	Low	Low	Low	Low
IFM 01 to 02	Low	Some	Low	Low	Low	Some
IKEMA	Low	Low	Low	Low	Low	Low
KEYNOTE-183	Low	Low	Low	Low	Some	Some

Trial name	D1 Randomization process	D2 Deviation from the intended interventions	D3 Missing data outcome	D4 Measurement of the outcome	D5 Selection of the reported results	Overall
LEPUS (MMY3009)	Low	Low	Low	Low	Low	Low
MM-003	Low	High	Low	Low	Low	High
MMY3001	Low	Low	Low	Low	Low	Low
MMY3022	Low	Some	High	Low	Some	High
NMSG 17/07	Low	Low	Low	Low	Some	Some
OCEAN	Low	Low	Low	Low	Low	Low
OPTIMISMM	Low	Low	Low	Low	Low	Low
OPTIMUM	Low	Low	Low	Low	Low	Low
PANORAMA 1	Low	Low	Low	Low	Low	Low
POLLUX	Low	Low	Low	Low	Low	Low
TOURMALINE-MM1	Low	Low	Low	Low	Low	Low
VANTAGE 068	Low	Low	Low	Low	Low	Low
NCT00017602	Some	Low	Low	Low	Low	Some
NCT01002248	Low	Low	Low	Low	Low	Low

MM = multiple myeloma; PFS = progression-free survival; r/r = relapsed and/or refractory.

Network Meta-Analysis

The research question is to evaluate the comparative efficacy and safety of drug combinations for both NDMM who are not eligible for autologous stem cell transplant as well as for those with relapse and refractory MM. Based on findings from the SLR, the HRs for PFS of selected studies were included in the NMA with RD (lenalidomide-dexamethasone) as the reference regimen for comparison of efficacy. As discussed previously that, given the lack of data on AEs and variations and missing data for the subgroups of interest (patients aged ≥ 75 years, patients with high-risk cytogenetics, and patients with an ECOG performance status of ≥ 2), an NMA could not be conducted to evaluate the comparative efficacy in these subgroups of interest as well as the comparative safety of these drug combinations.

Research Question 1: Newly Diagnosed Multiple Myeloma

The network for NDMM (refer to Figure 2) compared 27 treatment options, informed by 31 studies meeting the eligibility criteria of the clinical review. Clusters CRDa/CTDa, VMP, and RD are the only 3 clusters that are connected through a single therapy with the network, namely MP, VMP, and RD, respectively. All clusters between the MP and RD nodes include mainly older studies. A comparison of treatment effectiveness between the VMP and RD cluster is based on the relative performance of MP compared to RD. This comparison is informed by several clusters in the network. However, the VMP cluster is only connected

through a single study comparing MP to VMP (VISTA), marking the relative importance of this study to connect the VMP cluster.

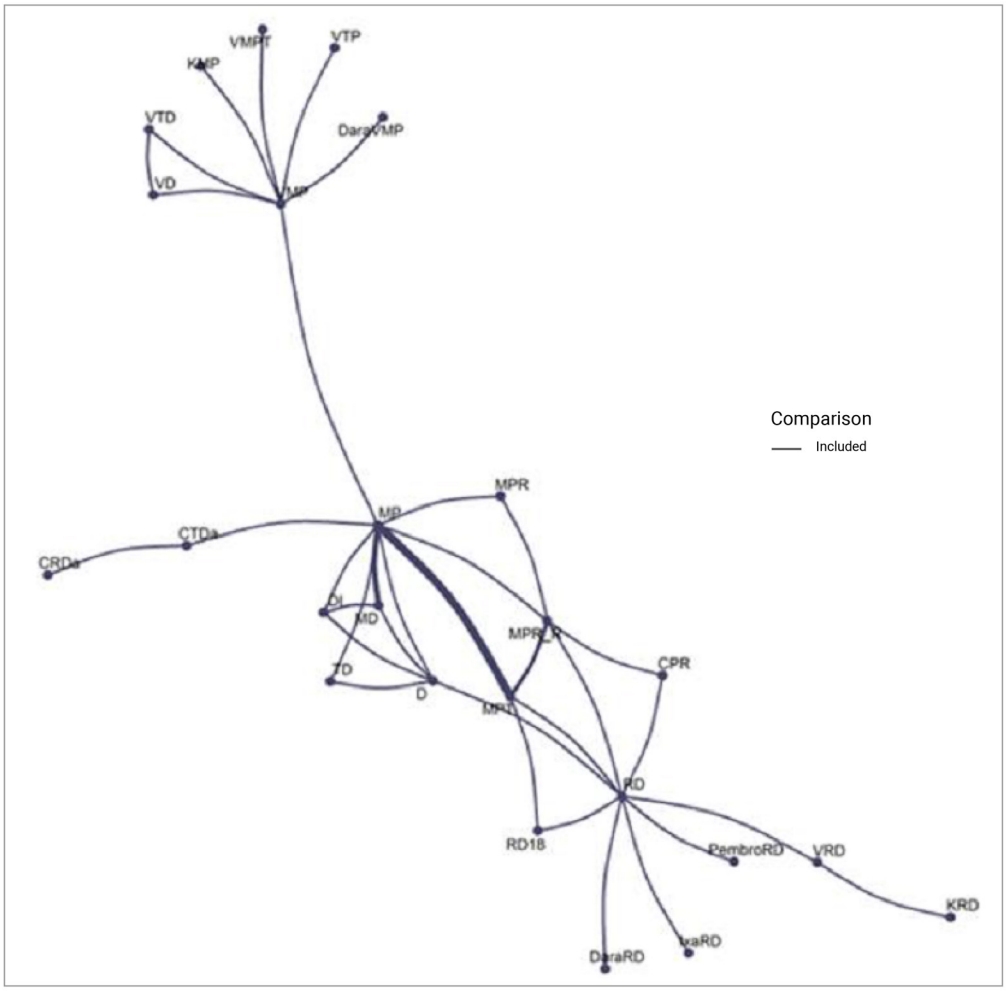
Figure 3 shows the NMA results of the base-case analysis. All regimens were ranked according to their estimated HR for PFS. Twelve regimens were estimated to be more favourable than the comparator, lenalidomide-dexamethasone (RD) based on the point estimates of the NMA, with HRs ranging from 0.38 to 0.99. Daratumumab-bortezomib-melphalan-prednisone (DaraVMP, HR: 0.38; 95%, 0.14 to 0.97), bortezomib-melphalan-prednisone-thalidomide (VMPT; HR: 0.52; 95%, 0.20 to 1.30), and daratumumab-lenalidomide-dexamethasone (DaraRD, HR: 0.53; 95%, 0.30 to 0.95) were more favourable than the comparator. Only 2 regimens (i.e., DaraVMP and DaraRD) were favoured in improving PFS relative to RD based on the 95% CrIs.

Thirteen regimens were estimated to be less favourable when compared to lenalidomide-dexamethasone (RD) based on the point estimates of the NMA and, in particular, results suggest that patients on dexamethasone-interferon alpha-2b (DI, HR: 2.10; 95% CrI, 1.10 to 3.90), dexamethasone (D, HR: 2.30; 95% CrI, 1.50 to 3.90) experienced decreased PFS relative to patients on RD based on the 95% CrIs.

Heterogeneity

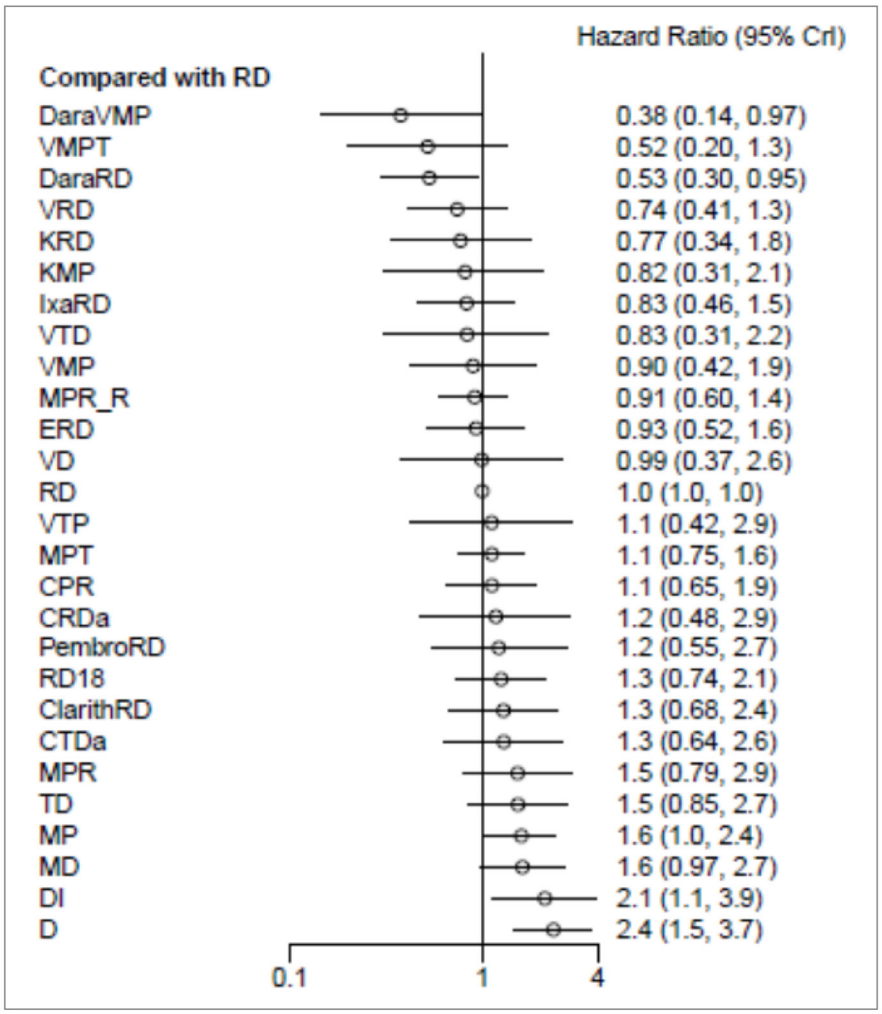
Our network (for the base-case analysis) comprised 11 comparisons that were informed only by a single RCT. For all of these comparisons, the HR obtained from the RCT equalled the HR obtained from the NMA. In addition, there were multiple treatments for which both direct and indirect evidence were available. A comparison of the HRs derived only from direct or indirect evidence revealed There were discrepancies in HRs, although the CI overlapped, resulting in P values of less than 0.05. The I^2 statistic, which was used to assess between-study heterogeneity, was 74% for the base-case analysis. According to the Cochrane Handbook for Systematic Reviews of Interventions (version 6.4, chapter 10.10), this value indicates substantial heterogeneity (I^2 range: 50% to 90%). However, for scenario 1, which was used in the economic analysis (as previously mentioned), the I^2 statistic was 31%, indicating only moderate heterogeneity (I^2 range: 30% to 60%). The I^2 statistic for the other scenario analyses ranged from 68% (scenario 3) to 89% (scenario 4).

Figure 2: Network for NDMM



a = attenuated; C = cyclophosphamide; Clarith = Clarithromycin; D = dexamethasone; Dara = daratumumab; E = elotuzumab; I = interferon alpha-2b; Ixa = ixazomib; K = carfilzomib; M = melphalan; P = prednisone; Pembro = pembrolizumab; R = lenalidomide; t = thalidomide; V = bortezomib.

Figure 3: NMA Results of the Base-Case Analysis for NDMM



a = attenuated; C = cyclophosphamide; Clarith = Clarithromycin; D = dexamethasone; Dara = daratumumab; E = elotuzumab; I = interferon alpha-2b; Ixa = ixazomib; K = carfilzomib; M = melphalan; P = prednisone; Pembro = pembrolizumab; R = lenalidomide; t = thalidomide; V = bortezomib.

Results of Sensitivity Analysis for NDMM

The NMA results of the scenario analyses are presented in Appendix 4. As discussed in the methods section, these scenarios have been designed to assess the sensitivity of the NMA results to the true estimates and address potential uncertainties due to risk of bias or other limitations.

In scenario 1 (Figure 6) where indirect evidence has been removed, the top 3 most favourable regimens as compared to lenalidomide-dexamethasone (RD) were: daratumumab-bortezomib-melphalan-prednisone (DaraVMP, HR: 0.47 95%; CrI, 0.18 to 1.30); daratumumab-lenalidomide-dexamethasone (DaraRD,HR:0.53; 95% CrI, 0.31 to 0.91) and bortezomib-melphalan-prednisone-thalidomide (VMPT, HR: 0.65 95; CrI, 0.25 to 1.70). However, the credible interval of these results has widened in this scenario, resulting in greater uncertainties and with some no longer excluding the null.

In scenario 2 (Figure 7) where RCTs judged to be at high risk of bias were excluded, the top 3 most favourable regimens were: daratumumab-bortezomib-melphalan-prednisone (DaraVMP, HR: 0.38 95% CrI, 0.13 to 1.00), bortezomib-melphalan-prednisone-thalidomide (VMPT,HR 0.52 95% CrI, 0.19 to 1.40), daratumumab-lenalidomide-dexamethasone (DaraRD, HR: 0.53; 95% CrI, 0.28 to 1.00). Again, the credible intervals of these results have widened, with greater uncertainties.

In scenario 3 (Figure 8) where RCTs were excluded if they were at high risk of bias or had concerns in at least 1 domain, the favourable regimens were daratumumab-bortezomib-melphalan-prednisone (DaraVMP, HR: 0.42; 95% CrI, 0.16 to 1.10), daratumumab-lenalidomide-dexamethasone (DaraRD, HR: 0.53; 95% CI, 0.30 to 0.94) and bortezomib-melphalan-prednisone-thalidomide (VMPT, HR: 0.58; 95% CrI, 0.22 to 1.50).

In scenario 4 (Figure 9) where RCTs were excluded if they included relapse or death as PFS event or did not report which events were incorporated in the definition of PFS, the 3 favourable regimens were daratumumab-bortezomib-melphalan-prednisone (DaraVMP, HR 0.44; 95% CI, 0.05 to 3.60), daratumumab-lenalidomide-dexamethasone (DaraRD, HR: 0.53; 95% CrI, 0.16 to 1.80) and ixazomib-lenalidomide-dexamethasone (IxaRD, HR: 0.83; 95% CrI, 0.24 to 2.80).

In scenario 5 (Figure 10) where RCTs were excluded if relapse was included event as PFS and / or excluded death as PFS event, the 3 favourable regimens were daratumumab-bortezomib-melphalan-prednisone (DaraVMP, HR: 0.39; 95% CrI, 0.10 to 1.50), daratumumab-lenalidomide-dexamethasone (DaraRD, HR: 0.53; 95% CrI, 0.24 to 1.20) and ixazomib-lenalidomide-dexamethasone (IxaRD, HR: 0.83; 95% CrI, 0.37 to 1.90).

It appears that in all 5 scenarios, both daratumumab-bortezomib-melphalan-prednisone (DaraVMP) and daratumumab-lenalidomide-dexamethasone (DaraRD) have been consistently ranked as 2 of the top 3 drug regimens when compared to lenalidomide (RD). However given widened with greater uncertainties, these results should be interpreted with caution.

The exclusion of RCTs based on the risk-of-bias assessment (scenarios 2 and 3) and the exclusion of RCTs based on the definition of PFS (scenarios 4 and 5) had only minor impact on the NMA results. In contrast, the exclusion of some indirect evidence based on expert opinion had a substantial impact (scenario 1). This scenario was used in the economic analysis based on feedback from the clinical experts.

Research Question 2: Relapsed and/or Refractory Multiple Myeloma

For the r/r MM population, the NMA conducted was based on the findings of HRs of PFS of the clinical review for r/r MM. Two separate networks were identified. One network (network A) consisted of 13 treatments informed by 13 studies, while the other (network B) consisted of 18 treatments informed by 18 studies (Table 7). There was no overlap between the 2 networks because none of the identified treatments in network A were present in a similar form in network B. Therefore, assumptions were necessary to create a connected network for r/r MM (Figure 4) and to facilitate a comparison of all currently relevant regimens. Assuming that the efficacy of bortezomib monotherapy (V) was equal to the efficacy of bortezomib/dexamethasone (VD) was considered reasonable, according to the clinical experts and a previous NMA in r/r MM.[12] However, it should be noted that this assumption is still being debated.[80,81] For example, Dimopolous et al.[81] stated that VD is likely to offer greater efficacy (in terms of response and delayed progression)

compared to D. Therefore, our assumption may potentially underestimate the relative effectiveness of the regimens in Network A compared to Network B.

Table 7: Separate Networks Including Regimens for r/r MM

Network	Regimens included in network
Network A	DaraVD, IsaKD with twice weekly K, KD with once weekly K, KD with twice weekly K, KDDara with twice weekly K, PanVD, PerVD, PomVD, SVD, TD, VCD, VD, and VeneVD
Network B	C, D, DaraPomD, DaraRD, ERD, IsaPomD, IxaRD, KRD with twice weekly K, MelD, ObliD, PembroPomD, PlitD, PomD, RD, T 200, T 400, T 100, and V

C = cyclophosphamide; D = dexamethasone; DaraPomD = daratumumab-pomalidomide-dexamethasone; DaraRD = daratumumab-lenalidomide-dexamethasone; DaraVD = daratumumab-bortezomib-dexamethasone; ERD = elotuzumab-lenalidomide-dexamethasone; IsaKD_twice weekly K = isatuximab-carfilzomib-dexamethasone with twice weekly of carfilzomib; IsaPomD = isatuximab-pomalidomide-dexamethasone; IxaRD = ixazomib-lenalidomide-dexamethasone; KD_once weekly_K = carfilzomib-dexamethasone with once weekly of carfilzomib; KD_twice_weekly_K = carfilzomib-dexamethasone with twice weekly of carfilzomib; KDDara_twice_weekly_K = carfilzomib-dexamethasone-daratumumab with twice weekly of carfilzomib; KRD_twice_weekly_K = carfilzomib-lenalidomide-dexamethasone with twice weekly of carfilzomib; MelD = melflufen-dexamethasone; ObliD = oblimersen sodium-dexamethasone; PanVD = panobonistat-bortezomib-dexamethasone; PembroPomD = pembrolizumab-pomalidomide-dexamethasone; PerVD = perifosine-bortezomib-dexamethasone; PlitD = plitidepsine-dexamethasone; PomD = pomalidomide-dexamethasone; PomVD = pomalidomide-bortezomib-dexamethasone; RD = lenalidomide-dexamethasone; SVD = selinexor-bortezomib-dexamethasone; T_100 = thalidomide 100 mg/day; T_200 = thalidomide 200mg/day; T_400 = thalidomide 400mg/day; TD = thalidomide-dexamethasone; V_or_VD = bortezomib or bortezomib-dexamethasone; V_plus_PLD = bortezomib plus pegylated liposomal doxorubicin; VCD = bortezomib-cyclophosphamide-dexamethasone; VeneVD = venetoclax-bortezomib-dexamethasone; VorV = vorinostat-bortezomib.

Figure 5 shows the NMA results of the base-case analysis. All regimens were ranked according to their estimated HR. The comparator was also lenalidomide-dexamethasone (RD).

Point estimates of effect (HR) showed a PFS benefit for 15 regimens, when compared with RD, with HRs ranging from 0.44 to 0.99; however, only 1 regimen (DaraRD, HR: 0.44; 95%, 0.28 to 0.70) was shown to have a statistically significant PFS benefit over RD. However, the following regimens also have broadly similar HRs when compared to RD: Isatuximab-carfilzomib-dexamethasone (IsaKd, HR: 0.44; 95%, 0.17 to 1.20), carfilzomib-dexamethasone-daratumumab (KdDara, HR: 0.49; 95% CrI, 0.20 to 1.20), daratumumb-bortezomib-dexamethasone (DaraVd, HR: 0.51; 95% CrI, 0.26 to 1.00)

Fifteen regimens were estimated to be less favourable when compared to lenalidomide-dexamethasone (RD) based on the point estimates of the NMA, and, in particular, results suggested that patients on dexamethasone (D, HR: 2.90; 95% CrI, 2.00 to 4.00) and oblimerson sodium-dexamethasone (OblinD, HR: 3.10; 95% CrI, 1.70 to 5.60) experienced decreased PFS benefit relative to patients on RD based on the 95% .

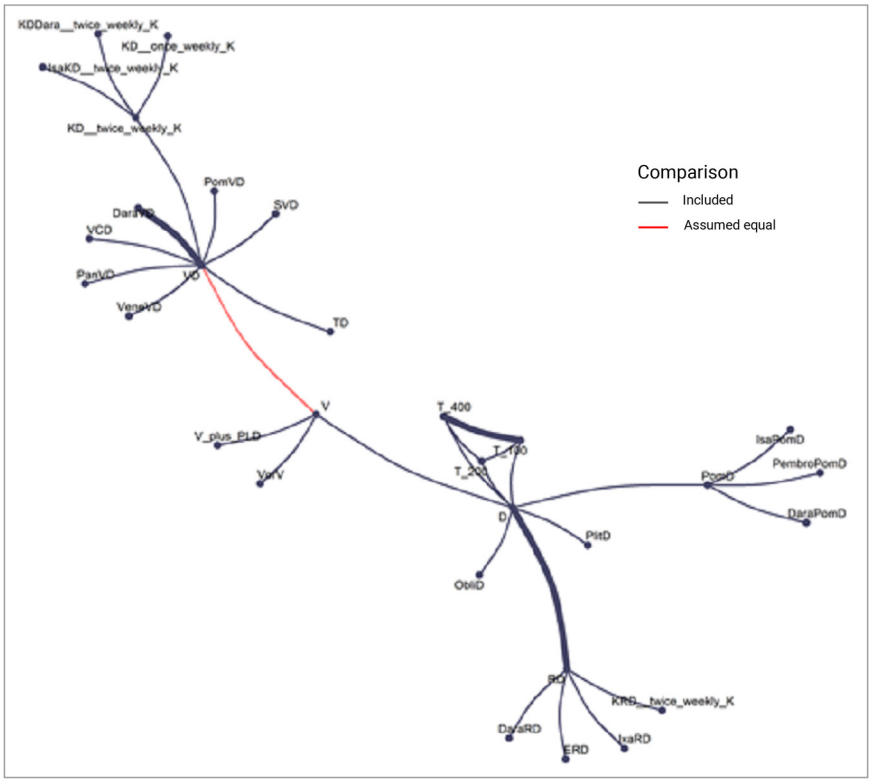
The NMA results of the scenario analyses are presented in Appendix 5. All scenarios had a large impact on the network. In scenarios 2 (Figure 11) and 5 (Figure 12), the pomalidomide/dexamethasone-based regimens had to be excluded because they were no longer connected. The RD-based regimens also had to be excluded in scenario 5. Consequently, a new comparator (dexamethasone) was required for this scenario. Scenarios 3 and 4 could not be conducted at all because the network was no longer connected.

As discussed previously that given the lack of data on AEs available from selected studies, an NMA could not be conducted to evaluate the comparative safety of these drug combinations.

Heterogeneity

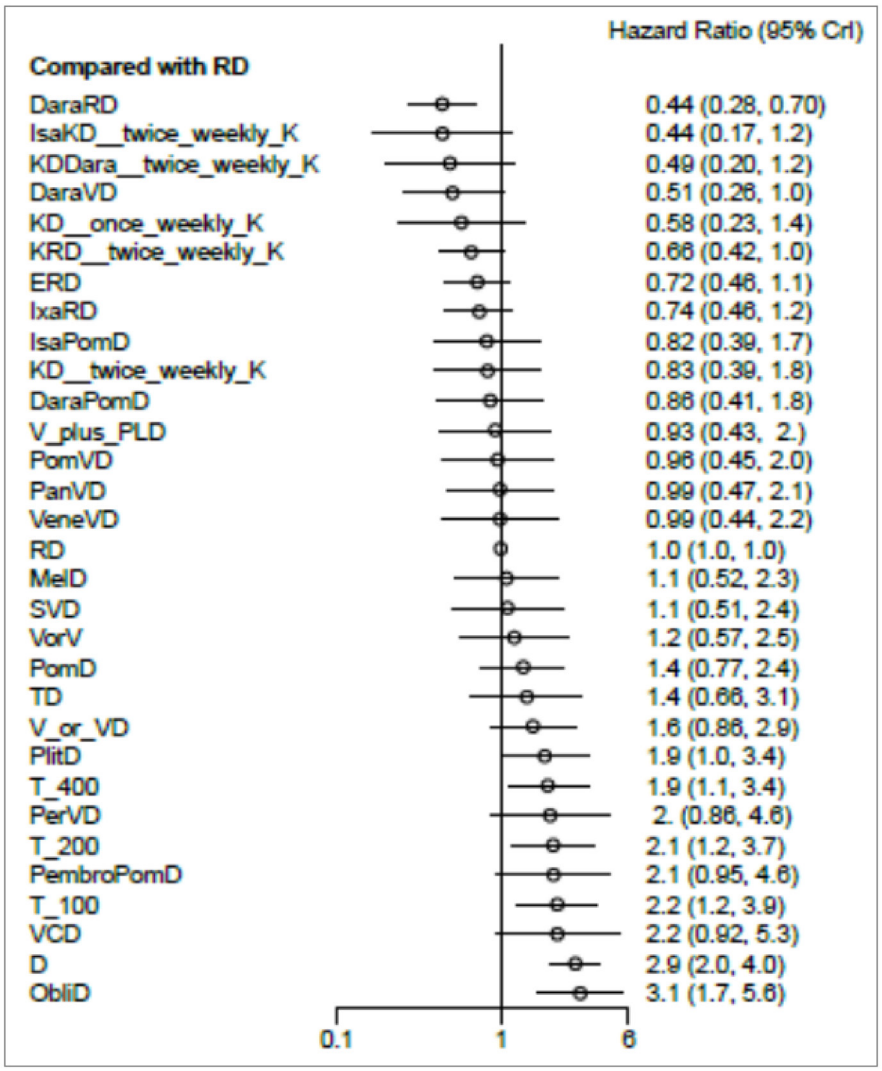
For all comparisons that were informed only by a single RCT, the HR obtained from the RCT equalled the HR obtained from the NMA. Only 1 comparison was informed by 2 RCTs:[69,70] RD versus D. Both RCTs comparing these regimens reported similar results. Therefore, the I^2 statistic was 0%. In addition, a very limited number of comparisons were informed by both direct and indirect evidence (Figure 4).

Figure 4: Network for r/r MM



D = dexamethasone; DaraPomD = daratumumab-pomalidomide-dexamethasone; DaraRD = daratumumab-lenalidomide-dexamethasone; DaraVD = daratumumab-bortezomib-dexamethasone; ERD = elotuzumab-lenalidomide-dexamethasone; IsaKD_twice weekly K = isatuximab-carfilzomib-dexamethasone with twice weekly of carfilzomib; IsaPomD = isatuximab-pomalidomide-dexamethasone; IxaRD = ixazomib-lenalidomide-dexamethasone; KD_once weekly_K = carfilzomib-dexamethasone with once weekly of carfilzomib; KD_twice_weekly_K = carfilzomib-dexamethasone with twice weekly of carfilzomib; KDDara_twice_weekly_K = carfilzomib-dexamethasone-daratumumab with twice weekly of carfilzomib; KRD_twice_weekly_K = carfilzomib-lenalidomide-dexamethasone with twice weekly of carfilzomib; MelD = melflufen-dexamethasone; ObliD = oblimersen sodium-dexamethasone; PanVD = panobonistat-bortezomib-dexamethasone; PembroPomD = pembrolizumab-pomalidomide-dexamethasone; PerVD = perifosine-bortezomib-dexamethasone; PlitD = plitidepsine-dexamethasone; PomD = pomalidomide-dexamethasone; PomVD = pomalidomide-bortezomib-dexamethasone; RD = lenalidomide-dexamethasone; SVD = selinexor-bortezomib-dexamethasone; T_100 = thalidomide 100 mg/day; T_200 = thalidomide 200mg/day; T_400 = thalidomide 400mg/day; TD = thalidomide-dexamethasone; V_or_VD = bortezomib or bortezomib-dexamethasone; V_plus_PLD = bortezomib plus pegylated liposomal doxorubicin; VCD = bortezomib-cyclophosphamide-dexamethasone; VeneVD = venetoclax-bortezomib-dexamethasone; VorV = vorinostat-bortezomib.

Figure 5: NMA Results of the Base-Case Analysis for r/r MM



D = dexamethasone; DaraPomD = daratumumab-pomalidomide-dexamethasone; DaraRD = daratumumab-lenalidomide-dexamethasone; DaraVD = daratumumab-bortezomib-dexamethasone; ERD = elotuzumab-lenalidomide-dexamethasone; IsaKD_twice weekly_K = isatuximab-carfilzomib-dexamethasone with twice weekly of carfilzomib; IsaPomD = isatuximab-pomalidomide-dexamethasone; IxaRD = ixazomib-lenalidomide-dexamethasone; KD_once weekly_K = carfilzomib-dexamethasone with once weekly of carfilzomib; KD_twice_weekly_K = carfilzomib-dexamethasone with twice weekly of carfilzomib; KDDara_twice_weekly_K = carfilzomib-dexamethasone-daratumumab with twice weekly of carfilzomib; KRD_twice_weekly_K = carfilzomib-lenalidomide-dexamethasone with twice weekly of carfilzomib; MelD = melflufen-dexamethasone; ObliD = oblimersen sodium-dexamethasone; PanVD = panobonistat-bortezomib-dexamethasone; PembroPomD = pembrolizumab-pomalidomide-dexamethasone; PerVD = perifosine-bortezomib-dexamethasone; PlitD = plitidepsine-dexamethasone; PomD = pomalidomide-dexamethasone; PomVD = pomalidomide-bortezomib-dexamethasone; RD = lenalidomide-dexamethasone; SVD = selinexor-bortezomib-dexamethasone; T_100 = thalidomide 100mg/day; T_200 = thalidomide 200mg/day; T_400 = thalidomide 400mg/day; TD = thalidomide-dexamethasone; V_or_VD = bortezomib or bortezomib-dexamethasone; V_plus_PLD = bortezomib plus pegylated liposomal doxorubicin; VCD = bortezomib-cyclophosphamide-dexamethasone; VeneVD = venetoclax-bortezomib-dexamethasone; VorV = vorinostat-bortezomib.

Results of the Sensitivity Analysis for r/r MM

The NMA results of the scenario analyses are presented in Appendix 5.

In scenario 2 (Figure 11) where RCTs that were judged to be at a high risk for bias were excluded, the top 3 regimens with lowest HRs for PFS as compared to lenalidomide-dexamethasone (RD) were: daratumumab-lenalidomide-dexamethasone (DaraRD, HR: 0.44; 95% CrI, 0.28 to 0.70); isatuximab-carfilzomib-dexamethasone (IsaKD, HR: 0.44; 95% CrI, 0.17 to 1.20) and carfilzomib-dexamethasone-daratumumab (KDDara, HR: 0.49; 95 CrI, 0.20 to 1.20).

In scenario 5 (Figure 12) where RCTs that included relapse as PFS event and / or excluded death as PFS event were excluded, the top 3 regimens were with lowest HRs for PFS as compared to lenalidomide-dexamethasone (RD) were: isatuximab-carfilzomib-dexamethasone (IsaKD, HR: 0.16; 95% CrI, 0.03 to 0.92), carfilzomib-dexamethasone-daratumumab (KDDara, HR: 0.17; 95% CrI, 0.03 to 0.99) and daratumumab-bortezomib-dexamethasone (DaraVD, HR: 0.18; 95% CrI, 0.05 to 0.63).

The results of the sensitivity analysis of these scenarios suggest that they had only a limited impact. Scenarios 3 and 4 could not be conducted because the network was no longer connected.

Health-Related Quality of Life

For HRQoL outcomes, there was a lack of usable data from the included RCTs. Hence, these findings were obtained through a review of CADTH Reimbursement Review Reports.

Of the 21 reviews conducted by CADTH, 15 included data on HRQoL; 4 in the NDMM population, and 11 in the r/r MM population.[22-30,33,34] A summary of characteristics of studies submitted to CADTH to support MM reviews that included data on HRQoL can be found in Table 8.

In the reviews of the NDMM population, the most commonly used HRQoL measure was the EORTC QLQ-C30 (4), and the EQ-5D (4), followed by the EORTC QLQ-MY20 (1), and FACT-Ntx (1).[22,23,30,34] In general, for reviews focusing on the NDMM population, the difference in HRQoL between treatment arms was evaluated, as well as the change from baseline to various time points based on cycle or month. The EORTC QLQ-C30 was used in all reviews in the newly diagnosed population. The mean baseline scores for the EORTC QLQ-C30 ranged from 49.6 to 56.9, and the reported change from baseline ranged from 1.5 to 11.3 points with the different treatments. Results for the EQ-5D were presented in 3 reviews for NDMM, however, the mean change in VAS results were only presented in 2 reviews, ranging from 3.7 to 10.1. The EORTC QLQ-MY20 was only included in the clinical guidance report of lenalidomide for MM,[30] in the newly diagnosed population, where results for change from baseline at 18 months were statistically significant for disease symptoms, but no statistically significant difference for side effects of treatment. Only 1 review included a trial that used the FACT-Ntx in the newly diagnosed population, presenting the change from baseline at 12 months, and the end of study.[34] Overall, interventions under review were generally favoured at earlier times of assessment compared to later times of assessment.

In the r/r MM population, the EORTC QLQ-C30 was the most frequently used HRQoL tool, used in the trials all reviews (11), followed by the EORTC QLQ-MY20 (10), the EQ-5D (7), and PGIS, QLQ-CIPN20, and FACT/GOG-Ntx (1 each).[24-29,33,37-40] Generally, HRQoL outcomes were exploratory, and subject to uncertainty due to low completion and compliance rates at later time points. Results of HRQoL in the r/r MM population were mostly reported for the EORTC QLQ-C30, particularly for Global Health Status, though reporting method

varied with some studies reporting between-group differences, and some reporting within-group differences for HRQoL measures. When reported, there was generally no clinically meaningful between-group differences in HRQoL for any measures evaluated.

Summary of Results

In this clinical review, the results from the NMA were only able to inform the comparative efficacy with PFS of different regimens used in NDMM and r/r MM. The data available were unable to inform on the comparative safety of these regimens. Analysis of subgroups of interest was also not feasible.

Research Question 1: Comparative Efficacy and Safety of Drug Combinations in Patients With Newly Diagnosed and Transplant-Ineligible Multiple Myeloma

For NDMM, 12 regimens trended toward having a favourable PFS when compared with RD (lenalidomide-dexamethasone), with HRs ranging from 0.38 to 0.99. The results for 2 regimens (i.e., DaraVMP and DaraRD) provided strong evidence to support a PFS benefit compared to RD based on the for the HR:

- daratumumab-bortezomib-melphalan-prednisone (DaraVMP, HR: 0.38; 95% CrI, 0.14 to 0.97),
- daratumumab-lenalidomide-dexamethasone (DaraRD, HR: 0.53; 95% CrI, 0.30 to 0.95).

Research Question 2: Comparative Efficacy and Safety of Drug Combinations in Patients With Relapsing-Refractory Multiple Myeloma

For r/r MM, 15 regimens trended toward having a favourable PFS when compared with RD, with HRs ranging from 0.44 to 0.99. The results for 1 regimen (i.e., DaraRD) provided strong evidence to support a PFS benefit compared to RD based on the for the HR:

- daratumumab-lenalidomide-dexamethasone (DaraRD; HR: 0.44; 95% CrI, 0.28 to 0.70).

Table 8: Summary of HRQoL Characteristics

Review	Year	Pivotal trial Name	Intervention	Comparator	HRQoL tools	HRQoL outcome	Time of Assessment
Newly Diagnosed MM							
Velcade (bortezomib)[34]	2013	Ludwig et al.,	VTD	VTDC	EORTC QLQ-C30, EQ-5D, FACT/ GOG-Ntx	CFB	Baseline, Day 1 of Cycle 2, 3, and 4
Revlimid (lenalidomide)[30]	2015	FIRST MM-015 E1A06	FIRST: Rd MM-015: MPL-L E1A06: MPL-L	FIRST: MPT MM-015: MPL-PBO, MP E1A06: MPT-T	EORTC QLQ-C30, QLQ-MY20, EQ-5D	Between-group difference, and CFB	Baseline, 12 months (E1A06), 64 weeks (MM-015), 18 months (FIRST), and end of treatment
Darzalex (daratumumab)[23]	2019	ALCYONE	DVMP	VMP	EORTC QLQ-C30, EQ-5D	Between-group difference, and CFB	Baseline, 3-, 6-, 9-, and 12 months during treatment, then every 6 months until progression
Darzalex (daratumumab) [22]	2020	MAIA	DRd	Rd	EORTC QLQ-C30, EQ-5D	Between-group difference, and CFB	Baseline, 3-, 6-, 9-, and 12 months during treatment, then every 6 months until progression
Relapsed and/or Refractory MM							
Pomalyst (pomalidomide) [28]	2014	MM-003	Pd	Dexamethasone	EORTC QLQ-C30, QLQ-MY20, EQ-5D	Between-group difference	Not reported
Kyprolis (carfilzomib) [25]	2016	ASPIRE	KRd	Rd	EORTC QLQ-C30, QLQ-MY20	Between-group difference, and CFB	Baseline, Day 1 of Cycle 3, 6, 12, and 18
Kyprolis (carfilzomib) [24]	2017	ENDEAVOUR	Kd	Vd	EORTC QLQ-C30, QLQ-MY20, FACT/ GOG-Ntx	Between-group difference, and CFB	Baseline, every 12 weeks until the end of treatment
Ninlaro (ixazomib) [26]	2017	TOURMALINE-MM1	ILd	Rd	EORTC QLQ-C30, QLQ-MY20	Between-group difference, and CFB	Not reported

Review	Year	Pivotal trial Name	Intervention	Comparator	HRQoL tools	HRQoL outcome	Time of Assessment
Ninlaro (ixazomib) [27]	2019	TOURMALINE-MM1	ILd	Rd	EORTC QLQ-C30, QLQ-MY20	Between-group difference, and CFB	Baseline, end of treatment
Pomalyst (pomalidomide)[29]	2019	OPTIMISMM	PVd	Vd	EORTC QLQ-C30, QLQ-MY20, EQ-5D	Between-group difference, and CFB	Baseline, Day 1 of every cycle, until treatment discontinuation
Sarclisa (isatuximab)[33]	2021	ICARIA-MM	IsaPD	Pd	EORTC QLQ-C30, QLQ-MY20, EQ-5D	Between-group difference (posthoc), and CFB	Baseline, and at each cycle
Idecabtagene Vicleucel (Abecma)[40]	2022	KarMMa	Idecabtagene vicleucel	NA	EORTC QLQ-C30, EQ-5D, EORTC QLQ-MY20	CFB	Baseline, months 1 through 9 and months 12 and 15
Sarclisa (isatuximab)[39]	2022	IKEMA	IKd	Kd	EORTC QLQ-C30, EQ-5D, EORTC QLQ-MY20	CFB	Baseline, Day 1 and 2 of each cycle until end of treatment
Selinexor (Xpovio)[38]	2022	BOSTON	SVd	Vd	EORTC QLQ-C30, EQ-5D, QLQ-CIPN20	Between-group difference	Baseline, and every cycle until end of treatment
Ciltacabtagene Autoleucel (Carvykti)[37]	2023	CARTITUDE-1	Ciltacabtagene autoleucel	NA	EORTC QLQ-C30, EQ-5D, EORTC QLQ-MY20, PGIS	CFB	Baseline to study day 100

CFB = change from baseline; DRd = daratumumab + lenalidomide + dexamethasone; DVMP = daratumumab + bortezomib + melphalan + prednisone; IKd = isatuximab + carfilzomib + dexamethasone; ILd = ixazomib + lenalidomide + dexamethasone; IsaPD = isatuximab + pomalidomide + dexamethasone; Kd = carfilzomib + dexamethasone; KRd = carfilzomib + lenalidomide + dexamethasone; MM = multiple myeloma; MPL = melphalan + prednisone + lenalidomide; MPL-L = melphalan + prednisone + lenalidomide with lenalidomide maintenance; MPT = melphalan + prednisone + thalidomide; MPT-t = melphalan + prednisone + thalidomide with thalidomide maintenance; NA = not applicable; PBO = placebo; Pd = pomalidomide + dexamethasone; PVd = pomalidomide + bortezomib + dexamethasone; Rd = lenalidomide + dexamethasone; SVd = selinexor + bortezomib + dexamethasone; Vd = bortezomib + dexamethasone; VTD = bortezomib + thalidomide + dexamethasone; VTDC = bortezomib + thalidomide + dexamethasone + cyclophosphamide.

Source: CADTH Clinical Guidance Reports for Multiple Myeloma.[22-30,33,34,37-40]

Limitations

One limitation of note is that based on the calculation of I^2, the test of heterogeneity for the base-case analysis of NDMM was 74%, which is interpreted to indicate strong heterogeneity. The I^2 for scenario 1 of the sensitivity analysis was calculated to be 31% and this scenario will be used for the economic analysis. For r/r MM, the I^2 was calculated to be 0%. Discrepancies in the level of heterogeneity detected in the NDMM network compared to the r/r MM network is likely due to the sparse network structure where the majority of comparisons in the network rely on evidence from a single RCT. In this situation, estimates of heterogeneity are often unstable and formal tests for heterogeneity are underpowered. However, descriptive assessments of heterogeneity through comparisons of baseline characteristics for potential effect modifiers to the network suggest that heterogeneity is likely present across the network which likely influence model estimates.

In addition, an assessment of proportional hazard across the network was not performed. Thus, the validity of the results reported by each NMA relies on the proportional hazards assumption across studies included in the network and the appropriateness of this assumption is unclear.

Health-Related Quality of Life

This outcome was informed by a review of CADTH reimbursement reports between January 2013 and June 2023. It was found that for both NDMM and r/r MM, the most commonly used HRQoL measure was the EORTC QLQ-C30. Overall, interventions reviewed for NDMM were generally positive for HRQoL outcome at earlier times of assessment compared to later times of assessment. For r/r MM, the reporting of this outcome varied in the methods of reporting. When reported, there was generally no clinically meaningful between-group differences in HRQoL for any measures evaluated.

Discussion

From this clinical review, it appears that the addition of daratumumab to the base-case comparator RD regimen (e.g., daratumumab-lenalidomide-dexamethasone, DaraRD) has consistently demonstrated improved HRs for PFS based on the NMA results for both NDMM and r/r MM. However, these results should be interpreted with caution, given the data were heterogeneous across studies, especially for the NDMM base-case analysis as the interpretation of these results depends on appropriateness of the proportional hazards assumption which has not been validated. It is recognized that patient characteristics such as the median age, cytogenetic risk status, and ECOG performance status are variable and inconsistent across the included studies. The characteristics of included studies also varied greatly with some being open label, many with multiple treatment arms as well as the difference in primary outcome measures and variable sample size range (e.g., 1 RCT with 115 patients[54] vs another RCT with 1,852 patients[82]). The median length of follow-up also vary greatly, with potential impact on PFS estimates where longer follow-up may lead to more favourable PFS estimates. For example, in CASTOR[83] where daratumumab-bortezomib-dexamethasone (DVd) was compared to bortezomib-dexamethasone (Vd), the duration of treatment with Vd was capped at 8 cycles, whereas in ENDEAVOUR,[67] where carfilzomib-dexamethasone (Kd) was compared to Vd, patients received Vd until disease progression or unacceptable toxicity, and more than 50% of the patients who

were treated with Vd received it for more than 6 months. In the OPTIMISMM[14] trial, which compared PomVd to Vd, patients received Vd until disease progression or unacceptable toxicity, however, the frequency of administration of Vd was reduced after cycle 8. In the r/r MM setting, the POLLUX[84] trial did not require patients to have prior exposure to lenalidomide. There were also inconsistencies in how many prior lines of therapies were required in some studies, which also resulted in patient characteristics being different in terms of their exposure to lenalidomide as well as whether they have been heavily pretreated before study enrolment.

Based on the current understanding of the pathophysiology of MM, these NMA results are consistent with the importance of multitarget approach in treating MM. In MM, there are various treatment classes with different mechanisms of action; including: IMiDs such as pomalidomide, lenalidomide and thalidomide which bind to an E3 ubiquitin ligase complex with cereblon and causing proteasome degradation of disease-related proteins; proteasome inhibitors (PIs) such as bortezomib, ixazomib, and carfilzomib inhibit the 20S proteasome, thereby also destroying disease-related proteins in MM; alkylating agents such as melphalan and cyclophosphamide work by inhibiting the transcription of DNA into RNA and stopping protein synthesis and causing cellular death; and glucocorticoid such as prednisone and dexamethasone repress target genes that are important in MM pathogenesis. There are also CD38 monoclonal antibodies (antiCD38) such as daratumumab and isatuximab that work by targeting and destroying CD38 expressed on all myeloma cells. Newer therapies also include selective inhibitors of nuclear export such as selinexor or chimeric antigen receptor (CAR) T-cells, such as idecabtagene vicleucel.[10]

The NMA results suggest that with a base comparator as lenalidomide-dexamethasone, adding a monoclonal antibody therapy that targets CD38 appears to improve treatment response, particularly with daratumumab. This appears to be applicable for transplant-ineligible patients with MM, both NDMM and r/r MM. Based on the NMA results, treating with monotherapy, specifically with dexamethasone may be suboptimal. As there are limitations in this study, the results should be further evaluated.

While the NMA could not be done on the safety evaluation as well as analyses of subgroups of interest such as patients aged 75 years or older, patients with high risk cytogenetics, and patients with an ECOG performance status of 2 or more, these areas will be further investigated through the use of real-world data as part of the economic analysis. In addition, the perspectives and experiences review have also highlighted the treatment burden in MM and how it has affected the patients' quality of life, including the experiences with the disease itself as well as the side effects of the treatment regimens.

Further, the clinical experts providing input on this CADTH review noted that Rd (lenalidomide-dexamethasone) may not be a relevant comparator from a clinical perspective as the current standard of care has evolved since the initiation of this study. The clinical experts highlighted that the front-line regimens for transplant-ineligible MM include lenalidomide-bortezomib-dexamethasone (RVd) or daratumumab-lenalidomide-dexamethasone (DRd). This is also reflected in the latest international clinical practice guidelines.[85] The relative effect of each treatment option versus RVd, DRd, and all other comparators are provided in Figure 14 (for NDMM) and in Figure 15 (for r/r MM) in Appendix 8.

For r/r MM, 1 of the main limitations is that the included studies did not differentiate whether patients received transplant in prior lines of treatment. This limitation can introduce bias as transplant eligibility status at diagnosis is a predictor of outcome in the treatment of relapsed disease.

In addition, subsequent treatment sequences in r/r MM must consider treatment effect including previous exposure to lenalidomide or refractory to lenalidomide therapy. Given this NMA did not conduct any sensitivity analyses to determine the treatment effect for patients who would be lenalidomide-exposed or refractory, these points are all acknowledged as limitations for this study.

In the economic analysis, the model has included 17 treatment sequences; of these, 3 sequences have used RVd as first-line regimen and 4 sequences have used DRd as first-line regimen. These results will be able to model treatment sequences reflective of current standard of care. Further these 17 treatment sequences have been carefully discussed to ensure they represent current clinical scenarios by incorporating different scenarios including being treatment refractory to previous treatments. In addition, the economic analysis has also incorporated real-world data by using survival data provided by Canadian Myeloma Research Group (CMRG) as comparison in the analysis.

Conclusions

Based on the NMA results from the clinical review, the following treatment regimens were found to be more favourable than the base comparator with RD (lenalidomide-dexamethasone) in transplant-ineligible MM. In NDMM, both DaraVMP (daratumumab-bortezomib-melphalan-prednisone) and DaraRD (daratumumab-lenalidomide-dexamethasone) have statistically significant differences of PFS when compared to RD. In r/r MM, DaraRD (daratumumab-lenalidomide-dexamethasone) was statistically significantly different in PFS when compared to RD. These results suggest that adding daratumumab in a regimen for NDMM or r/r MM appears to offer PFS benefits. Due to various limitations of the analysis, such evidence should be interpreted with caution and further studies to validate the results would be recommended.

Perspectives and Experiences Review

This section addresses the following research question: What are the perspectives and experiences of patients with newly diagnosed and transplant-ineligible or r/r MM on expectations of treatment, treatment decision-making, experiences of treatment, and barriers to accessing or receiving treatment across the course of their cancer?

Patient Input

Information Gathering

Myeloma Canada has existed for over 15 years to support the growing number of Canadians diagnosed with myeloma each year, and those living longer than ever with the disease through access to new and innovative therapies. Myeloma Canada has collected data on the impact of myeloma and its treatments on patients and caregivers by conducting surveys, and regularly contributes patient group input to CADTH.

In April and May 2021, Myeloma Canada circulated a survey by email and social media to the MM patient community in Canada. The survey received 555 responses, including 107 patients living with myeloma who were ineligible for a stem cell transplant. Advanced age was the most frequent response as to why they had not received a transplant.

Additionally, Myeloma Canada collated the results of 6 previous surveys circulated to provide input to drugs entering CADTH's Reimbursement Reviews:

- carfilzomib (2016, 344 respondents)
- daratumumab administered by a subcutaneous injection (2020, 247 respondents)
- daratumumab with lenalidomide and dexamethasone (2019, 216 respondents)
- idecabtagene vicleucel (2021, 388 respondents)
- isatuximab with pomalidomide and dexamethasone (2020, 375 respondents)
- pomalidomide with bortezomib and dexamethasone (2019, 174 respondents)
- refer to the original input provided by Myeloma Canada.

Results

Experiences Living With MM

Many individuals who have MM will experience loss of autonomy and independence. The severity of their condition might mean that they require a caregiver or family member to assist them in completing day-to-day life tasks. Importantly, this affects their ability to work, exercise, and travel, which are key concerns reported by patients. These concerns may also be exacerbated by the additional restrictions imposed on severely immunocompromised patients because of COVID-19.

Patient Expectations and Preferences With Treatment

Dynamism of Disease and of Treatment

MM oscillates between periods of disease dormancy (remission) and periods of cancer growth (relapse) which require treatment. The process of finding a "right treatment" to curb disease progression, is constant as the "right treatment" for any single case of myeloma is always changing.

Managing Disease Symptoms With Minimal Treatment Side Effects

When weighing treatment options, patients are looking for a treatment that will limit myeloma growth and symptoms without imposing side effects intolerable to the point that they are detrimental to their quality of life. As described by 1 person, "treatment that allows some quality of life, not just existing" and by another as "treatments that are not too difficult with side effects, so I may retain my lifestyle and mobility."

Therefore, a good quality of life means striking a balance between manageable myeloma symptoms and minimal treatment side effects. As such, patients report that the risk of infection due to immunodeficiency caused by the disease and due to treatment regimens, is a key concern, along with fatigue, pain, and mobility. Shortness of breath, confusion, neuropathy, nausea, stomach issues, and insomnia are also troublesome side effects that patients want to avoid.

Administering Treatment in the Least Invasive Way

Transplant-ineligible MM patients receive treatment through 3 main routes of administration: orally, subcutaneous injection, and by IV transfusion. Because treatments delivered orally are self-administered, they require fewer hospital trips. This reduces the burden placed on patients, especially those who live in rural or remote areas that need to travel further to receive treatment. Conversely, IV infusions are the least desirable route of administration for most patients because they demand considerably more time and involve out-of-pocket expenses (e.g., travel, parking). As described by 1 person, "much easier to plan a day around a 5-minute injection than 7 hours of IV."

Lessening Financial Implications

Coverage of drug costs is the most widely reported financial impact on patients and it varies from 1 person to the next, based in part, on where they live. Whether a treatment will be covered by provincial and territorial and private health care plans is a consideration for most patients. Additional costs involved include maintenance therapy and expenses involved in travelling to receive treatment. The frequency of these visits differs, but patients report weekly or monthly trips most often.

Offering a Holistic Approach to Choosing Treatment

The response to treatment is different for each patient and for each, a treatment that does not work initially, might be effective as their disease evolves. Finding a right treatment to curb disease progression is an unrelenting exercise.

For this reason, patients' conversations with their health care providers must extend beyond the effectiveness of a therapy, to include the impact it will have on patients' emotional, mental, physical, and intellectual selves. And this may vary and need to be reevaluated at different stages in their lives and different stages in their treatment journey.

Patients also express a desire for mental health-related side effects of MM and its treatments, such as anxiety and depression, to be openly discussed with their prescribing physician, and for support to be offered.

Qualitative Evidence Synthesis

Study Design

A rapid qualitative evidence synthesis was conducted. Primary qualitative studies were synthesized using a framework approach.[86] The review objective was to understand and describe patients' experiences with and perspectives around the treatment of transplant-ineligible and r/r MM.

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, CINAHL and Scopus. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was MM. CADTH-developed search filters were applied to limit retrieval to qualitative studies. Where possible, retrieval

was limited to the human population. The search was also limited to English-language documents published between January 1, 2016 and May 31, 2021.

An update search was conducted on July 6, 2023 to capture any articles published or made available since the initial search date.

Selection Criteria

Selected publications were primary English-language qualitative studies or the qualitative component of mixed method studies. For the purpose of this review, qualitative studies or qualitative components are those that use both qualitative data collection methods (e.g., documents, interviews, or participant observation) and qualitative data analysis methods (e.g., constant comparative method, content analysis). Studies that only used surveys as a method of data collection were excluded.

Studies with multiple publications using the same dataset were included if they report on distinct research questions. Table 9 describes the selection criteria used, built using the Sample, Phenomenon of Interest, Design, Evaluation, Research (SPIDER) criteria for framing qualitative evidence synthesis research questions.[86] Studies with a mixed sample (i.e., transplant eligible and NDMM, transplant eligible MM, and the sample of interest) were included so long as they did include participants from the sample of interest. Studies that included patient and health care provider and/or family carers were included but only direct patient participant accounts were used in the analysis.

Table 9: Inclusion Criteria for Qualitative Evidence Synthesis

Sample	Phenomenon of interest	Design	Evaluation	Research type
People living with newly diagnosed transplant-ineligible or relapsed and/or refractory MM	Treatment of newly diagnosed transplant-ineligible or relapsed and/or refractory MM	Any qualitative design	• Expectations of treatment • Decision-making around treatment • Experiences with treatment • Barriers to accessing or receiving treatment	Primary qualitative studies or the qualitative component of mixed method studies (excludes surveys)

MM = multiple myeloma.

Screening and Selecting Studies for Inclusion

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 9. Publications were excluded if they did not meet the selection criteria outlined in Table 9, they were duplicate publications reporting on the same data and same findings, or were published before 2016.

Data Extraction

One reviewer extracted data describing study and participants characteristics for each included publication using a priori developed electronic data extraction forms. Data extraction forms were built a priori to capture key study and participant characteristics and are reported in Table 14 in Appendix 10 and are summarized narratively.

Critical Appraisal

The critical appraisal was conducted by the primary reviewer who followed Krefting's[87] approach for assessing trustworthiness in qualitative research. The trustworthiness of the study results was evaluated by asking questions around how the research methods shaped how the research team arrived at their findings or results. This was done with a particular focus on 4 guiding questions: Were the study authors true to their participants (credibility)? Does the analysis make sense in light of the data presented (confirmability)? Is the analysis consistent across study findings (dependability)? Is the analysis relevant to the research question of this review (transferability)?[87] Results of the critical appraisal were used to understand the methodological and conceptual limitations of the included publications in specific relation to the research questions. The results of the critical appraisal are reported narratively and general notes on trustworthiness and transferability (i.e., high, moderate, low) are reported on in Table 14 in Appendix 10.

Data Analysis

Descriptive Analysis

A descriptive analysis of study characteristics was conducted. The results are presented in tabular form and are accompanied by a narrative summary. The purpose of the descriptive analysis was to describe the set of included studies and understand the range of types of programs, participants, methods, and data that informed the synthesis.

Data Synthesis

A framework synthesis was used to organize and analyze results of the included studies.[88] The a priori framework consisted of concepts from project scoping and the research question. These included expectations of treatment, decision-making around treatment, experiences with treatment, and barriers to accessing or receiving treatment. The type of MM, the duration of illness and the number of relapses were considered when conducting the analysis.

One reviewer conducted the analysis. Included primary studies were read and re-read to identify key findings and concepts that mapped on the a priori framework. Analytic memos were made which noted details and observations about the study's methodology, findings, and interpretations, and connections to other studies and concepts in the framework. Mind mapping techniques were used to explore how emerging concepts mapped across study findings and across concepts,[89] and the initial framework was modified as new concepts emerged from the preliminary analysis. Using these techniques, concepts were re-ordered and organized into thematic categories. Rereading, memoing, and diagramming continued until themes were appropriately described and supported by data from the included publications. During the analysis, issues with transferability and the results of the critical appraisal were considered to aid with interpretation.

Once the analysis was stable (i.e., that further rereading of memos and primary studies was not leading to changes in structure or description of findings), data triangulation with relevant qualitative evidence syntheses and patient input was done to strengthen the credibility and dependability of this review's findings.[90] The objective of the analysis was to identify and describe thematic categories that offer insight

into the experiences with and perspectives on the treatment of MM from the perspectives of patients with newly diagnosed and transplant-ineligible and r/r disease.

Reflexivity

Reflexivity is an epistemological principle and approach in qualitative research that recognizes the role of the researcher as an instrument.[91] Reflexive practices and techniques are those that allow for and facilitate making researcher's observations and interpretations transparent and explicit versus implicit and unacknowledged. This study employed the reflexive practices of memoing and dialogue between the qualitative reviewer and other members of the health technology assessment (HTA) team to probe and position reviewers in relation to the analysis. Further, the qualitative reviewer explored additional empirical sources (e.g., published qualitative reviews) and patient engagement activities to identify possible alternate concepts, connections and interpretations within the preliminary findings and data.

Results

Quantity of Research Available

A total of 696 citations were identified in the literature search. Following screening of titles and abstracts, 672 citations were excluded and 24 potentially relevant reports from the electronic search were retrieved for full-text review. Of these potentially relevant articles, 14 publications were excluded, and 10 primary qualitative studies met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA[92] flow chart of the study selection.

Descriptive Analysis of Study and Participant Characteristics

Additional details regarding the characteristics of included publications and their participants are provided in Appendix 10.

Study Design, Data Collection, and Data Analysis

Four primary studies were of a qualitative descriptive design.[93-96] Four studies did not report or describe the study design used.[97-100] One was a phenomenological study,[101] and another was a descriptive exploratory study.[102]

Four primary studies collected data using semistructured interviews.[93,97,99,101] One used in-depth interviews,[96] and another used unstructured interviews to collect data.[98] Two studies used focus groups.[94,102] One study used both in-depth interviews and focus groups,[95] and another used semistructured interviews, questionnaires, verbal rating scales and patient-completed graphic diagrams to collect data.[100]

Two primary studies used content analysis,[93,97] 2 studies used thematic content analysis,[99,102] 2 studies used thematic analysis,[94,96] and 1 each used a phenomenological approach,[101] Colizzi's descriptive framework[98] and a blended approach using aspects of qualitative description and grounded theory[95] One study did not report or describe the data analysis method.[100]

Country of Origin

Three studies were conducted in Ireland.[94,96,98] Two studies were conducted in the US[93,97] and 2 studies were conducted in Australia.[101,102]

One study each was conducted in Germany,[99] Canada,[95] and France.[100]

Study Participants

Eight studies included adult patients,[94-99,101,102] and 2 studies included adult patients and their health care providers.[93,100] Two primary studies included patients who had transplant-ineligible NDMM and r/r MM.[97,101] Three studies included patients with relapsed MM.[94,96,100] One study included patients with r/r MM who had 2 or more relapses and had been treated with either bortezomib and/or carfilzomib and either lenalidomide, pomalidomide, or thalidomide or any combination of these 3.[95]

Three studies included patients living with MM not further specified,[93,99,102] and 1 study included patients living with MM for over a year.[98]

Summary of Critical Appraisal

Overall, the set of included primary studies was judged to be of low to moderate in terms of their trustworthiness. Of the included studies, 3 were assessed as low trustworthiness,[97,99,100] 5 as moderately trustworthy,[94-96,98,101] and 2 as highly trustworthy.[93,102]

The primary studies assessed as low quality typically did not have reported methods to ensure the collection of rich data or document an analytic approach that was with the principles and practices of qualitative methodologies.[97,99,100] The studies that were assessed as being of moderate quality frequently had findings that were not fully or richly described, and/or were not entirely supported by data or the connections between themes and subthemes not consistently well-described. The 2 studies assessed as high quality had detailed description of methods and of findings that were consistently well-described and supported by data.[93,102]

Of the included primary studies, 4 were judged to be highly transferable as they had samples, settings, and research questions relating to phenomena of interest that were relevant to this review.[94,95,98,101] Three studies were assessed to be of low transferability due to issues with trustworthiness[97,99] or lack of patient-focused findings or data.[96] Two studies were assessed to be of moderate transferability, 1 due to issues in trustworthiness[100] and 2 due to a nonrelevant population in the sample.[93,102]

Data Synthesis

Experiences with Treatment

Symptoms and Related Impact on Patients' Lives

Participants reported that, in many cases, they did not know whether to attribute their symptoms to their treatment or their disease[97,101] with some exceptions, most notably steroids. Fatigue, peripheral neuropathy, risk of infection (due to low blood cell count), diarrhea were all raised as symptoms that patients struggled with in their daily life.

Fatigue was experienced as profound low energy, which left participants unable to do activities of daily living, for example cooking, as well as those activities that gave them meaning and pleasure.[93-95,97,98,101,102] As 1 participant described: "I was very, very tired. Sometimes, I'd sit in my armchair for 5 to 10 minutes and have a short nap, and then I feel better. But I am always very tired, all day long. I can no longer work around the house as I used to, do what I used to do – it's fatigue, physical, and I can no longer do much" (p. e4).[97]

Peripheral neuropathy was described as painful but also difficult in that it affected balance, mobility, and fine motor skills.[93-95,97,98,101,102] Patients feared they would trip over things or not be able to move as intended. This affected patients' ability to move about their homes and also affected their daily functioning.[95,102] For some, this meant that they could no longer drive or walk, reducing their independent ability to leave their home: "I couldn't even get toothpaste out of a tube, it affected my strength in my hands and feet. I was driving along one day, and I couldn't feel the controls, the pedals, so, I've given up driving, which, again, is a very frustrating thing to do" (p. 10).[102]

The risk of infection due to neutropenia was a source of worry for patients, who sought to avoid it by reducing their social activities and outings.[93,95,97,98] This was also the aspect of the disease patients wanted most controlled according to input provided by Myeloma Canada. Like other symptoms, this affected patients ability to engage with their family and friends and do the activities that gave them pleasure: "My main problem with that was that because of it dropping my blood counts, my platelets, and neutrophil so low, I had to really think about where I wanted to go and what I wanted to do and I was really totally kind of [giving] up things that I love" (p. 155).[93] Patients reported at times they were left feeling isolated from their own family and unable to visit with their grandchildren.[95]

Diarrhea affected participants' diets, their ability to sleep and be rested, and its unpredictability meant that they often chose not to go out or only did so with additional planning.[93,95,98] Managing diarrhea required managing their diets and planning social activities to account for potential urgency. As 1 participant described it, "I have to think of the nearby facilities before I go out. You know, the diarrhea from the medications can catch you out sometimes, it just comes on so quick" (p. 106).[98] Others chose to not go out at all: "I just want to go to church and everything. I miss my fellow members and everything, but I just, I'm just afraid to go then... like I said, with this diarrhea and everything, I didn't want to go and have a... you know... I don't want to be embarrassed" (p. 155).[93]

Pain, particularly bone pain, and the worry about fractures, meant that participants had reduced ability to engage in sports and leisure activities they once enjoyed.[93,97,101] It also affected their social roles, for example, 1 grandparent described: "I can't mind my grandchildren now due to my back [pain]. I can't lift of carry them."

The 1 area where patients seemed able to make a clear link between symptoms and treatment was the use of steroids. Participants found the effects of steroids – the swings in mood, energy, sleep disturbance, and the irritability that came with it added to the instability in their life.[94,95,98,101] Its emotional impact was profound for some: "My emotions broke down when I started the steroids, I had to see the psych oncology team because I just couldn't cope" (p. 106). [98]

Taken together, patients reported that their symptoms had huge impact on multiple dimensions of their lives.[93,97,98,101] This impact was social, in their ability to fulfill their roles (e.g., as a worker, as a grandparent) and ability to socialize with friends, family, and community.[95,97,98] In both the literature and patient input submitted to CADTH, physically, fatigue, peripheral neuropathy, risk of infection, diarrhea, and pain affect affected their ability to move and made it difficult to leave their homes, to do activities that gave them meaning or pleasure, or even routine activities of daily living.[93,97,98,101] The inability to do things as they used to and the activities that they enjoyed affected them emotionally, even as patients described a variety of coping

strategies to adjust to their new normal.[93,95,98,100-102] This was reflected in the input received by Myeloma Canada as well. Individuals reported experiencing loss of autonomy and independence. Depending on the severity of their condition, some require a caregiver or family member to assist them in completing day-to-day tasks. Importantly, this affects their ability to work, exercise, and travel, which are key concerns reported by patients. These concerns may also be exacerbated by the additional restrictions imposed on severely immunocompromised patients because of COVID-19.

Living with a noncurable condition meant participants were always engaged in the management of their condition, physically and emotionally.[95] Patients described how living with r/r MM was experienced as work that included developing emotional coping strategies, continually adjusting expectations about what activities they could engage in, and lifestyle behaviours such as diet and exercise to maintain their health as best as they could.[95,98,101] In light of constant need for treatment while living with a noncurable disease, patients described that they desired to live a normal life and carry out normal or typical activities, even if these needed to be adjusted.[95]

Expectations of and Decision-Making Around Treatment

Hoping for Remission and Waiting for Relapse

Remission was valued for the time it enabled patients to be with family and friends and for offering the ability to live a more normal life.[95,100,102] In other words, remission was a time when patients felt their lives had returned to some form of normalcy, in part because they were no longer occupied with treatment requiring frequent visits with health care providers.[95,100,102] However, patients described their perspectives and experiences of remission often in light of its relapse and further treatment. One patient described how: "I just felt that I need to put my life on hold again; my life revolved around the 6-weekly visit to the hospital" (p. 79).[100]

Relapse was described as having the effect of putting their lives on hold,[100] highlighting how it disrupted their ability to live their lives in ways that felt normal or natural to them. They recounted that living with a condition that entailed multiple relapses meant a life of emotional ups and downs:[95,98]

"You're on a drug and it works, and then you relapse and go into remission and then relapse again. The emotional roller-coaster is so hard... Was told before Christmas I only had a few months to live. Mentally, I was ready to die and then the numbers went down again on the drug I'm on now... so I've had to readjust my thinking. So hard to get my head around it, my funeral was arranged and everything. It's so different to other cancers as there's not as many remissions/relapses. That's what (sic) so had to adjust to" (p. 107).[98]

Patients varied in their emotional responses to each individual relapse. Some, as experienced patients, felt prepared to undergo what laid ahead of them: "The first relapse, I didn't take as good as I did the second one. I just thought 'Oh, I've got to go through all that again'... I was more able to cope the second time round; both physically and emotionally" (p. 79).[100] Others found the prospect of more treatment devastating, particularly when they felt treatment options were becoming less and less, or the symptoms were more debilitating with subsequent relapses.[98,100,102] One patient put it succinctly: "There is this darker force there now. I'm anxious

that I'm running out of time, or that the combination of drugs won't work anymore. I'm afraid to look ahead" (p. 107).[98]

Similarly, patients surveyed by Myeloma Canada expressed wanting a treatment that would offer them a good quality of life and help them achieve a long remission. Specifically, a treatment that would limit myeloma growth and symptoms without imposing side effects intolerable to the point that they would be detrimental to their quality of life.

Changes in Treatment Expectations and Decision-Making Over Time

Worries about narrowing treatment options and debilitating or worsening symptoms with relapse points to the way that patients' experiences of and views on treatment change over time.[95,97,100] As 1 patient described it: "[w]hen I was diagnosed my [children were in grade school] and I was [under 40 years] old, so life expectancy was #1,... whereas 25 years later life expectancy is not that great, [physical and cognitive side effects, and the effects of dex] are more important... Quality of life is more important" (p. 6).[95]

Patients reflected on the physical, emotional, and social impact of the disease and its treatment when thinking about what they sought out of treatment: "So, like in the end you know, we were, we all recognize that there is no cure so we look for a treatment that gives us the best quality of life and in that you know, we want to still have a good physical capacity and good mental capacity as best we can, right? That's what we strove for and as we live longer with the disease, we strive for even more of that." (p. 6)[95]

The importance of what patients termed quality of life comes into further view in some accounts where they were experiencing suffering: "You feel very unsure, all this suffering. If I come off this and then a year later, I am dead then you think 'well what is the... point.?'" (p. 2438).[101] Patients wanted a holistic approach to their treatment, 1 that accounted for their whole person not just their physical condition:[98,102] "The whole being is important. You know, it affects the whole person, treatment should include the physical and psychological, like why go through treatment to get a remission if the quality of life then isn't addressed. Some nurses were great, they talk to me not just the disease" (p. 107).[98]

This was echoed in the patient input received by Myeloma Canada, whereby patients described finding a right treatment to curb disease progression as an unrelenting exercise that should consider the impact on their emotional, mental, physical, and intellectual selves. And this may vary and need to be reevaluated at different stages in their lives and different stages in their treatment journey. Patients also expressed a desire for mental health-related side effects of MM and its treatments, such as anxiety and depression, to be openly discussed with their prescribing physician, and for support to be offered.

Barriers to Accessing or Receiving Treatment

Treatment Required to Travel and Sometimes Temporary Relocation

Patients noted that travel and temporary relocation to be close to their treatment facility created logistical and financial burdens.[97,101] Costs considerations raised by participants included parking costs[101] and those due to temporary relocation.[97] Travel to medical appointments was also logistically difficult as patients lost or experienced a reduction in their physical mobility due to symptoms or the inability to drive.[101]

Over half of individuals surveyed by Myeloma Canada reported receiving their present treatment at a cancer centre. The frequency of these visits differed, but patients reported weekly or monthly trips most often. Alternatively, oral therapies require fewer hospital trips. According to surveyed individuals, oral treatment options reduce the burden placed on patients, especially those who live in rural or remote areas that need to travel further to receive treatment. Conversely, IV infusions were the least desirable route of administration for most patients because they demand considerably more time and involve out-of-pocket expenses (e.g., travel, parking).

The Financial Impact of Living With Constant Treatment

Study patients described being under chronic financial pressures.[93,95,101] These pressures came from increased cost (e.g., travel and relocation)[101] and loss of income from being unable to work.[93,95] Patients described being forced to leave work due to symptoms, notably pain and fatigue and the number of medical appointments they had to attend.[95] This greatly reduced some patients' discretionary or disposable income: "I have no finances [laughter] any more. Yeah, I mean it. I have no money other than what goes toward medicine... I basically live on disability income, so I can't contribute to anything other than staying alive" (p. 155).[93]

Individuals surveyed by Myeloma Canada expressed similar concerns. Coverage of drug costs was the most widely reported financial impact on patients and it varied from 1 person to the next, based in part on where they lived. Additional costs included maintenance therapy and expenses involved in travelling to receive treatment.

Summary of Results

This rapid qualitative review included 10 primary studies exploring the experiences and perspectives of patients with MM on their treatment. Fatigue, peripheral neuropathy, risk of infection (due to low blood cell count), diarrhea were all raised as symptoms that patients struggled within their daily life. These affected multiple dimensions of their lives, including their social roles, social relations, and ability to engage in activities of daily living and those that gave them pleasure or meaning. Patients valued remissions because of the time gave to be with family and friends and because it enabled them to live a more normal life, in part because they were no longer occupied with frequent visits to health care providers for treatment. Relapse meant patients had to put their lives on hold and a departure from a normal life. MM with its multiple relapses meant patients felt they lived a life of emotional ups and downs.

Patients' experiences of and views on treatment changed over time, with each new relapse bringing worries about narrowing treatment options and debilitating or worsening symptoms. When thinking about treatment, patients considered the physical, emotional, and social impact of the disease and its treatment and wanted a holistic approach that considered their whole being and not just their physical condition. Patients identified challenges they faced in accessing treatment, including the need to travel to health care facilities or temporarily locate near them, and the chronic financial strain that living with constant treatment caused.

The small number of included studies affected the ability to describe patients' perspectives and experiences, particularly around treatment expectations and decision-making. The limited number of included studies

and lack of detailed reporting of patients' place in their cancer journey (e.g., duration of illness, number of lines of treatment) and the lack of longitudinal qualitative data meant that this review was unable to explore how individual's treatment decision-making changes over time. Further, it was not possible to distinguish the experiences of those with newly diagnosed and treatment-ineligible MM from those who were relapsed and/or refractory. As a result, the findings reported here should be interpreted with these limitations in mind, specifically, that they do not encompass or capture all experiences relating to treatment of newly diagnosed and treatment-ineligibility and r/r MM. This review used a framework synthesis approach and was guided by a prespecified conceptual framework. While this allowed for efficiency in the analysis by targeting specific aspects of treatment experiences that were relevant to this HTA, it risked not capturing potentially valuable findings outside of this framework. The revision of the framework in response to emergent findings and additional data sources (i.e., patient engagement and an additional qualitative evidence synthesis) helped mitigate this risk.

Note that the updated search conducted on July 6, 2023 identified additional studies that met the inclusion criteria. Six primary qualitative studies were identified that explore the expectations or experiences related to treatment, decision-making around treatment, and barriers to accessing or receiving treatment, for people with r/r MM, or who were newly diagnosed but transplant-ineligible. Two mixed methods studies meeting the inclusion criteria were identified. However, none were deemed as able to add new insights to the pre-existing qualitative rapid review and, for this reason, a reference list will serve as the sole update to the existing rapid review (refer to Appendix 11).

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Appendix 1: NMA — Literature Search Strategy

Note that this appendix has not been copy-edited.

Embase

('multiple myeloma'/de OR 'myeloma'/de OR 'myeloma cell'/de OR (myelom*):ab,ti,kw) AND (bortezomib/mj OR lenalidomide/mj OR bendamustine/mj OR daratumumab/mj OR carfilzomib/mj OR panobinostat/mj OR thalidomide/mj OR prednisone/mj OR dexamethasone/mj/exp OR melphalan/mj OR (bortezomib OR lenalidomid* OR bendamustin* OR daratumumab* OR carfilzomib* OR panobinostat* OR belrapzo* OR bendamustin* OR bendeka* OR thalidomid* OR prednison* OR dexamethason* OR melphalan* OR cc-5013 OR cc5013 OR cdc-501 OR cdc-5013 OR cdc501 OR cdc5013 OR cimet-3393 OR cytostasan* OR darzalex* OR enmd-0997 OR enmd0997 OR farydak* OR humax-CD38 OR imet-3393 OR imet3393 OR imid-3 OR imid3 OR kyprolis* OR lbh-589 OR lbh-589a OR lbh-589b OR lbh589 OR lbh589a OR lbh589b OR ldp-341 OR ldp341 OR levact* OR mg-341 OR mg341 OR mln-341 OR mln341 OR nvp-lbh-589 OR nvp-lbh589 OR panobinostat-lactate* OR pr-171 OR pr171 OR ps-341 OR ps341 OR revimid* OR revlimid* OR ribomustin* OR ribomustine* OR ribovact* OR sdx-105 OR sdx105 OR syp-1512 OR syp1512 OR treanda* OR velcade* OR zimet-3393 OR zimet3393 OR contergan OR distaval OR isomin OR k-17 OR kedavon OR kevadon OR neurosedin OR neurosedyne OR nsc-66847 OR sedalis OR shin-naito OR softenon OR synovir OR talimol OR talizer OR telagan OR telargan OR thado OR thalidomid* OR thalix OR thalomid* OR adrecort* OR adrenocot* OR aeroseb-dex* OR aflucoson* OR aflucosone* OR alanine-nitrogen-mustard* OR alfalyl* OR alkeran* OR anaflogistico* OR ancortone* OR arcodexan* OR artrosone* OR azium* OR bidexol* OR biocortone* OR calonat* OR cb3025* OR cb-3025* OR cebedex* OR cetadexon* OR colisone* OR colofoam* OR corsona* OR cortan* OR cortastat* OR cortidelt* OR cortidex* OR cortidexason* OR cortidron* OR cortiprex* OR cortisumman* OR cutason* OR dacorten* OR dacortin* OR dalalone* OR danasone* OR decacortin* OR decadeltoson* OR decaderm* OR decadion* OR decadran* OR decadron* OR decaesadril* OR decaject* OR decamethasone* OR decasone* OR decaspray* OR decasterolone* OR decdan* OR decilone* OR decofluor* OR decortancyl* OR decortin* OR decortisyl* OR de-cortisyl* OR dectancyl* OR dehydrocortison* OR dekacort* OR dekortin* OR delitisone* OR dellacort* OR delladec* OR deltacorten* OR deltacortison* OR deltacorton* OR delta-dome* OR deltafluoren* OR deltafluorene* OR deltasone* OR deltison* OR deltisona* OR deltra* OR dergramin* OR deronil* OR desacort* OR desacortone* OR desadrene* OR desalark* OR desameton* OR desigdron* OR de-sone-la* OR dexacen-4* OR dexachel* OR dexacort* OR dexacortal* OR dexacorten* OR dexacortin* OR dexacortisyl* OR dexa-cortisyl* OR dexa-dabrosan* OR dexadabroson* OR dexadecadrol* OR dexadrol* OR dexagel* OR dexagen* OR dexahelvacort* OR dexakorti* OR dexa-korti* OR dexalien* OR dexalocal* OR dexame* OR dexamecortin* OR dexameson* OR dexamesone* OR dexametason* OR dexameth* OR dexamethason* OR dexamethazon* OR dexamethonium* OR dexamonozon* OR dexane* OR dexano* OR dexa-p* OR dexapot* OR dexa-scherosan* OR dexascheroson* OR dexascherozon* OR dexa-scherozon* OR dexascherozone* OR dexa-scherozone* OR dexason* OR dexasone* OR dexinoral* OR dexionil* OR dexmethsone* OR dexona* OR dexone* OR dexpak-taperpak* OR dextelan* OR dextenza* OR dextrasone* OR dexycu* OR dezone* OR diadreson* OR di-adreson* OR dibasona* OR doxamethasone* OR drazone* OR encorton* OR enkorton* OR esacortene* OR evomela* OR

exadion* OR exadione* OR ex-s1* OR fernisone* OR firmalone* OR fluormethylprednisolon* OR fluormethylprednisolone* OR fluormethyl-prednisolone* OR fluormone* OR fluorocort* OR fluorodelta* OR fluoromethylprednisolone* OR fortecortin* OR gammacorten* OR gammacortene* OR grosodexon* OR grosodexone* OR hemady* OR hexadecadiol* OR hexadecadrol* OR hexadiol* OR hexadrol* OR hostacortin* OR insone* OR isnacort* OR isoptodex* OR isopto-dex* OR isoptomaxidex* OR isopto-maxidex* OR levofalan* OR levo-ortho-sarcolysine* OR levo-phenylalanine-mustard* OR levo-sarcolysin* OR liquid-pred* OR lodotra* OR lokalison-f* OR loverine* OR l-phenylalanine-mustard* OR l-sarcolysin* OR luxazone* OR marvidione* OR maxidex* OR mediamethasone* OR megacortin* OR me-korti* OR melfalan* OR melphalan-hydrochloride* OR melphalon* OR melphelan* OR mephameson* OR mephamesone* OR meprison* OR metacortandracin* OR metasolon* OR metasolone* OR methazone-ion* OR methazonion* OR methazon-ion* OR methazonione* OR meticorten* OR metisone-lafi* OR mexasone* OR millicorten* OR millicortenol* OR mk125* OR mk-125* OR mymethasone* OR neoforderx* OR neofordex* OR nisomethasona* OR nisona* OR novocort* OR nsc10023* OR nsc-10023* OR nsc34521* OR nsc-34521* OR nsc8806* OR nsc-8806* OR oftan-dexa* OR opticorten* OR opticortinol* OR oradexan* OR oradexon* OR oradexone* OR orasone* OR orgadrone* OR orisane* OR ozurdex* OR panafcort* OR paracort* OR pehacort* OR phenylalanine-2037* OR pidexon* OR policort* OR posurdex* OR precort* OR prednicen* OR prednicorm* OR prednicot* OR prednidib* OR predni-f* OR prednison* OR prednitone* OR prodexona* OR prodexone* OR pronison* OR pronizone* OR pulmison* OR rayos* OR rectodelt* OR sanamethasone* OR santenson* OR santeson* OR sawasone* OR servisone* OR sk15673* OR sk-15673* OR solurex* OR spoloven* OR steerometz* OR sterapred* OR sterasone* OR thilodexine* OR triamcimetil* OR ultracorten* OR urtilone* OR vexamet* OR visumetazone* OR visumethazone* OR winpred* OR ixazomib* OR isatuximab* OR cyclophosphamid* OR pomalidomid* OR idecabtagen* OR vicleucel* OR elotuzumab* OR Abecma* OR Actimid* OR B-518 OR B518 OR bb-2121 OR bb2121 OR bms-901608 OR bms901608 OR carloxan OR CC4047 OR CC-4047 OR Chloroethylaminophenylalanine OR ciclofosfamida OR ciclolen OR cicloxal OR clafen OR cycloblastin* OR cyclo-cell OR cyclofos-amide OR cyclofosfamid* OR cyclophar OR cyclophosphan* OR cyclostin OR cycloxan OR cyphos OR cytophosphan* OR cytoxan OR D2UX06XLB5 OR empliciti OR endocyclo-phosphate OR endoxan* OR enduxan* OR Fiasone OR genoxal OR Hu-38SB19 OR Hu38SB19 OR huluc63 OR Ide-cel OR IMID-3 OR IMID3 OR Imidan OR Imnovid* OR Isomin OR Kevadon OR ledoxan* OR mitoxan OR MLN-9708 OR MLN9708 OR Neaufatin OR neosan OR neosar OR Neosedyn OR Neosydyn OR Nerosedyn OR Neufatin OR Neurodyn OR Neurosedin OR Nevrodyn OR noristan OR nsc-26271 OR nsc-2671 OR pdl-063 OR pdl063 OR Pomalyst* OR prednisolone-f OR procytox* OR R30772KCU0 OR SAR-650984 OR SAR650984 OR Sarclisa* OR semdoxan OR sendoxan OR syklofosfamid OR Turbinaire OR Valgraine OR Wojtab OR ((((new* NEAR/3 diagnos*) OR first-line OR untreat* OR naive)) AND (transplant* NEAR/6 (ineligib* OR non-eligib* OR not-eligib*))) OR ((relaps* OR refractor*) NEAR/3 myeloma*)):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT (juvenile/exp NOT adult/exp) AND [english]/lim AND ('randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR 'pragmatic trial'/exp OR 'phase 3 clinical trial'/exp OR 'randomized controlled trial (topic)'/exp OR 'controlled clinical trial (topic)'/exp OR Randomization/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR Placebo/exp OR 'control group'/exp OR 'systematic review'/exp OR 'systematic review (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis (topic)'/exp OR 'biomedical technology assessment'/exp OR ((random* or sham or placebo*) OR ((singl* or doubl*) NEXT/1 (blind* or dumm* or mask*)) OR

((tripl* or trebl*) NEXT/1 (blind* or dumm* or mask*)) OR (control* NEAR/3 (study or studies or trial* or group*)) OR (Nonrandom* or non-random* or quasi-random* or quasirandom*) OR allocated OR ((open-label) NEAR/5 (study or studies or trial*)) OR ((equivalence or superiority or non-inferiority or noninferiority) NEAR/3 (study or studies or trial*)) OR pragmatic-stud* OR ((pragmatic or practical) NEAR/3 trial*) OR ((quasiexperimental or quasi-experimental) NEAR/3 (study or studies or trial*)) OR (phase NEXT/1 (III or 3) NEAR/3 (study or studies or trial*)) OR ((systematic* NEAR/3 (review* or overview*)) or (methodologic* NEAR/3 (review* or overview*))) OR ((quantitative NEAR/3 (review* or overview* or synthes*)) or (research NEAR/3 (integrati* or overview*))) OR ((integrative NEAR/3 (review* or overview*)) or (collaborative NEAR/3 (review* or overview*)) or (pool* NEAR/3 analy*)) OR (data-synthes* or data-extraction* or data-abstraction*) OR (handsearch* or hand-search*) OR (mantel-haenszel or peto or der-simonian or dersimonian or fixed-effect* or latin-square*) OR (met-analy* or met-analy* or technology-assessment* or HTA or HTAs or technology-overview* or technology-appraisal*) OR (meta-regression* or metaregression*) OR (meta-analy* or metaanaly* or systematic-review* or biomedical-technology-assessment* or bio-medical-technology-assessment*) OR (medline or cochrane or pubmed or medlars or embase or cinahl) OR (cochrane or (health NEAR/2 technology-assessment) or evidence-report) OR (comparative NEAR/3 (efficacy or effectiveness)) OR (outcomes-research or relative-effectiveness) OR ((indirect or indirect-treatment or mixed-treatment or bayesian) NEAR/3 comparison*) OR (meta-analysis or systematic-review) OR (multi* NEAR/3 treatment NEAR/3 comparison*) OR (mixed NEAR/3 treatment NEAR/3 (meta-analy* or metaanaly*)) OR Umbrella-review* OR (multi* NEAR/2 paramet* NEAR/2 evidence NEAR/2 synthesis) OR (multiparamet* NEAR/2 evidence NEAR/2 synthesis) OR (multi-paramet* NEAR/2 evidence NEAR/2 synthesis)):ab,ti)

Ovid MEDLINE

(Multiple Myeloma/ OR (myelom*).ab,ti,kw.) AND (Bortezomib/ OR Lenalidomide/ OR Bendamustine Hydrochloride/ OR daratumumab.nm. OR carfilzomib.nm. OR Panobinostat/ OR Thalidomide/ OR Prednisone/ OR Dexamethasone/ OR Melphalan/ OR (bortezomib OR lenalidomid* OR bendamustin* OR daratumumab* OR carfilzomib* OR panobinostat* OR belrapzo* OR bendamustin* OR bendeka* OR thalidomid* OR prednison* OR dexamethason* OR melphalan* OR cc-5013 OR cc5013 OR cdc-501 OR cdc-5013 OR cdc501 OR cdc5013 OR cimet-3393 OR cytostasan* OR darzalex* OR enmd-0997 OR enmd0997 OR farydak* OR humax-CD38 OR imet-3393 OR imet3393 OR imid-3 OR imid3 OR kyprolis* OR lbh-589 OR lbh-589a OR lbh-589b OR lbh589 OR lbh589a OR lbh589b OR ldp-341 OR ldp341 OR levact* OR mg-341 OR mg341 OR mln-341 OR mln341 OR nvp-lbh-589 OR nvp-lbh589 OR panobinostat-lactate* OR pr-171 OR pr171 OR ps-341 OR ps341 OR revimid* OR revlimid* OR ribomustin* OR ribomustine* OR ribovact* OR sdx-105 OR sdx105 OR syp-1512 OR syp1512 OR treanda* OR velcade* OR zimet-3393 OR zimet3393 OR contergan OR distaval OR isomin OR k-17 OR kedavon OR kevadon OR neurosedin OR neurosedyne OR nsc-66847 OR sedalis OR shin-naito OR softenon OR synovir OR talimol OR talizer OR telagan OR telargan OR thado OR thalidomid* OR thalix OR thalomid* OR adrecort* OR adrenocot* OR aeroseb-dex* OR aflucoson* OR aflucosone* OR alanine-nitrogen-mustard* OR alfalyl* OR alkeran* OR anaflogistico* OR ancortone* OR arcodexan* OR artrosone* OR azium* OR bidexol* OR biocortone* OR calonat* OR cb3025* OR cb-3025* OR cebedex* OR cetadexon* OR colisone* OR colofoam* OR corsona* OR cortan* OR cortastat* OR cortidelt* OR cortidex* OR cortidexason* OR cortidron* OR cortiprex* OR cortisumman* OR cutason* OR dacorten* OR

dacortin* OR dalalone* OR danasone* OR decacortin* OR decadeltoson* OR decaderm* OR decadion* OR decadran* OR decadron* OR decaesadril* OR decaject* OR decamethasone* OR decasone* OR decaspray* OR decasterolone* OR decdan* OR decilone* OR decofluor* OR decortancyl* OR decortin* OR decortisyl* OR de-cortisyl* OR dectancyl* OR dehydrocortison* OR dekacort* OR dekortin* OR delitisone* OR dellacort* OR delladec* OR deltacorten* OR deltacortison* OR deltacorton* OR delta-dome* OR deltafluoren* OR deltafluorene* OR deltasone* OR deltison* OR deltisona* OR deltra* OR dergramin* OR deronil* OR desacort* OR desacortone* OR desadrene* OR desalark* OR desameton* OR desigdron* OR de-sone-la* OR dexacen-4* OR dexachel* OR dexacort* OR dexacortal* OR dexacorten* OR dexacortin* OR dexacortisyl* OR dexa-cortisyl* OR dexa-dabrosan* OR dexadabroson* OR dexadecadrol* OR dexadrol* OR dexagel* OR dexagen* OR dexahelvacort* OR dexakorti* OR dexa-korti* OR dexalien* OR dexalocal* OR dexame* OR dexamecortin* OR dexameson* OR dexamesone* OR dexametason* OR dexameth* OR dexamethason* OR dexamethazon* OR dexamethonium* OR dexamonozon* OR dexane* OR dexano* OR dexa-p* OR dexapot* OR dexa-scherosan* OR dexascheroson* OR dexascherozon* OR dexa-scherozon* OR dexascherozone* OR dexa-scherozone* OR dexason* OR dexasone* OR dexinoral* OR dexionil* OR dexmethsone* OR dexona* OR dexone* OR dexpak-taperpak* OR dextelan* OR dextenza* OR dextrasone* OR dexycu* OR dezone* OR diadreson* OR di-adreson* OR dibasona* OR doxamethasone* OR drazone* OR encorton* OR enkorton* OR esacortene* OR evomela* OR exadion* OR exadione* OR ex-s1* OR fernisone* OR firmalone* OR fluormethylprednisolon* OR fluormethylprednisolone* OR fluormethyl-prednisolone* OR fluormone* OR fluorocort* OR fluorodelta* OR fluoromethylprednisolone* OR fortecortin* OR gammacorten* OR gammacortene* OR grosodexon* OR grosodexone* OR hemady* OR hexadecadiol* OR hexadecadrol* OR hexadiol* OR hexadrol* OR hostacortin* OR insone* OR isnacort* OR isoptodex* OR isopto-dex* OR isoptomaxidex* OR isopto-maxidex* OR levofalan* OR levo-ortho-sarcolysine* OR levo-phenylalanine-mustard* OR levo-sarcolysin* OR liquid-pred* OR lodotra* OR lokalison-f* OR loverine* OR l-phenylalanine-mustard* OR l-sarcolysin* OR luxazone* OR marvidione* OR maxidex* OR mediamethasone* OR megacortin* OR me-korti* OR melfalan* OR melphalan-hydrochloride* OR melphalon* OR melphelan* OR mephameson* OR mephamesone* OR meprison* OR metacortandracin* OR metasolon* OR metasolone* OR methazone-ion* OR methazonion* OR methazon-ion* OR methazonione* OR meticorten* OR metisone-lafi* OR mexasone* OR millicorten* OR millicortenol* OR mk125* OR mk-125* OR mymethasone* OR neoforderx* OR neofordex* OR nisomethasona* OR nisona* OR novocort* OR nsc10023* OR nsc-10023* OR nsc34521* OR nsc-34521* OR nsc8806* OR nsc-8806* OR oftan-dexa* OR opticorten* OR opticortinol* OR oradexan* OR oradexon* OR oradexone* OR orasone* OR orgadrone* OR orisane* OR ozurdex* OR panafcort* OR paracort* OR pehacort* OR phenylalanine-2037* OR pidexon* OR policort* OR posurdex* OR precort* OR prednicen* OR prednicorm* OR prednicot* OR prednidib* OR predni-f* OR prednison* OR prednitone* OR prodexona* OR prodexone* OR pronison* OR pronizone* OR pulmison* OR rayos* OR rectodelt* OR sanamethasone* OR santenson* OR santeson* OR sawasone* OR servisone* OR sk15673* OR sk-15673* OR solurex* OR spoloven* OR steerometz* OR sterapred* OR sterasone* OR thilodexine* OR triamcimetil* OR ultracorten* OR urtilone* OR vexamet* OR visumetazone* OR visumethazone* OR winpred* OR ixazomib* OR isatuximab* OR cyclophosphamid* OR pomalidomid* OR idecabtagen* OR vicleucel* OR elotuzumab* OR Abecma* OR Actimid* OR B-518 OR B518 OR bb-2121 OR bb2121 OR bms-901608 OR bms901608 OR carloxan OR CC4047 OR CC-4047 OR Chloroethylaminophenylalanine OR ciclofosfamida OR ciclolen OR cicloxal OR

clafen OR cycloblastin* OR cyclo-cell OR cyclofos-amide OR cyclofosfamid* OR cyclophar OR cyclophosphan* OR cyclostin OR cycloxan OR cyphos OR cytophosphan* OR cytoxan OR D2UX06XLB5 OR empliciti OR endocyclo-phosphate OR endoxan* OR enduxan* OR Fiasone OR genoxal OR Hu-38SB19 OR Hu38SB19 OR huluc63 OR Ide-cel OR IMID-3 OR IMID3 OR Imidan OR Imnovid* OR Isomin OR Kevadon OR ledoxan* OR mitoxan OR MLN-9708 OR MLN9708 OR Neaufatin OR neosan OR neosar OR Neosedyn OR Neosydyn OR Nerosedyn OR Neufatin OR Neurodyn OR Neurosedin OR Nevrodyn OR noristan OR nsc-26271 OR nsc-2671 OR pdl-063 OR pdl063 OR Pomalyst* OR prednisolone-f OR procytox* OR R30772KCU0 OR SAR-650984 OR SAR650984 OR Sarclisa* OR semdoxan OR sendoxan OR syklofosfamid OR Turbinaire OR Valgraine OR Wojtab OR ((((new* ADJ3 diagnos*) OR first-line OR untreat* OR naive)) AND (transplant* ADJ6 (ineligib* OR non-eligib* OR not-eligib*))) OR ((relaps* OR refractor*) ADJ3 myeloma*)).ab,ti.) NOT ((exp child/ OR exp infant/ OR pediatrics/ OR adolescent/) NOT exp adult/) AND english.la. NOT (exp animals/ NOT humans/) AND (Randomized Controlled Trial/ OR Controlled Clinical Trial/ OR Pragmatic Clinical Trial/ OR Pragmatic Clinical Trials as Topic/ OR Clinical Trial, Phase III/ OR Clinical Trials, Phase III as Topic/ OR Randomized Controlled Trials as Topic/ OR Controlled Clinical Trials as Topic/ OR Random Allocation/ OR Double-Blind Method/ OR Single-Blind Method/ OR Placebos/ OR Control Groups/ OR Systematic Review/ OR Systematic Reviews as Topic/ OR Meta-Analysis/ OR Network Meta-Analysis/ OR Meta-Analysis as Topic/ OR Technology Assessment, Biomedical/ OR ((random* or sham or placebo*) OR ((singl* or doubl*) ADJ (blind* or dumm* or mask*)) OR ((tripl* or trebl*) ADJ (blind* or dumm* or mask*)) OR (control* ADJ3 (study or studies or trial* or group*)) OR (Nonrandom* or non-random* or quasi-random* or quasirandom*) OR allocated OR ((open-label) ADJ5 (study or studies or trial*)) OR ((equivalence or superiority or non-inferiority or noninferiority) ADJ3 (study or studies or trial*)) OR pragmatic-stud* OR ((pragmatic or practical) ADJ3 trial*) OR ((quasiexperimental or quasi-experimental) ADJ3 (study or studies or trial*)) OR (phase ADJ (III or 3) ADJ3 (study or studies or trial*)) OR ((systematic* ADJ3 (review* or overview*)) or (methodologic* ADJ3 (review* or overview*))) OR ((quantitative ADJ3 (review* or overview* or synthes*)) or (research ADJ3 (integrati* or overview*))) OR ((integrative ADJ3 (review* or overview*)) or (collaborative ADJ3 (review* or overview*)) or (pool* ADJ3 analy*)) OR (data-synthes* or data-extraction* or data-abstraction*) OR (handsearch* or hand-search*) OR (mantel-haenszel or peto or der-simonian or dersimonian or fixed-effect* or latin-square*) OR (met-analy* or met-analy* or technology-assessment* or HTA or HTAs or technology-overview* or technology-appraisal*) OR (meta-regression* or metaregression*) OR (meta-analy* or metaanaly* or systematic-review* or biomedical-technology-assessment* or bio-medical-technology-assessment*) OR (medline or cochrane or pubmed or medlars or embase or cinahl) OR (cochrane or (health ADJ2 technology-assessment) or evidence-report) OR (comparative ADJ3 (efficacy or effectiveness)) OR (outcomes-research or relative-effectiveness) OR ((indirect or indirect-treatment or mixed-treatment or bayesian) ADJ3 comparison*) OR (meta-analysis or systematic-review) OR (multi* ADJ3 treatment ADJ3 comparison*) OR (mixed ADJ3 treatment ADJ3 (meta-analy* or metaanaly*)) OR Umbrella-review* OR (multi* ADJ2 paramet* ADJ2 evidence ADJ2 synthesis) OR (multiparamet* ADJ2 evidence ADJ2 synthesis) OR (multi-paramet* ADJ2 evidence ADJ2 synthesis)).ab,ti.)

Cochrane Central Register of Clinical Trials

((myelom*):ab,ti,kw) AND ((bortezomib OR lenalidomid* OR bendamustin* OR daratumumab* OR carfilzomib* OR panobinostat* OR belrapzo* OR bendamustin* OR bendeka* OR thalidomid* OR prednison* OR dexamethason* OR melphalan*):ab,ti)

Appendix 2: NMA — List of Included Studies

Note that this appendix has not been copy-edited.

Newly Diagnosed Multiple Myeloma

ALCYONE (NCT02195479)

Mateos MV, Cavo M, Blade J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. *Lancet*. 2020;395(10218):132-141. PubMed

Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. *New Engl J Med*. 2018;378(6):518-528. PubMed

CLARION (NCT01818752)

Facon T, Lee JH, Moreau P, et al. Carfilzomib or bortezomib with melphalan-prednisone for transplant-ineligible patients with newly diagnosed multiple myeloma. *Blood*. 2019;133(18):1953-1963. PubMed

E1A06 (NCT00602641)

Stewart AK, Jacobus S, Fonseca R, et al. Melphalan, prednisone, and thalidomide vs melphalan, prednisone, and lenalidomide (ECOG E1A06) in untreated multiple myeloma. *Blood*. 2015;126(11):1294-1301. PubMed

E5A93 – Not Included in NMA

Kyle RA, Jacobus S, Friedenberg WR, Slabber CF, Rajkumar SV, Greipp PR. The treatment of multiple myeloma using vincristine, carmustine, melphalan, cyclophosphamide, and prednisone (VBMCP) alternating with high-dose cyclophosphamide and α2β interferon versus VBMCP: results of a phase III eastern cooperative oncology group study E5A93. *Cancer*. 2009;115(10):2155-2164. PubMed

EMN01 (NCT01093196)

Bringhen S, D'Agostino M, Paris L, et al. Lenalidomide-based induction and maintenance in elderly newly diagnosed multiple myeloma patients: updated results of the EMN01 randomized trial. *Haematologica*. 2020;105(7):1937-1947. PubMed

Magarotto V, Bringhen S, Offidani M, et al. Triplet vs doublet lenalidomide-containing regimens for the treatment of elderly patients with newly diagnosed multiple myeloma. *Blood*. 2016;127(9):1102-1108. PubMed

ENDURANCE (NCT01863550)

Kumar SK, Jacobus SJ, Cohen AD, et al. Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol*. 2020;21(10):1317-1330. PubMed

FIRST (NCT00689936)

Facon T, Dimopoulos MA, Dispenzieri A, et al. Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. *Blood*. 2018;131(3):301-310. PubMed

Hulin C, Belch A, Shustik C, et al. Updated outcomes and impact of age with lenalidomide and low-dose dexamethasone or melphalan, prednisone, and thalidomide in the randomized, phase III FIRST trial. *J Clin Oncol*. 2016;34(30):3609-3617. PubMed

Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. *New Engl J Med*. 2014;371(10):906-917. PubMed

GBRAM0002 (NCT01532856) – Not included in NMA

Hungria VTM, Crusoé EQ, Maiolino A, et al. Phase 3 trial of three thalidomide-containing regimens in patients with newly diagnosed multiple myeloma not transplant-eligible. *Ann Hematol*. 2016;95(2):271-278. PubMed

GEM2005 (NCT00443235)

Mateos MV, Oriol A, Martínez-López J, et al. GEM2005 trial update comparing VMP/VTP as induction in elderly multiple myeloma patients: do we still need alkylators? *Blood*. 2014;124(12):1887-1893. PubMed

Mateos MV, Oriol A, Martínez-López J, et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. *Lancet Oncol*. 2010;11(10):934-941. PubMed

GIMEMA MM-03-05 (NCT01063179)

Palumbo A, Bringhen S, Larocca A, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: updated follow-up and improved survival. *J Clin Oncol*. 2014;32(7):634-640. PubMed

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GISMM2001-A (NCT00232934)

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HOVON 49

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HOVON 87

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IFM 01/01 (NCT00644306)

Hulin C, Facon T, Rodon P, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. *J Clin Oncol*. 2009;27(22):3664-3670. PubMed

IFM 95-01

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JCOG9301 – Not Included in NMA

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KEYNOTE-185 (NCT02579863)

Usmani SZ, Schjesvold F, Oriol A, et al. Pembrolizumab plus lenalidomide and dexamethasone for patients with treatment-naive multiple myeloma (KEYNOTE-185): a randomised, open-label, phase 3 trial. *Lancet Haematol*. 2019;6(9):e448-e458. PubMed

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MM-015 (NCT00405756)

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MM-PETHEMA 96

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MY.7

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Myeloma XI (NCT01554852)

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NMSG 12 (NCT00218855)

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S0232 (NCT00064038)

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S0777 (NCT00644228)

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S9210 – Not Included in NMA

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TOURMALINE-MM2 (NCT01850524)

Facon T, Venner CP, Bahlis NJ, et al. Oral ixazomib, lenalidomide, and dexamethasone for transplant-ineligible patients with newly diagnosed multiple myeloma. *Blood*. 2021;137(26):3616-3628. PubMed

UPFRONT (NCT00507416)

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VISTA (NCT00111319)

Miguel JFS, Schlag R, Khuageva NK, et al. Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma. *J Clin Oncol*. 2013;31(4):448-455. PubMed

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NCT00205751

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Ludwig 2005 – Not Included in NMA

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Relapsed and/or Refractory Multiple Myeloma

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APEX (NCT00048230)

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APOLLO (NCT03180736)

Dimopoulos MA, Terpos E, Boccadoro M, et al. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2021;22(6):801-812. PubMed

A.R.R.O.W. (NCT02412878)

Dimopoulos MA, Niesvizky R, Weisel K, et al. Once- versus twice-weekly carfilzomib in relapsed and refractory multiple myeloma by select patient characteristics: phase 3 A.R.R.O.W. study subgroup analysis. *Blood Cancer J.* 2020;10(3):35. – *Subgroup analysis* PubMed

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ASPIRE (NCT01080391)

Siegel DS, Dimopoulos MA, Ludwig H, et al. Improvement in overall survival with carfilzomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma. *J Clin Oncol*. 2018;36(8):728-734. PubMed

Dimopoulos MA, Stewart AK, Masszi T, et al. Carfilzomib, lenalidomide, and dexamethasone in patients with relapsed multiple myeloma categorised by age: secondary analysis from the phase 3 ASPIRE study. *Br J Haematol*. 2017;177(3):404-413. – *Subgroup analysis* PubMed

Dimopoulos MA, Stewart AK, Masszi T, et al. Carfilzomib-lenalidomide-dexamethasone vs lenalidomide- dexamethasone in relapsed multiple myeloma by previous treatment. *Blood Cancer J.* 2017;7(4):e554. – *Subgroup analysis* PubMed

Avet-Loiseau H, Fonseca R, Siegel D, et al. Carfilzomib significantly improves the progression-free survival of high-risk patients in multiple myeloma. *Blood*. 2016;128(9):1174-1180. – *Subgroup analysis* PubMed

Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *New Engl J Med*. 2015;372(2):142-152. PubMed

BELLINI (NCT02755597)

Kumar SK, Harrison SJ, Cavo M, et al. Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol*. 2020;21(12):1630-1642. PubMed

BOSTON (NCT03110562)

Richard S, Chari A, Delimpasi S, et al. Selinexor, bortezomib, and dexamethasone versus bortezomib and dexamethasone in previously treated multiple myeloma: Outcomes by cytogenetic risk. *Am J Hematol*. 2021; In press. – *Subgroup analysis* PubMed

Auner HW, Gavriatopoulou M, Delimpasi S, et al. Effect of age and frailty on the efficacy and tolerability of once-weekly selinexor, bortezomib, and dexamethasone in previously treated multiple myeloma. *Am J Hematol*. 2021; 96(6):708-718. – *Subgroup analysis* PubMed

Grosicki S, Simonova M, Spicka I, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. *Lancet*. 2020;396(10262):1563-1573. PubMed

CANDOR (NCT03158688)

Dimopoulos M, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. *Lancet*. 2020;396(10245):186-197. PubMed

CASTOR (NCT02136134)

Mateos MV, Sonneveld P, Hungria V, et al. Daratumumab, bortezomib, and dexamethasone versus bortezomib and dexamethasone in patients with previously treated multiple myeloma: three-year follow-up of CASTOR. *Clin Lymphoma Myeloma Leukemia*. 2020;20(8):509-518. PubMed

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CC-5013-MM-009 (NCT00056160)

Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *New Engl J Med*. 2007;357(21):2133-2142. PubMed

CC-5013-MM-010 (NCT00424047)

Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *New Engl J Med*. 2007;357(21):2123-2132. PubMed

E1A95 (NCT00002878) – Not included in NMA

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ELOQUENT-2 (NCT01239797)

Dimopoulos MA, Lonial S, White D, et al. Elotuzumab, lenalidomide, and dexamethasone in RRMM: final overall survival results from the phase 3 randomized ELOQUENT-2 study. *Blood Cancer J.* 2020;10(9):91. PubMed

Dimopoulos MA, Lonial S, Betts KA, et al. Elotuzumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended 4-year follow-up and analysis of relative progression-free survival from the randomized ELOQUENT-2 trial. *Cancer*. 2018;124(20):4032-4043. PubMed

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Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. *New Engl J Med*. 2015;373(7):621-631. PubMed

ENDEAVOR (NCT01568866)

Orlowski RZ, Moreau P, Niesvizky R, et al. Carfilzomib-dexamethasone versus bortezomib-dexamethasone in relapsed or refractory multiple myeloma: updated overall survival, safety, and subgroups. *Clin Lymphoma Myeloma Leuk*. 2019;19(8):522-530. e1. PubMed

Goldschmidt H, Moreau P, Ludwig H, et al. Carfilzomib–dexamethasone versus subcutaneous or intravenous bortezomib in relapsed or refractory multiple myeloma: secondary analysis of the phase 3 ENDEAVOR study. *Leuk Lymphoma*. 2018;59(6):1364-1374. PubMed

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Moreau P, Joshua D, Chng WJ, et al. Impact of prior treatment on patients with relapsed multiple myeloma treated with carfilzomib and dexamethasone vs bortezomib and dexamethasone in the phase 3 ENDEAVOR study. *Leukemia*. 2017;31(1):115-122. – *Subgroup analysis* PubMed

Chng WJ, Goldschmidt H, Dimopoulos MA, et al. Carfilzomib-dexamethasone vs bortezomib-dexamethasone in relapsed or refractory multiple myeloma by cytogenetic risk in the phase 3 study ENDEAVOR. *Leukemia*. 2017;31(6):1368-1374. – *Subgroup analysis* PubMed

Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): and randomised, phase 3, open-label, multicentre study. *Lancet Oncol*. 2016;17(1):27-38. PubMed

FOCUS (NCT01302392) – Not included in NMA

Hájek R, Masszi T, Petrucci MT, et al. A randomized phase III study of carfilzomib vs low-dose corticosteroids with optional cyclophosphamide in relapsed and refractory multiple myeloma (FOCUS). *Leukemia*. 2017;31(1):107-114. PubMed

ICARIA-MM (NCT02990338)

Harrison SJ, Perrot A, Alegre A. et al. Subgroup analysis of ICARIA-MM study in relapsed/refractory multiple myeloma patients with high-risk cytogenetics. *Br J Haematol*. 2021;194(1):120-131. – *Subgroup analysis* PubMed

Bringhen S, Pour L, Vorobyev V, et al. Isatuximab plus pomalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma according to prior lines of treatment and refractory status: ICARIA-MM subgroup analysis. *Leuk Res*. 2021;104:106576. – *Subgroup analysis* PubMed

Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. *Lancet*. 2019;394(10214):2096-2107. PubMed

IFM 01-02

Yakoub-Agha I, Mary JY, Hulin C, et al. Low-dose vs. high-dose thalidomide for advanced multiple myeloma: a prospective trial from the Intergroupe Francophone du Myélome. *Eur J Haematol*. 2012;88(3):249-259. PubMed

IKEMA (NCT03275285)

Moreau P, Dimopoulos MA, Mikhael J, et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. *Lancet*. 2021;397(10292):2361-2371. PubMed

KEYNOTE-183 (NCT02576977)

Mateos MV, Blacklock H, Schjesvold F, et al. Pembrolizumab plus pomalidomide and dexamethasone for patients with relapsed or refractory multiple myeloma (KEYNOTE-183): a randomised, open-label, phase 3 trial. *Lancet Haematol*. 2019;6(9):e459-e469. PubMed

LEPUS/MMY3009 (NCT03234972)

Lu J, Fu W, Li W, et al. Daratumumab, Bortezomib, and Dexamethasone Versus Bortezomib and Dexamethasone in Chinese Patients with Relapsed or Refractory Multiple Myeloma: Phase 3 LEPUS (MMY3009) Study. *Clin Lymphoma Myeloma Leuk*. 2021; In press. PubMed

MM-003 (NCT01311687)

Dimopoulos MA, Weise KC, Song KW, et al. Cytogenetics and long-term survival of patients with refractory or relapsed and refractory multiple myeloma treated with pomalidomide and low-dose dexamethasone. *Haematologica*. 2015;100(10):1327-1333. PubMed

San Miguel JF, Weisel KC, Song KW, et al. Impact of prior treatment and depth of response on survival in MM-003, a randomized phase 3 study comparing pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed/refractory multiple myeloma. *Haematologica*. 2015;100(10):1334-1339. – *Subgroup analysis* PubMed

Miguel JS, Weisel K, Moreau P, 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;14(11):1055-1066. PubMed

MMY3001 (NCT00103506)

Orlowski RZ, Nagler A, Sonneveld P, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. *J Clin Oncol*. 2007;25(25):3892-3901. PubMed

MMY3002 (NCT00813150)

Kropff M, Vogel M, Bisping G, et al. Bortezomib and low-dose dexamethasone with or without continuous low-dose oral cyclophosphamide for primary refractory or relapsed multiple myeloma: a randomized phase III study. *Ann Hematol*. 2017;96(11):1857-1866. PubMed

MMY3033 (NCT01910987) – Not included in NMA

Terpos E, Gobbi M, Potamianou A, Lahaye M, Couturier C, Cavo M. Retreatment and prolonged therapy with subcutaneous bortezomib in patients with relapsed multiple myeloma: a randomized, controlled, phase III study. *Eur J Haematol*. 2018;100(1):10-19. PubMed

NMSG 17/07 (NCT00602511)

Hjorth M, Hjertner O, Knudsen LM, et al. Thalidomide and dexamethasone vs. bortezomib and dexamethasone for melphalan refractory myeloma: a randomized study. *Eur J Haematol*. 2012;88(6):485-496. PubMed

OPTIMISMM (NCT01734928)

Dimopoulos M, Weisel K, Moreau P, et al. Pomalidomide, bortezomib, and dexamethasone for multiple myeloma previously treated with lenalidomide (OPTIMISMM): outcomes by prior treatment at first relapse. *Leukemia*. 2021;35(6):1722-1731. PubMed

OPTIMUM (NCT00452569)

Kropff M, Baylon HG, Hillengass J, et al. Thalidomide versus dexamethasone for the treatment of relapsed and/or refractory multiple myeloma: results from optimum, a randomized trial. *Haematologica*. 2012;97(5):784-790. PubMed

PANORAMA 1 (NCT01023308)

San-Miguel JF, Hungria VTM, Yoon SS, et al. Overall survival of patients with relapsed multiple myeloma treated with panobinostat or placebo plus bortezomib and dexamethasone (the PANORAMA 1 trial): a randomised, placebo-controlled, phase 3 trial. *Lancet Haematol*. 2016;3(11):e506-e515. PubMed

San-Miguel JF, Hungria VTM, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. *Lancet Oncol*. 2014;15(11):1195-1206. PubMed

POLLUX (NCT02076009)

Kaufman JL, Dimopoulos MA, White D, et al. Daratumumab, lenalidomide, and dexamethasone in relapsed/refractory myeloma: a cytogenetic subgroup analysis of POLLUX. *Blood Cancer J.* 2020;10(11):111. – *Subgroup analysis* PubMed

Bahlis NJ, Dimopoulos MA, White DJ, et al. Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of POLLUX, a randomized, open-label, phase 3 study. *Leukemia*. 2020;34(7):1875-1884. PubMed

Dimopoulos MA, San-Miguel J, Belch A, et al. Daratumumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of POLLUX. *Haematologica*. 2018;103(12):2088-2096. PubMed

Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *New Engl J Med*. 2016;375(14):1319-1331. PubMed

TOURMALINE-MM1 (NCT01564537)

Mateos MV, Masszi T, Grzasko N, et al. Impact of prior therapy on the efficacy and safety of oral ixazomiblenalidomide-dexamethasone vs. placebo-lenalidomide-dexamethasone in patients with relapsed/refractory multiple myeloma in TOURMALINE-MM1. *Haematologica*. 2017;102(10):1767-1775. – *Subgroup analysis* PubMed

Avet-Loiseau H, Bahlis NJ, Chng WJ, et al. Ixazomib significantly prolongs progression-free survival in high-risk relapsed/refractory myeloma patients. *Blood*. 2017;130(24):2610-2618. – *Subgroup analysis* PubMed

Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. *New Engl J Med*. 2016;374(17):1621-1634. PubMed

VANTAGE 088 (NCT00773747)

Dimopoulos M, Siegel DS, Lonial S, et al. Vorinostat or placebo in combination with bortezomib in patients with multiple myeloma (VANTAGE 088): a multicentre, randomised, double-blind study. *Lancet Oncol*. 2013;14(11):1129-1140. PubMed

NCT00017602

Chanan-Khan A, Niesvizky R, Hohl RJ, et al. Phase III randomised study of dexamethasone with or without oblimersen sodium for patients with advanced multiple myeloma. *Leuk Lymphoma*. 2009;50(4):559-565. PubMed

Appendix 3: NMA — List of Ongoing Studies Without Published Results

Note that this appendix has not been copy-edited.

Newly Diagnosed Multiple Myeloma

ARUMM (NCT02112175)

CEPHEUS (NCT03652064)

E1A05 (NCT00522392)

FiTNEss (NCT03720041)

IMROZ (NCT03319667)

MM-027

RV-MM-PI-0752 (NCT02215980)

Relapsed and/or Refractory Multiple Myeloma

AMN003 (NCT03143049)

CheckMate 602 (NCT02726581)

DREAMM-3 (NCT04162210)

DREAMM-7 (NCT04246047)

DREAMM-8 (NCT04484623)

KarMMa-3 (NCT03651128)

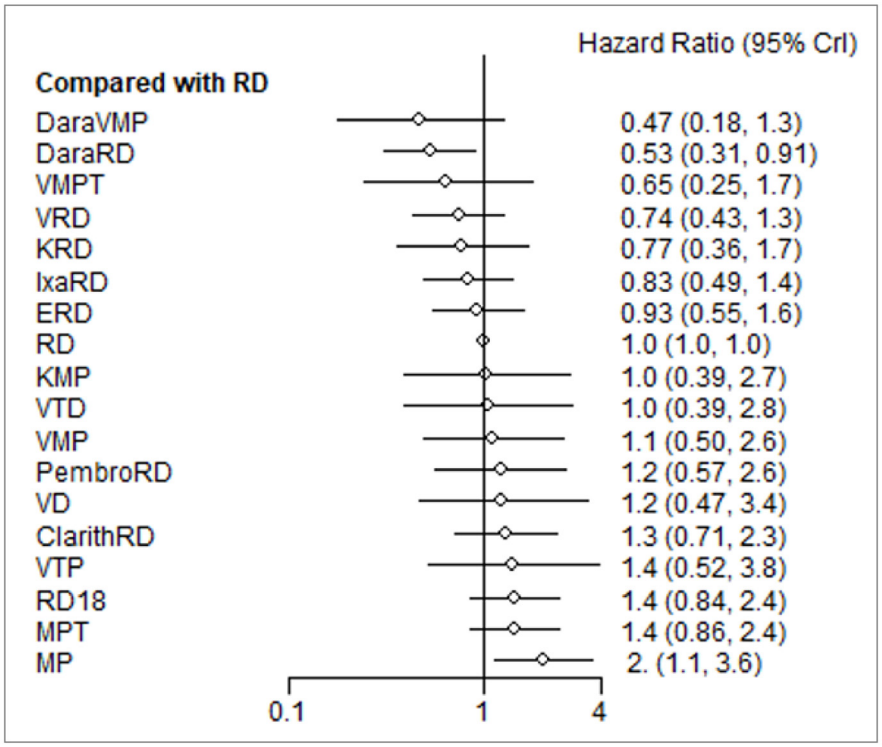
LIGHTHOUSE (NCT04649060)

NCT03440411

Appendix 4: NMA Scenario Analyses for NDMM

Note that this appendix has not been copy-edited.

Figure 6: NMA Analysis for NDMM — Scenario 1



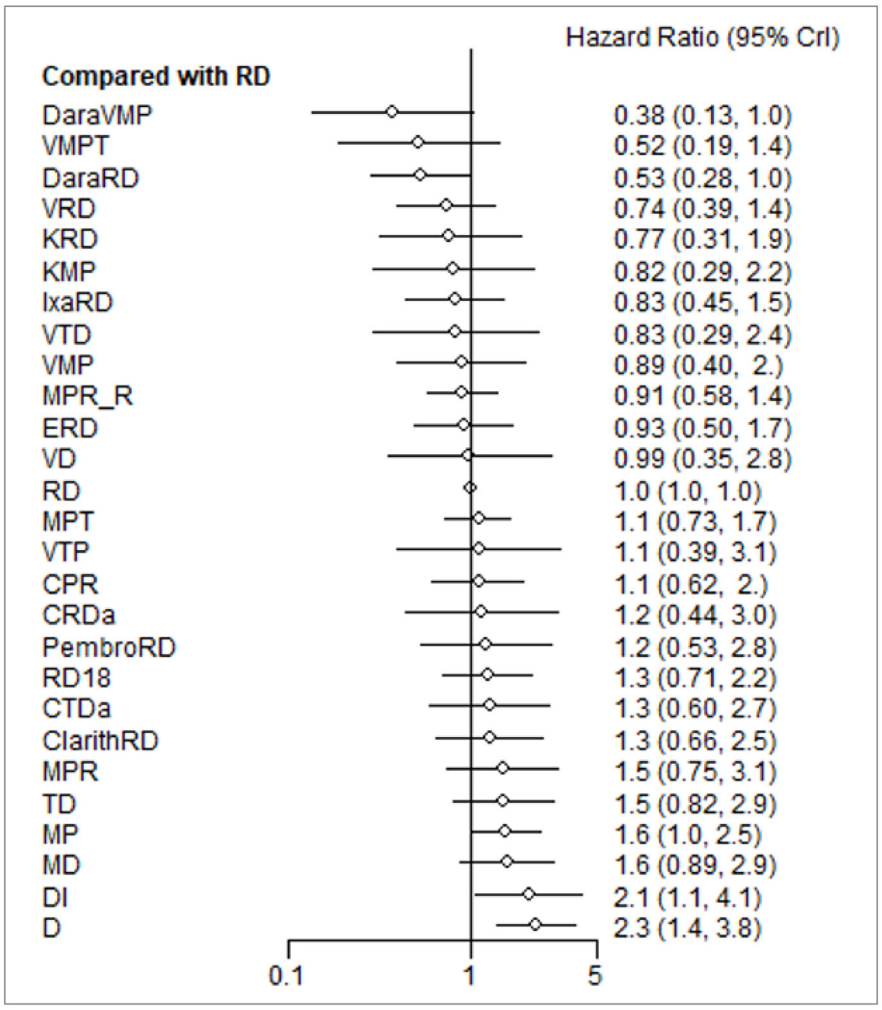
a = attenuated; C = cyclophosphamide; Clarith = Clarithromycin; D = dexamethasone; Dara = daratumumab; E = elotuzumab; I = interferon alpha-2b; Ixa = ixazomib; K = carfilzomib; M = melphalan; P = prednisone; Pembro = pembrolizumab; R = lenalidomide; t = thalidomide; V = bortezomib.

ClarithRD = clarithromycin-lenalidomide-dexamethasone; CPR = cyclophosphamide-prednisone-lenalidomide; CRDa = attenuated cyclophosphamide-lenalidomide-dexamethasone; CTDa = attenuated cyclophosphamide-thalidomide-dexamethasone;

D = dexamethasone; DaraRD = daratumumab-lenalidomide-dexamethasone; DaraVMP = daratumumab-bortezomib-melphalan-prednisone; DI = dexamethasone-interferon alpha-2b; ERD = elotuzumab-lenalidomide-dexamethasone; IxaRD = ixazomib-lenalidomide-dexamethasone;

KRD = carfilzomib-lenalidomide-dexamethasone; KMP = carfilzomib-melphalan-prednisone; MD = melphalan-dexamethasone; MP = melphalan-prednisone; MPR = melphalan-prednisone-lenalidomide; MPR_R = melphalan-prednisone-lenalidomide, followed by lenalidomide maintenance; MPT = melphalan-prednisone-thalidomide; PembroRD = pembrolizumab-lenalidomide-dexamethasone; RD = lenalidomide-dexamethasone; RD18 = lenalidomide-dexamethasone for 18 4-week cycles; TD = thalidomide-dexamethasone; VD = bortezomib-dexamethasone; VMP = bortezomib-melphalan-prednisone; VMPT = bortezomib-melphalan-prednisone-thalidomide; VRD = bortezomib-lenalidomide-dexamethasone; VTD = bortezomib-thalidomide-dexamethasone; VTP = bortezomib-thalidomide-prednisone.

Figure 7: NMA Analysis for NDMM — Scenario 2

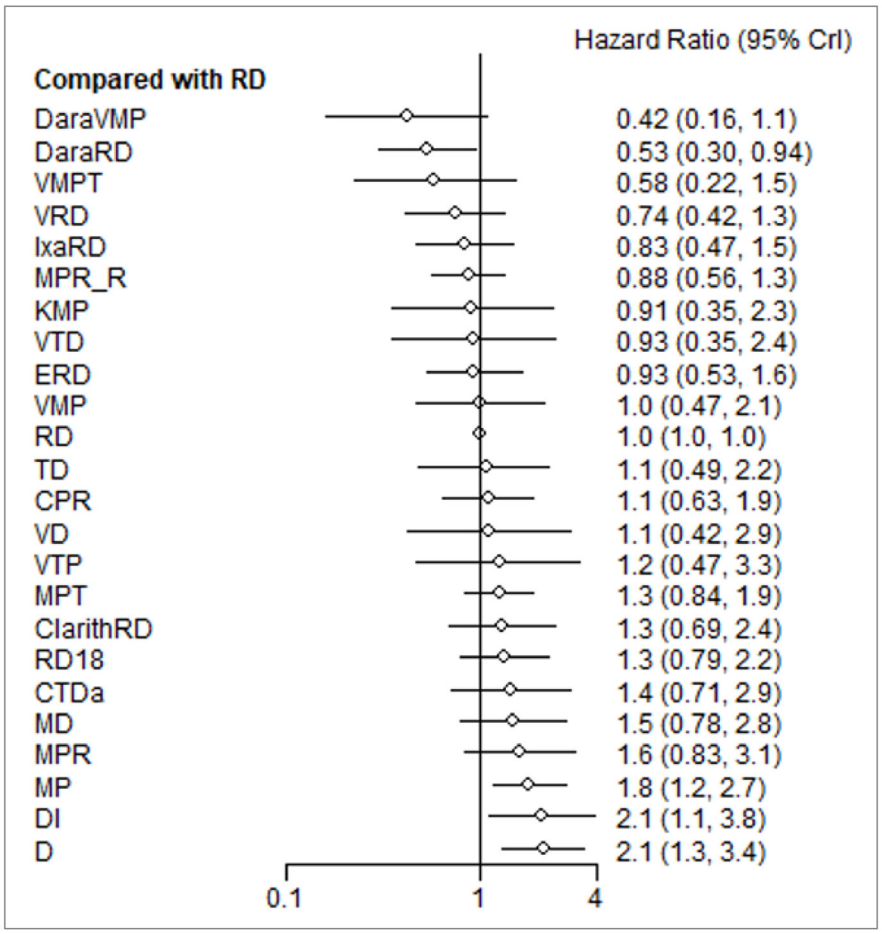


a = attenuated; C = cyclophosphamide; Clarith = Clarithromycin; D = dexamethasone; Dara = daratumumab; E = elotuzumab; I = interferon alpha-2b; Ixa = ixazomib; K = carfilzomib; M = melphalan; P = prednisone; Pembro = pembrolizumab; R = lenalidomide; t = thalidomide; V = bortezomib.

ClarithRD = clarithromycin-lenalidomide-dexamethasone; CPR = cyclophosphamide-prednisone-lenalidomide; CRDa = attenuated cyclophosphamide-lenalidomide-dexamethasone; CTDa = attenuated cyclophosphamide-thalidomide-dexamethasone;

D = dexamethasone; DaraRD = daratumumab-lenalidomide-dexamethasone; DaraVMP = daratumumab-bortezomib-melphalan-prednisone; DI = dexamethasone-interferon alpha-2b; ERD = elotuzumab-lenalidomide-dexamethasone; IxaRD = ixazomib-lenalidomide-dexamethasone; KRD = carfilzomib-lenalidomide-dexamethasone; KMP = carfilzomib-melphalan-prednisone; MD = melphalan-dexamethasone; MP = melphalan-prednisone; MPR = melphalan-prednisone-lenalidomide; MPR_R = melphalan-prednisone-lenalidomide, followed by lenalidomide maintenance; MPT = melphalan-prednisone-thalidomide; PembroRD = pembrolizumab-lenalidomide-dexamethasone; RD = lenalidomide-dexamethasone; RD18 = lenalidomide-dexamethasone for 18 4-week cycles; TD = thalidomide-dexamethasone; VD = bortezomib-dexamethasone; VMP = bortezomib-melphalan-prednisone; VMPT = bortezomib-melphalan-prednisone-thalidomide; VRD = bortezomib-lenalidomide-dexamethasone; VTD = bortezomib-thalidomide-dexamethasone; VTP = bortezomib-thalidomide-prednisone.

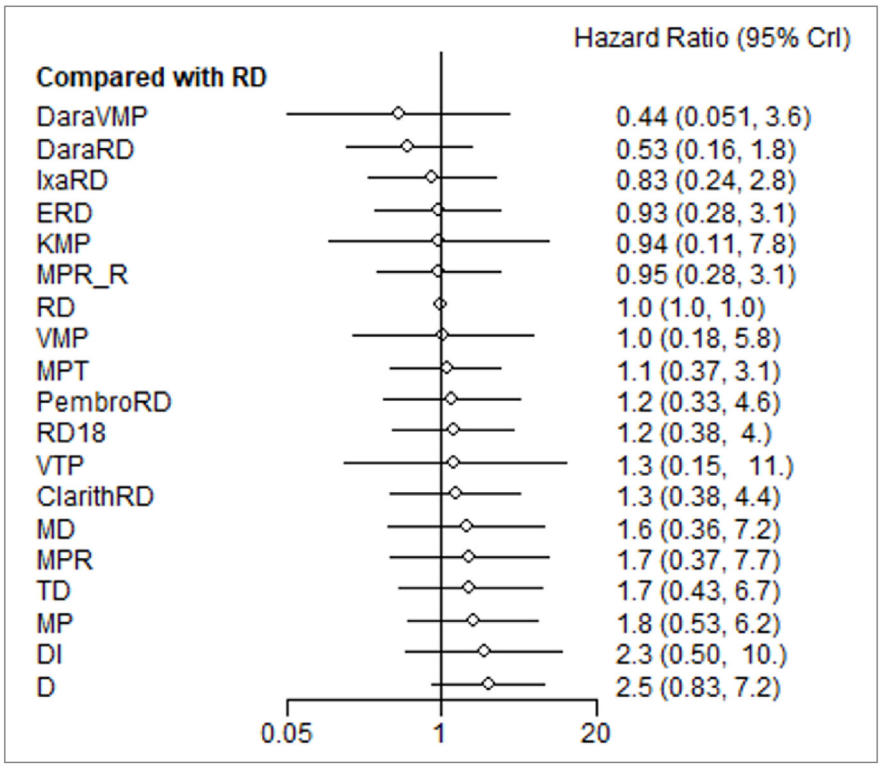
Figure 8: NMA Analysis for NDMM — Scenario 3



a = attenuated; C = cyclophosphamide; Clarith = Clarithromycin; D = dexamethasone; Dara = daratumumab; E = elotuzumab; I = interferon alpha-2b; Ixa = ixazomib; K = carfilzomib; M = melphalan; P = prednisone; Pembro = pembrolizumab; R = lenalidomide; t = thalidomide; V = bortezomib.

ClarithRD = clarithromycin-lenalidomide-dexamethasone; CPR = cyclophosphamide-prednisone-lenalidomide; CRDa = attenuated cyclophosphamide-lenalidomide-dexamethasone; CTDa = attenuated cyclophosphamide-thalidomide-dexamethasone;D = dexamethasone; DaraRD = daratumumab-lenalidomide-dexamethasone; DaraVMP = daratumumab-bortezomib-melphalan-prednisone; DI = dexamethasone-interferon alpha-2b; ERD = elotuzumab-lenalidomide-dexamethasone; IxaRD = ixazomib-lenalidomide-dexamethasone;KRD = carfilzomib-lenalidomide-dexamethasone; KMP = carfilzomib-melphalan-prednisone; MD = melphalan-dexamethasone; MP = melphalan-prednisone; MPR = melphalan-prednisone-lenalidomide; MPR_R = melphalan-prednisone-lenalidomide, followed by lenalidomide maintenance; MPT = melphalan-prednisone-thalidomide; PembroRD = pembrolizumab-lenalidomide-dexamethasone; RD = lenalidomide-dexamethasone; RD18 = lenalidomide-dexamethasone for 18 4-week cycles; TD = thalidomide-dexamethasone; VD = bortezomib-dexamethasone; VMP = bortezomib-melphalan-prednisone; VMPT = bortezomib-melphalan-prednisone-thalidomide; VRD = bortezomib-lenalidomide-dexamethasone; VTD = bortezomib-thalidomide-dexamethasone; VTP = bortezomib-thalidomide-prednisone.

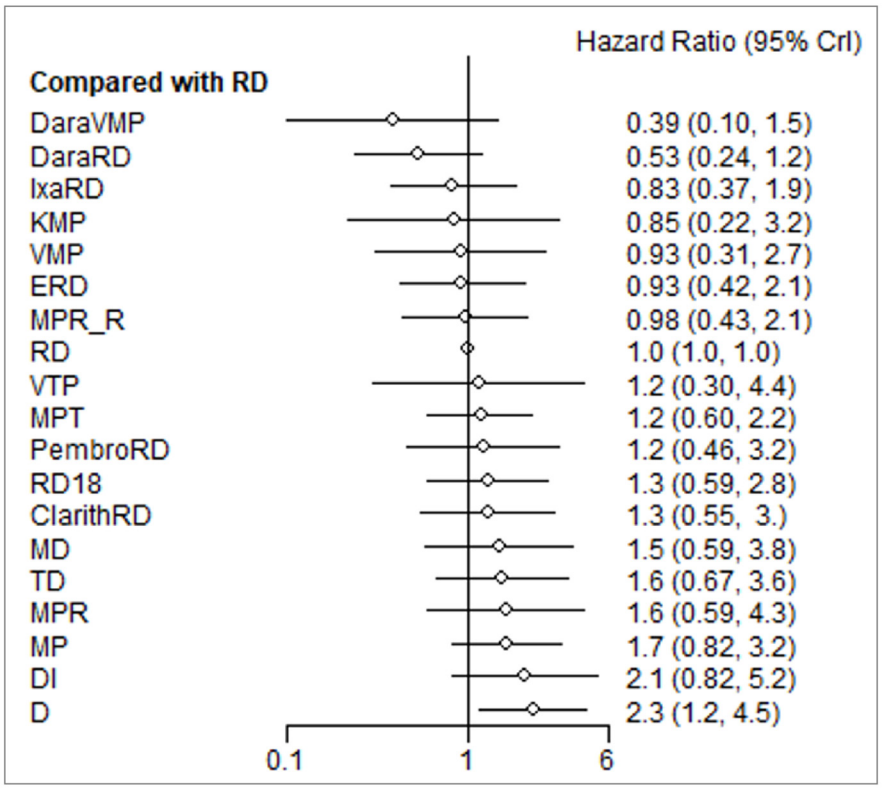
Figure 9: NMA Analysis for NDMM — Scenario 4



a = attenuated; C = cyclophosphamide; Clarith = Clarithromycin; D = dexamethasone; Dara = daratumumab; E = elotuzumab; I = interferon alpha-2b; Ixa = ixazomib; K = carfilzomib; M = melphalan; P = prednisone; Pembro = pembrolizumab; R = lenalidomide; t = thalidomide; V = bortezomib.

ClarithRD = clarithromycin-lenalidomide-dexamethasone; CPR = cyclophosphamide-prednisone-lenalidomide; CRDa = attenuated cyclophosphamide-lenalidomide-dexamethasone; CTDa = attenuated cyclophosphamide-thalidomide-dexamethasone;D = dexamethasone; DaraRD = daratumumab-lenalidomide-dexamethasone; DaraVMP = daratumumab-bortezomib-melphalan-prednisone; DI = dexamethasone-interferon alpha-2b; ERD = elotuzumab-lenalidomide-dexamethasone; IxaRD = ixazomib-lenalidomide-dexamethasone;KRD = carfilzomib-lenalidomide-dexamethasone; KMP = carfilzomib-melphalan-prednisone; MD = melphalan-dexamethasone; MP = melphalan-prednisone; MPR = melphalan-prednisone-lenalidomide; MPR_R = melphalan-prednisone-lenalidomide, followed by lenalidomide maintenance; MPT = melphalan-prednisone-thalidomide; PembroRD = pembrolizumab-lenalidomide-dexamethasone; RD = lenalidomide-dexamethasone; RD18 = lenalidomide-dexamethasone for 18 4-week cycles; TD = thalidomide-dexamethasone; VD = bortezomib-dexamethasone; VMP = bortezomib-melphalan-prednisone; VMPT = bortezomib-melphalan-prednisone-thalidomide; VRD = bortezomib-lenalidomide-dexamethasone; VTD = bortezomib-thalidomide-dexamethasone; VTP = bortezomib-thalidomide-prednisone.

Figure 10: NMA Analysis for NDMM — Scenario 5



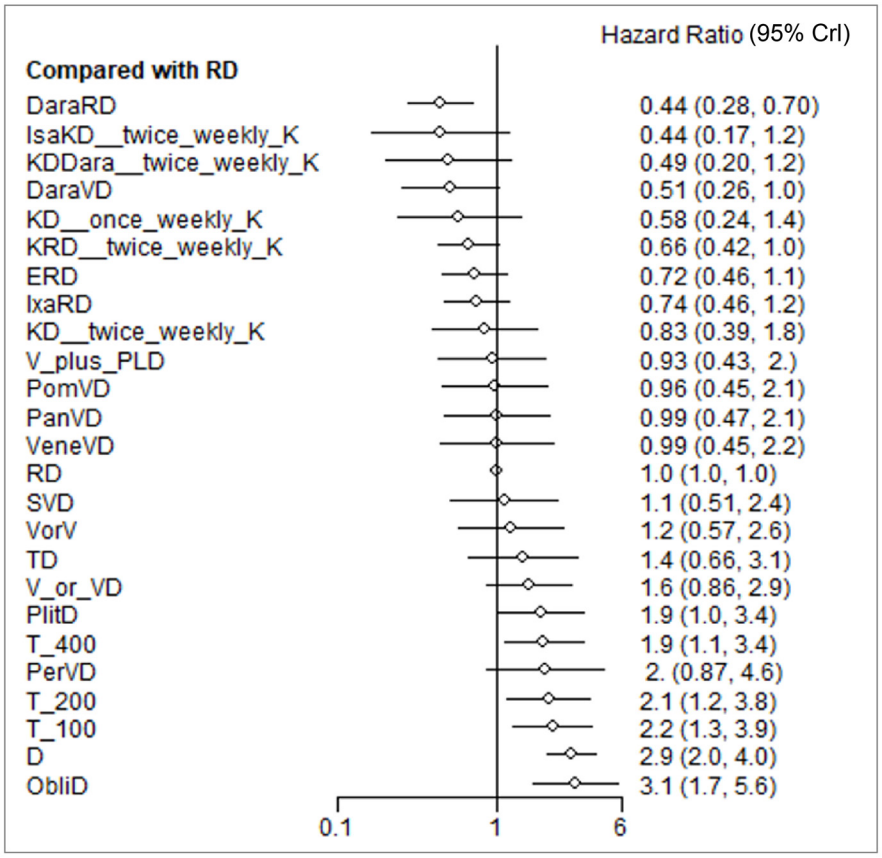
a = attenuated; C = cyclophosphamide; Clarith = Clarithromycin; D = dexamethasone; Dara = daratumumab; E = elotuzumab; I = interferon alpha-2b; Ixa = ixazomib; K = carfilzomib; M = melphalan; P = prednisone; Pembro = pembrolizumab; R = lenalidomide; t = thalidomide; V = bortezomib.

ClarithRD = clarithromycin-lenalidomide-dexamethasone; CPR = cyclophosphamide-prednisone-lenalidomide; CRDa = attenuated cyclophosphamide-lenalidomide-dexamethasone; CTDa = attenuated cyclophosphamide-thalidomide-dexamethasone;D = dexamethasone; DaraRD = daratumumab-lenalidomide-dexamethasone; DaraVMP = daratumumab-bortezomib-melphalan-prednisone; DI = dexamethasone-interferon alpha-2b; ERD = elotuzumab-lenalidomide-dexamethasone; IxaRD = ixazomib-lenalidomide-dexamethasone;KRD = carfilzomib-lenalidomide-dexamethasone; KMP = carfilzomib-melphalan-prednisone; MD = melphalan-dexamethasone; MP = melphalan-prednisone; MPR = melphalan-prednisone-lenalidomide; MPR_R = melphalan-prednisone-lenalidomide, followed by lenalidomide maintenance; MPT = melphalan-prednisone-thalidomide; PembroRD = pembrolizumab-lenalidomide-dexamethasone; RD = lenalidomide-dexamethasone; RD18 = lenalidomide-dexamethasone for 18 4-week cycles; TD = thalidomide-dexamethasone; VD = bortezomib-dexamethasone; VMP = bortezomib-melphalan-prednisone; VMPT = bortezomib-melphalan-prednisone-thalidomide; VRD = bortezomib-lenalidomide-dexamethasone; VTD = bortezomib-thalidomide-dexamethasone; VTP = bortezomib-thalidomide-prednisone.

Appendix 5: NMA Scenario Analyses for r/r Multiple Myeloma

Note that this appendix has not been copy-edited.

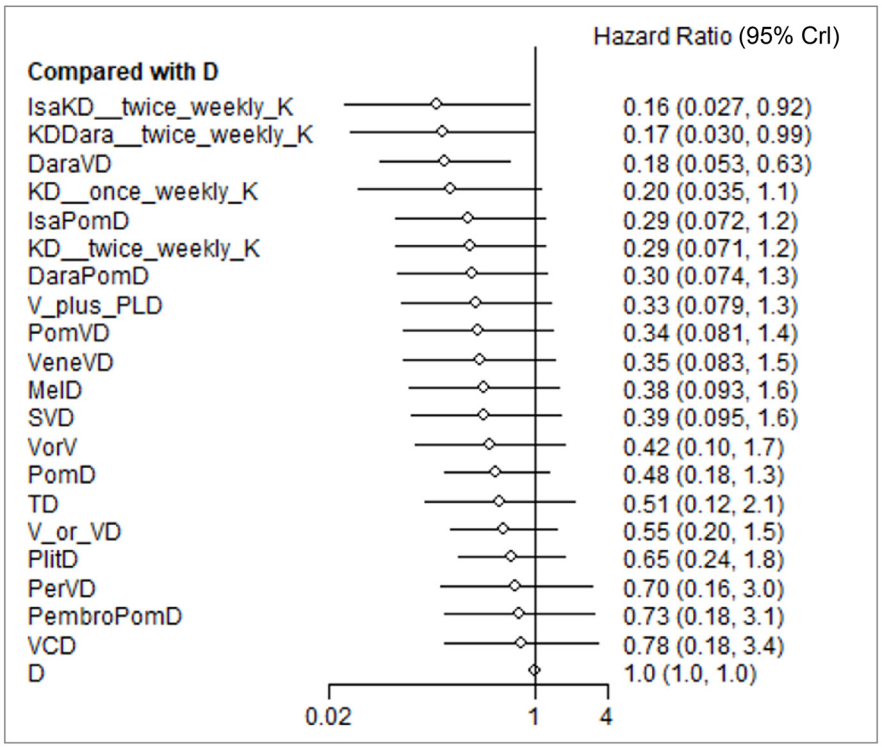
Figure 11: NMA Analysis for r/r MM — Scenario 2



C = cyclophosphamide; D = dexamethasone; Dara = daratumumab; E = elotuzumab; Isa = isatuximab; Ixa = ixazomib; K = carfilzomib; Mel = melflufen; Obli = oblimersen sodium; Pan = panobonistat; Pembro = pembrolizumab; Per = perifosine; PLD = pegylated liposomal doxorubicin; Plit = plitidepsine; Pom = pomalidomide; R = lenalidomide; S = selinexor; t = thalidomide; V = bortezomib; Vene = venetoclax; Vor = vorinostat.D = dexamethasone; DaraPomD = daratumumab-pomalidomide-dexamethasone; DaraRD = daratumumab-lenalidomide-dexamethasone; DaraVD = daratumumab-bortezomib-dexamethasone; ERD = elotuzumab-lenalidomide-dexamethasone; IsaKD_twice weekly_K = isatuximab-carfilzomib-dexamethasone with twice weekly of carfilzomib; IsaPomD = isatuximab-pomalidomide-dexamethasone; IxaRD = ixazomib-lenalidomide-dexamethasone; KD_once weekly_K = carfilzomib-dexamethasone with once weekly of carfilzomib; KD_twice_weekly_K = carfilzomib-dexamethasone with twice weekly of carfilzomib; KDDara_twice_weekly_K = carfilzomib-dexamethasone-daratumumab with twice weekly of carfilzomib; KRD_twice_weekly_K = carfilzomib-lenalidomide-dexamethasone with twice weekly of carfilzomib; MelD = melflufen-dexamethasone; ObliD = oblimersen sodium-dexamethasone

PanVD = panobonistat-bortezomib-dexamethasone; PembroPomD = pembrolizumab-pomalidomide-dexamethasone; PerVD = perifosine-bortezomib-dexamethasone; PlitD = plitidepsine-dexamethasone; PomD = pomalidomide-dexamethasone; PomVD = pomalidomide-bortezomib-dexamethasone;RD = lenalidomide-dexamethasone; SVD = selinexor-bortezomib-dexamethasone; T_100 = thalidomide 100 mg/day; T_200 = thalidomide 200 mg/day; T_400 = thalidomide 400mg/day; TD = thalidomide-dexamethasone; V_or_VD = bortezomib or bortezomib-dexamethasone; V_plus_PLD = bortezomib plus pegylated liposomal doxorubicin; VCD = bortezomib-cyclophosphamide-dexamethasone; VeneVD = venetoclax-bortezomib-dexamethasone; VorV = vorinostat-bortezomib.

Figure 12: NMA Analysis for r/r MM — Scenario 5



C = cyclophosphamide; D = dexamethasone; Dara = daratumumab; E = elotuzumab; Isa = isatuximab; Ixa = ixazomib; K = carfilzomib; Mel = melflufen; Obli = oblimersen sodium; Pan = panobonistat; Pembro = pembrolizumab; Per = perifosine; PLD = pegylated liposomal doxorubicin; Plit = plitidepsine; Pom = pomalidomide; R = lenalidomide; S = selinexor; t = thalidomide; V = bortezomib; Vene = venetoclax; Vor = vorinostat; D = dexamethasone; DaraPomD = daratumumab-pomalidomide-dexamethasone; DaraRD = daratumumab-lenalidomide-dexamethasone; DaraVD = daratumumab-bortezomib-dexamethasone; ERD = elotuzumab-lenalidomide-dexamethasone; IsaKD_twice weekly_K = isatuximab-carfilzomib-dexamethasone with twice weekly of carfilzomib; IsaPomD = isatuximab-pomalidomide-dexamethasone; IxaRD = ixazomib-lenalidomide-dexamethasone; KD_once weekly_K = carfilzomib-dexamethasone with once weekly of carfilzomib; KD_twice_weekly_K = carfilzomib-dexamethasone with twice weekly of carfilzomib; KDDara_twice_weekly_K = carfilzomib-dexamethasone-daratumumab with twice weekly of carfilzomib; KRD_twice_weekly_K = carfilzomib-lenalidomide-dexamethasone with twice weekly of carfilzomib; MelD = melflufen-dexamethasone; ObliD = oblimersen sodium-dexamethasonePanVD = panobonistat-bortezomib-dexamethasone; PembroPomD = pembrolizumab-pomalidomide-dexamethasone; PerVD = perifosine-bortezomib-dexamethasone; PlitD = plitidepsine-dexamethasone; PomD = pomalidomide-dexamethasone; PomVD = pomalidomide-bortezomib-dexamethasone;RD = lenalidomide-dexamethasone; SVD = selinexor-bortezomib-dexamethasone; T_100 = thalidomide 100mg/day; T_200 = thalidomide 200 mg/day; T_400 = thalidomide 400mg/day; TD = thalidomide-dexamethasone; V_or_VD = bortezomib or bortezomib-dexamethasone; V_plus_PLD = bortezomib plus pegylated liposomal doxorubicin; VCD = bortezomib-cyclophosphamide-dexamethasone; VeneVD = venetoclax-bortezomib-dexamethasone; VorV = vorinostat-bortezomib.

Appendix 6: NMA — Extracted Data for Study Characteristics and Patient Characteristics

Table 10: Extracted Data — Study Characteristics NDMM

Trial name	NCT number	First author's last name	Publication year	Experimental arm(s)	Comparator arm(s)	Maintenance therapy		Enrolment period	Blinding	Primary outcome(s)
						Experimental arm(s)	Comparator arm(s)			
ALCYONE	NCT02195479	Mateos	2020	DaraVMP	VMP	Dara	NA	Feb 2015 - Jul 2016	Open-label	PFS
CLARION	NCT01818752	Facon	2019	KMP	VMP	NA	NA	July 2013 - Jun 2015	Open-label	PFS
E1A06	NCT00602641	Stewart	2015	MPT	MPR	T	R	Feb 2008 - Nov 2011	Open-label	PFS
ELOQUENT-1	NCT01335399	Dimopoulos	2022	ERD	RD	NA	NA	Aug 2011 - Jun 2014	Open-label	PFS
EMN01	NCT01093196	Bringhen	2020	MPR CPR	RD	R or RP	R or RP	Aug 2009 - Sep 2012	Open-label	PFS
ENDURANCE (E1A11)	NCT01863550	Kumar	2020	KRD	VRD	Indefinite R or limited (2 years) R	Indefinite R or limited (2 years) R	Dec 2013 - Feb 2019	Open-label	PFS
FIRST (MM-02)	NCT00689936	Facon	2018	RD continuous RD18	MPT	NA	NA	Aug 2008 - Mar 2011	Open-label	PFS
GEM2005	NCT00443235	Mateos	2014	VMP	VTP	VT or VP	VT or VP	Mar 2006 - Oct 2008	Open-label	RR
GEM-CLARIDEX	NCT02575144	Puig	2021	ClarithRD	RD	NA	NA	Jul 2015 - May 2019	Open-label	PFS
GIMEMA MM-03 to 05	NCT01063179	Palumbo	2014	VMPT	VMP	VT	NA	May 2006 - Jan 2009	Open-label	PFS

Trial name	NCT number	First author's last name	Publication year	Experimental arm(s)	Comparator arm(s)	Maintenance therapy		Enrolment period	Blinding	Primary outcome(s)
						Experimental arm(s)	Comparator arm(s)			
GISMM2001-A	NCT00232934	Palumbo	2008	MPT	MP	T	NA	Jan 2002 - May 2005	Open-label	RR PFS
HOVON 49	NA	Wijermans	2010	MPT	MP	T	NA	Sep 2002 - Jul 2007	Open-label	EFS
HOVON 87	NA	Zweegman	2016	MPR	MPT	R	T	Mar 2009 - Oct 2012	Open-label	PFS
IFM 01/01	NCT00644306	Hulin	2009	MPT	MP (+ PLC)	NA	NA	Apr 2002 - Dec 2006	Double-blinded	OS
IFM 95 to 01	NA	Facon	2006	MP	MD D DI	NA	NA	Jun 1995 - Sep 1998	Open-label	OS
KEYNOTE-185	NCT02579863	Usmani	2019	PembroRD	RD	NA	NA	Jan 2016 - Jun 2017	Open-label	PFS
MAIA (MMY3008)	NCT02252172	Facon	2021	DaraRD	RD	NA	NA	Mar 2015 - Jan 2017	Open-label	PFS
MM-015	NCT00405756	Palumbo	2012	MPR	MPR MP	MPR: R	MPR: PLC MP: PLC	Feb 2007 - Sep 2008	Double-blinded	PFS
MM-PETHEMA 96	NA	Hernández	2004	MP	MD	DI	DI	NR	NR	NR
MRC Myeloma IX	NA	Morgan	2013	CTD (attenuated)	MP	T or no maintenance	T or no maintenance	Jun 2003 - Nov 2007	Open-label	PFS OS
MY.7	NA	Shustik	2006	MP	MD	D or observation	D or observation	Jun 1995 - Jul 2003	Open-label	OS
Myeloma XI	NCT01554852	Jackson	2020	CRD (attenuated)	CTD (attenuated)	R, VorR, or observation	R, VorR, or observation	May 2010 - Apr 2016	Open-label	PFS OS

Trial name	NCT number	First author's last name	Publication year	Experimental arm(s)	Comparator arm(s)	Maintenance therapy		Enrolment period	Blinding	Primary outcome(s)
						Experimental arm(s)	Comparator arm(s)			
NMSG 12	NCT00218855	Waage	2010	MPT	MP	T	PLC	Jan 2002 - May 2007	Double-blinded	OS
S0232	NCT00064038	Zonder	2010	RD	D (+ PLC)	RD	D (+ PLC)	Oct 2004 - Apr 2007	Double-blinded	PFS
S0777	NCT00644228	Durie	2020	VRD	RD	RD	RD	Apr 2008 - Feb 2012	Open-label	PFS
THAL-MM-03	NCT00057564	Rajkumar	2008	TD	D (+ PLC)	NA	NA	Mar 2003 - Apr 2005	Double-blinded	TTP
TMSG-2005 to 001	NCT00934154	Beksac	2010	MPT	MP	NA	NA	Feb 2006 - Jun 2009	Open-label	Response Toxicities
TOURMALINE-MM2	NCT01850524	Facon	2021	IxaRD	RD (+ PLC)	NA	NA	May 2013 - Dec 2015	Double-blinded	PFS
UPFRONT	NCT00507416	Niesvizky	2015	VD VTD	VMP	VD: V VTD: V	VMP: V	Jun 2007 - Mar 2010	Open-label	PFS
VISTA	NCT00111319	San Miguel	2013	VMP	MP	NA	NA	Dec 2004 - Sep 2006	Open-label	TTP
NA	NCT00205751	Ludwig	2009	TD	MP	T + I or I	T + I or I	Aug 2001 - Oct 2007	Open-label	PFS Tolerance

Note this table has not been copy-edited.

Table 11: Extracted Data — Patient Characteristics and Outcomes for NDMM

Trial name	Sample size (ITT population)		Median age (in years)		Proportion of male patients		Median (IQR) follow-up (in months)		HR for PFS (95% CI)	HR for TTP (95% CI)
	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)		
ALCYONE	350	356	71	71	46%	47%	40.1 (37.4 to 43.1)		0.42 (0.34 to 0.51)	NR
CLARION	478	477	72	72	51%	50%	22 (NR)		0.91 (0.75 to 1.10)	0.84 (0.68 to 1.04)
E1A06	154	152	76	77	56%	53%	40.7 (NR)		0.84 (0.64 to 1.09)	NR
ELOQUENT-1	374	374	73	73	56%	54%	70.6 (35.1 to 79.2)		0.93 (0.77 to 1.12)	0.85 (0.69 to 1.05)
EMN01	MPR: 218 CPR: 222	RD: 222	MPR: 74 CPR: 73	RD: 73	MPR: 50% CPR: 48%	RD: 49%	71 (NR)		MPR vs. RD: 0.84 (0.68 to 1.04) MPR vs. CPR: 0.78 (0.63 to 0.96) CPR vs. RD: NR	NR
ENDURANCE (E1A11)	545	542	65	64	60%	58%	9 (5 to 23)		1.04 (0.83 to 1.31)	0.97 (0.75 to 1.24)
FIRST (MM-02)	RD continuous: 535 RD18: 541	MPT: 547	RD continuous: 73 RD18: 73	MPT: 73	RD continuous: 55% RD18: 50%	MPT: 52%	67 (range: 0 to 87)		RD continuous vs. MPT: 0.69 (0.59 to 0.79) RD	NR

Trial name	Sample size (ITT population)		Median age (in years)		Proportion of male patients		Median (IQR) follow-up (in months)		HR for PFS (95% CI)	HR for TTP (95% CI)
	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)		
									continuous vs. RD18: 0.70 (0.60 to 0.81)	
GEM2005	130	130	73	73	53%	47%	72 (NR)		0.80 (0.61 to 1.04)[a]	NR
GEM-CLARIDEX	143	143	75	76	50%	45%	19 (range: 0 to 54)		1.29 (0.92 to 1.82)	NR
GIMEMA MM-03 to 05	254	257	71	71	51%	47%	54 (NR)		0.58 (0.47 to 0.71)	NR
GISMM2001-A	167	164	72	72	NR	NR	38.4 (range: 0.2 to 69.5)	37.7 (range: 0 to 72.3)	0.63 (0.48 to 0.81)	0.57 (0.44 to 0.75)
HOVON 49	165	168	72	73	57%	55%	39 (NR)		0.79 (0.62 to 1.00)[b]	NR
HOVON 87	319	318	73	72	58%	51%	36 (NR)		0.87 (0.72 to 1.04)	NR
IFM 01/01	113	116	79		38%	53%	47.5 (NR)		0.61 (0.46 to 0.82)[b]	NR
IFM 95 to 01	MP: 122	MD: 118 D: 127 DI: 121	MP: 70	MD: 69 D: 70 DI: 69	MP: 57%	MD: 47% D: 50% DI: 50%	82.8 (SE: 1.6)		DI vs. D: 0.93 (0.72 to 1.20)[c] MD vs. D: 0.57 (0.44 to 0.74)[c] MP vs. D: 0.67 (0.52 to 0.87)[c]	NR

Trial name	Sample size (ITT population)		Median age (in years)		Proportion of male patients		Median (IQR) follow-up (in months)		HR for PFS (95% CI)	HR for TTP (95% CI)
	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)		
									MD vs. DI: 0.62 (0.48 to 0.80)[c] MP vs. DI: 0.73 (0.56 to 0.94)[c] MD vs. MP: 0.85 (0.66 to 1.10)[c]	
KEYNOTE-185	151	150	74	74	46%	47%	6.6 (3.4 to 9.6)		1.22 (0.67 to 2.22)	0.55 (0.20 to 1.50)
MAIA (MMY3008)	368	369	73	74	51%	53%	56.6 (53.0 to 60.1)	55.9 (52.5 to 59.4)	0.53 (0.43 to 0.66)	NR
MM-015	MPR(R): 152	MPR: 153 MP: 154	MPR(R): 71	MPR: 71 MP: 72	MPR(R): 47%	MPR: 54% MP: 49%	30 (range: 1 to 47)		MPR(R) vs. MPR: 0.47 (0.33 to 0.67)[c] MPR(R) vs. MP: 0.37 (0.26 to 0.52)[c] MP vs. MPR: 1.27 (0.94 to 1.73)[c]	NR
MM-PETHEMA 96	96	100	74	74	42%	43%	53.6 (21.3 to 76.7)		0.98 (0.74 to 1.32) [c,d]	NR
MRC Myeloma IX	426	423	73	73	57%	55%	70.8 (NR)		0.81 (0.69 to 0.94)	NR

Trial name	Sample size (ITT population)		Median age (in years)		Proportion of male patients		Median (IQR) follow-up (in months)		HR for PFS (95% CI)	HR for TTP (95% CI)
	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)		
MY.7	234	232	71	71	43%	38%	62.4 (NR)		0.88 (0.72 to 1.07)	NR
Myeloma XI	928	924	75	74	55%	58%	50 (48 to 78)		0.91 (0.83 to 1.01)	NR
NMSG 12	182	175	75	74	51%	61%	42 (NR)		0.89 (0.70 to 1.13)[b]	NR
S0232	97	95	NR	NR	55%	58%	45.4 (NR)		0.56 (0.39 to 0.79)[a]	NR
S0777	235	225	63	63	63%	53%	84 (NR)		0.74 (96% Wald CI: 0.59 to 0.93)	NR
THAL-MM-03	235	235	Mean: 64	Mean: 64	50%	51%	17 (NR)	18 (NR)	0.50 (0.38 to 0.64)	0.43 (0.32 to 0.58)
TMSG-2005 to 001	58	57	69	72	60%	47%	23 (NR)		0.70 (0.42 to 1.17)[b]	NR
TOURMALINE-MM2	351	354	73	74	49%	51%	53.3 (NR)	55.8 (NR)	0.83 (0.68 to 1.02)	0.74 (0.59 to 0.93)
UPFRONT	VD: 168 VTD: 167	VMP: 167	VD: 75 VTD: 73	VMP: 72	VD: 60% VTD: 42%	VMP: 54%	VD: 44.3 (24.7 to 53.3) VTD: 41.3 (21.1 to 49.1)	VMP: 43.4 (35.2 to 54.3)	VD vs. VMP: 1.11 (0.84 to 1.48)[c] VTD vs. VMP: 0.93 (0.69 to 1.26)[c] VD vs. VTD:	NR

Trial name	Sample size (ITT population)		Median age (in years)		Proportion of male patients		Median (IQR) follow-up (in months)		HR for PFS (95% CI)	HR for TTP (95% CI)
	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)		
									1.20 (0.89 to 1.61)[c]	
VISTA	344	338	71	71	51%	49%	60.1 (range: 0 to 74)		0.56 (0.40 to 0.79)[a]	0.48 (NR)
NCT00205751	145	143	72	72	51%	49%	28.1 (range: 1 to 70)		1.30 (0.95 to 1.78)	1.26 (0.88 to 1.80)

C = cyclophosphamide; CI = confidence interval; Clarith = Clarithromycin; D = dexamethasone; Dara = daratumumab; E = elotuzumab; HR = hazard ratio; I = interferon alpha-2b; IQR = interquartile range; Ixa = ixazomib; K = carfilzomib; M = melphalan; NA = not applicable/available; NCT = national clinical trial; NR = not reported; P = prednisone; Pembro = pembrolizumab; PFS = progression-free survival; PLC = placebo; R = lenalidomide; t = thalidomide; TTP = time to progression; V = bortezomib; Vor = vorinostat.

Note this table has not been copy-edited.

[a]Obtained from Blommestein et al.[11]

[b]Retrieved from Fayers et al.[16]

[c]Estimated following the methodology as described by Guyot et al.[17]

[d]EFS (defined as the time between the start of therapy and disease progression, relapse, death, or last follow-up).

Table 12: Extracted Data — Study Characteristics for r/r MM

Trial name	NCT number	First author's last name	Publication year	Experimental arm(s)	Comparator arm(s)	Maintenance therapy		Enrolment period	Blinding	Primary outcome(s)
						Experimental arm(s)	Comparator arm(s)			
ADMYRE	NCT01102426	Spicka	2019	PlitD	D	NA	NA	Jun 2010 - May 2015	Open-label	PFS
APEX	NCT00048230	Richardson	2005	V	D	NA	NA	Jun 2002 - Oct 2003	Open-label	TTP
APOLLO	NCT03180736	Dimopoulos	2021	DaraPomD	PomD	NA	NA	Jun 2017 - Jun 2019	Open-label	PFS

Trial name	NCT number	First author's last name	Publication year	Experimental arm(s)	Comparator arm(s)	Maintenance therapy		Enrolment period	Blinding	Primary outcome(s)
						Experimental arm(s)	Comparator arm(s)			
A.R.R.O.W.	NCT02412878	Moreau	2018	KD (once-weekly K)	KD (twice-weekly K)	NA	NA	Sep 2015 - Aug 2016	Open-label	PFS
ASPIRE	NCT01080391	Siegel	2018	KRD (twice-weekly K)	RD	NA	NA	Jul 2010 - Mar 2012	Open-label	PFS
BELLINI	NCT02755597	Kumar	2020	VeneVD	VD (+ PLC)	NA	NA	Jul 2016 - Oct 2017	Double-blinded	PFS
BOSTON	NCT03110562	Grosicki	2020	SVD	VD	NA	NA	Jun 2017 - Feb 2019	Open-label	PFS
CANDOR	NCT03158688	Usmani	2022	KDDara (twice-weekly K)	KD (twice-weekly K)	NA	NA	Jun 2017 - Jun 2018	Open-label	PFS
CASTOR	NCT02136134	Sonneveld	2022	DaraVD	VD	Dara	NA	Sep 2014 - Sep 2015	Open-label	PFS
CC-5013-MM-009	NCT00056160	Weber	2007	RD	D (+ PLC)	NA	NA	Feb 2003 - Apr 2004	Double-blinded	TTP
CC-5013-MM-010	NCT00424047	Dimopoulos	2007	RD	D (+ PLC)	NA	NA	Sep 2003 - Sep 2004	Double-blinded	TTP
ELOQUENT-2	NCT01239797	Dimopoulos	2020	ERD	RD	NA	NA	Jun 2011 - Nov 2012	Open-label	ORR PFS
ENDEAVOUR	NCT01568866	Orlowski	2019	KD (twice-weekly K)	VD	NA	NA	Jun 2012 - Jun 2014	Open-label	PFS
ICARIA-MM	NCT02990338	Richardson	2022	IsaPomD	PomD	NA	NA	Jan 2017 - Feb 2018	Open-label	PFS
IFM 01 to 02		Yakoub-Agha	2012	T	T	NA	NA	Dec 2001 - Oct 2004	Open-label	OS
IKEMA	NCT03275285	Moreau	2021	IsaKD (twice-weekly K)	KD (twice-weekly K)	NA	NA	Nov 2017 - Mar 2019	Open-label	PFS

Trial name	NCT number	First author's last name	Publication year	Experimental arm(s)	Comparator arm(s)	Maintenance therapy		Enrolment period	Blinding	Primary outcome(s)
						Experimental arm(s)	Comparator arm(s)			
KEYNOTE-183	NCT02576977	Mateos	2019	PembroPomD	PomD	NA	NA	Jan 2016 - Jun 2017	Open-label	PFS OS
LEPUS (MMY3009)	NCT03234972	Fu	2023	DaraVD	VD	NA	NA	Dec 2017 - Aug 2019	Open-label	PFS
MM-003	NCT01311687	Dimopoulos	2015	PomD	D	NA	NA	Mar 2011 - Aug 2012	Open-label	PFS
MMY3001	NCT00103506	Orlowski	2016	V + PLD	V	NA	NA	Dec 2004 - Mar 2006	Open-label	TTP
MMY3022	NCT00813150	Kropff	2017	VCD	VD	NA	NA	Dec 2008 - Dec 2010	Open-label	TTP
NMSG 17/07	NCT00602511	Hjorth	2012	TD	VD	NA	NA	Oct 2007 - Sep 2010	Open-label	PFS
OCEAN	NCT03151811	Schjesvold	2022	MelD	PomD	NA	NA	Jun 2017 - Sep 2020	Open-label	PFS
OPTIMISMM	NCT01734928	Richardson	2019	PomVD	VD	NA	NA	Jan 2013 - May 2017	Open-label	PFS
OPTIMUM	NCT00452569	Kropff	2011	T	D	NA	NA	Mar 2006 - Jan 2009	Open-label	TTP
PANORAMA 1	NCT01023308	San-Miguel	2016	PanVD	VD (+ PLC)	NA	NA	Jan 2010 - Feb 2012	Double-blinded	PFS
POLLUX	NCT02076009	Bahlis	2020	DaraRD	RD	NA	NA	Jun 2014 - Jul 2015	Open-label	PFS
TOURMALINE-MM1	NCT01564537	Richardson	2021	IxaRD	RD (+ PLC)	NA	NA	Aug 2012 - May 2014	Double-blinded	PFS
VANTAGE 088	NCT00773747	Dimopoulos	2013	VorV	V (+ PLC)	NA	NA	Dec 2008 - Sep 2011	Double-blinded	PFS

Trial name	NCT number	First author's last name	Publication year	Experimental arm(s)	Comparator arm(s)	Maintenance therapy		Enrolment period	Blinding	Primary outcome(s)
						Experimental arm(s)	Comparator arm(s)			
—	NCT00017602	Chanan-Khan	2009	ObliD	D	NA	NA	Mar 2001 - Apr 2003	Open-label	TTP
—	NCT01002248	Richardson	2020	PerVD	VD (+ PLC)	NA	NA	Mar 2010 - Mar 2013	Double-blinded	PFS

Note this table has not been copy-edited.

Table 13: Extracted Data — Patient Characteristics and Outcomes for r/r MM

Trial name	Sample size (ITT population)		Median age (in years)		Proportion of male patients		Median (IQR) follow-up (in months)		HR for PFS (95% CI)	HR for TTP (95% CI)
	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)		
ADMYRE	171	84	64	65	57%	42%	NR	NR	0.65 (0.48 to 0.89)	NR
APEX	333	336	62	61	56%	60%	8.3 (NR)		NR	0.55 (0.41 to 0.74)
APOLLO	151	153	67	68	52%	54%	16.9 (14.4 to 20.6)		0.63 (0.47 to 0.85)	NR
A.R.R.O.W.	240	238	66	66	55%	54%	12.6 (11.7 to 13.8)	12.0 (10.5 to 12.6)	0.69 (0.54 to 0.88)	0.66 (0.50 to 0.85)
ASPIRE	396	396	64	65	54%	59%	48.8 (NR)	48.0 (NR)	0.66 (0.55 to 0.78)	NR

Trial name	Sample size (ITT population)		Median age (in years)		Proportion of male patients		Median (IQR) follow-up (in months)		HR for PFS (95% CI)	HR for TTP (95% CI)
	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)		
BELLINI	194	97	66	65	50%	57%	18.7 (16.6 to 21.0)		0.63 (0.44 to 0.90)	0.55 (0.38 to 0.79)
BOSTON	195	207	66	67	59%	56%	13.2 (6.2 to 19.8)	16.5 (9.4 to 19.8)	0.70 (0.53 to 0.93)	NR
CANDOR	312	154	64	65	57%	59%	27.8 (25.6 to 29.5)	27.0 (13.2 to 28.6)	0.59 (0.45 to 0.78)	0.50 (0.37 to 0.67)
CASTOR	251	247	64	64	55%	60%	72.6 (NR)		0.31 (0.25 to 0.40)	NR
CC-5013-MM-009	177	176	64	62	60%	59%	26.2 (NR)	12.9 (NR)	NR	0.35 (0.27 to 0.47)
CC-5013-MM-010	176	175	63	64	59%	59%	16.4 (NR)		NR	0.35 (0.27 to 0.46)
ELOQUENT-2	321	325	67	66	60%	59%	Minimum: 70.6		0.72 (0.60 to 0.87)	NR
ENDEAVOUR	464	465	65	65	52%	49%	44.3 (NR)	43.7 (NR)	0.53 (0.44 to 0.65)	NR
ICARIA-MM	154	153	68	66	58%	46%	35.3 (33.5 to 37.4)		0.60 (0.46 to 0.78)	NR

Trial name	Sample size (ITT population)		Median age (in years)		Proportion of male patients		Median (IQR) follow-up (in months)		HR for PFS (95% CI)	HR for TTP (95% CI)
	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)		
IFM 01 to 02	195	205	NR	NR	46%	49%	36 (NR)		0.82 (0.67 to 1.01)	NR
IKEMA	179	123	65	63	56%	55%	20.7 (19.4 to 22.1)		0.53 (99% CI, 0.32 to 0.89)	NR
KEYNOTE-183	125	124	65	67	62%	63%	7.8 (4.0 to 10.5)	8.6 (5.1 to 11.1)	1.53 (1.05 to 2.22)	NR
LEPUS (MMY3009)	141	70	61	61	60%	60%	25.1 (range: 0 to 42.1)		0.35 (0.24 to 0.51)	0.34 (0.22 to 0.51)
MM-003	302	153	64	65	60%	57%	15.4 (NR)		0.48 (0.39 to 0.60)	NR
MMY3001	324	322	61	62	58%	54%	103 (NR)		0.59 (0.46 to 0.76)	0.55 (0.43-.071)
MMY3022	47	46	Mean: 71	Mean: 68	55%	54%	24 (NR)		NR	1.41 (0.84 to 2.33)
NMSG 17/07	67	64	71	71	42%	64%	16 (4 to 47)	15 (4 to 21)	0.92 (0.68 to 1.25)	NR

Trial name	Sample size (ITT population)		Median age (in years)		Proportion of male patients		Median (IQR) follow-up (in months)		HR for PFS (95% CI)	HR for TTP (95% CI)
	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)		
OCEAN	246	249	68	68	57%	56%	19.8 (12.0 to 25.0)	18.6 (11.8 to 23.7)	0.79 (0.64 to 0.98)	NR
OPTIMISMM	281	278	67	68	55%	53%	15.9 (9.9 to 21.7)		0.61 (0.49 to 0.77)	NR
OPTIMUM	T 100: 121 T 200: 122 T 400: 130	126	T 100: 64 T 200: 63 T 400: 65	63	T 100: 45% T 200: 46% T 400: 59%	45%	NR	NR	T 400 vs. D: 0.74 (0.55 to 1.00)	T 100 vs. D: 0.74 (0.57 to 0.97) T 200 vs. D: 0.73 (0.56 to 0.95) T 400 vs. D: 0.71 (0.54 to 0.92) T 200 vs. T 100: 0.98 (0.75 to 1.29) T 400 vs. T 100: 0.95 (0.73 to 1.25) T 400 vs. T 200: 0.97 (0.74 to 1.27)
PANORAMA 1	387	381	63	63	52%	54%	6.47 (1.81 to 13.47)	5.59 (2.14 to 11.30)	0.63 (0.52 to 0.76)	NR

Trial name	Sample size (ITT population)		Median age (in years)		Proportion of male patients		Median (IQR) follow-up (in months)		HR for PFS (95% CI)	HR for TTP (95% CI)
	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)	Experimental arm(s)	Comparator arm(s)		
POLLUX	286	283	65	65	NR	NR	44.3 (range: 0 to 50.9)		0.44 (0.35 to 0.55)	NR
TOURMALINE-MM1	360	362	66	66	58%	56%	85.0 (NR)	85.1 (NR)	0.74 (0.59 to 0.94)	NR
VANTAGE 088	317	320	61	63	60%	58%	14.2 (NR)		0.77 (0.64 to 0.94)	0.79 (0.64 to 0.96)
—	110	114	59	65	53%	56%	NR	NR	NR	1.07 (0.88 to 1.61)
—	69	66	NR	NR	60%	56%	11.0 (NR)	9.2 (NR)	1.27 (0.82 to 1.97)	NR

C = Cyclophosphamide; CI = confidence interval; D = Dexamethasone; Dara = Daratumumab; E = Elotuzumab; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; IQR = interquartile range; Isa = Isatuximab; Ixa = Ixazomib; K = Carfilzomib; M = Melphalan; NA = Not applicable; NCT = national clinical trial; NE = Not estimable; NR = Not reported; Obli = Oblimersen sodium; Pan = Panobonistat; Pembro = Pembrolizumab; PFS = progression-free survival; PLC = Placebo; PLD = Pegylated liposomal doxorubicin; Plit = Plitidepsine; Pom = Pomalidomide; R = Lenalidomide; S = Selinexor; t = Thalidomide; TTP = time to progression; V = Bortezomib; Vene = Venetoclax; Vor = Vorinostat.

[a]Obtained from Van Beurden-Tan et al.[12]

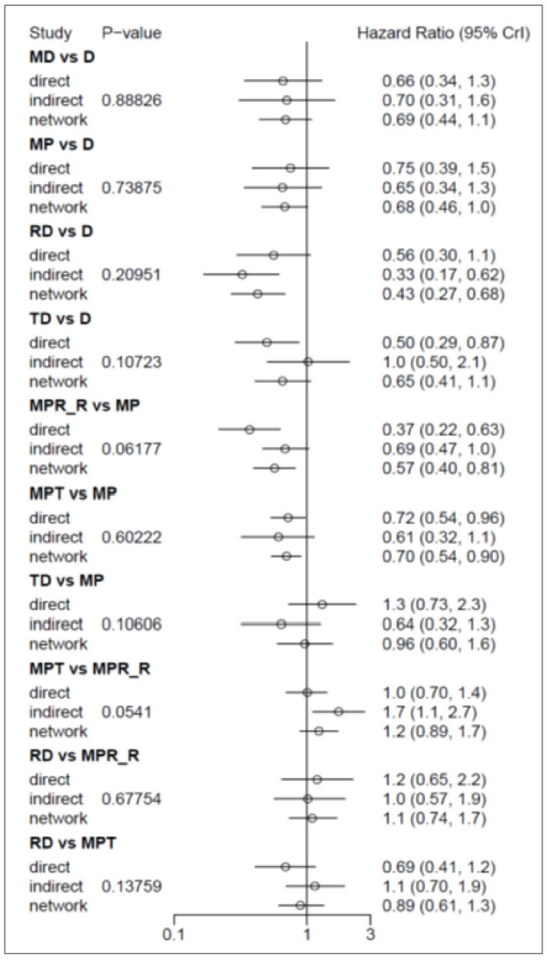
[b]Estimated following the methodology as described by Guyot et al.[17]

Note that this table has not been copy-edited.

Appendix 7: NMA — Direct Versus Indirect Evidence for NDMM

Note that this appendix has not been copy-edited.

Figure 13: Direct Versus Indirect Evidence for NDMM



D = dexamethasone; MD = melphalan-dexamethasone; MP = melphalan-prednisone; MPR_R = melphalan-prednisone-lenalidomide, followed by lenalidomide maintenance; MPT = melphalan-prednisone-thalidomide; RD = lenalidomide-dexamethasone; TD = thalidomide-dexamethasone.

Appendix 8: NMA — Base-Case Analysis With HR

Note that this appendix has not been copy-edited.

Figure 14: Pairwise Base-Case Analysis for NDMM

NDMM	DaraVMP	DaraRD	VMPT	VRD	KRD	IxaRD	KMP	VTD	MPR_R	VMP	ERD	RD	VD	MPT	CPR	VTP	CRDa	PembroRD	RD18	ClarithRD	CTDa	MPR	TD	MD	MP	DI	D
DaraVMP		1.41	1.38	1.97	2.05	2.20	2.16	2.22	2.42	2.38	2.47	2.65	2.64	2.98	2.98	2.98	3.13	3.24	3.34	3.43	3.43	4.05	4.07	4.30	4.24	5.62	6.24
DaraRD	0.71		0.98	1.40	1.45	1.57	1.54	1.57	1.72	1.69	1.75	1.89	1.88	2.12	2.12	2.11	2.23	2.30	2.37	2.43	2.44	2.89	2.90	3.06	3.02	4.00	4.43
VMPT	0.72	1.02		1.42	1.48	1.60	1.57	1.61	1.76	1.72	1.79	1.92	1.91	2.16	2.15	2.15	2.26	2.35	2.42	2.48	2.49	2.93	2.95	3.12	3.08	4.07	4.52
VRD	0.51	0.72	0.70		1.04	1.12	1.10	1.13	1.23	1.21	1.26	1.35	1.34	1.51	1.51	1.51	1.59	1.65	1.70	1.74	1.75	2.06	2.07	2.19	2.16	2.86	3.17
KRD	0.49	0.69	0.67	0.96		1.08	1.06	1.08	1.18	1.16	1.21	1.30	1.29	1.46	1.45	1.45	1.53	1.58	1.63	1.67	1.68	1.98	1.99	2.10	2.08	2.75	3.05
IxaRD	0.45	0.64	0.63	0.89	0.93		0.98	1.01	1.10	1.08	1.12	1.21	1.20	1.35	1.35	1.35	1.42	1.47	1.51	1.56	1.56	1.84	1.85	1.95	1.93	2.55	2.83
KMP	0.46	0.65	0.64	0.91	0.95	1.02		1.02	1.12	1.10	1.14	1.23	1.22	1.38	1.38	1.37	1.44	1.50	1.54	1.58	1.59	1.88	1.88	1.99	1.96	2.60	2.88
VTD	0.45	0.64	0.62	0.89	0.92	0.99	0.98		1.09	1.07	1.11	1.20	1.19	1.34	1.34	1.34	1.41	1.46	1.50	1.54	1.55	1.83	1.84	1.95	1.92	2.54	2.82
MPR_R	0.41	0.58	0.57	0.81	0.84	0.91	0.89	0.91		0.98	1.02	1.09	1.09	1.23	1.23	1.23	1.29	1.34	1.37	1.41	1.42	1.67	1.68	1.78	1.75	2.32	2.57
VMP	0.42	0.59	0.58	0.83	0.86	0.92	0.91	0.93	1.02		1.04	1.12	1.11	1.25	1.25	1.25	1.31	1.36	1.40	1.44	1.44	1.70	1.71	1.81	1.78	2.36	2.62
ERD	0.41	0.57	0.56	0.80	0.83	0.89	0.88	0.90	0.98	0.96		1.08	1.07	1.21	1.21	1.20	1.27	1.32	1.35	1.39	1.39	1.64	1.65	1.74	1.72	2.28	2.53
RD	0.38	0.53	0.52	0.74	0.77	0.83	0.82	0.83	0.91	0.90	0.93		0.99	1.12	1.12	1.12	1.18	1.22	1.26	1.29	1.30	1.53	1.53	1.62	1.60	2.12	2.35
VD	0.38	0.53	0.52	0.74	0.77	0.83	0.82	0.84	0.92	0.90	0.94	1.01		1.13	1.13	1.13	1.18	1.22	1.26	1.29	1.30	1.54	1.54	1.63	1.61	2.13	2.36
MPT	0.34	0.47	0.46	0.66	0.69	0.74	0.73	0.74	0.81	0.80	0.83	0.89	0.89		1.00	1.00	1.05	1.09	1.12	1.15	1.15	1.36	1.37	1.45	1.43	1.89	2.10
CPR	0.34	0.47	0.46	0.66	0.69	0.74	0.73	0.74	0.81	0.80	0.83	0.89	0.89	1.00		1.00	1.05	1.09	1.12	1.15	1.16	1.36	1.37	1.45	1.43	1.89	2.09
VTP	0.34	0.47	0.46	0.66	0.69	0.74	0.73	0.75	0.82	0.80	0.83	0.89	0.89	1.00	1.00		1.05	1.09	1.12	1.15	1.16	1.36	1.37	1.45	1.43	1.89	2.10
CRDa	0.32	0.45	0.44	0.63	0.65	0.70	0.69	0.71	0.78	0.76	0.79	0.85	0.84	0.95	0.95	0.95		1.04	1.07	1.10	1.10	1.30	1.30	1.38	1.36	1.80	1.99
PembroRD	0.31	0.43	0.43	0.61	0.63	0.68	0.67	0.68	0.75	0.73	0.76	0.82	0.82	0.92	0.92	0.92	0.97		1.03	1.06	1.06	1.25	1.26	1.33	1.31	1.74	1.92
RD18	0.30	0.42	0.41	0.59	0.61	0.66	0.65	0.67	0.73	0.71	0.74	0.80	0.79	0.89	0.89	0.89	0.94	0.97		1.03	1.03	1.22	1.22	1.29	1.27	1.69	1.87
ClarithRD	0.29	0.41	0.40	0.57	0.60	0.64	0.63	0.65	0.71	0.70	0.72	0.77	0.77	0.87	0.87	0.87	0.91	0.95	0.97		1.00	1.18	1.19	1.26	1.24	1.64	1.82
CTDa	0.29	0.41	0.40	0.57	0.60	0.64	0.63	0.64	0.71	0.69	0.72	0.77	0.77	0.87	0.87	0.87	0.91	0.94	0.97	1.00		1.18	1.19	1.25	1.24	1.64	1.81
MPR	0.25	0.35	0.34	0.48	0.50	0.54	0.53	0.55	0.60	0.59	0.61	0.65	0.65	0.73	0.73	0.73	0.77	0.80	0.82	0.85	0.85		1.00	1.06	1.05	1.39	1.54
TD	0.25	0.34	0.34	0.48	0.50	0.54	0.53	0.54	0.59	0.58	0.61	0.65	0.65	0.73	0.73	0.73	0.77	0.80	0.82	0.84	0.84	1.00		1.06	1.04	1.38	1.53
MD	0.23	0.33	0.32	0.46	0.48	0.51	0.50	0.51	0.56	0.55	0.57	0.62	0.61	0.69	0.69	0.69	0.73	0.75	0.77	0.80	0.80	0.94	0.95		0.99	1.31	1.45
MP	0.24	0.33	0.33	0.46	0.48	0.52	0.51	0.52	0.57	0.56	0.58	0.63	0.62	0.70	0.70	0.70	0.74	0.76	0.79	0.81	0.81	0.96	0.96	1.01		1.32	1.47
DI	0.18	0.25	0.25	0.35	0.36	0.39	0.39	0.39	0.43	0.42	0.44	0.47	0.47	0.53	0.53	0.53	0.56	0.58	0.59	0.61	0.61	0.72	0.72	0.77	0.75		1.11
D	0.16	0.23	0.22	0.32	0.33	0.35	0.35	0.36	0.39	0.38	0.40	0.43	0.42	0.48	0.48	0.48	0.50	0.52	0.53	0.55	0.55	0.65	0.65	0.69	0.68	0.90	

a = attenuated; C = cyclophosphamide; Clarith = Clarithromycin; D = dexamethasone; Dara = daratumumab; E = elotuzumab; I = interferon alpha-2b; Ixa = ixazomib; K = carfilzomib; M = melphalan; P = prednisone; Pembro = pembrolizumab; R = lenalidomide; t = thalidomide; V = bortezomib.

ClarithRD = clarithromycin-lenalidomide-dexamethasone; CPR = cyclophosphamide-prednisone-lenalidomide; CRDa = attenuated cyclophosphamide-lenalidomide-dexamethasone; CTDa = attenuated cyclophosphamide-thalidomide-dexamethasone; D = dexamethasone; DaraRD = daratumumab-lenalidomide-dexamethasone; DaraVMP = daratumumab-bortezomib-melphalan-prednisone; DI = dexamethasone-interferon alpha-2b; ERD = elotuzumab-lenalidomide-dexamethasone; IxaRD = ixazomib-lenalidomide-dexamethasone; KRD = carfilzomib-lenalidomide-dexamethasone; KMP = carfilzomib-melphalan-prednisone; MD = melphalan-dexamethasone; MP = melphalan-prednisone; MPR = melphalan-prednisone-lenalidomide; MPR_R = melphalan-prednisone-lenalidomide, followed by lenalidomide maintenance; MPT = melphalan-prednisone-thalidomide; PembroRD = pembrolizumab-lenalidomide-dexamethasone; RD = lenalidomide-dexamethasone; RD18 = lenalidomide-dexamethasone for 18 4-week cycles; TD = thalidomide-dexamethasone; VD = bortezomib-dexamethasone; VMP = bortezomib-melphalan-prednisone; VMPT = bortezomib-melphalan-prednisone-thalidomide; VRD = bortezomib-lenalidomide-dexamethasone; VTD = bortezomib-thalidomide-dexamethasone; VTP = bortezomib-thalidomide-prednisone.

Figure 15: Pairwise Base-Case Analysis for r/r MM

RRMM	DaraRD	IsaKD__twice_weekly_K	KDDara__twice_weekly_K	DaraVD	KD__once_weekly_K	KRD__twice_weekly_K	ERD	IxaRD	IsaPomD	KD__twice_weekly_K	DaraPomD	V_plus_PLD	PomVD	PanVD	VeneVD	RD	MelD	SVD	VorV	PomD	TD	V_or_VD	PlitD	T_400	PerVD	PembroPomD	T_200	VCD	T_100	D	ObliD
DaraRD		1.00	1.11	1.15	1.31	1.50	1.64	1.68	1.87	1.89	1.96	2.10	2.18	2.25	2.25	2.27	2.46	2.50	2.75	3.12	3.28	3.57	4.21	4.40	4.55	4.77	4.74	5.03	5.03	6.49	6.94
IsaKD__twice_weekly_K	1.00		1.11	1.15	1.30	1.50	1.63	1.68	1.86	1.89	1.96	2.10	2.17	2.25	2.25	2.27	2.46	2.50	2.74	3.11	3.28	3.56	4.20	4.38	4.53	4.75	4.72	5.03	5.01	6.47	6.93
KDDara__twice_weekly_K	0.90	0.90		1.04	1.17	1.34	1.47	1.51	1.68	1.70	1.76	1.89	1.96	2.02	2.02	2.04	2.21	2.24	2.47	2.79	2.95	3.21	3.78	3.94	4.07	4.28	4.25	4.52	4.51	5.82	6.22
DaraVD	0.87	0.87	0.97		1.13	1.30	1.42	1.46	1.62	1.64	1.70	1.82	1.89	1.95	1.95	1.97	2.14	2.17	2.38	2.70	2.85	3.10	3.66	3.81	3.94	4.13	4.11	4.36	4.36	5.63	6.01
KD__once_weekly_K	0.77	0.77	0.85	0.88		1.15	1.25	1.29	1.43	1.45	1.50	1.61	1.67	1.72	1.72	1.74	1.89	1.91	2.11	2.39	2.51	2.74	3.23	3.36	3.48	3.65	3.62	3.86	3.85	4.97	5.32
KRD__twice_weekly_K	0.67	0.67	0.74	0.77	0.87		1.09	1.12	1.24	1.26	1.31	1.40	1.45	1.50	1.50	1.51	1.64	1.67	1.83	2.07	2.19	2.38	2.81	2.93	3.03	3.18	3.16	3.36	3.35	4.32	4.63
ERD	0.61	0.61	0.68	0.70	0.80	0.92		1.03	1.14	1.15	1.20	1.29	1.33	1.37	1.38	1.39	1.50	1.53	1.68	1.90	2.01	2.18	2.57	2.69	2.77	2.91	2.89	3.07	3.07	3.96	4.24
IxaRD	0.59	0.60	0.66	0.69	0.78	0.89	0.97		1.11	1.12	1.17	1.25	1.29	1.34	1.34	1.35	1.47	1.48	1.63	1.85	1.95	2.12	2.50	2.62	2.70	2.83	2.82	2.99	2.99	3.85	4.13
IsaPomD	0.54	0.54	0.60	0.62	0.70	0.80	0.88	0.90		1.01	1.05	1.12	1.16	1.20	1.20	1.22	1.32	1.34	1.47	1.67	1.76	1.91	2.26	2.35	2.43	2.55	2.53	2.69	2.69	3.47	3.71
KD__twice_weekly_K	0.53	0.53	0.59	0.61	0.69	0.79	0.87	0.89	0.99		1.04	1.11	1.15	1.19	1.19	1.20	1.30	1.32	1.45	1.65	1.74	1.89	2.23	2.33	2.40	2.52	2.50	2.66	2.66	3.43	3.67
DaraPomD	0.51	0.51	0.57	0.59	0.67	0.76	0.83	0.86	0.95	0.96		1.07	1.11	1.14	1.15	1.16	1.25	1.28	1.40	1.59	1.67	1.82	2.15	2.24	2.31	2.43	2.41	2.56	2.56	3.30	3.54
V_plus_PLD	0.48	0.48	0.53	0.55	0.62	0.71	0.78	0.80	0.89	0.90	0.93		1.04	1.07	1.07	1.08	1.17	1.19	1.30	1.48	1.56	1.70	2.00	2.09	2.16	2.26	2.25	2.39	2.39	3.08	3.30
PomVD	0.46	0.46	0.51	0.53	0.60	0.69	0.75	0.77	0.86	0.87	0.90	0.97		1.03	1.03	1.04	1.13	1.15	1.26	1.43	1.51	1.64	1.94	2.02	2.09	2.19	2.17	2.31	2.31	2.98	3.19
PanVD	0.44	0.45	0.50	0.51	0.58	0.67	0.73	0.75	0.83	0.84	0.87	0.94	0.97		1.00	1.01	1.10	1.11	1.22	1.38	1.46	1.59	1.88	1.95	2.02	2.12	2.10	2.24	2.23	2.89	3.09
VeneVD	0.44	0.45	0.50	0.51	0.58	0.67	0.73	0.75	0.83	0.84	0.87	0.93	0.97	1.00		1.01	1.09	1.11	1.22	1.38	1.46	1.59	1.87	1.95	2.02	2.12	2.10	2.23	2.23	2.88	3.08
RD	0.44	0.44	0.49	0.51	0.58	0.66	0.72	0.74	0.82	0.83	0.86	0.93	0.96	0.99	0.99		1.08	1.10	1.21	1.37	1.44	1.57	1.85	1.94	2.00	2.10	2.08	2.21	2.21	2.85	3.06
MelD	0.41	0.41	0.45	0.47	0.53	0.61	0.66	0.68	0.76	0.77	0.80	0.85	0.88	0.91	0.91	0.92		1.01	1.12	1.27	1.33	1.45	1.71	1.79	1.85	1.94	1.92	2.04	2.04	2.63	2.82
SVD	0.40	0.40	0.45	0.46	0.52	0.60	0.65	0.67	0.75	0.76	0.78	0.84	0.87	0.90	0.90	0.91	0.99		1.10	1.25	1.31	1.43	1.69	1.76	1.82	1.91	1.89	2.02	2.01	2.59	2.78
VorV	0.36	0.36	0.41	0.42	0.48	0.55	0.60	0.61	0.68	0.69	0.71	0.77	0.79	0.82	0.82	0.83	0.90	0.91		1.13	1.19	1.30	1.53	1.60	1.65	1.73	1.72	1.83	1.83	2.36	2.53
PomD	0.32	0.32	0.36	0.37	0.42	0.48	0.53	0.54	0.60	0.61	0.63	0.68	0.70	0.72	0.72	0.73	0.79	0.80	0.88		1.05	1.15	1.35	1.41	1.46	1.53	1.52	1.62	1.61	2.08	2.23
TD	0.30	0.31	0.34	0.35	0.40	0.46	0.50	0.51	0.57	0.58	0.60	0.64	0.66	0.68	0.69	0.69	0.75	0.76	0.84	0.95		1.09	1.28	1.34	1.38	1.45	1.44	1.53	1.53	1.98	2.11
V_or_VD	0.28	0.28	0.31	0.32	0.37	0.42	0.46	0.47	0.52	0.53	0.55	0.59	0.61	0.63	0.63	0.64	0.69	0.70	0.77	0.87	0.92		1.18	1.23	1.27	1.33	1.33	1.41	1.41	1.82	1.95
PlitD	0.24	0.24	0.26	0.27	0.31	0.36	0.39	0.40	0.44	0.45	0.47	0.50	0.52	0.53	0.53	0.54	0.58	0.59	0.65	0.74	0.78	0.85		1.04	1.08	1.13	1.12	1.20	1.19	1.54	1.65
T_400	0.23	0.23	0.25	0.26	0.30	0.34	0.37	0.38	0.43	0.43	0.45	0.48	0.50	0.51	0.51	0.52	0.56	0.57	0.63	0.71	0.75	0.81	0.96		1.03	1.08	1.08	1.14	1.14	1.47	1.58
PerVD	0.22	0.22	0.25	0.25	0.29	0.33	0.36	0.37	0.41	0.42	0.43	0.46	0.48	0.49	0.50	0.50	0.54	0.55	0.60	0.69	0.72	0.79	0.93	0.97		1.05	1.04	1.11	1.11	1.43	1.53
PembroPomD	0.21	0.21	0.23	0.24	0.27	0.31	0.34	0.35	0.39	0.40	0.41	0.44	0.46	0.47	0.47	0.48	0.52	0.52	0.58	0.65	0.69	0.75	0.88	0.92	0.95		0.99	1.06	1.05	1.36	1.45
T_200	0.21	0.21	0.24	0.24	0.28	0.32	0.35	0.36	0.39	0.40	0.41	0.44	0.46	0.48	0.48	0.48	0.52	0.53	0.58	0.66	0.69	0.75	0.89	0.93	0.96	1.01		1.06	1.06	1.37	1.46
VCD	0.20	0.20	0.22	0.23	0.26	0.30	0.33	0.33	0.37	0.38	0.39	0.42	0.43	0.45	0.45	0.45	0.49	0.50	0.55	0.62	0.65	0.71	0.84	0.87	0.90	0.95	0.94		1.00	1.29	1.38
T_100	0.20	0.20	0.22	0.23	0.26	0.30	0.33	0.33	0.37	0.38	0.39	0.42	0.43	0.45	0.45	0.45	0.49	0.50	0.55	0.62	0.65	0.71	0.84	0.87	0.90	0.95	0.94	1.00		1.29	1.38

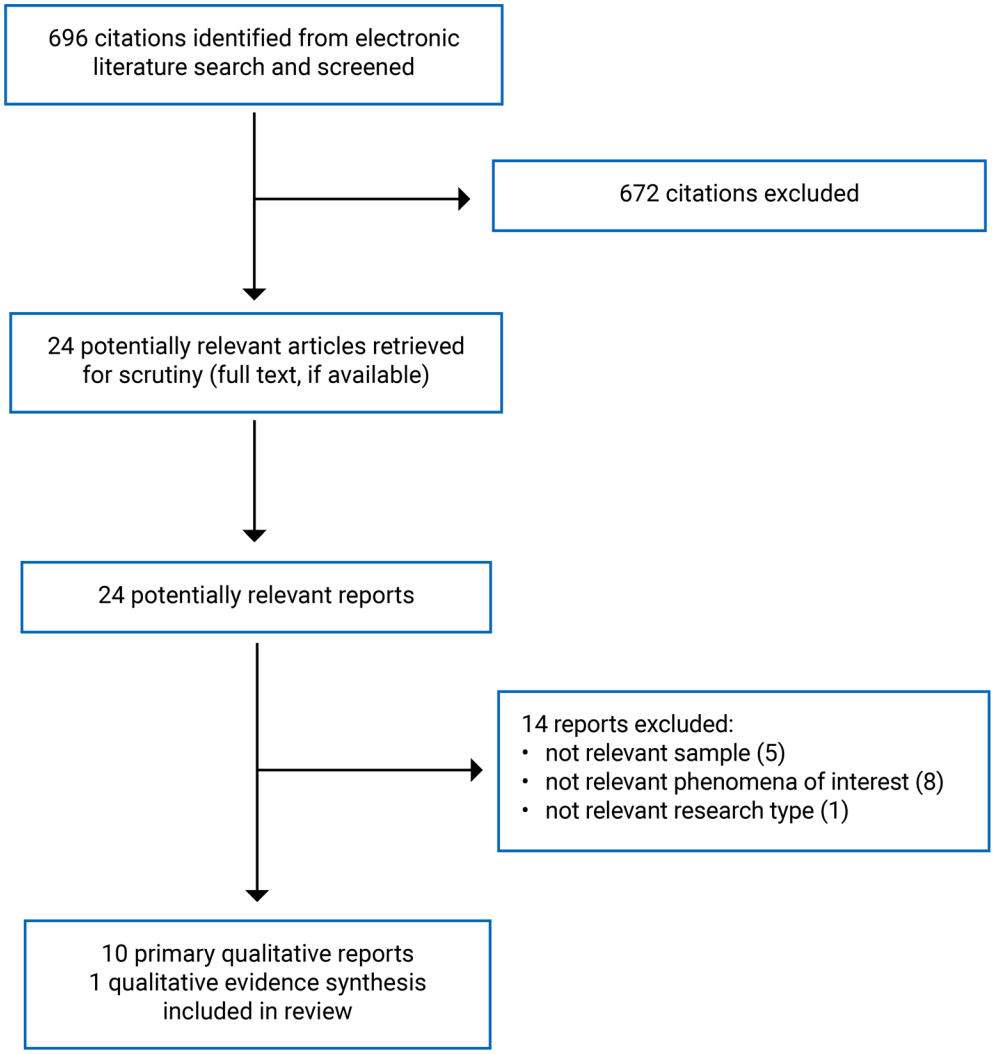
C = cyclophosphamide; D = dexamethasone; Dara = daratumumab; E = elotuzumab; Isa = isatuximab; Ixa = ixazomib; K = carfilzomib; Mel = melflufen; Obli = oblimersen sodium; Pan = panobonistat; Pembro = pembrolizumab; Per = perifosine; PLD = pegylated liposomal doxorubicin; Plit = plitidepsine; Pom = pomalidomide; R = lenalidomide; S = selinexor; t = thalidomide; V = bortezomib; Vene = venetoclax; Vor = vorinostat.

D = dexamethasone; DaraPomD = daratumumab-pomalidomide-dexamethasone; DaraRD = daratumumab-lenalidomide-dexamethasone; DaraVD = daratumumab-bortezomib-dexamethasone; ERD = elotuzumab-lenalidomide-dexamethasone; IsaKD_twice weekly_K = isatuximab-carfilzomib-dexamethasone with twice weekly of carfilzomib; IsaPomD = isatuximab-pomalidomide-dexamethasone; IxaRD = ixazomib-lenalidomide-dexamethasone; KD_once weekly_K = carfilzomib-dexamethasone with once weekly of carfilzomib; KD_twice_weekly_K = carfilzomib-dexamethasone with twice weekly of carfilzomib; KDDara_twice_weekly_K = carfilzomib-dexamethasone-daratumumab with twice weekly of carfilzomib; KRD_twice_weekly_K = carfilzomib-lenalidomide-dexamethasone with twice weekly of carfilzomib; MelD = melflufen-dexamethasone; ObliD = oblimersen sodium-dexamethasone; PanVD = panobonistat-bortezomib-dexamethasone; PembroPomD = pembrolizumab-pomalidomide-dexamethasone; PerVD = perifosine-bortezomib-dexamethasone; PlitD = plitidepsine-dexamethasone; PomD = pomalidomide-dexamethasone; PomVD = pomalidomide-bortezomib-dexamethasone; RD = lenalidomide-dexamethasone; SVD = selinexor-bortezomib-dexamethasone; T_100 = thalidomide 100mg/day; T_200 = thalidomide 200mg/day; T_400 = thalidomide 400mg/day; TD = thalidomide-dexamethasone; V_or_VD = bortezomib or bortezomib-dexamethasone; V_plus_PLD = bortezomib plus pegylated liposomal doxorubicin; VCD = bortezomib-cyclophosphamide-dexamethasone; VeneVD = venetoclax-bortezomib-dexamethasone; VorV = vorinostat-bortezomib.

Appendix 9: Qualitative Evidence Synthesis — Selection of Included Studies

Note that this appendix has not been copy-edited.

Figure 16: Selection of Included Studies



Appendix 10: Qualitative Evidence Synthesis: Characteristics of Included Publications and Their Patients

Table 14: Characteristics of Included Publications and Their Patients, and Results of Critical Appraisal of Included Studies

Author, year, country	Funding	Study objectives	Inclusion criteria	Description of study patients	Study design, method of data collection, and analysis	Judgment on trustworthiness and transferability
He, 2021, US[97]	Janssen Global Services	To conduct an exploratory investigation into concepts that could form attributes that influence treatment choices for patients with MM	Patients with MM residing in the UK, France, or Germany with a physician confirmed diagnosis	A total of 30 patients with MM, 6 with transplant ineligible NDMM, 12 with transplant eligible NDMM, and 12 with r/r MM Mean age of 60.3 years (sd 10.7) 15 (50%) were female 24 (80%) had an ECOG performance status of 0 or 1 15 (50%) were on their first-line of therapy	NR; semistructured interviews; content analysis	Low. While sampling is well-described, interview methods are only partially designed to collect rich qualitative data (i.e., open-ended questions). The most substantial limitation is that the findings are focused on presenting the distribution of concepts/experiences across subtypes of MM. This is an inappropriate use of qualitative methods. No exploration of the meaning of experiences for participants, nor their intersections and interconnections. Transferability is low due to issues with trustworthiness.
Hermann, 2021, Germany[99]	None declared	To explore the facilitators and barriers	Patients with MM receiving outpatient care at the Charité--	20 patients with MM Average age of 63.3 years (range of 39 to 79 years) 8 (40%) female participants	NR; face-to-face semistructured interviews; thematic content analysis	Low. Conceptual assumptions underlying the study are not described (i.e., prognostic acceptance,

Author, year, country	Funding	Study objectives	Inclusion criteria	Description of study patients	Study design, method of data collection, and analysis	Judgment on trustworthiness and transferability
		for prognostic acceptance	Universitätsmedizin Berlin	10 patients (x%) were > 5 years since diagnosis 13 patients (x%) had received < 5 lines of treatment, 4 had more than 5 lines of treatment		what it is, why it is assumed to be good). Findings are described with very limited detail and no supporting data are provided. Low transferability due to low trustworthiness and study focus on prognostic acceptance vs. disease and treatment experiences.
LeBlanc, 2021, US[93]	National Institute of Nursing research of the National Institutes of Health	To explore the ways in which multiple myeloma affects an individual's life	Patients with MM from 1 cancer treatment centre and clinicians from 2 cancer treatment centres in North Carolina	15 patients with MM Mean age of 63.7 years 7 (47%) female Mean months since diagnosis 71.9 (range 8 to 144) Duration of MM not reported 10 (67%) of patients were had received a transplant	Cross-sectional qualitative descriptive study; semistructured interviews; content analysis	High. Methods for the collection and analysis of data well documented. Study findings are support by data and their dimensions well-described. Moderate transferability to this review due to inclusion of high proportion of transplant-eligible MM patients.
Cuffe, 2020, Ireland[98]	None declared	To understand patients' experiences of living with multiple myeloma for more than 1 year	Patients with MM being cared for in a hematology clinic in an urban acute teaching hospital	6 patients who had MM for more than one year Median age of 67.5 years 4 (67%) were female 2 participants were in remission, 4 were relapsed Time since diagnosis ranged from 2 to 6 years	NR; unstructured interviews; Colizzi's descriptive framework	Moderate. While the authors describe achieving saturation with 6 interviews, this is likely due to the high-level descriptive nature of their themes. Findings are supported by data; primary concern is around the limited investigation on how time played a role in people's experience of MM as a

Author, year, country	Funding	Study objectives	Inclusion criteria	Description of study patients	Study design, method of data collection, and analysis	Judgment on trustworthiness and transferability
						chronic condition. Limited probing around relapse/ remission experiences. Transferability is high as study objectives and setting are relevant to this review.
de Wet, 2019, Australia[101]	The Western Australian Cancer and Palliative Care Network	To explore the experiences of patients with MM of their illness and treatment	Patients receiving care for their MM at a hematology unit at single tertiary care hospital	15 patients with NDMM or r/r MM Mean age of 62 years (51 to 74 years) 4 (27%) participants were female Mean time since diagnosis = 2.7 years Mean number of 1.7 lines of therapy (range of 1 to 5)	Phenomenology; semistructured interviews; phenomenological approach	Moderate. Well-described methods for the collection of rich data for their analysis. Findings are supported by data; primary concern is around some overlap and dissonance in some subthemes. Transferability is high as study objectives and setting are relevant to this review.
Parsons, 2019, Canada[95]	Janssen, Inc.	To develop an in-depth understanding of patients' lived experience of r/r MM and its treatment and to identify which features of treatment were most important to them	People living with r/r MM across Canada recruited through Myeloma Canada	32 participants with r/r MM who had 2 or more relapses and had been treated with either bortezomib and/ or carfilzomib AND either lenalidomide, pomalidomide, or thalidomide or any combination of these 3 Mean age of 66 years (range of 51 to 83 years) 10 (31%) of participants were women	Qualitative description; in-depth telephone interviews and in-person focus groups; data analysis approach combined features of qualitative description with grounded theory	Moderate. Methods well described. Unclear why they inclusion criteria included the specific drug combination and some findings were assessed to be lacking in rich description and data to support them. Transferability is high as study objectives and setting are relevant to this review.

Author, year, country	Funding	Study objectives	Inclusion criteria	Description of study patients	Study design, method of data collection, and analysis	Judgment on trustworthiness and transferability
Cormican, 2018, Republic of Ireland[94]	Health Research Board of Ireland	To explore which symptoms relapsed myeloma patients experience and what self-care strategies are used	Patients with a diagnosis of r/r MM and having failed at least one treatment	15 patients with r/r MM Average age was 66 years (range of 51 to 80 years) Participants had an average of 3 lines of treatments	Descriptive qualitative study; focus groups; thematic analysis	Moderate. Some use of methods to increase trustworthiness including reflexive practices however the analysis is not richly described. Transferability is high as study objectives and setting are relevant to this review.
Monterosso, 2018, Australia[102]	Cancer and Palliative Care Research and Evaluation Unit, Western Australian Cancer and Palliative Care Network	To establish the unmet needs and preferences for survivorship in a cohort of patients with MM 6 to 49 months postdiagnosis	Patients with MM who were treated at a large tertiary cancer centre in Western Australia	14 patients with MM Mean age of 57 years 7 (50%) participants were female Mean time since diagnosis was 31 months (range 6 to 49 months) 7 (50%) participants had at least 2 lines of treatment	Descriptive exploratory study; focus groups; thematic content analysis	High. Detailed description of sampling and recruitment and methods of analysis and techniques to improve rigour. Findings are overall well-described and supported by the data. Transferability is moderate as study population is patients with MM broadly.
Hulin, 2017, France[100]	Celgene International	To expand the current knowledge on how relapse in MM affects both patients and physicians	Patients with r/r MM and their hematologists in the UK, France, Germany, Italy, and Spain	50 patients with r/r MM Mean age of 71 years (range 51 to 85) 22 (44%) were female Median number of relapses 1 (range 1 to 5)	NR; semistructured interviews and structured questionnaires, verbal rating scales, and patient-completed graphic diagrams; NR	Low. Trustworthiness was affected primarily due to the lack of reporting of methods of data analysis, which affects interpretation of how they derived their findings. Findings themselves are not richly described nor are their interconnections. Transferability is moderate due to issues with trustworthiness.

Author, year, country	Funding	Study objectives	Inclusion criteria	Description of study patients	Study design, method of data collection, and analysis	Judgment on trustworthiness and transferability
Cormican, 2016, Republic of Ireland[96]	None declared	To explore whether there were different opinions on the current management of relapsed myeloma between patients and health care professionals	Patients with relapsed MM who have received at least one treatment recruited through outpatient hematology departments and health care professionals	8 patients with relapsed MM Age range was 55 to 85 years 2 (25%) were female	Descriptive qualitative; in-depth interviews; thematic analysis	Moderate. Collection of multiple sources of data improves credibility, and the analysis is well-described and supported by data. Transferability is low due to limited patient-focused findings.

MM = multiple myeloma; NDMM = newly diagnosed multiple myeloma; r/r MM = relapsed and/or refractory multiple myeloma; sd = standard deviation; ECOG = Eastern Cooperative Oncology Group; DCE = discrete choice experiment; NR = not reported.

Note: This table has not been copy-edited.

Appendix 11: Qualitative Evidence Synthesis — Additional Studies Identified During the Updated Search on July 6, 2023

Note that this appendix has not been copy-edited.

Primary Qualitative Reviews

Rowland S, Forbes R, Howell D, et al. Psychosocial and supportive care needs of individuals with advanced myeloma. *Can Oncol Nurs J.* 2023;33(2):215-222. PubMed: PM37152822 PubMed

Cohen AD, Hari P, Htut M, et al. Patient Perceptions Regarding Ciltacabtagene Autoleucel Treatment: Qualitative Evidence From Interviews With Patients With Relapsed/Refractory Multiple Myeloma in the CARTITUDE-1 Study. Clin Lymphoma Myeloma Leuk. 2023 01;23(1):68-77. PubMed:PM36357295

Blejec S, Cytryn R, Yagnik R, Bickell NA, Lin JJ. Facilitators of Multiple Myeloma Treatment: A Qualitative Study. Oncol Nurs Forum. 2023 04 21;50(3):372-380. PubMed: PM37155979

Nathwani N, Bell J, Cherepanov D, et al. Patient perspectives on symptoms, health-related quality of life, and treatment experience associated with relapsed/refractory multiple myeloma. *Support Care Cancer.* 2022 Jul;30(7):5859-5869. PubMed: PM35364733 PubMed

Crawford R, Gries KS, Valluri S, et al. The patient experience of relapsed refractory multiple myeloma and perspectives on emerging therapies. Cancer Rep (Hoboken). 2022 11;5(11):e1603. PubMed: PM35168299

Pritlove C, Jassi M, Burns B, McCurdy A. The work of managing multiple myeloma and its implications for treatment-related decision making: a qualitative study of patient and caregiver experiences. *BMC Cancer.* 2021 Jul 08;21(1):793. PubMed: PM34238260 PubMed

Mixed Methods Reviews

Delforge M, Otero PR, Shah N, et al. Analysis of patient-reported experiences up to 2 years after receiving idecabtagene vicleucel (ide-cel, bb2121) for relapsed or refractory multiple myeloma: Longitudinal findings from the phase 2 KarMMa trial. Leuk Res. 2023 06;129:107074. PubMed: PM37087950.

Shah N, Delforge M, San-Miguel J, et al. Patient experience before and after treatment with idecabtagene vicleucel (ide-cel, bb2121): qualitative analysis of patient interviews in the KarMMa trial. Leuk Res. 2022 09;120:106921. PubMed: PM35930999.

Pharmacoeconomic Review

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Abbreviations

AE	adverse event
ASCT	autologous stem cell transplant
CarDex	carfilzomib plus dexamethasone
CarLenDex	carfilzomib plus lenalidomide plus dexamethasone
CMRG	Canadian Multiple Myeloma Research Group
CyBorDex	cyclophosphamide plus bortezomib plus dexamethasone
DaraBorDex	daratumumab plus bortezomib plus dexamethasone
DaraCyBorDex	daratumumab plus cyclophosphamide plus bortezomib plus dexamethasone
DaraLenDex	daratumumab plus lenalidomide plus dexamethasone
DaraMphBorPred	daratumumab plus melphalan plus bortezomib plus prednisone
ECOG	Eastern Cooperative Oncology Group
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
IsaPomDex	isatuximab plus pomalidomide plus dexamethasone
ISS	international staging system
LenBorDex	lenalidomide plus bortezomib plus dexamethasone
LenDex	Lenalidomide plus dexamethasone
LY	life-year
MM	multiple myeloma
NMA	network meta-analysis
OS	overall survival
PFS	progression-free survival
PomBorDex	pomalidomide plus bortezomib plus dexamethasone
PomDex	pomalidomide plus dexamethasone
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
TTP	time to progression
WTP	willingness to pay

Economic Analysis and Economic Evaluation

An economic evaluation was performed to assess the cost-effectiveness of various treatment sequences for patients transplant ineligible with multiple myeloma (MM) who are transplant ineligible. This economic evaluation assessed the lifetime costs, health outcomes, and cost-effectiveness of various treatment sequences for patients with MM who are transplant ineligible. A protocol was written a priori and followed in this review. The scope and analytical approach taken in the economic evaluation were based on the availability of data identified from the clinical review.

Type of Economic Evaluation

The economic evaluation is a cost-effectiveness analysis with outcomes expressed as life-years (LYs) and a cost-utility analysis with outcomes expressed as quality-adjusted life-years (QALYs).

Target Populations and Setting

The target population are patients living in Canada with MM who are transplant ineligible. To ensure the analysis was representative of the MM population in Canada, Canada's Drug and Health Technology Agency (CADTH) collaborated with the Canadian Multiple Myeloma Research Group (CMRG) to use real-world evidence to inform the analysis.

Treatment

The following treatment sequences were considered in the economic analysis in consultation with the pCODR Provincial Advisory Group at the time of protocol development for the model. Since finalization of these sequences, several treatments have received positive CADTH recommendations for MM such as selinexor in combination with bortezomib and dexamethasone, isatuximab in combination with carfilzomib and dexamethasone, and ciltacabtagene autoleucel. These therapies were not considered in this analysis. Although the protocol originally intended to analyze 3 lines of therapies, based on discussions with experts and drug plans alongside data available from CMRG, a decision was made to analyze up to 4 lines of therapies. Overall, 17 treatment sequences were evaluated. Table 1 outlines what lines of therapies were analyzed in each treatment sequence.

Table 1: List of Treatment Sequences Evaluated

Sequence number	1L therapy	2L therapy	3L therapy	4L therapy
1	DaraCyBorDex	LenDex	PomBorDex	CarDex
2	DaraCyBorDex	CarLenDex	PomBorDex	None[1]
3	DaraMphBorPred	LenDex	PomBorDex	CarDex
4	DaraLenDex	PomBorDex	CarDex	None[1]
5	DaraLenDex	CyBorDex	PomDex	None[1]
6	DaraLenDex	CarDex	PomBorDex	None[1]
7	CyBorDex	CarLenDex	PomBorDex	DaraBorDex

Sequence number	1L therapy	2L therapy	3L therapy	4L therapy
8	CyBorDex	DaraLenDex	PomBorDex	DaraBorDex
9	CyBorDex	LenDex	PomDex	DaraBorDex
10	LenBorDex	DaraBorDex	PomBorDex	CarDex
11	LenBorDex	PomBorDex	CarDex	DaraBorDex
12	LenBorDex	DaraBorDex	CarDex	PomBorDex
13	LenBorDex	CarDex	IsaPomDex	None[1]
14	LenDex	DaraBorDex	CarDex	PomDex
15	LenDex	CyBorDex	PomDex	DaraBorDex
16	LenDex	CyBorDex	IsaPomDex	CarDex
17	LenDex	CarDex	PomBorDex	DaraBorDex

1L = first line; 2L = second line; 3L = third line; 4L = forth line; CarDex = carfilzomib and dexamethasone; CarLenDex = carfilzomib, lenalidomide, and dexamethasone; CyBorDex = cyclophosphamide, bortezomib, and dexamethasone; DaraBorDex = daratumumab, bortezomib, and dexamethasone; DaraCyBorDex = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; DaraLenDex = daratumumab, lenalidomide, and dexamethasone; DaraMphBorPred = daratumumab, melphalan, bortezomib, and dexamethasone; IsaPomDex = isatuximab, pomalidomide, and bortezomib; LenDex = lenalidomide and dexamethasone; LenBorDex = lenalidomide, bortezomib, and dexamethasone; PomBorDex = pomalidomide; bortezomib and dexamethasone; PomDex = pomalidomide and bortezomib.

One these sequences were originally analyzed as 3 lines with patients not receiving a 4L therapy, as there was no data on what outcomes would be like for those on 4L who do not receive any therapy it was assumed these patients would receive outcomes and costs equivalent to those who receive LenDex as a 4L therapy in CMRG data.

Of the 17 treatment sequences outlined in Table 1, sequences 2, 4, 5, 6, and 13 stop at 3 lines of therapy. No data could be gathered on the outcomes of patients who do not receive therapy after failing a third line of therapy. In consultation with experts, it was noted that these patients may be retreated with a prior regimen or receive a recently approved therapy such as selinexor. As selinexor was not included in the original protocol, an assumption was made that these patients would experience costs and health outcomes equivalent to LenDex in the 4L setting. This introduced a clear bias for these strategies; health outcomes and costs in the 4L setting will likely be different in these patients. Therefore, it was deemed inappropriate to compare strategies which stopped at 3L to strategies which continue onto 4L as there is insufficient evidence to inform these comparisons. When analyzing the results, strategies which stop at 3L are only compared against each other and the same for 4L strategies.

Perspective

The analysis was conducted from the perspective of the public health care payer in Canada.

Time Horizon and Discounting

The model has a lifetime horizon. Discount rates of 1.5% for both costs and QALYs were applied as per CADTH guidelines.

Model Structure

The economic model used in this study is an adaptation of a previously peer-reviewed published patient-level simulation model for patients with transplant-ineligible MM.[1] The model is a discrete event simulation with up to 4 treatment lines modelled. For the first-, second-, and third-line treatments, possible events are either the start of the next line of treatment or death. Only time to death is modelled once a simulated patient enters fourth-line treatment. A graphical representation of the model is depicted in Figure 1.

Seven distinct transitions were defined, as depicted in Figure 1. These transition numbers are summarized in Table 2.

Figure 1: A Graphical Representation on the Economic Model

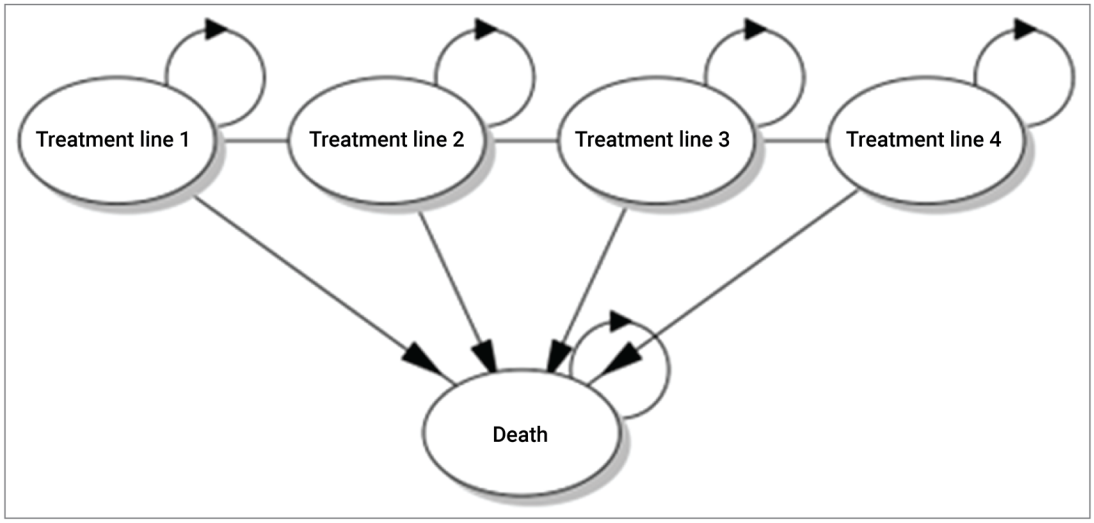


Table 2: Transition Numbers of the Model and Corresponding Model States

Transition number	From model state	To model state
1	Treatment line 1	Treatment line 2
2	Treatment line 1	Death
3	Treatment line 2	Treatment line 3
4	Treatment line 2	Death
5	Treatment line 3	Treatment line 4
6	Treatment line 3	Death
7	Treatment line 4	Death

All simulated patients start with treatment line 1 and can receive up to 3 subsequent treatment lines — patients can thus receive a maximum of 4 treatment lines. Some patients may not receive all 4 treatment lines, as they may die before they would receive a subsequent line of treatment. From any treatment line,

patients can die and transition to the absorbing state of death. Upon reaching fourth line it is assumed patients remain on therapy until death as the analysis does not allow for consideration of a fifth line of therapy. This approach may overestimate costs in the fourth-line setting, dependent on what treatments, if any, are received in the fifth line in clinical practice. However, it was felt this would not have a major impact on overall cost-effectiveness conclusions as this assumption applies to all lines and the minority of patients will make it to fourth line.

Alternate model structures were considered but were deemed inappropriate for the decision problem. In oncology, a partition survival model (PSM) is a common approach for modelling the cost-effectiveness of treatments. However, a PSM structure is very restrictive.[2,3] For this decision problem, the cost-effectiveness of treatment sequences, not individual lines of therapy, is being assessed. Therefore, the impact a treatment has on overall survival for example will depend on what treatment is given next in the sequence. A PSM was not considered sufficiently flexible to account for this across multiple lines of therapy.

Data Inputs

Four different types of model input parameters can be distinguished in the model:

- patient characteristics and baseline survival curves for overall survival and time to next treatment for patients receiving lenalidomide and dexamethasone in each line (1 to 4) based on data from CMRG
- relative treatment effects versus lenalidomide and dexamethasone based on a network meta-analysis
- health state utilities
- resource use and costs.

All these input parameters are described in the subsequent sections of this report.

Patient Characteristics and Baseline Survival Estimates From CMRG

To ensure the model reflected the MM population in Canada, a collaboration with the CMRG and CADTH was initiated. On behalf of the Optimal Pharmacotherapy for Transplant-Ineligible Multiple Myeloma Therapeutic Review project team, CADTH requested an analysis of the real-world data in the CMRG National Database for inclusion in the economic model. CADTH provided the necessary R-code compiled by Erasmus School of Health Policy and Management, which was then executed onsite at the CMRG. In this way, it was ensured that all patient-level data stayed on site and that the results of this analysis could not be traced back to individual patients.

Data from CMRG included survival times and patient characteristics. The latter were used as covariates for several regression models. The survival times data included the time to next treatment line(s), time to death or last time of follow-up, treatment line status, and death status. All data were prepared with the R package mstate (version 0.3.2),[4] and analyzed with the R packages survival (version 3.4.0) and flexsurv (version 2.2).[5,6] R-code to fit the models was based on previously written code by the Decision Analysis in R for Technologies in Health group.[7-9]

One additional consideration with the CMRG data was assessing treatment effects between different treatments. As with all observational data, the CMRG data are prone to bias when considering treatment

effects due to the absence of random treatment allocation. The patient baseline characteristics at the start of therapy for lines 1 to 4 per treatment were requested to assess the risk of potential bias due to confounding.

To ensure data were relevant to the decision problem, patients should be autologous stem cell transplant (ASCT) ineligible and initiating a first line of therapy for MM. To achieve this the following filters were applied by CMRG:

- filter for patients that received line 1 treatment with intent marked as Non-ASCT
- remove all non-MM related diagnosis including MGUS
- remove patients that receive an ASCT in any subsequent line of therapy
- initiation of line 1 therapy between January 2007 to December 2020 to ensure a sufficient length of follow-up
- age cut-off of 65 years or older
- remove patients who initiated therapy with no follow-up (0 days) and patients with MM diagnosis posttherapy initiation (receiving therapy for a previous malignancy).

Once the target population was identified the following data were collected:

- age
- gender
- lines 1, 2, 3, and 4 therapy names and start date of treatments
- date of death and last follow-up
- baseline lab values for patients initiating lines 1 to 3: B2M (nmol/L), albumin (g/L), creatinine (µmol/L), calcium (mmol/L), LDH (U/L), hemoglobin (g/L), platelets (E + 9/L), and White blood cell count (E + 9/L)
- international staging system (ISS) at diagnosis
- cytogenetics t4:14, t14:16, Del17p, t11:14 at diagnosis
- MM heavy chain type at diagnosis
- MM light chain at diagnosis
- medical history, comorbidities at diagnosis (yes/no).

Due to large numbers of missing data only the following baseline lab values could be used to inform the regression analysis: hemoglobin, white blood count, platelets, and creatine. Any analysis comparing relative efficacy between different treatment regimens was considered inappropriate as it was not possible to adjust for even known confounders. Baseline characteristics at initiation of first-line therapy are shown in Table 3.

For illustrative purposes, to be able to plot survival curves based on parametric models estimated on CMRG data, a “standard patient” was created based on the most often observed values for all covariates outlined in Table 4. For treatment “no lenalidomide plus dexamethasone” was selected. This, therefore, estimates how long the average patient with MM who did not receive lenalidomide plus dexamethasone is expected

to survive and/or remain on therapy for each given line. Treatment modifiers can be applied based on data from the NMA.

Table 3: Baseline Population Characteristics at Initiation of Line 1 Therapy

Characteristic	Gender		
	Female, N = 922	Male, N = 1,226	All, N = 2,148
Age (years)			
Mean (SD)	76.1 (6.28)	75.6 (6.28)	75.8 (6.29)
Median (IQR)	75.0 (71.0, 80.0)	75.0 (71.0, 80.0)	75.0 (71.0, 80.0)
Range	65 to 99	65 to 94	65 to 99
Hemoglobin			
Mild	323 (35.0%)	378 (30.8%)	701 (32.6%)
Moderate	318 (34.5%)	362 (29.5%)	680 (31.7%)
Normal	144 (15.6%)	301 (24.6%)	445 (20.7%)
Severe	76 (8.2%)	95 (7.7%)	171 (8.0%)
Unknown	61 (6.6%)	90 (7.3%)	151 (7.0%)
White blood count			
Mild	144 (15.6%)	235 (19.2%)	379 (17.6%)
Moderate	41 (4.4%)	69 (5.6%)	110 (5.1%)
Normal	641 (69.5%)	772 (63.0%)	1,413 (65.8%)
Severe	7 (0.8%)	12 (1.0%)	19 (0.9%)
Unknown	89 (9.7%)	138 (11.3%)	227 (10.6%)
Platelets			
Mild	106 (11.5%)	226 (18.4%)	332 (15.5%)
Moderate	11 (1.2%)	21 (1.7%)	32 (1.5%)
Normal	697 (75.6%)	848 (69.2%)	1,545 (71.9%)
Severe	16 (1.7%)	12 (1.0%)	28 (1.3%)
Unknown	92 (10.0%)	119 (9.7%)	211 (9.8%)
Creatinine			
Mild	166 (18.0%)	324 (26.4%)	490 (22.8%)
Moderate	116 (12.6%)	198 (16.2%)	314 (14.6%)
Normal	503 (54.6%)	490 (40.0%)	993 (46.2%)
Severe	58 (6.3%)	108 (8.8%)	166 (7.7%)
Unknown	79 (8.6%)	106 (8.6%)	185 (8.6%)
Treatment			
Lenalidomide	192 (20.8%)	244 (19.9%)	436 (20.3%)

Characteristic	Gender		
	Female, N = 922	Male, N = 1,226	All, N = 2,148
No lenalidomide	730 (79.2%)	981 (80.1%)	1,711 (79.7%)
Unknown	0	1	1

Table 4: Standard Patient per Transition

Transition number	Age	Sex	Treatment	Hemoglobin	White blood count	Platelet	Creatinine
1 (line 1 to line 2)	76	Male	No LenDex	Mild	Normal	Normal	Normal
2 (line 1 to death)	76	Male	No LenDex	Mild	Normal	Normal	Normal
3 (line 2 to line 3)	78	Male	No LenDex	Mild	Normal	Normal	Normal
4 (line 2 to death)	78	Male	No LenDex	Mild	Normal	Normal	Normal
5 (line 3 to line 4)	79	Male	No LenDex	Mild	Normal	Normal	Normal
6 (line 3 to death)	79	Male	No LenDex	Mild	Normal	Normal	Normal
7 (line 4 to death)	80	Male	No LenDex	Mild	Normal	Normal	Normal

LenDex = lenalidomide and dexamethasone.

Conducting Survival Analysis

To derive how much time is spent within each state of the model, survival analysis was conducted on the data by the CMRG, per treatment line (lines 1 to 4). To extrapolate the empirical survival curves for both time to next treatment (TTNT) and overall survival (OS) beyond the observed time frame, we used several parametric survival distributions from the R package flexsurv (version 2.2).[6] The following distributions were considered:

- generalized gamma
- Weibull
- gamma
- exponential
- log logistic
- log normal
- Gompertz.

Analyses of the empirical data were guided by a five-stepped approach outlined by the National Institute for Health and Care Excellence, Decision Support Unit technical support document 14.[10] These steps were:

- considering how to model the treatment effect over time
- considering which parametric models are appropriate given the shape of the hazard functions and the survival curves
- considering internal validity through visual inspection and statistical tests of fit

- considering external validity by comparing the extrapolations to background mortality and/or data from other studies, assessing the plausibility of extrapolated long-term treatment effects, and clinical validity of the extrapolations
- choosing the most appropriate model and completing sensitivity analysis using alternative plausible models.

Internal validity (step 3) was assessed through the goodness-of-fit criteria (i.e., the Akaike's Information Criterion [AIC] and the Bayesian Information Criterion [BIC]). The lowest values for both AIC and BIC indicated a relative better fit of the parametric distribution to the empirical data when compared to all other fitted distribution for the same treatment arm. External validity (step 4) was ensured by consulting clinical experts in the field of hematology-oncology.

Time-To-Event Analysis

Table 5 summarizes data from the CMRG database that was used to inform the survival analysis for each model transition.

For transitions that pertain to time to next therapy (transitions 1, 3 and 5) the number of events and time-to-event relate to the number of patients who failed their current line of therapy and moved on to the next line. Patients were censored if they were lost to follow-up or died before moving to the next treatment line.

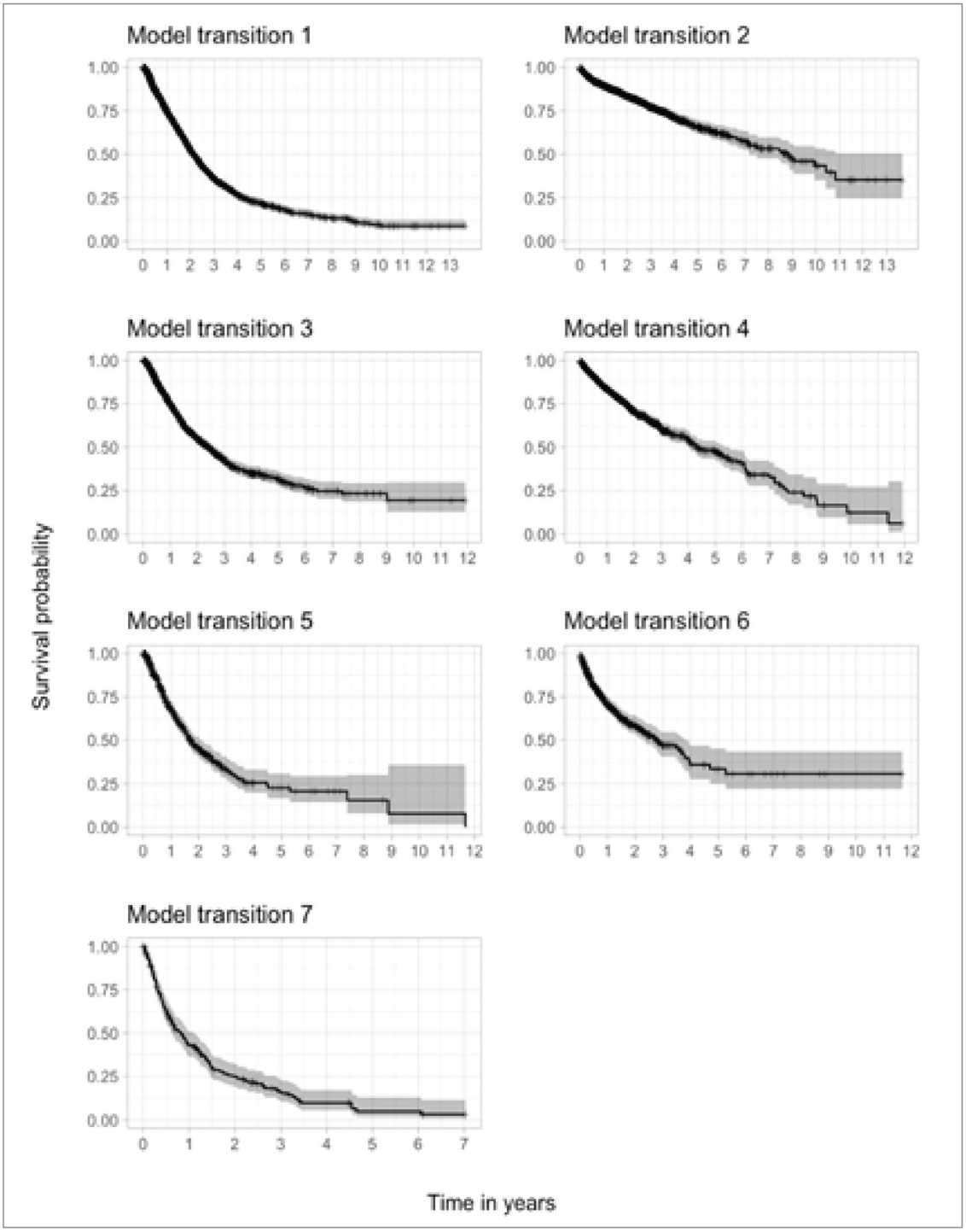
For transitions that pertain to death on a given line (transitions 2, 4, 6 and 7) the number of events and time-to-event relate to the number of patients who died on their current line. Patients were censored if they were lost to follow-up or moved to the next line of therapy.

Table 5: Summary Statistics of the Time-to-Event Analysis

Transition number	Number of patients	Number of events	Median time-to-event in days	Lower 95% confidence limit	Upper 95% confidence limit	Censored
1 (line 1 to line 2)	2,148	1,253	780	739	839	882
2 (line 1 to death)	2,148	378	3,225	2,620	NA	1,762
3 (line 2 to line 3)	1,250	549	886	789	969	696
4 (line 2 to death)	1,250	353	1,578	1,471	2,018	896
5 (line 3 to line 4)	546	230	634	558	768	316
6 (line 3 to death)	546	184	1,017	829	1,386	351
7 (line 4 to death)	214	162	301	225	407	50

Figure 2 depicts the empirical Kaplan-Meier curves for the different transitions within the model. Survival analysis was conducted on these curves to extrapolate beyond the period for which data were available. CADTH notes that data for all transitions was fairly mature with over 50% of events having occurred across all 7 transitions.

Figure 2: Empirical Survival for Each Model Transition for Patients as Observed in CMRG



Choosing Covariates

Survival analysis was conducted for each transition using 3 different survival formulas for each parametric survival model:

- An intercept only model – this model does not control for any covariates and therefore only provides an average estimate across all patients.
- A model using age, sex, and treatment dichotomized into lenalidomide and dexamethasone versus no lenalidomide and dexamethasone as covariates — this model is the same as model 1 above while also controlling for age, sex, and whether the patients received lenalidomide and dexamethasone.
- A model using age, sex, treatment dichotomized into lenalidomide and dexamethasone versus no lenalidomide and dexamethasone, and laboratory values (i.e., hemoglobin, white blood count, platelet count, and creatinine) grouped in mild, normal, moderate, severe, and unknown as covariates — this model is the same as model 2 above while also controlling for laboratory values as available at start line 1.

For each model 7 parametric forms were fitted. As can be seen in Table 6, not all models could be estimated for all transitions. Most models could be fitted to the data except for the Gompertz model in most cases.

Model Fit Based on Visual Inspection

AIC values are summarized in Table 7. Bold text highlights the parametric fit with the lowest AIC value.

BIC values are summarized in Table 8. Bold text highlights the parametric fit with the lowest BIC value.

Table 6: Parametric Functions Estimated per Model Transition and According to Covariates Used

Transition number	Exponential	Gamma	Generalized gamma	Gompertz	Weibull	Log logistic	Log normal
Intercept							
1	Estimated	Estimated	Estimated	Not estimated	Estimated	Estimated	Estimated
2	Estimated	Estimated	Estimated	Not estimated	Estimated	Estimated	Estimated
3	Estimated	Estimated	Estimated	Not estimated	Estimated	Estimated	Estimated
4	Estimated	Estimated	Estimated	Not estimated	Estimated	Estimated	Estimated
5	Estimated	Estimated	Estimated	Not estimated	Estimated	Estimated	Estimated
6	Estimated	Estimated	Estimated	Not estimated	Estimated	Estimated	Estimated
7	Estimated	Estimated	Estimated	Estimated	Estimated	Estimated	Estimated
Age and sex and treatment (LenDex vs. no LenDex)							
1	Estimated	Estimated	Estimated	Not estimated	Estimated	Estimated	Estimated
2	Estimated	Estimated	Estimated	Not estimated	Estimated	Estimated	Estimated
3	Estimated	Estimated	Estimated	Not estimated	Estimated	Estimated	Estimated
4	Estimated	Estimated	Estimated	Not estimated	Estimated	Estimated	Estimated

Transition number	Exponential	Gamma	Generalized gamma	Gompertz	Weibull	Log logistic	Log normal
5	Estimated	Estimated	Estimated	Not estimated	Estimated	Estimated	Estimated
6	Estimated	Estimated	Estimated	Not estimated	Estimated	Estimated	Estimated
7	Estimated	Estimated	Estimated	Estimated	Estimated	Estimated	Estimated
Age and sex and treatment (LenDex vs. no LenDex) and lab values							
1	Estimated	Estimated	Estimated	Not estimated	Estimated	Estimated	Estimated
2	Estimated	Estimated	Estimated	Not estimated	Estimated	Estimated	Estimated
3	Estimated	Estimated	Estimated	Not estimated	Estimated	Estimated	Estimated
4	Estimated	Estimated	Estimated	Not estimated	Estimated	Estimated	Estimated
5	Estimated	Estimated	Estimated	Not estimated	Estimated	Estimated	Estimated
6	Estimated	Estimated	Estimated	Not estimated	Estimated	Estimated	Estimated
7	Not estimated	Estimated	Estimated	Estimated	Estimated	Not estimated	Not estimated

LenDex = lenalidomide and dexamethasone.

Table 7: AIC Values per Model Transition and According to Covariates Used

Transition number	Exponential	Gamma	Generalized gamma	Gompertz	Weibull	Log logistic	Log normal
Intercept							
1	20,326.83	20,312.34	**20,236.93**	NA	20,323.09	20,240.56	20,240.1
2	7,039.50	**7,023.91**	7,025.77	NA	7,024.02	7,028.52	7,035.15
3	9,044.51	9,044.59	**8,978.58**	NA	9,046.49	8,994.23	8,978.65
4	**6,128.01**	6,129.25	6,131.21	NA	6,129.23	6,137.82	6,147.06
5	3,655.06	3,653.44	3,628.62	NA	3,655.94	3,634.60	**3,627.20**
6	3,006.56	2,995.05	2,978.99	NA	2,991.68	2,983.23	**2,977.22**
7	2,352.12	2,352.83	2,339.56	2,345.25	2,350.87	2,341.00	**2,337.73**
Age and sex and treatment (LenDex vs no LenDex)							
1	20,260.45	20,243.56	**20,180.17**	NA	20,254.43	20,186.05	20,186.73
2	6,926.70	**6,918.39**	6,919.41	NA	6,919.31	6,931.01	6,959.77
3	9,035.37	9,034.42	8,975.71	NA	9,037.01	8,990.65	**8,974.99**
4	**6,132.12**	6,133.54	6,135.55	NA	6,133.52	6,143.08	6,152.12
5	3,658.64	3,656.52	3,630.73	NA	3,659.2	3,637.71	**3,629.62**
6	2,992.88	2,985.23	2,975.17	NA	2,983.09	2,977.89	**2,973.17**
7	2,331.54	2,333.26	2,320.14	2,328.51	2,332.12	2,322.31	**2,318.18**
Age and sex and treatment (LenDex vs no LenDex) and lab values							
1	19,037.6	19,008.79	**18,976.75**	NA	19,019.69	18,986.71	18,992.41
2	6,504.22	**6,502.71**	6,503.1	NA	6,503.25	6,515.14	6,546.3

Transition number	Exponential	Gamma	Generalized gamma	Gompertz	Weibull	Log logistic	Log normal
3	8,124.73	8,118.35	8,079.4	NA	8,122.77	8,090.49	**8,077.66**
4	4,502.39	4,504.54	4,501.13	NA	4,504.34	**4,498.85**	4,502.25
5	3,155.95	3,154.08	**3,120.2**	NA	3,156.59	3,133.24	3,123.74
6	2,696.87	2,692.22	2,672.76	NA	2,689.34	2,677.21	**2,671.99**
7	NA	2,066.04	**2,060.51**	2,065.72	2,066.40	NA	NA

AIC = Akaike's Information Criterion, LenDex = lenalidomide and dexamethasone.

Note: Bold text with grey shading represents lowest AIC value.

The parametric distributions that converged are plotted on the empirical Kaplan-Meier curves to determine their visual fit. Since all patient-related data were stripped from the model objects estimated with flexsurv, the parametric curves for the visual inspection can only be plotted when new (pseudo) patient data are provided for each model parameter. For visual inspection, a "standard" patient was created based on the most often observed data from the CMRG summary statistics. The characteristics of the "standard" patient are summarized in Table 4. The plots shown in Figure 3 outline the survival functions for the "standard" patient and not the entire cohort. This illustrates how the survival of the average patient compares to Kaplan-Mier curves for the entire cohort. However, patients with different characteristics will have different survival curves based on their characteristics.

Table 8: BIC Values per Model Transition and According to Covariates

Transition number	Exponential	Gamma	Generalized gamma	Gompertz	Weibull	Log logistic	Log normal
Intercept							
1	20,332.50	20,323.68	20,253.95	NA	20,334.43	20,251.90	**20,251.45**
2	7,045.18	**7,035.26**	7,042.79	NA	7,035.36	7,039.87	7,046.50
3	9,049.65	9,054.85	8,993.97	NA	9,056.76	9,004.50	**8,988.91**
4	**6,133.14**	6,139.51	6,146.61	NA	6,139.49	6,148.08	6,157.32
5	3,659.36	3,662.04	3,641.53	NA	3,664.54	3,643.20	**3,635.80**
6	3,010.87	3,003.66	2,991.90	NA	3,000.29	2,991.84	**2,985.83**
7	2,355.48	2,359.57	2,349.65	2,351.98	2,357.6	2,347.73	**2,344.46**
Age and sex and treatment (LenDex vs. no LenDex)							
1	20,283.14	20,271.92	20,214.2	NA	20,282.79	**20,214.41**	20,215.09
2	6,949.39	**6,946.75**	6,953.44	NA	6,947.67	6,959.36	6,988.13
3	9,055.89	9,060.07	9,006.50	NA	9,062.66	9,016.31	**9,000.64**
4	**6,152.64**	6,159.19	6,166.34	NA	6,159.18	6,168.73	6,177.77
5	3,675.85	3,678.03	3,656.54	NA	3,680.71	3,659.23	**3,651.14**
6	3,010.09	3,006.75	3,000.98	NA	3,004.60	2,999.41	**2,994.68**
7	2,344.99	2,350.06	2,340.31	2,345.32	2,348.92	2,339.12	**2,334.98**

Transition number	Exponential	Gamma	Generalized gamma	Gompertz	Weibull	Log logistic	Log normal
Age and sex and treatment (LenDex vs. no LenDex) and lab values							
1	19,149.91	19,126.71	**19,100.29**	NA	19,137.61	19,104.63	19,110.33
2	**6,616.53**	6,620.63	6,626.64	NA	6,621.17	6,633.06	6,664.23
3	8,223.56	8,222.12	8,188.11	NA	8,226.54	8,194.25	**8,181.42**
4	4,601.22	4,608.31	4,609.83	NA	4,608.10	4,602.62	**4,606.01**
5	3,239.75	3,242.07	3,212.39	NA	3,244.59	3,221.24	**3,211.74**
6	2,780.67	2,780.21	2,764.94	NA	2,777.34	2,765.20	**2,759.98**
7	NA	2,134.77	**2,132.52**	2,134.45	2,135.13	NA	NA

BIC = Bayesian Information Criterion, LenDex = lenalidomide and dexamethasone.

Note: Bold text with grey shading represents lowest BIC value.

Summary of Selected Parametric Models

The plots for each model transition number and converged models are depicted in Figure 3. To plot the parametric distributions, the "standard patient," as outlined in Table 4 was used.

For the final analysis, models for the first treatment (i.e., transitions 1 and 2) are based on the model adjusted for age, sex, treatment, and lab values, while time in all other treatment lines (i.e., lines 2 to 4 and transitions 3 to 7) were estimated using the model adjusted for age, sex, and treatment. Due to missing data in later lines adjustment for lab values in these transitions was not feasible as these values are expected to vary over time. In consultation with clinical experts and based on best parametric fit, given the maturity of data, the parametric fit applied to each transition is detailed in Table 9. As a scenario analysis, we used the Weibull distribution for all transitions. Figure 4 outlines the chosen parametric fit for each transition number for the 'standard' patient as outlined in Table 4.

Figure 3: Empirical and Extrapolated Survival for Model Transition Number

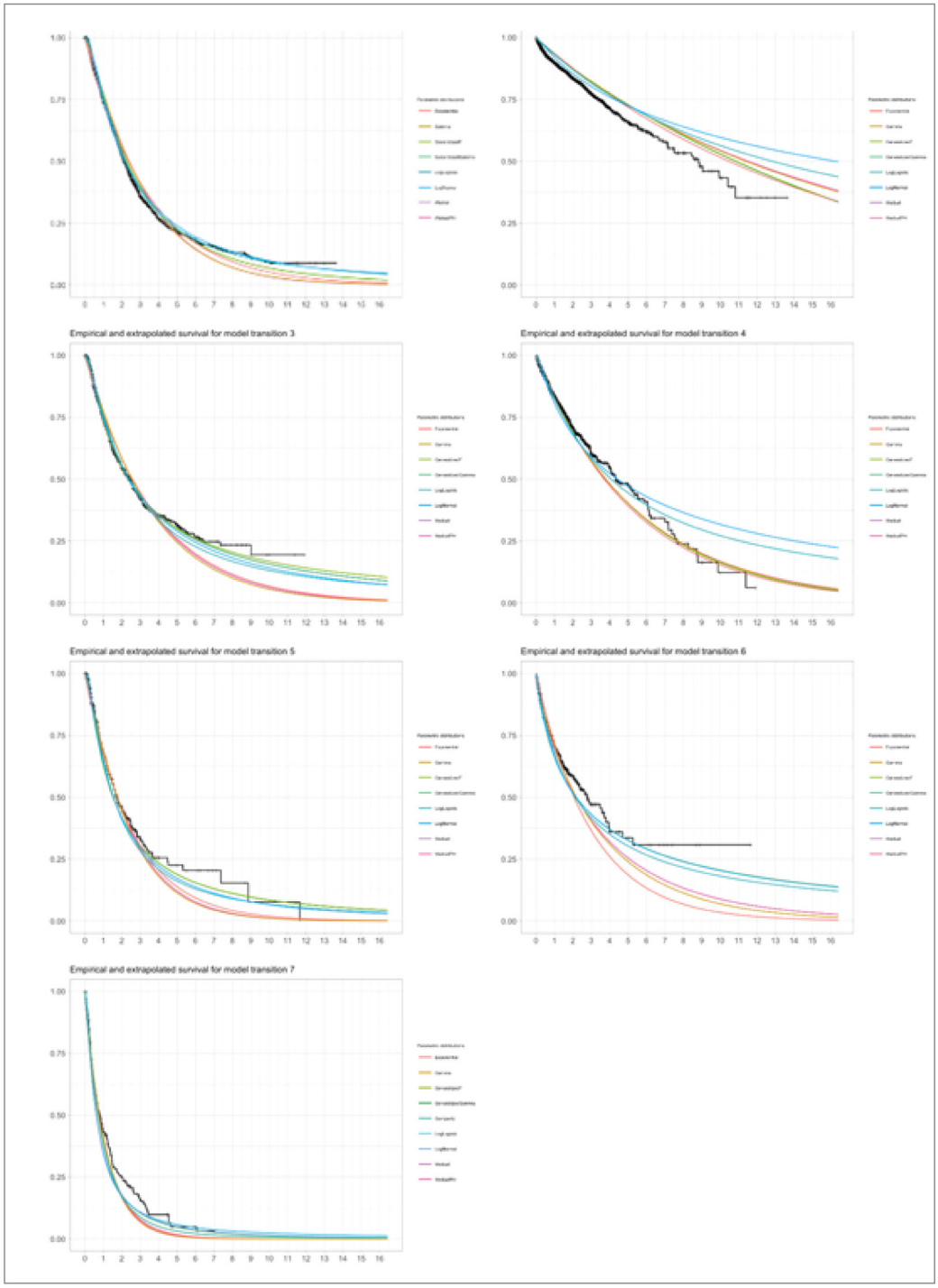


Table 9: Chosen Parametric Model for Each Transition

Transition number	Model	Parametric fit Base case	Parametric fit Scenario Alternative distributions
1 (line 1 to line 2)	Age + sex + treatment + lab values model	Generalized gamma	Weibull
2 (line 1 to death)		Exponential	Weibull
3 (line 2 to line 3)	Age + sex + treatment	Weibull	Weibull
4 (line 2 to death)		Exponential	Weibull
5 (line 3 to line 4)		Lognormal	Weibull
6 (line 3 to death)		Lognormal	Weibull
7 (line 4 to death)		Lognormal	Weibull

Accounting for Correlation Between Characteristics

As the model is a discrete event simulation, at the beginning of each model run the model assigns a set of patient characteristics that determine baseline survival estimates based on age, sex, and lab values. One way to determine what these baseline characteristics are is to randomly allocate each characteristic based on descriptive summary data provided by CMRG, however this assumes independence among all characteristics, i.e., a patient's age is uninformative when predicting gender and severity of condition. This may not be the case for many variables. To overcome this, the CMRG provided CADTH with bootstrapped data for 5,000 iterations with replacement. This process randomly selects a patient from the database, notes their characteristics and then selects another patient. This process was repeated 5,000 times. This enables the model to account for the correlation between variables when selecting baseline patient characteristics.

Relative Treatment Effects

The effect of treatment was based on the results from a network meta-analysis (NMA), which estimated the hazard ratios for each specific therapy based on whether it was used in a treatment-naive or treatment experienced population (full methods from this NMA can be found in the CADTH clinical report). From this NMA, hazard ratios for progression-free survival (PFS) were identified for each treatment. If a treatment was used in the first-line setting, the hazard ratio (HR) from the treatment-naive NMA was used. If the treatment was used in a later line (2L+) then the HR from the treatment experienced NMA was used. In total 12 treatments were considered, which are summarized in Table 10.

To use results from the NMA in the economic analysis several assumptions needed to be made.

First, the NMA only gives the results for PFS. PFS is a composite outcome that includes both time to progression (TTP) and death before progression. The model treats these 2 events as 2 distinct outcomes. Therefore, a HR is needed for both TTP and time to death before progression. Some trials used to inform the NMA reported the HR for TTP as well as PFS. However, this information was not frequently reported

and therefore a NMA could not be conducted on TTP alone. As PFS comprises both TTP and time to death before progression the difference between TTP and PFS is influenced by 2 factors:

- The number of deaths that occur *before progression* as a proportion of total PFS events. As the number of events due to progression, as a proportion of total events which also includes deaths before progression, trends to 100% the HRs for TTP and PFS become equal;
- The difference the treatment has on TTP and time to death before progression. If the HR for TTP is equal to the HR for time to death before progression, then the HR for PFS will equal the HR for TTP.

Table 10: Employed HRs from the NMA for Model Transitions in the Base Case

Treatment	PFS (first-line setting)	PFS (second line or further settings)
LenDex	Reference	Reference
LenBorDex	0.74	NA
DaraCyBorDex	0.47	NA
DaraMphBorPred	0.47	NA
DaraLenDex	0.53	0.44
DaraBorDex	NA	0.51
CyBorDex	1.12	2.21
CarDex	NA	0.83
CarLenDex	NA	0.66
PomBorDex	NA	0.96
PomDex	NA	1.37
IsaPomDex	NA	0.82

HR = hazard ratio; CarDex = carfilzomib and dexamethasone; CarLenDex = carfilzomib, lenalidomide, and dexamethasone; CyBorDex = cyclophosphamide, bortezomib, and dexamethasone; DaraBorDex = daratumumab, bortezomib, and dexamethasone; DaraCyBorDex = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; DaraLenDex = daratumumab, lenalidomide, and dexamethasone; DaraMphBorPred = daratumumab, melphalan, bortezomib, and dexamethasone; HR = hazard ratio; IsaPomDex = isatuximab, pomalidomide, and bortezomib; LenDex = lenalidomide and dexamethasone; LenBorDex = lenalidomide, bortezomib, and dexamethasone; NA = not applicable (as this treatment was not assessed in that given line of therapy given the proposed sequences outlined in Table 1); NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival; PomBorDex = pomalidomide; bortezomib and dexamethasone; PomDex = pomalidomide and bortezomib.

For item 1, based on data that could be extracted from trials and in consultation with clinical experts, progression is the main event that influences the PFS statistic likely comprising of over 75% of events. For item 2, based on data extracted from the trials and in consultation with clinical experts it is not expected that there would be large relative differences between treatments when looking at time to death before progression. Clinically if a treatment is not delaying progression, it is unlikely to have a substantial impact on survival. Based on this it is expected that the HR for TTP will be slightly lower than the HR for PFS.

From the NMA every trial that reported both TTP and PFS was extracted. In the treatment-naive NMA, TTP was consistently lower than PFS for all trials it was reported (Table 11). The TTP HR was reported to be around 90% lower than the HR for PFS. This equated to an HR that was 0.04 to 0.07 lower when looking at TTP versus PFS. The difference was even smaller in the treatment experienced group (Table 12). This was due to progression being an even more common event relative to death before progression. In studies

conducted in patients who are treatment experienced the TTP HR was on average 95% lower with an absolute difference of 0.01 to 0.08. One trial reported the HR for TTP was slightly higher than the HR for PFS (0.79 versus 0.77).

In the base-case analysis TTP was assumed to equal PFS and the HR for time to death before progression was assumed to be 1 for all treatments (i.e., assuming time to death before progression was similar to the data as observed in the CMRG). A treatment could therefore only improve OS by delaying time to next therapy. It is acknowledged that this assumption will underestimate the benefit of all treatments. To explore the impact of this, the following scenario analyses was conducted:

- In treatment-naive patients, the HR for TTP was assumed to be 0.10 lower than the HR for PFS. In treatment experienced patients the HR for TTP was assumed to be 0.05 lower than the HR for PFS. This was informed by the upper limits differences between TTP and PFS for studies that reported both.

Second, an assumption had to be made regarding the efficacy of each therapy for a given treatment line. Trials conducted in the MM space tend to be conducted in patients who are treatment naive or treatment experienced (relapsed and/or refractory). For patients who are treatment experienced the model requires further specification as to which line of therapy the treatment is being used. This level of granularity is not provided consistently across trials and as it may not be a stratified outcome at baseline, results from these subgroup analyses are highly uncertain. It was therefore assumed that a treatment would have the same efficacy in line 2 as it would line 3. Experts noted that as patients often become frailer as they move down treatment lines, and more intensive therapies may be less effective. To explore this, a scenario analysis was conducted to explore the impact of an alternative assumption in which the HR for PFS of carfilzomib and daratumumab combinations was less effective for third line and subsequent lines (i.e., the HR was 10% and 20% higher).

In the 4L setting patients do not receive a further line of therapy in the model and therefore the only impact a treatment may have in the model is on mortality. A study by Etekal et al.[11] explored the potential correlation between OS and PFS in the MM space. In the relapsed and/or refractory space the study notes that 58% of the variation in OS was due to changes in progression. A linear trend was estimated in the study by looking at the reported OS HR compared to the PFS HR. The output from this has been translated in Table 13. For example, based on the output from the linear regression plot, a PFS HR of 0.5 approximately translates to an OS HR of 0.78, a PFS HR of 0.8 translates to an OS HR of 0.94. Therefore, any PFS HR below 0.9 may predict some improvement in OS.

Figure 4: Empirical Survival for Model Transition Number

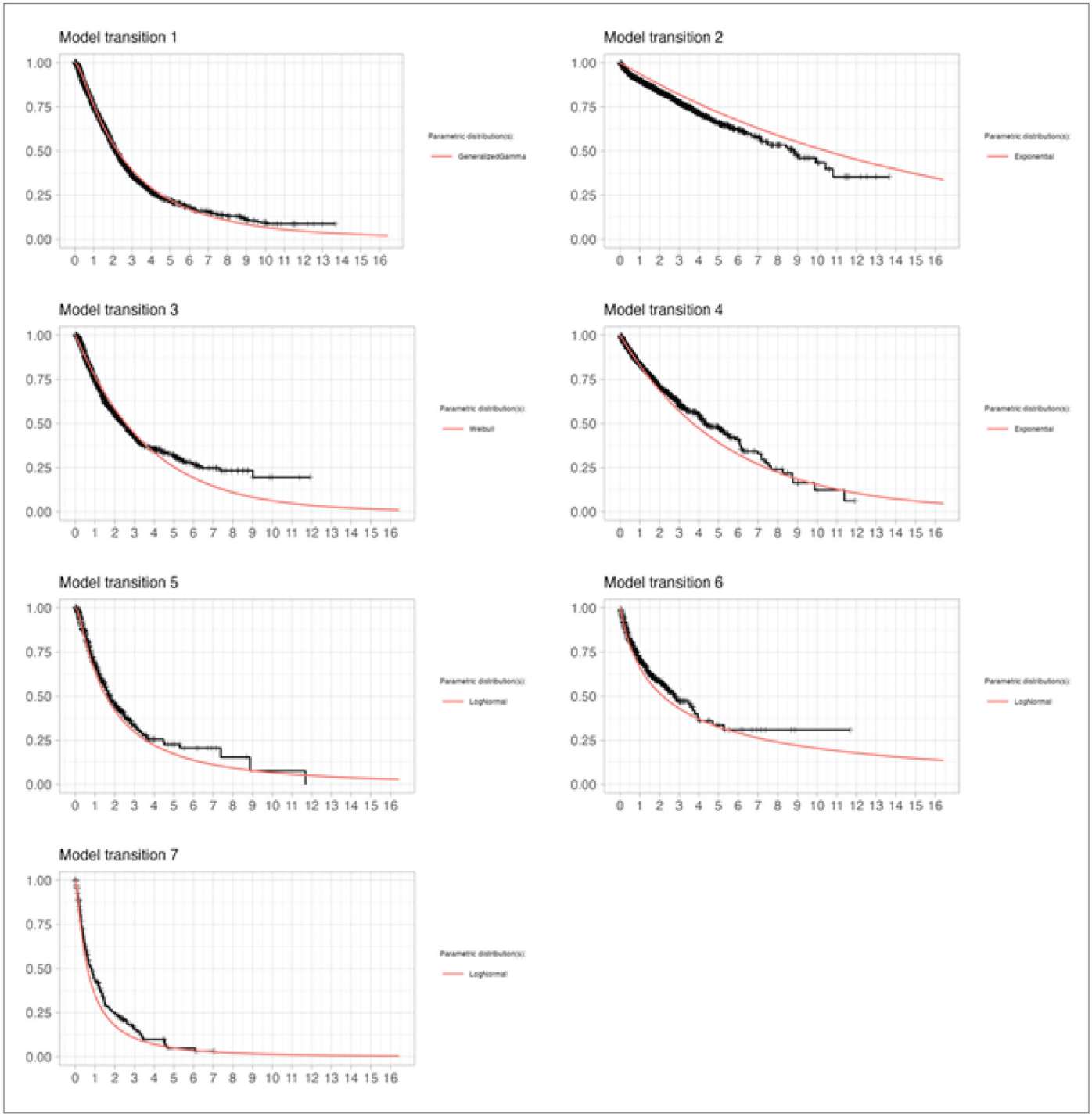


Table 11: Difference in HRs for PFS and TTP in Treatment-Naive Trials

Trial name	PFS HR	TTP HR	Difference (as a %)	Absolute difference
CLARION	0.91	0.84	92%	0.07
ENDURANCE	1.04	0.97	93%	0.07
GISMM2001-A	0.63	0.57	90%	0.06
THAL-MM-03	0.50	0.43	86%	0.07
TOURMALINE-MM2	0.83	0.74	89%	0.09
VISTA	0.56	0.48	86%	0.08
NCT00205751	1.30	1.26	97%	0.04

HR = hazard ratio, PFS = progression-free survival, TTP = time to progression.

Table 12: Difference in HR for PFS and TTP in Treatment Experienced Trials

Trial name	PFS HR	TTP HR	Difference (as a %)	Absolute difference
ARROW	0.69	0.66	96%	0.03
BELLINI	0.63	0.55	87%	0.08
LEPUS	0.35	0.34	97%	0.01
MMY3001	0.59	0.55	93%	0.04
OPTIMUM	0.74	0.71	96%	0.03
VANTAGE	0.77	0.79	103%	−0.02

HR = hazard ratio, PFS = progression-free survival, TTP = time to progression.

Table 13: Output From Linear Regression Plots for OS and PFS HRs

PFS HR	OS HR
0.1	0.55
0.2	0.61
0.3	0.67
0.4	0.72
0.5	0.78
0.6	0.83
0.7	0.89
0.8	0.94

HR = hazard ratio, OS = overall survival; PFS = progression-free survival.

In the base case, treatments in the 4L setting improve OS by assuming a correlation between PFS and OS. Input from clinical experts noted that in the 4L setting many patients would be triple refractory. Outcomes in this group tend to be poor and therefore the efficacy of a therapy will likely be substantially worse in this group of patients. Given the high degree of uncertainty regarding relative efficacy in the 4L setting to explore

this, a scenario analysis was conducted. In the 4L setting treatment efficacy was assumed to be equivalent among all treatment alternatives (HR = 1). We refer to this as Scenario "HR in subsequent lines to 1."

Given the above assumptions, the base case model utilizes the following HR (Table 14) for each transition in the model for each treatment sequence.

Population Mortality

In the CMRG data, all-cause mortality was captured and there was substantial follow-up for OS. Nevertheless, to avoid the possibility that patients could reach implausible ages, it was assumed that they could not become older than 110 years and this was the maximum age implemented in the model in the base case.

Table 14: PFS HRs from NMA for Model Transitions in the Base Case

Treatment	HR for TTNT relative to LenDex in each line			
	Line 1	Line 2	Line 3	Line 4 (HR applied to OS)
CyBorDex	1.12	2.21	NA	NA
DaraBorDex	NA	**0.51**	NA	**0.51 (0.78)**
DaraCyBorDex	**0.47**	NA	NA	NA
DaraLenDex	**0.53**	**0.44**	NA	NA
DaraMphBorPred	**0.47**	NA	NA	NA
LenBorDex	**0.74**	NA	NA	NA
LenDex	Reference	Reference	Reference	Reference
CarDex	NA	**0.83**	**0.83**	**0.83 (0.96)**
CarLenDex	NA	**0.66**	NA	NA
PomDex	NA	NA	1.37	1.37 (1.23)
PomBorDex	NA	**0.96**	**0.96**	**0.96 (1.00)**
IsaPomDex	NA	NA	**0.82**	NA

CarDex = carfilzomib and dexamethasone; CarLenDex = carfilzomib, lenalidomide, and dexamethasone; CyBorDex = cyclophosphamide, bortezomib, and dexamethasone; DaraBorDex = daratumumab, bortezomib, and dexamethasone; DaraCyBorDex = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; DaraLenDex = daratumumab, lenalidomide, and dexamethasone; DaraMphBorPred = daratumumab, melphalan, bortezomib, and dexamethasone; HR = hazard ratio; IsaPomDex = isatuximab, pomalidomide, and bortezomib; LenDex = lenalidomide and dexamethasone; LenBorDex = lenalidomide, bortezomib, and dexamethasone; NA = not applicable (as this treatment was not assessed in that given line of therapy given the proposed sequences outlined in Table 1); NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival; PomBorDex = pomalidomide; bortezomib and dexamethasone; PomDex = pomalidomide and bortezomib.

Note: Bold text with grey shading treatments that have a point estimate better than LenDex from the NMA (note uncertainty in the point estimate is accounted for in the PSA).

Utilities

Estimates of utilities were derived from the literature as the CMRG did not collect these data. A systematic review by Golicki et al.[12] gathered data on EQ-5D health state utility scores in MM. Results from these studies show a large degree of variability of utility scores within and across different MM health states. From this review, 1 study conducted in Canada[13] was identified that analyzed MM utility scores using a Canada value set. This study showed that utility was estimated to be 0.78 with slight variability depending on time from diagnosis and time on treatment. The lowest utility score identified from the study was 0.75 for individuals 3 months before starting therapy (0.75) though patient numbers informing this were small (n = 16). This

study did not look at utility changes dependent on the line of therapy. Only 1 study identified in the review by Golicki et al. analyzed utility scores by line of therapy. A study by Acaster et al[14] reported utility scores in a UK cohort by first, second, and a later line of therapy. The results showed that utility increased for those moving to second line and then decreased by later lines. Given small numbers (n = 12) this result is highly uncertain. Given the potential for survivor bias, whereby individuals who are healthier go onto later lines this may limit the reliability of a cross sectional cohort study that does not look at how utilities change over time given numerous lines of progression.

A study by Hatswell et al[15] performed a systematic review of the literature alongside registry and trial data to inform utility values by line of therapy. The paper's preferred approach demonstrated a high degree of variability of utility values within each health state. For an individual who was ASCT ineligible and on first-line therapy, utility was estimated to be 0.62 (95% CI, 0.456 to 0.786). For an individual who was on second-line therapy this decreased to 0.59 (95% CI, 0.568 to 0.612). For third line this decreased to 0.58 (95% CI, 0.275 to 0.880). For fourth line and beyond utility again further decreased to 0.469 (95% CI, 0.021 to 0.918). The study shows that estimates of utility scores for a given line of therapy are highly uncertain. The study concludes this is due to variability in the underlying data that informs the analysis.

Overall, there is a high degree of uncertainty regarding how utility changes as patients receive subsequent lines of therapy. Achieving disease stability and preventing constant movement through lines of therapy is likely to improve patient utility. If a patient therefore fails a line of therapy but then achieves stability on a subsequent line then it is plausible that utility will improve for that patient. In the base-case analysis CADTH assumed no reduction in utility as the patient progresses through lines of therapy and explored this assumption through scenario analyses. Patient utility as taken from Naik et al[15] was used to inform baseline utility (0.78), this was then age adjusted using a Canada value set. A scenario analysis was conducted in which utility decrements were implemented for later lines of therapy (L2 −0.03, L3 −0.04, L4 to 0.15). We refer to this as Scenario "Utility decrements in later lines."

Resource Use and Costs

Treatment Costs

Treatment costs consisted of drug acquisition costs and drug administration costs. Drug acquisition costs were calculated as a function of unit drug prices, dosing, and treatment duration. Drug prices were taken from different sources and are summarized in Table 15 (together with their sources). To establish the cost of each regimen CADTH reached out to all participating public drug plans to establish what were the most prescribed dosing schedules for each regimen. For most regimens there was consistency regarding how each drug was administered as part of a regimen. The following discrepancies were noted:

- For dexamethasone there was discrepancy regarding how often it is administered and at what dose. As the purpose of this exercise was to determine treatment costs and as dexamethasone is such a low-cost treatment alternative dexamethasone dosing schedules have minimal impacts on cost. This was therefore not determined to be a large concern.
- For DaraCyBorDex there was variability regarding when daratumumab would be administered twice per 28-day cycle as opposed to 4 times. Some schedules drop down to 2 administrations

of daratumumab per cycle at cycle 3 before going down to 1 administration per cycle at cycle 7. Other schedules continue giving daratumumab 4 times per cycle until cycle 4. Given this equates to 2 additional administrations of daratumumab for 1 cycle this small discrepancy in cost was not deemed to be of concern.

- For DaraMphBorPred there is limited information due to its limited use across Canada. The product monograph from Cancer Care Ontario (CCO) is also for the IV version of daratumumab and not the routinely used subcutaneous version. It was assumed that daratumumab would be given subcutaneously, the same as other regimens (such as DaraLenDex), and administration of bortezomib, melphalan and prednisone would be administered as per the product monograph from CCO.
- For LenBorDex CCO notes that lenalidomide is to be given for days 1 to 14 per 21-day cycle. Other plans note than lenalidomide is given for 21 days in a 28-week cycle. As there was more consistency on administration for 28-day cycles this was chosen in the base case. Likewise, the discrepancy does not have a substantial impact on cost as 1 regimen has patients taking a treatment every 2 of 3 days whereas the other has patients taking treatment every 3 of 4 days.
- For carfilzomib regimens there was the most potential variability in administration across Canada. In consultation with clinical experts, it was noted that the once weekly regimen was more frequently administered. This was especially important as once weekly versus twice weekly carfilzomib has differing levels of efficacy according to trials included in the NMA. For CarDex carfilzomib was assumed to be administered at a starting dose of 20 mg/kg^2 followed by weekly administration of 70kg/m^2. For CarLenDex carfilzomib was assumed to be administered at a starting dose of 20 mg/kg^2 followed by weekly administration of 56 kg/m^2.

These costs are based on public list prices and confidential pricing agreements with the pan Canadian Pharmaceutical Alliance (pCPA) exists for many of the comparators. Likewise, some treatments, such as pomalidomide, have patents due to expire. The cost of these regimens will decrease substantially when generics enter the market. As the cost per cycle changes over time for many of the considered regimens, for illustrative purposes, the information in Table 15 is presented in Figure 5. This figure outlines the cumulative cost over time for each regimen in Table 15 and demonstrates how the cumulative cost can change. DaraBorDex and DaraBorMphPred have been excluded from the graph to allow for the figure to be less crowded as well as the costs being close to DaraCyBorD. In the model, cumulative costs over time will look different as the model accounts for treatment discontinuation, discounting, and a more accurate patient weight.

Table 15: CADTH Cost Comparison Table for Therapies for Patients With MM Who Are Transplant Ineligible

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage (per 28 day cycle)	Daily cost ($)	28-day cost ($)
Cyclophosphamide + bortezomib + dexamethasone (CyBorDex) [28 day cycle]						
Bortezomib[a]	3.5 mg	Injection	654.31	1.5 mg/m^2 on days 1, 8, 15, 22	93	2,617
Cyclophosphamide	50 mg	Tablet	0.4773	300 mg/m^2 on days 1, 8, 15, 22	0.75	21
Dexamethasone[b]	0.5 mg 4 mg	Tablet	0.1564 0.6112	40 mg on days 1, 8, 15, 22	0.87	24
Cyclophosphamide + bortezomib + dexamethasone regimen					95	2,663
Daratumumab + bortezomib + dexamethasone (DaraBorDex) [28 day cycle]						
Bortezomib[a]	3.5 mg	Injection	654.31	**Cycle 1 to 8** 1.5 mg/m^2 on days 1, 4, 8, 11 **Cycle 9+:** Not administered	Cycles 1 to 8: 93 Cycles 9+: 0	Cycles 1 to 8: 2,617 Cycles 9+: 0
Daratumumab	1,800	Injection	$7,310	**Cycle 1 to 2** 1,800 mg on days 1, 8, 15, 22 **Cycle 3 to 4** 1,800 mg on days 1, 15 **Cycle 5+** 1,800 mg on days 1	Cycles 1, 2: 1,044 Cycles 3, 4: 522 Cycles 5+: 261	Cycles 1, 2: 29,240 Cycles 3, 4: 14,620 Cycles 5+: 7,310
Dexamethasone[b]	4 mg	Tablet	0.6112	**Cycle 1 to 8** 40 mg on days 1, 8, 15, 22 **Cycle 9+** 40 mg on days 1	Cycles 1 to 8: 0.87 Cycles 9+: 0.22	Cycles 1 to 8: 24 Cycles 9+: 6
Daratumumab + bortezomib + dexamethasone regimen					Cycles 1, 2: 1,139 Cycles 3, 4: 616 Cycles 5, 6, 7, 8: 355 Cycle 9+: 261	Cycles 1, 2: 31,882 Cycles 3, 4: 17,262 Cycles 5, 6, 7 8: 9,952 Cycle 9+: 7,316

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage (per 28 day cycle)	Daily cost ($)	28-day cost ($)
Daratumumab + cyclophosphamide + bortezomib + dexamethasone (DaraCyBorDex) [28 day cycle]						
Bortezomib[a]	3.5 mg	Injection	654.31	**Cycle 1 to 8** 1.5 mg/m^2 on days 1, 8, 15, 22 Cycle 9+: Not administered	Cycle 1 to 8: 93 Cycle 9+: 0	Cycle 1 to 8: 2,617 Cycle 9+: 0
Cyclophosphamide	25 mg 50 mg	Tablet	0.3545 0.4773	**Cycle 1 to 8** 300 mg/m^2 on days 1, 8, 15, 22 **Cycle 9+:** Not administered	Cycle 1 to 8: 1 Cycle 9+: 0	Cycle 1 to 8: 21 Cycle 9+: 0
Daratumumab	1,800	Injection	$7,310	**Cycle 1 to 2** 1,800 mg on days 1, 8, 15, 22 **Cycle 3 to 6** 1,800 mg on days 1,15 **Cycle 7+** 1,800 mg on days: 1	Cycle 1 to 2: 1,044 Cycle 3 to 6: 522 Cycle 7+: 261	Cycle 1 to 2: 29,240 Cycle 3 to 6: 14,620 Cycle 7+: 7,310
Dexamethasone[b]	4 mg	Tablet	0.6112	**Cycle 1 to 8** 40 mg on days 1, 8, 15, 22 **Cycle 9+** 40 mg on days 1	Cycles 1 to 8: 0.87 Cycles 9+: 0.22	Cycles 1 to 8: 24 Cycles 9+: 6
Daratumumab + cyclophosphamide + bortezomib + dexamethasone regimen					Cycles 1, 2: 1,139 Cycles 3 to 6: 617 Cycles 7 to 8: 356 Cycle 9+: 261	Cycles 1, 2: 31,903 Cycles 3 to 6: 17,283 Cycles 7 to 8: 9,973 Cycle 9+: 7,316
Daratumumab + lenalidomide + dexamethasone (DaraLenDex) [28 day cycle]						
Daratumumab	1,800	Injection	$7,310	**Cycle 1 to 2** 1,800 mg on days 1, 8, 15, 22 **Cycle 3 to 4** 1,800 mg on days 1, 15	Cycle 1 to 2: 1,044 Cycle 3 to 4: 522 Cycle 5+: 261	Cycle 1 to 2: 29,240 Cycle 3 to 4: 14,620 Cycle 5+: 7,310

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage (per 28 day cycle)	Daily cost ($)	28-day cost ($)
				Cycle 5+ 1,800 mg on days 1		
Dexamethasone[b]	0.5 mg 4 mg	Tablet	0.1564 0.6112	40 mg on days 1, 8, 15, 22	0.87	24
Lenalidomide	25	Tablet	106	25 mg on days 1 to 21	79.50	2,226
Daratumumab + lenalidomide + dexamethasone regimen					Cycle 1 to 2: 1,125 Cycle 3 to 4: 603 Cycle 5+: 341	Cycle 1 to 2: 31,490 Cycle 3 to 4: 16,870 Cycle 5+: 9,560
Daratumumab + melphalan + bortezomib + prednisone (DaraMphBorPred)[c] [42 day cycle for melphalan, prednisone and bortezomib, 28-day cycle for daratumumab from cycle 10+]						
Bortezomib[a]	3.5 mg	Injection	654.31	**Cycle 1** 1.3 mg/m^2 on days 1, 4, 8, 11, 22, 25, 29, 32 **Cycle 2 to 9** 1.3 mg/m2 on days 1, 8, 22, 29 **Cycle 10+:** Not administered	Cycle 1: 125 Cycle 2 to 9: 62 Cycle 10+: 0	Cycle 1: 3,490 Cycle 2 to 9: 1,745 Cycle 10+: 0
Daratumumab	1,800	Injection	7,310	**Cycle 1** 1,800 mg on days 1, 8, 15, 22, 29, 36 **Cycle 2 to 9** 1,800 mg on days 1, 22 **Cycle 10+** 1,800 mg on days 1	Cycle 1 to 2: 1,044 Cycle 2 to 9: 348 Cycle 10+: 261	Cycle 1 to 2: 29,240 Cycle 2 to 9: 9,747 Cycle 10+: 7,310
Melphalan	2 mg	Tablet	2.02	**Cycle 1 to 9** 9 mg/m^2 on days 1, 2, 3, 4 **Cycle 10+** Not administered	Cycle 1 to 9: 2 Cycle 10+: 0	Cycle 1 to 9: 43 Cycle 10+: 0

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage (per 28 day cycle)	Daily cost ($)	28-day cost ($)
Prednisone	5 mg 50 mg	Tablet	0.02 0.17	**Cycle 1 to 9** 60 mg/m^2 on days 1, 2, 3, 4 **Cycle 10+:** Not administered	Cycle 1 to 9: 0.03 Cycle 10+: 0	Cycle 1 to 9: 0.93 Cycle 10+: 0
Daratumumab + melphalan + bortezomib + prednisone regimen					Cycle 1 to 2: 1,170 Cycle 2 to 9: 412 Cycle 10+: 261	Cycle 1 to 2: 32,774 Cycle 2 to 9: 11,536 Cycle 10+: 7,310
Lenalidomide + bortezomib + dexamethasone (LenBorDex) [28 day cycle]						
Bortezomib[a]	3.5 mg	Injection	654.31	**Cycle 1 to 8** 1.3 mg/m^2 on days 1, 8, 15, 22 **Cycle 9+:** Not administered	Cycle 1 to 8: 93 Cycle 9+: 0	Cycle 1 to 8: 2,617 Cycle 9+: 0
Lenalidomide	25	Tablet	106	25 mg on days 1 to 21	80	2,226
Dexamethasone[b]	0.5 mg 4 mg	Tablet	0.1564 0.6112	40 mg on days 1, 8, 15, 22	0.87	24
Lenalidomide + bortezomib + dexamethasone regimen					Cycle 1 to 8: 174 Cycle 9+: 80	Cycle 1 to 8: 4,868 Cycle 9+: 2,250
Lenalidomide + dexamethasone (LenDex) [28 day cycle]						
Lenalidomide	25	Tablet	106	25 mg on days 1 to 21	80	2,226
Dexamethasone[b]	0.5 mg 4 mg	Tablet	0.1564 0.6112	40 mg on days 1, 8, 15, 22	0.87	24
Lenalidomide + dexamethasone regimen					80	2,250
Carfilzomib + dexamethasone (CarDex) – weekly [28 day cycle]						
Carfilzomib	10 mg 30 mg 60 mg	Injection	255.5500[c] 766.6590 1,533.3300	**Cycle 1** 20 mg/m^2 on days 1 70 mg/m^2 on days 8, 15 **Cycle 2+** 70 mg/m^2 on days 1, 8, 15	Cycle 1: 292 Cycle 2+: 329	Cycle 1: 8,178 Cycle 2+: 9,200

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage (per 28 day cycle)	Daily cost ($)	28-day cost ($)
Dexamethasone[b]	0.5 mg 4 mg	Tablet	0.1564 0.6112	40 mg on days 1, 8, 15, 22	0.87	24
Carfilzomib + dexamethasone regimen					Cycle 1: 293 Cycle 2+: 329	Cycle 1: 8,202 Cycle 2+: 9,224
Carfilzomib + lenalidomide + dexamethasone (CarLenDex)[d] [28 day cycle]						
Carfilzomib	10 mg 30 mg 60 mg	Injection	255.5500[c] 766.6590 1,533.3300	**Cycle 1** 20 mg/m^2 on days 1 56 mg/m^2 on days 8, 15 **Cycle 2+** 56 mg/m^2 on days 1, 8, 15 **Cycle 18+:** Not administered	Cycle 1: 219 Cycle 2 to 18: 274 Cycle 18+: 0	Cycle 1: 6,133 Cycle 2+: 7,667 Cycle 18+: 0
Lenalidomide	25	Tablet	106	25 mg on days 1 to 21	80	2,226
Dexamethasone[b]	0.5 mg 4 mg	Tablet	0.1564 0.6112	40 mg on days 1, 8, 15, 22	4	24
Carfilzomib + lenalidomide + dexamethasone regimen					Cycle 1: 299 Cycle 2 to 18: 354 Cycle 18+: 80	Cycle 1: 8,384 Cycle 2 to 18: 9,917 Cycle 18+: 2,250
Pomalidomide + dexamethasone (PomDex) [28 day cycle length]						
Pomalidamide	4 mg	Tablet	500	4 mg on Days: 1 to 21	375.00	10,500
Dexamethasone[b]	0.5 mg 4 mg	Tablet	0.1564 0.6112	40 mg on Days: 1, 8, 15, 22	0.87	24
Pomalidomide + dexamethasone regimen					376	10,525
Pomalidomide + bortezomib + dexamethasone (PomBorDex) [28 day cycle length]						
Bortezomib	3.5 mg	Injection	654.31	1.3 mg/m^2 on days 1, 8, 15, 22	93.47	2,617
Pomalidomide	4 mg	Tablet	500	4 mg on days 1 to 21	375	10,500

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage (per 28 day cycle)	Daily cost ($)	28-day cost ($)
Dexamethasone[b]	4 mg	Tablet	0.1564 0.6112	40 mg on days 1, 8, 15, 22	0.87	24
Pomalidomide + bortezomib + dexamethasone regimen					469	13,142
Isatuximab + pomalidomide + dexamethasone (IsaPomDex) [28 day cycle length]						
Dexamethasone[b]	0.5 mg 4 mg	Tablet	0.1564 0.6112	40 mg on days 1, 8, 15, 22	0.87	24
Pomalidomide	4 mg	Tablet	500	4 mg on days 1 to 21	375	10,500
Isatuximab	120 mg	Solution for IV	757.90	**Cycle 1** 10 mg/kg on days 1, 8, 15, 22 **Cycle 2+** 10 mg/kg on days 1, 15	Cycle 1: 758 Cycle 2+: 379	Cycle 1: 10,611 Cycle 2+: 21,221
Isatuximab + pomalidomide + dexamethasone					Cycle 1: 1,134 Cycle 2+: 755	Cycle 1: 31,746 Cycle 2+: 21,135

MM = multiple myeloma.

[a]It was noted a higher dose of 1.5 mg/m^2 is sometimes adopted for bortezomib.

[b]It was noted lower doses of dexamethasone are recommended for patients over the age of 70 and its use beyond certain cycle lengths is discretionary.

[c]The DaraMphBorPred is rarely used in practice in Canada and the monograph is for an IV form of daratumumab which is rarely used. Here the subcutaneous version of daratumumab is assumed, aligning with all other regimens.

[d]Alternative carfilzomib doses are used such as 70mg/kg^2 though only administered on days 1, 8 in cycles 13 to 18.

In the model simulation, when a required target dose could only be achieved by combining several pills or vials, the lowest cost combination was considered. The lowest cost drug combination for a single target dose was allowing for up to 10 different combinations to reach the target dose. The choice for the maximum combinations was made to reduce computational intensity and because it was assumed that a reduced regimen complexity is favourable in clinical practice. Since some drugs are administered based on the patients' body weight in kilogram (kg) or body surface areas (BSA), the function to calculate drug combination prices accounts for either kg or BSA of each simulated patient in the model. For illustrative purposes, in Table 15 all costs are calculated assuming a weight is 75 kg and BSA of 1.8 m^2 for the treatment duration. In the model, these costs are calculated based on the specific characteristics of each simulated patient.

Administration Costs

The costs associated with drug administration were sourced from the Ontario Schedule of Benefits: Physician services under the Health Insurance Act, and varied based on the method of administration. Each subcutaneous application was calculated at $75, as stipulated by Code: G345. If multiple subcutaneous applications occur on a single day, the $75 cost was only applied once. Oral treatment administration costs, as per Code: G388, were $25.75 and only eligible for reimbursement once every 21 days, up to a limit of 6 months. This stipulation was integrated into the model that predicts precise patient treatment days, thereby accurately estimating the cost of oral drug administration. IV drug applications were priced at $125, consisting of $105 for the administration and $20 for the preparation of the dose by a pharmacy technician. These costs were validated with participating CADTH drug plans to ensure broad generalizability across jurisdictions. It was noted that isatuximab was an exception due to a considerably longer chair time (around 2 hours) compared to other IV applications (approximately 30 minutes). Based on drug plan input, the standard administration cost of $105 for isatuximab was tripled for the initial 2 doses ($315) and doubled ($210) for subsequent administrations.

Other Health Care Utilization Costs

Final costs to consider were those associated with the management of MM. The costs outlined in Table 16 were identified and validated with clinical experts. One consideration was whether these costs would vary as a patient moves through treatment lines. A study by De Oliveira et al[16] showed that costs in myeloma are high at initial (first 6 months) and terminal (last 6 months) phases of the disease and are approximately $15,000 annually in between. This estimate does include drug costs however, which are considered separately in this analysis. Just using the resource estimates below will likely underestimate total health system costs incurred across the patient lifetime but will unlikely have a substantial impact on cost-effectiveness conclusions as there is insufficient data to show how resource utilization varies between treatment lines in Canada.

Table 16: MM Management Costs

Item	Code	Unit cost ($)	Yearly use
Hematologist clinical visit	A616[a]	$105.25	12 (once per month)
Full blood count	L393[b]	$3.98	12 (once per month)
TSH	L341[b]	$3.58	4 (once every 3 months)
Urea nitrogen (BUN)	L251[b]	$1.28	12 (once per month)
Sodium	L226[b]	$1.16	12 (once per month)
SGPT (ALT)	L223[b]	$1.28	12 (once per month)
SGOT (AST)	L222[b]	$1.28	12 (once per month)
Protein	L208[b]	$1.16	12 (once per month)
Potassium	L204[b]	$1.16	12 (once per month)
Phosphatase, alkaline	L191[b]	$1.28	12 (once per month)
Glucose, quantitative	L111[b]	$1.28	12 (once per month)
Creatinine	L067[b]	$1.28	12 (once per month)
CO_2 content, CO_2 combining power, bicarbonate (measured, not calculated)	L061[b]	$1.28	12 (once per month)
Chloride	L053[b]	$1.28	12 (once per month)
Calcium	L045[b]	$1.16	12 (once per month)
Bilirubin, total	L030[b]	$1.28	12 (once per month)
Glomerular filtration rate	L004[b]	$1.55	12 (once per month)
Electrophoresis, serum - including total protein	L085[b]	$17.58	12 (once per month)
Gammopathy Screen by immunoelectrophoresis or immunofixation Serum Urine	L575[b]	$25.66	12 (once per month)

MM = multiple myeloma.

[a]Unit costs obtained from Ontario Ministry of Health Schedule of Benefits Physician Services Under the Health Insurance Act 2023.

[b]Unit costs obtained from Ontario Ministry of Health Schedule of Benefits For Laboratory Services 2023.

Adverse Events

When considering health care utilization and quality of life impact from treatment related adverse events (AEs) were identified as an important consideration. In consultation with clinical experts the following AEs were noted as being the most notable to consider across treatments based on their prevalence, expected difference between treatments, and or severity: respiratory infections, neuropathy, diarrhea, cardiotoxicity, thrombotic events. These outcomes could not be robustly explored using the NMA. To further explore this, product monographs for bortezomib, lenalidomide, daratumumab, carfilzomib, isatuximab and pomalidomide were analyzed from BC Cancer (Table 17). Rates of severe events for the mentioned AEs were noted for each treatment. This constitutes a naive comparison and not a formal comparison of AEs; this does not account for potential confounding across the studies by which the AE data were gathered. Likewise, Table 17 is not comprehensive as many other AEs are reported in the product monograph. The below exercise was therefore performed for illustrative purposes.

Table 17: Rates of Selected Severe Side Effects Across Treatments

Treatment	Thrombocytopenia %	Diarrhea %	Peripheral neuropathy %	Pneumonia %	URTI %	Neutropenia %	Infusion related reaction %
Bortezomib[17]	30	7 to 8	8 to14	5	NR[a]	14 to16	NR (SC)
Lenalidomide[18]	53	5	< 1	10	1	62	NR (oral)
Daratumumab[19]	14 to 18	< 1	4	6	2	12 to 20	< 2 for initial and < 1 for subsequent injections (if given SC)
Carfilzomib[20]	9 to 25	1	1	6 to 11	1 to 3	8 to 10	4
Isatuximab[21]	25 to 31	2	NR	22 to 26	3 to 9	20 to 85	1 to 5
Pomalidomide[22]	9 to 22	1	1	2 to 15	1 to 2	22 to 48	NR (oral)

NR = not reported, SC = subcutaneous; URTI = upper respiratory tract infection.

[a]No severe rates reported, nonsevere reported as 18%.

Highlighted Cells Indicate the Highest Reported Incidence

Across treatments there is variability in the rate of AEs. Even for a single treatment such as daratumumab or isatuximab for example, the rate of neutropenia is highly variable. Table 17 is only a limited view on a select number of AEs. For each therapy, the product monographs report many other AEs, with some not reported above deemed severe and clinically important. Likewise, the above constitutes a naive comparison among all treatments. As evidence to inform AEs was limited and highly variable, they were not explicitly incorporated into the analysis. Implicitly a poor AE profile will influence time to next therapy which has been incorporated into the analysis, but the quality-of-life impact and cost associated with AEs has not.

Probabilistic Sensitivity Analysis

Probabilistic Sensitivity Analysis (PSA) was conducted to evaluate the uncertainty around the effect estimates, namely, LYs and QALYs derived from the economic model simulation. The variability in HRs obtained from the NMA was explored using the same sample population as for the base case.

For each of the 5,000 simulated patients, a total of 100 HRs per treatment sequence were applied to capture the inherent variability in treatment effects. This approach facilitated a comprehensive exploration of the parameter uncertainty associated with the different treatment sequences. This application of the HRs resulted in a total of 500,000 PSA simulations for each of the 17 treatment sequence, ensuring a thorough examination of the stochastic uncertainty of the model outcomes. The PSA was executed across all 17 treatment sequences, thereby providing a broad-spectrum understanding of the uncertainty prevailing across different treatment pathways.

HRs from the NMA were varied based on their upper and lower credibility intervals, using a truncated log normal distribution. It was therefore assumed that the logarithmic HRs would follow a normal distribution. Upper and lower truncation bounds were based on the upper and lower credibility intervals in the NMA, respectively. The truncated log normal distribution was based on the EnvStats package (Version 2.7.0) in R.

Base-Case Analysis Results

The aggregated results of the model simulation are summarized in Table 18, grouped by four- and three-line treatment sequences.

Table 18: Aggregated Results of the Model Simulation, Grouped by Four- and Three-Line Treatment Sequences

Sequence name	Total discounted costs ($)	Total discounted QALYs	Incremental discounted costs ($)	Incremental QALYs	Sequential ICER ($/QALY)	Status
4L setting						
CyBorDex,LenDex,PomDex, DaraBorDex	405,734	4.88	Reference			ND
LenBorDex,DaraBorDex, PomBorDex,CarDex	557,848	5.30	152,114	0.42	362,156	ND
DaraCyBorDex,LenDex, PomBorDex,CarDex	836,601	5.72	278,753	0.42	663,698	[a]
CyBorDex,CarLenDex, PomBorDex,DaraBorDex	498,147	4.98	Extendedly dominated			ED
LenBorDex,PomBorDex, CarDex,DaraBorDex	611,277	5.34	Extendedly dominated			ED
LenDex,CyBorDex,PomDex, DaraBorDex	428,795	4.83	Dominated			D
LenDex,DaraBorDex,CarDex, PomDex	520,581	4.88	Dominated			D
LenDex,CyBorDex, IsaPomDex,CarDex	549,597	4.71	Dominated			D
LenBorDex,DaraBorDex, CarDex,PomBorDex	559,193	5.29	Dominated			D
LenDex,CarDex,PomBorDex, DaraBorDex	591,209	5.02	Dominated			D
CyBorDex,DaraLenDex, PomBorDex,DaraBorDex	660,480	5.05	Dominated			D
DaraMphBorPred,LenDex, PomBorDex,CarDex	830,684	5.72	[a]			[a]
3L setting						
LenBorDex,CarDex, IsaPomDex,LenDex	543,514	5.19	Reference			ND
DaraCyBorDex,CarLenDex, PomBorDex,LenDex	808,689	5.78	265,175	0.59	448,964	ND

Sequence name	Total discounted costs ($)	Total discounted QALYs	Incremental discounted costs ($)	Incremental QALYs	Sequential ICER ($/QALY)	Status
DaraLenDex,CyBorDex, PomDex,LenDex	830,150	5.37		Dominated		D
DaraLenDex,CarDex, PomBorDex,LenDex	992,776	5.59		Dominated		D
DaraLenDex,PomBorDex, CarDex,LenDex	1,016,503	5.58		Dominated		D

CarDex = carfilzomib and dexamethasone; CarLenDex = carfilzomib, lenalidomide, and dexamethasone; CyBorDex = cyclophosphamide, bortezomib, and dexamethasone; D = dominated; DaraBorDex = daratumumab, bortezomib, and dexamethasone; DaraCyBorDex = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; DaraLenDex = daratumumab, lenalidomide, and dexamethasone; DaraMphBorPred = daratumumab, melphalan, bortezomib, and dexamethasone; ED = extendedly dominated; ICER = incremental cost-effectiveness ratios; IsaPomDex = isatuximab, pomalidomide, and bortezomib; LenDex = lenalidomide and dexamethasone; LenBorDex = lenalidomide, bortezomib, and dexamethasone; ND = nondominated; PomBorDex = pomalidomide; bortezomib and dexamethasone; PomDex = pomalidomide and bortezomib; QALY = quality-adjusted life-year.

[a] DaraMphBorPred dominates DaraCyBorDex however costs for this option were highly uncertain due to lack of use across Canada. The results are presented here for transparency though should be interpreted with caution.

Effectiveness of Sequences

In the 4L setting, 2 sequences were identified as most effective: DaraCyBorDex,LenDex,PomBorDex,CarDex and DaraMphBorPred,LenDex,PomBorDex,CarDex (total QALYs: 5.72 each). In the 3L setting, DaraCyBorDex,CarLenDex,PomBorDex,LenDex yielded the highest QALYs (5.78).

Cost-Effectiveness

Dominated sequences (i.e., sequences that were more expensive but yielding lower QALYs) were excluded from the sequential analysis calculations. Extendedly dominated alternatives were then excluded thereafter. A strategy is extendedly dominated if better health outcomes and lower cost to the health service can be achieved through a combination of 2 other strategies. For example, if giving 50% of patients strategy A and 50% of patients strategy C resulted in better outcomes and lower costs than giving everyone strategy B, we would say therapy B is extendedly dominated. The incremental cost-effectiveness ratios (ICERs) were calculated based on comparisons of moving to increasingly costly but increasingly effective alternatives that are neither dominated nor extendedly dominated.

In the 4L setting, CyBorDex,LenDex,PomDex,DaraBorDex was selected as the reference sequence since this was the sequences with the lowest total cost ($405,734). The ICER was $362,156 per QALY gained for LenBorDex,DaraBorDex,PomBorDex,CarDex compared to the reference sequence. The ICER of the most effective sequence, DaraCyBorDex,LenDex,PomBorDex,CarDex, was $663,698 per QALY gained compared to LenBorDex,DaraBorDex,PomBorDex,CarDex. Remaining strategies were either dominated or extendedly dominated.

In the 3L setting, the ICER for DaraCyBorDex,CarLenDex,PomBorDex,LenDex was $448,964 per QALY gained when compared to LenBorDex,CarDex,IsaPomDex,LenDex (i.e., the reference sequence). Remaining strategies were either dominated or extendedly dominated.

Figure 5 and Figure 6 show the cost-effectiveness with the efficient frontier for the four- and three-line treatment sequences, respectively.

Figure 5: Cumulative Cost Over Time for Each Regimen Assuming No Treatment Discontinuation

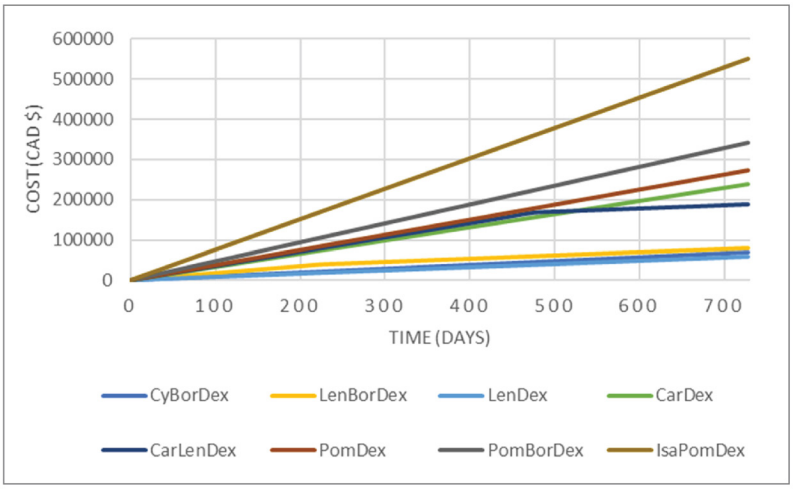
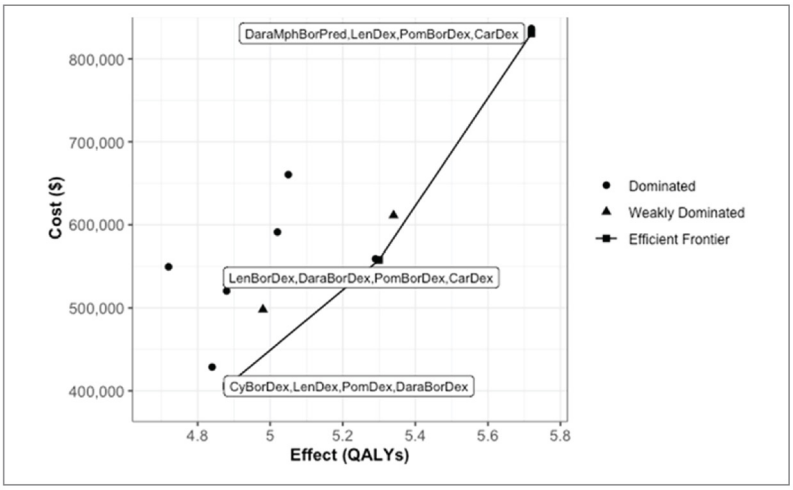


Figure 6: Cost-Effectiveness for Four-Line Treatment Sequences



Effectiveness per Line

Table 19 summarizes the disaggregated results for modelled mean time per treatment line (conditional on starting that line) and time to death (in years), grouped by four- and three-line treatment sequences. The sequences are arranged in descending order based on their time to death, which means that the sequence with the longest time to death is ranked first. In the 4L setting, the mean time to death ranged from 6.09 years for LenDex,CyBorDex,IsaPomDex,CarDex to 7.38 years for both DaraCyBorDex,LenDex,PomBorDex,CarDex and DaraMphBorPred,LenDex,PomBorDex,CarDex. The time in the

first line was substantially longer for both daratumumab-based regimens (5.14 years each) than for regimens without daratumumab (ranging from 2.87 to 3.87 years).

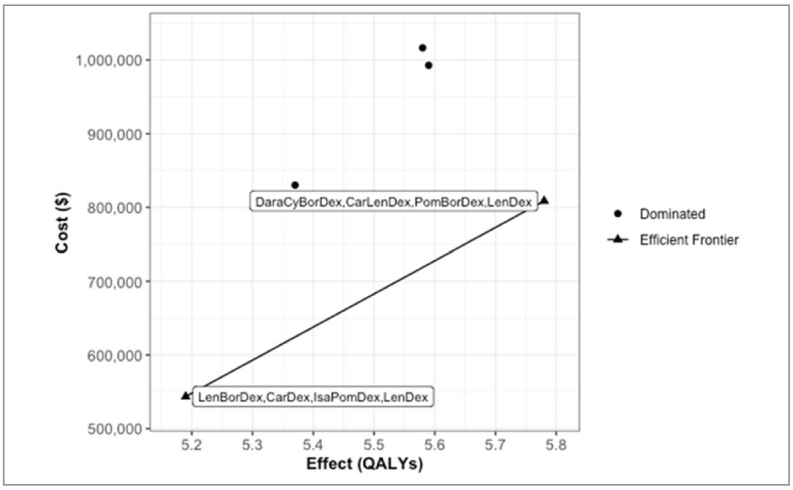
Table 19: Mean Discounted Time per Treatment Line (in Years), Conditional on Starting that Line, Grouped by Four- and Three-Line Treatment Sequences

Sequence name	Time in line 1	Time in line 2	Time in line 3	Time from line 4 until death	Time to death
4L setting					
DaraCyBorDex,LenDex,PomBorDex,CarDex	5.14	2.03	1.55	3.45	7.38
DaraMphBorPred,LenDex,PomBorDex,CarDex	5.14	2.03	1.55	3.45	7.38
LenBorDex,PomBorDex,CarDex,DaraBorDex	3.87	2.17	1.79	4.35	6.89
LenBorDex,DaraBorDex,PomBorDex,CarDex	3.87	2.98	1.53	3.69	6.84
LenBorDex,DaraBorDex,CarDex,PomBorDex	3.87	2.98	1.70	3.44	6.82
CyBorDex,DaraLenDex,PomBorDex,DaraBorDex	2.87	3.24	1.61	4.53	6.52
LenDex,CarDex,PomBorDex,DaraBorDex	3.13	2.41	1.63	4.35	6.48
CyBorDex,CarLenDex,PomBorDex,DaraBorDex	2.87	2.72	1.63	4.44	6.43
CyBorDex,LenDex,PomDex,DaraBorDex	2.87	2.18	1.30	4.25	6.30
LenDex,DaraBorDex,CarDex,PomDex	3.13	3.04	1.77	2.72	6.29
LenDex,CyBorDex,PomDex,DaraBorDex	3.13	1.28	1.31	4.14	6.24
LenDex,CyBorDex,IsaPomDex,CarDex	3.13	1.28	1.94	3.27	6.09
3L setting					
DaraCyBorDex,CarLenDex,PomBorDex,LenDex	5.14	2.54	1.47	3.50	7.46
DaraLenDex,CarDex,PomBorDex,LenDex	4.80	2.28	1.51	3.45	7.22
DaraLenDex,PomBorDex,CarDex,LenDex	4.80	2.10	1.73	3.34	7.20
DaraLenDex,CyBorDex,PomDex,LenDex	4.80	1.20	1.21	3.28	6.94
LenBorDex,CarDex,IsaPomDex,LenDex	3.87	2.35	1.76	3.35	6.69

CarDex = carfilzomib and dexamethasone; CarLenDex = carfilzomib, lenalidomide, and dexamethasone; CyBorDex = cyclophosphamide, bortezomib, and dexamethasone; DaraBorDex = daratumumab, bortezomib, and dexamethasone; DaraCyBorDex = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; DaraLenDex = daratumumab, lenalidomide, and dexamethasone; DaraMphBorPred = daratumumab, melphalan, bortezomib, and dexamethasone; IsaPomDex = isatuximab, pomalidomide, and bortezomib; LenDex = lenalidomide and dexamethasone; LenBorDex = lenalidomide, bortezomib, and dexamethasone; PomBorDex = pomalidomide; bortezomib and dexamethasone; PomDex = pomalidomide and bortezomib.

In the 3L setting, the time to death ranged from 6.69 years for LenBorDex,CarDex,IsaPomDex,LenDex to 7.46 years for DaraCyBorDex,CarLenDex,PomBorDex,LenDex. The time in the first line was substantially longer for both daratumumab-based regimens (4.80 years for DaraLenDex and 5.14 years for DaraCyBorDex) than for LenBorDex (3.87 years).

Figure 7: Cost-Effectiveness for Three-Line Treatment Sequences



Costs

The disaggregated results for modelled costs for drug acquisition, administration, and monitoring are summarized in Table 20 and Table 21, grouped by four- and three-line treatment sequences, respectively. The tables outline what proportion of total cost can be attributed to each drug. In the 4L analysis, the total costs ranged from $405,734 for CyBorDex,LenDex,PomDex,DaraBorDex to $836.601 for DaraCyBorDex,LenDex,PomBorDex,CarDex. Acquisition costs were the main cost driver for all sequences, accounting for, on average, 95% of the total costs. Total costs were much higher for sequences which included daratumumab-based regimens in the first line ($836,601 for DaraCyBorDex,LenDex,PomBorDex,CarDex) than for regimens without daratumumab ($428,795 for LenDex,CyBorDex,IsaPomDex,CarDex). In the 3L analysis, the total costs ranged from $543,514 for LenBorDex,CarDex,IsaPomDex,LenDex to $1,016,503 for DaraLenDex,PomBorDex,CarDex,LenDex. Acquisition costs were the main cost driver for all sequences, accounting for, on average, 96% of the total costs. Overall, daratumumab constitutes the majority of costs, even when used in the fourth-line setting. When used in the first-line setting daratumumab makes up 64 to 69% of total lifetime drug costs.

Table 20: Proportion of Total Costs Attributed to Each Drug (Strategies That Use 4 Unique Lines of Therapy)

Strategy	Total costs ($)	Total costs ($) attributable to									
		Dara	Cy	Bor	Dex	Len	Mph and Pred	Car	Pom	Isa	Monitoring/ admin
CyBorDex,CarLenDex, PomBorDex, DaraBorDex	498,147	110,638	847	125,184	1,843	58,283	0	84,187	89,069	0	28,095
CyBorDex,DaraLenDex, PomBorDex, DaraBorDex	660,480	370,661	859	119,877	2,180	69,416	0	0	71,002	0	26,485
CyBorDex,LenDex, PomDex, DaraBorDex	405,734	145,172	811	104,355	1,866	46,781	0	0	84,880	0	21,869
DaraCyBorDex,LenDex, PomBorDex, CarDex	836,601	564,455	167	39,153	1,506	31,958	0	92,612	76,382	0	30,369
DaraMphBorPred,LenDex, PomBorDex, CarDex	830,684	553,817	0	43,196	914	31,898	581	92,621	76,423	0	31,234
LenBorDex,DaraBorDex, CarDex, PomBorDex	559,193	220,769	0	46,972	1,733	112,741	0	69,620	80,971	0	26,394
LenBorDex,DaraBorDex, PomBorDex, CarDex	557,848	220,740	0	43,066	1,674	112,741	0	87,749	65,101	0	26,777
LenBorDex,PomBorDex, CarDex, DaraBorDex	611,277	107,340	0	67,179	2,201	112,741	0	99,638	193,041	0	29,158
LenDex,CarDex, PomBorDex, DaraBorDex	591,209	115,168	0	28,437	2,128	91,105	0	229,921	95,953	0	28,496
LenDex,CyBorDex, IsaPomDex, CarDex	420,016	0	252	31,291	2,394	91,105	0	138,857	103,660	152,850	29,149
LenDex,CyBorDex, PomDex, DaraBorDex	428,795	173,062	257	38,163	1,758	91,105	0	0	104,883	0	19,553

Strategy	Total costs ($)	Total costs ($) attributable to									
		Dara	Cy	Bor	Dex	Len	Mph and Pred	Car	Pom	Isa	Monitoring/ admin
LenDex,DaraBorDex, CarDex, PomDex	520,581	246,912	0	13,223	1,614	91,105	0	77,671	68,196	0	21,864

CarDex = carfilzomib and dexamethasone; CarLenDex = carfilzomib, lenalidomide, and dexamethasone; CyBorDex = cyclophosphamide, bortezomib, and dexamethasone; DaraBorDex = daratumumab, bortezomib, and dexamethasone; DaraCyBorDex = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; DaraLenDex = daratumumab, lenalidomide, and dexamethasone; DaraMphBorPred = daratumumab, melphalan, bortezomib, and dexamethasone; IsaPomDex = isatuximab, pomalidomide, and bortezomib; LenDex = lenalidomide and dexamethasone; LenBorDex = lenalidomide, bortezomib, and dexamethasone; PomBorDex = pomalidomide; bortezomib and dexamethasone; PomDex = pomalidomide and bortezomib.

Table 21: Proportion of Total Costs Attributed to Each Drug (Strategies That Use 3 Unique Lines of Therapy)

Strategy	Total costs ($)	Total costs ($) attributable to									
		Dara	Cy	Bor	Dex	Len	Mph and Pred	Car	Pom	Isa	Monitoring/ admin
DaraCyBorDex, CarLenDex, PomBorDex,LenDex	808,689	564,465	162	35,421	1,213	57,255	0	59,115	61,541	0	29,517
DaraLenDex,CarDex, PomBorDex,LenDex	992,776	532,038	0	18,565	2,482	159,837	0	174,232	73,962	0	31,670
DaraLenDex,CyBorDex, PomDex,LenDex	830,150	532,038	166	23,576	2,324	169,102	0	0	79,030	0	23,908
DaraLenDex,PomBorDex, CarDex,LenDex	1,016,503	532,038	0	41,168	2,745	159,184	0	86,403	164,064	0	30,902
LenBorDex,CarDex, IsaPomDex,LenDex	543,514	0	0	14,829	2,085	133,550	0	204,773	63,856	94,486	29,935

CarDex = carfilzomib and dexamethasone; CarLenDex = carfilzomib, lenalidomide, and dexamethasone; CyBorDex = cyclophosphamide, bortezomib, and dexamethasone; DaraBorDex = daratumumab, bortezomib, and dexamethasone; DaraCyBorDex = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; DaraLenDex = daratumumab, lenalidomide, and dexamethasone; DaraMphBorPred = daratumumab, melphalan, bortezomib, and dexamethasone; IsaPomDex = isatuximab, pomalidomide, and bortezomib; LenDex = lenalidomide and dexamethasone; LenBorDex = lenalidomide, bortezomib, and dexamethasone; PomBorDex = pomalidomide; bortezomib and dexamethasone; PomDex = pomalidomide and bortezomib.

Table 22: Aggregated Results of the Model Simulation, Grouped by Four- and Three-Line Treatment Sequences

Sequence name	Total discounted costs ($)	Total discounted QALYs	Incremental discounted costs ($)	Incremental QALYs	Sequential ICER ($/QALY)
4L setting					
CyBorDex,LenDex,PomDex,DaraBorDex	403,504	4.96	Reference		
LenBorDex,DaraBorDex,PomBorDex,CarDex	557,232	5.4	153,728	0.44	348,921
DaraCyBorDex,LenDex,PomBorDex,CarDex	850,871	5.82	293,639	0.42	699,140
CyBorDex,CarLenDex,PomBorDex,DaraBorDex	495,956	5.08	Extendedly dominated		
LenBorDex,DaraBorDex,CarDex,PomBorDex	556,147	5.38	Extendedly dominated		
LenBorDex,PomBorDex,CarDex,DaraBorDex	605,880	5.44	Extendedly dominated		
LenDex,CyBorDex,IsaPomDex,CarDex	554,515	4.84	Dominated		
LenDex,CyBorDex,PomDex,DaraBorDex	428,042	4.91	Dominated		
LenDex,DaraBorDex,CarDex,PomDex	521,756	4.97	Dominated		
LenDex,CarDex,PomBorDex,DaraBorDex	588,250	5.11	Dominated		
CyBorDex,DaraLenDex,PomBorDex,DaraBorDex	651,635	5.14	Dominated		
DaraMphBorPred,LenDex,PomBorDex,CarDex	844,885	5.82	[a]		
3L setting					
LenBorDex,CarDex,IsaPomDex,LenDex	544,404	5.32	Reference		
DaraCyBorDex,CarLenDex,PomBorDex,LenDex	820,377	5.88	275,973	0.56	494,543
DaraLenDex,CyBorDex,PomDex,LenDex	849,130	5.47	Dominated		
DaraLenDex,CarDex,PomBorDex,LenDex	1,009,173	5.69	Dominated		
DaraLenDex,PomBorDex,CarDex,LenDex	1,031,905	5.68	Dominated		

CarDex = carfilzomib and dexamethasone; CarLenDex = carfilzomib, lenalidomide, and dexamethasone; CyBorDex = cyclophosphamide, bortezomib, and dexamethasone; DaraBorDex = daratumumab, bortezomib, and dexamethasone; DaraCyBorDex = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; DaraLenDex = daratumumab, lenalidomide, and dexamethasone; DaraMphBorPred = daratumumab, melphalan, bortezomib, and dexamethasone; IsaPomDex = isatuximab, pomalidomide, and bortezomib; LenDex = lenalidomide and dexamethasone; LenBorDex = lenalidomide, bortezomib, and dexamethasone; ND = nondominated; PomBorDex = pomalidomide; bortezomib and dexamethasone; PomDex = pomalidomide and bortezomib; QALY = quality-adjusted life-year.

[a] DaraMphBorPred dominates DaraCyBorDex however costs for this option were highly uncertain due to lack of use across Canada. The results are presented here for transparency though should be interpreted with caution.

Table 23: Overview of Scenario Analyses

Description	Number of model simulations	Choice of parametric survival functions	Hazard ratios	Utilities
Base case	5,000	Based on BIC and clinical plausibility	NMA HR applied to TTP with correction for 4L therapies	Age decrements
Alternative distributions	5,000	All Weibull	NMA HR applied to TTP with correction for 4L therapies	Age decrements

Description	Number of model simulations	Choice of parametric survival functions	Hazard ratios	Utilities
Decrements for TTP	5,000	Based on BIC and clinical plausibility	NMA HR with improved HRs for TTP transitions (−0.10 in line 1 and −0.05 for lines 2,3, and 4)	Age decrements
HR decrements for carfilzomib and daratumumab treatments	5,000	Based on BIC and clinical plausibility on BIC	NMA HR with decrement for carfilzomib and daratumumab treatment in 3L and 4L setting. With 1.1 in third line and 1.2 in subsequent lines	Age decrements
HR in subsequent lines to 1	5,000	Based on BIC and clinical plausibility	NMA scenario 1 HR in subsequent lines set to 1	Age decrements
Utility decrements in later lines	5,000	Based on BIC and clinical plausibility	NMA HR applied to TTP with correction for 4L therapies	Utility decrements per line

BIC = Bayesian Information Criterion; HR = hazard ratio; NMA = network meta-analysis; TTP = time to progression.

Assessment of Uncertainty

PSA Results

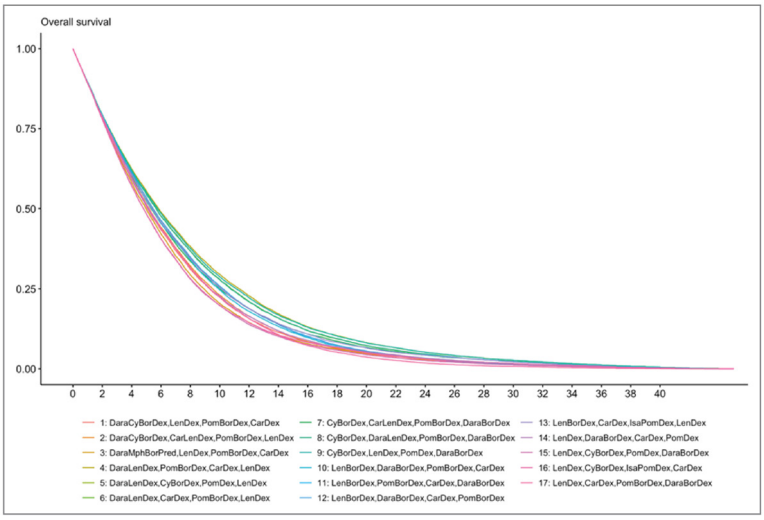
As the analysis is conducted as a patient-level simulation, uncertainty concerning heterogeneity of the population of people in Canada with MM has been captured. However, there remains outstanding uncertainty for other parameters in the model such as relative effects between treatments. Aggregated results of the model simulation are summarized in Table 24, grouped by four-line (4L) and three-line (3L) treatment sequences, respectively. Incremental costs and QALYs Results were similar to the deterministic results though the total costs and QALYs for each strategy was consistently higher in the probabilistic analysis. Figure 9 outlines the uncertainty associated with estimation of LYs for each strategy.

Scenario Analyses

An overview of all conducted scenario analyses is provided in Table 24.

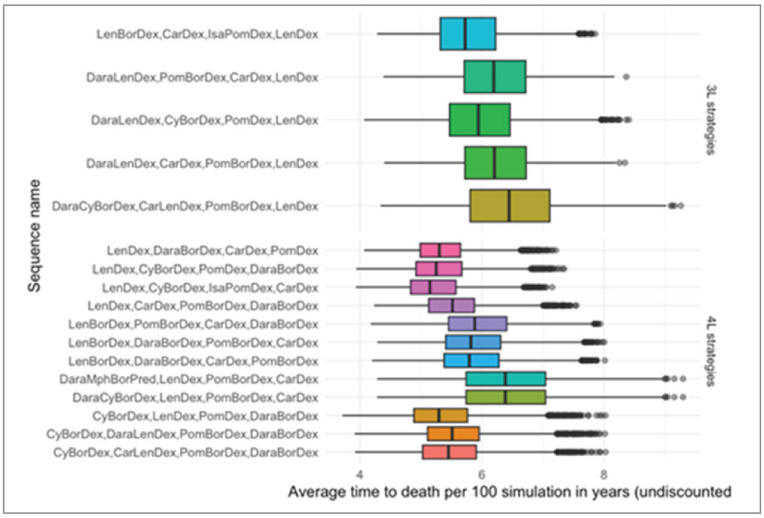
Figure 8 Depicts the modelled OS of the simulated patients for each treatment sequence.

Figure 8: Modelled OS of the Simulated Patients for Each Treatment Sequence



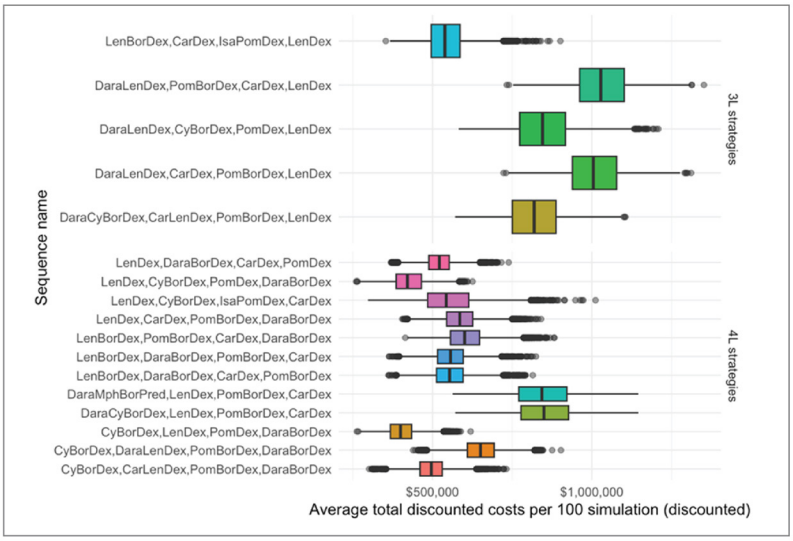
OS = overall survival.

Figure 9: Boxplots of the Estimated Time to Death in the Probabilistic Sensitivity Analysis



CarDex = carfilzomib and dexamethasone; CarLenDex = carfilzomib, lenalidomide, and dexamethasone; CyBorDex = cyclophosphamide, bortezomib, and dexamethasone; DaraBorDex = daratumumab, bortezomib, and dexamethasone; DaraCyBorDex = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; DaraLenDex = daratumumab, lenalidomide, and dexamethasone; DaraMphBorPred = daratumumab, melphalan, bortezomib, and dexamethasone; IsaPomDex = isatuximab, pomalidomide, and bortezomib; LenDex = lenalidomide and dexamethasone; LenBorDex = lenalidomide, bortezomib, and dexamethasone; PomBorDex = pomalidomide; bortezomib and dexamethasone; PomDex = pomalidomide and bortezomib.

Figure 10: Boxplots of the Estimated Total Costs in The Probabilistic Sensitivity Analysis



CarDex = carfilzomib and dexamethasone; CarLenDex = carfilzomib, lenalidomide, and dexamethasone; CyBorDex = cyclophosphamide, bortezomib, and dexamethasone; DaraBorDex = daratumumab, bortezomib, and dexamethasone; DaraCyBorDex = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; DaraLenDex = daratumumab, lenalidomide, and dexamethasone; DaraMphBorPred = daratumumab, melphalan, bortezomib, and dexamethasone; IsaPomDex = isatuximab, pomalidomide, and bortezomib; LenDex = lenalidomide and dexamethasone; LenBorDex = lenalidomide, bortezomib, and dexamethasone; PomBorDex = pomalidomide; bortezomib and dexamethasone; PomDex = pomalidomide and bortezomib.

Table 24 represents the cost-effectiveness results for the scenario "Alternative distributions." In this scenario, a Weibull function was selected for all transitions (instead of only for transition 3). The Weibull function shows lower survival estimates for all transitions, resulting in lower life-years and consequently lower QALYs and costs for all sequences. However, the impact of the alternative distributions differs across sequences. For some transitions, the differences between alternative parametric distributions are smaller, hence the smaller impact. While there were changes in the status of sequences that were dominated or extendedly dominated, the status of nondominated sequences remained unchanged. Although the Weibull function is commonly used for modelling survival in multiple myeloma, the BIC statistics and visual fit showed that the base case distributions provide a better fit to the data. In addition, the follow-up in CMRG is sufficiently long to ensure that most of the events of interest (i.e., the start of new therapy or death) were observed. Therefore, this scenario may show an underestimation of the outcomes.

Table 24: Aggregated Results of the Scenario "Alternative Distributions," Grouped by Four- and Three-Line Treatment Sequences

Sequence name	Total costs ($)	Total QALYs	Incremental costs ($)	Incremental QALYs	Sequential ICER ($/QALY)
4L setting					
CyBorDex,LenDex,PomDex,DaraBorDex	372,577	4.68	Reference		
LenBorDex,DaraBorDex,PomBorDex,CarDex	537,263	5.18	164,686	0.50	327,198
DaraCyBorDex,LenDex,PomBorDex,CarDex	795,676	5.51	258,413	0.33	783,070
CyBorDex,CarLenDex,PomBorDex,DaraBorDex	461,360	4.79	Extendedly dominated		
LenDex,DaraBorDex,CarDex,PomDex	505,984	4.82	Extendedly dominated		
LenDex,CyBorDex,IsaPomDex,CarDex	490,895	4.48	Dominated		
LenDex,CyBorDex,PomDex,DaraBorDex	390,679	4.58	Dominated		
LenBorDex,DaraBorDex,CarDex,PomBorDex	537,379	5.17	Dominated		
LenDex,CarDex,PomBorDex,DaraBorDex	559,513	4.84	Dominated		
LenBorDex,PomBorDex,CarDex,DaraBorDex	579,641	5.09	Dominated		
CyBorDex,DaraLenDex,PomBorDex,DaraBorDex	634,862	4.93	Dominated		
DaraMphBorPred,LenDex,PomBorDex,CarDex	789,739	5.51	[a]		
3L setting					
LenBorDex,CarDex,IsaPomDex,LenDex	522,873	5.02	Reference		
DaraCyBorDex,CarLenDex,PomBorDex,LenDex	785,734	5.61	333,533	0.59	448,640
DaraLenDex,CyBorDex,PomDex,LenDex	803,375	5.16	Dominated		
DaraLenDex,CarDex,PomBorDex,LenDex	969,674	5.41	Dominated		
DaraLenDex,PomBorDex,CarDex,LenDex	992,231	5.37	Dominated		

CarDex = carfilzomib and dexamethasone; CarLenDex = carfilzomib, lenalidomide, and dexamethasone; CyBorDex = cyclophosphamide, bortezomib, and dexamethasone; DaraBorDex = daratumumab, bortezomib, and dexamethasone; DaraCyBorDex = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; DaraLenDex = daratumumab, lenalidomide, and dexamethasone; DaraMphBorPred = daratumumab, melphalan, bortezomib, and dexamethasone; IsaPomDex = isatuximab, pomalidomide, and bortezomib; LenDex = lenalidomide and dexamethasone; LenBorDex = lenalidomide, bortezomib, and dexamethasone; PomBorDex = pomalidomide; bortezomib and dexamethasone; PomDex = pomalidomide and bortezomib' QALY = quality-adjusted life-year.

[a] DaraMphBorPred dominates DaraCyBorDex however costs for this option were highly uncertain due to lack of use across Canada. The results are presented here for transparency though should be interpreted with caution.

Table 25 represents the cost-effectiveness results for the scenario "Decrements for TTP." Assuming a higher relative treatment effect results in higher QALYs for all sequences. This is especially the case in sequences with effective treatments in the first line, since the decrement in transition 1 was larger (−0.10) than in transitions 3, 5 and 7 (−0.05). In the 4L setting, the total QALYs for the most effective treatment sequences, DaraMphBorPred,LenDex,PomBorDex,CarDex and DaraCyBorDex,LenDex,PomBorDex,CarDex, increased by more than 0.3. However, the total costs also increased by almost $50,000. While in theory the HRs from the base case for PFS might underestimate the TTP and more favourable outcomes might be expected, the outcomes of this scenario are likely optimistic since none of the randomized controlled trials that reported both PFS and TTP showed a difference in HRs 0f 0.10 (Table 11; range 0.04 to 0.09).

Table 25: Aggregated Results of the Scenario Decrements for TTP, Grouped by Four- and Three-Line Treatment Sequences

Sequence name	Total costs ($)	Total QALYs	Incremental costs ($)	Incremental QALYs	Sequential ICER ($/QALY)
4L setting					
CyBorDex,LenDex,PomDex,DaraBorDex	414,427	4.87	Reference		
LenBorDex,DaraBorDex,PomBorDex,CarDex	553,530	5.53	139,103	0.65	212,643
DaraCyBorDex,LenDex,PomBorDex,CarDex	886,017	6.07	332,487	0.54	615,717
LenDex,CyBorDex,PomDex,DaraBorDex	440,704	4.92	Extendedly dominated		
CyBorDex,CarLenDex,PomBorDex,DaraBorDex	502,664	4.97	Extendedly dominated		
LenBorDex,DaraBorDex,CarDex,PomBorDex	544,141	5.47	Extendedly dominated		
LenBorDex,PomBorDex,CarDex,DaraBorDex	607,208	5.56	Dominated		
LenDex,CyBorDex,IsaPomDex,CarDex	568,776	4.78	Dominated		
LenDex,DaraBorDex,CarDex,PomDex	522,413	4.91	Dominated		
LenDex,CarDex,PomBorDex,DaraBorDex	603,756	5.10	Dominated		
CyBorDex,DaraLenDex,PomBorDex,DaraBorDex	669,048	5.01	Dominated		
DaraMphBorPred,LenDex,PomBorDex,CarDex	880,387	6.07	[a]		
3L setting					
LenBorDex,CarDex,IsaPomDex,LenDex	541,087	5.40	Reference		
DaraCyBorDex,CarLenDex,PomBorDex,LenDex	852,700	6.12	311,613	0.72	432,712
DaraLenDex,CyBorDex,PomDex,LenDex	891,056	5.67	Dominated		
DaraLenDex,CarDex,PomBorDex,LenDex	1,042,379	5.86	Dominated		
DaraLenDex,PomBorDex,CarDex,LenDex	1,065,766	5.87	Dominated		

CarDex = carfilzomib and dexamethasone; CarLenDex = carfilzomib, lenalidomide, and dexamethasone; CyBorDex = cyclophosphamide, bortezomib, and dexamethasone; DaraBorDex = daratumumab, bortezomib, and dexamethasone; DaraCyBorDex = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; DaraLenDex = daratumumab, lenalidomide, and dexamethasone; DaraMphBorPred = daratumumab, melphalan, bortezomib, and dexamethasone; IsaPomDex = isatuximab, pomalidomide, and bortezomib; LenDex = lenalidomide and dexamethasone; LenBorDex = lenalidomide, bortezomib, and dexamethasone; PomBorDex = pomalidomide; bortezomib and dexamethasone; PomDex = pomalidomide and bortezomib; QALY = quality-adjusted life-year.

[a] DaraMphBorPred dominates DaraCyBorDex however costs for this option were highly uncertain due to lack of use across Canada. The results are presented here for transparency though should be interpreted with caution.

Table 26 represents the cost-effectiveness results for the scenario "HR decrements for Car and Dara treatments." In this scenario, only the outcomes for third- and fourth-line carfilzomib and daratumumab-based regimens are altered (i.e., lower effectiveness is assumed). All 4L sequences include either carfilzomib and/or daratumumab as third- and/or fourth-line treatment and consequently QALYs are lower for all sequences. Regarding the 3L sequences, there is only 1 sequence (i.e., DaraLenDex,PomBorDex,CarDex,LenDex) slightly altered as it includes carfilzomib as third-line treatment; however, the status of this sequence remains dominated. Given that almost all (4L) or only 1 (3L) sequence is influenced, the impact of this scenario is relatively small.

Table 26: Aggregated Results of the Scenario HR decrements for Car and Dara treatments, Grouped by Four- and Three-Line Treatment Sequences

Sequence name	Total costs ($)	Total QALYs	Incremental costs ($)	Incremental QALYs	Sequential ICER ($/QALY)
4L setting					
CyBorDex,LenDex,PomDex,DaraBorDex	380,222	4.70	Reference		
LenBorDex,DaraBorDex,CarDex,PomBorDex	557,566	5.27	177,344	0.58	308,091
DaraCyBorDex,LenDex,PomBorDex,CarDex	818,238	5.62	260,672	0.35	744,777
CyBorDex,CarLenDex,PomBorDex,DaraBorDex	479,792	4.85	Extendedly dominated		
LenDex,DaraBorDex,CarDex,PomDex	517,408	4.86	Extendedly dominated		
LenBorDex,DaraBorDex,PomBorDex,CarDex	541,454	5.22	Extendedly dominated		
LenDex,CyBorDex,IsaPomDex,CarDex	519,739	4.56	Dominated		
LenDex,CyBorDex,PomDex,DaraBorDex	397,201	4.60	Dominated		
LenDex,CarDex,PomBorDex,DaraBorDex	571,451	4.88	Dominated		
LenBorDex,PomBorDex,CarDex,DaraBorDex	589,334	5.19	Dominated		
CyBorDex,DaraLenDex,PomBorDex,DaraBorDex	646,093	4.95	Dominated		
DaraMphBorPred,LenDex,PomBorDex,CarDex	812,321	5.62	[a]		
3L setting					
LenBorDex,CarDex,IsaPomDex,LenDex	543,514	5.19	Reference		
DaraCyBorDex,CarLenDex,PomBorDex,LenDex	808,689	5.78	265,175	0.59	449,290
DaraLenDex,CyBorDex,PomDex,LenDex	830,150	5.37	Dominated		
DaraLenDex,CarDex,PomBorDex,LenDex	992,776	5.59	Dominated		
DaraLenDex,PomBorDex,CarDex,LenDex	1,011,255	5.57	Dominated		

CarDex = carfilzomib and dexamethasone; CarLenDex = carfilzomib, lenalidomide, and dexamethasone; CyBorDex = cyclophosphamide, bortezomib, and dexamethasone; DaraBorDex = daratumumab, bortezomib, and dexamethasone; DaraCyBorDex = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; DaraLenDex = daratumumab, lenalidomide, and dexamethasone; DaraMphBorPred = daratumumab, melphalan, bortezomib, and dexamethasone; IsaPomDex = isatuximab, pomalidomide, and bortezomib; LenDex = lenalidomide and dexamethasone; LenBorDex = lenalidomide, bortezomib, and dexamethasone; PomBorDex = pomalidomide; bortezomib and dexamethasone; PomDex = pomalidomide and bortezomib; QALY = quality-adjusted life-year.

[a] DaraMphBorPred dominates DaraCyBorDex however, costs for this option were highly uncertain due to lack of use across Canada. The results are presented here for transparency though should be interpreted with caution.

Table 27 represents the cost-effectiveness results for the scenario "HR in 4L to 1." Since this only has an impact on fourth-line treatments for which no LenDex effectiveness was assumed, the outcomes of the 3L sequences are the same as the base case.

Regarding the 4L sequences, all sequences with fourth-line treatments that were more effective than LenDex (i.e., DaraBorDex and CarDex), the QALYs and costs are lower, with a larger decrease in QALYs for the sequences including the most effective fourth-line treatment (i.e., DaraBorDex). Since it is unlikely that DaraBorDex and CarDex show no additional gain, the results of this scenario are believed to underestimate the outcomes.

Table 27: Aggregated Results of the Scenario "HR in 4L set to 1," Grouped by Four- and Three-Line Treatment Sequences

Sequence name	Total costs ($)	Total QALYs	Incremental costs ($)	Incremental QALYs	Sequential ICER ($/QALY)
4L setting					
CyBorDex, LenDex, PomDex, DaraBorDex	372,207	4.64	Reference		
LenBorDex, DaraBorDex, PomBorDex, CarDex	554,016	5.28	181,809	0.64	283,290
LenBorDex, DaraBorDex, CarDex, PomBorDex	562,696	5.30	8,680	0.02	459,582
DaraCyBorDex, LenDex, PomBorDex, CarDex	832,243	5.69	269,547	0.39	691,146
LenDex, CyBorDex, IsaPomDex, CarDex	542,513	4.68	Extendedly dominated		
CyBorDex, CarLenDex, PomBorDex, DaraBorDex	473,843	4.81	Extendedly dominated		
LenDex, DaraBorDex, CarDex, PomDex	540,741	4.98	Extendedly dominated		
LenDex, CyBorDex, PomDex, DaraBorDex	387,412	4.53	Dominated		
LenDex, CarDex, PomBorDex, DaraBorDex	565,121	4.83	Dominated		
LenBorDex, PomBorDex, CarDex, DaraBorDex	587,715	5.17	Dominated		
CyBorDex, DaraLenDex, PomBorDex, DaraBorDex	641,379	4.91	Dominated		
DaraMphBorPred, LenDex, PomBorDex, CarDex	826,326	5.69	[a]		
3L setting					
LenBorDex, CarDex, IsaPomDex, LenDex	543,514	5.19	Reference		
DaraCyBorDex, CarLenDex, PomBorDex, LenDex	808,689	5.78	265,175	0.59	449,290
DaraLenDex, CyBorDex, PomDex, LenDex	830,150	5.37	Dominated		
DaraLenDex, CarDex, PomBorDex, LenDex	992,776	5.59	Dominated		
DaraLenDex, PomBorDex, CarDex, LenDex	1,016,503	5.58	Dominated		

CarDex = carfilzomib and dexamethasone; CarLenDex = carfilzomib, lenalidomide, and dexamethasone; CyBorDex = cyclophosphamide, bortezomib, and dexamethasone; DaraBorDex = daratumumab, bortezomib, and dexamethasone; DaraCyBorDex = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; DaraLenDex = daratumumab, lenalidomide, and dexamethasone; DaraMphBorPred = daratumumab, melphalan, bortezomib, and dexamethasone; IsaPomDex = isatuximab, pomalidomide, and bortezomib; LenDex = lenalidomide and dexamethasone; LenBorDex = lenalidomide, bortezomib, and dexamethasone; PomBorDex = pomalidomide; bortezomib and dexamethasone; PomDex = pomalidomide and bortezomib; QALY = quality-adjusted life-year.

[a] DaraMphBorPred dominates DaraCyBorDex however costs for this option were highly uncertain due to lack of use across Canada. The results are presented here for transparency though should be interpreted with caution.

Table 28 represents the cost-effectiveness results for the scenario "Utility decrements in later lines." In this scenario, LYs and costs are not altered since only the utility values are changed. Consequently, only the QALY outcomes are changed, i.e., lower for all sequences. Additional utility decrements in later lines have a larger impact on sequences with more effective treatments in later lines of therapy and causes the sequence LenBorDex,PomBorDex,CarDex,DaraBorDex to be dominated instead of extendedly dominated. While lower health-related quality of life in later lines of therapy is expected, data to inform utility decrements are highly uncertain and hence outcomes should be interpreted with caution.

Table 28: Aggregated Results of the Scenario Utility Decrements in Later Lines, Grouped by Four- and Three-Line Treatment Sequences

Sequence name	Total costs ($)	Total QALYs	Incremental costs ($)	Incremental QALYs	Sequential ICER ($/QALY)
4L setting					
CyBorDex,LenDex,PomDex,DaraBorDex	405,734	4.66	Reference		
LenBorDex,DaraBorDex,PomBorDex,CarDex	557,848	5.17	152,114	0.51	295,786
DaraCyBorDex,LenDex,PomBorDex,CarDex	836,601	5.61	278,753	0.44	633,530
CyBorDex,CarLenDex,PomBorDex,DaraBorDex	498,147	4.79	Extendedly dominated		
LenDex,CyBorDex,IsaPomDex,CarDex	549,597	4.53	Dominated		
LenDex,CyBorDex,PomDex,DaraBorDex	428,795	4.59	Dominated		
LenDex,DaraBorDex,CarDex,PomDex	520,581	4.75	Dominated		
LenBorDex,DaraBorDex,CarDex,PomBorDex	559,193	5.16	Dominated		
LenDex,CarDex,PomBorDex,DaraBorDex	591,209	4.83	Dominated		
LenBorDex,PomBorDex,CarDex,DaraBorDex	611,277	5.17	Dominated		
CyBorDex,DaraLenDex,PomBorDex,DaraBorDex	660,480	4.88	Dominated		
DaraMphBorPred,LenDex,PomBorDex,CarDex	830,684	5.61	[a]		
3L setting					
LenBorDex,CarDex,IsaPomDex,LenDex	543,514	5.05	Reference		
DaraCyBorDex,CarLenDex,PomBorDex,LenDex	808,689	5.68	265,175	0.63	421,979
DaraLenDex,CyBorDex,PomDex,LenDex	830,150	5.23	Dominated		
DaraLenDex,CarDex,PomBorDex,LenDex	992,776	5.48	Dominated		
DaraLenDex,PomBorDex,CarDex,LenDex	1,016,503	5.47	Dominated		

CarDex = carfilzomib and dexamethasone; CarLenDex = carfilzomib, lenalidomide, and dexamethasone; CyBorDex = cyclophosphamide, bortezomib, and dexamethasone; DaraBorDex = daratumumab, bortezomib, and dexamethasone; DaraCyBorDex = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; DaraLenDex = daratumumab, lenalidomide, and dexamethasone; DaraMphBorPred = daratumumab, melphalan, bortezomib, and dexamethasone; IsaPomDex = isatuximab, pomalidomide, and bortezomib; LenDex = lenalidomide and dexamethasone; LenBorDex = lenalidomide, bortezomib, and dexamethasone; PomBorDex = pomalidomide; bortezomib and dexamethasone; PomDex = pomalidomide and bortezomib; QALY = quality-adjusted life-year.

[a] DaraMphBorPred dominates DaraCyBorDex however costs for this option were highly uncertain due to lack of use across Canada. The results are presented here for transparency though should be interpreted with caution.

Validation With the MAIA Study

Given its prominence in the literature, clinical experts noted that the MAIA study should be used as 1 means of testing the external validity of the model. The MAIA trial compared DaraLenDex and LenDex in the first-line transplant ineligible setting. For this analysis, the effectiveness of LenDex in clinical practice, regarding OS and TTNT, is obtained from CMRG and given the data are very mature the model does not extrapolate these outcomes substantially. Therefore, for LenDex in the first line the model mostly replicates the real-world data from CMRG. In the CMRG data, 20% of the patients received LenDex as first-line treatment. The outcomes of first-line LenDex from the health economic model shows the outcomes if all CMRG patients would have received LenDex. Based on the CMRG data, the economic model estimates the average time in line 1 is 3.2

years (38 months) for patients who receive LenDex. The median time is 2.1 years (25 months). The MAIA study showed higher median PFS for LenDex to be 2.9 years (34.4 months). One reason for this is the difference in OS in the real-world evidence versus the trial where patients in the trial had better OS than in the real world. Lower baseline survival, as observed in CMRG, causes the absolute survival of all sequences to be lower and likewise decreases the time spent on treatment. There are some differences in patient and disease characteristics between the CMRG and MAIA population that should be noted. The CMRG patients were older (median age 76 vs 74) and patients below 65 years old (1% in MAIA) were not included. Other deviations observed are a higher proportion of high-risk patients and more patients with stage III disease. ISS and cytogenetic risk had too many missing values to be included in the parametric survival models, hence the analysis does not account for this but this might explain the lower median survival observed for all CMRG patients assuming treatment with LenDex.

Although there were absolute differences between the MAIA study and the predicted model output, there were similarities. First, in the first 2 years of the MAIA trial there are small insignificant differences in OS. After 2 years the OS curves begin to diverge. This also occurs in the model, supporting the notion that PFS is likely the main driver of OS differences. As patients move to later lines the rate of mortality increases. This means there is a lag between progression and mortality increases which is shown in the MAIA trial and the model output. Second, the absolute difference in OS between LenDex first-line sequences (followed by no daratumumab in subsequent lines) versus DaraLenDex first-line sequences is close to what was seen in the MAIA study. For example, at 4 years the absolute difference in the cohort alive is approximately 8% in the MAIA study. In the model output, at 4 years the difference is approximately 6%. Therefore, although there are differences between the model output and the MAIA data this will unlikely have a substantial impact on conclusions of cost-effectiveness. Finally, it should be noted that this analysis is not an exact replication of the MAIA trial as there was no fixed protocol on what subsequent therapies could be received in subsequent lines in the MAIA trial. For example, some patients went on to receive ASCT or re-treatment with lenalidomide which is not considered in this analysis. There is therefore no expectation for the current model results to exactly mirror the MAIA conclusions though output should be broadly similar. It is plausible that the economic analysis may underestimate the cost-effectiveness of daratumumab in the first line, however this has been explored through multiple scenario analyses.

Summary of Economic Results

The results of the analysis provide insights into the cost-effectiveness of various strategies used to manage MM in patients who are transplant ineligible.

Given its clinical efficacy, as evidenced in the NMA, and large cost relative to other therapies, the role of daratumumab within the treatment pathway was seen of being of particular importance. In the base-case analysis, strategies that use daratumumab in the first-line setting generate between 5.37 to 5.78 QALYs (approximately 7.0 to 7.5 LYs). These strategies also produced the highest costs to the health system. Overall, strategies that use daratumumab in the first line have lifetime health care costs of $808,689 to $1,016,503 per patient. One reason for this disparity in cost is due to the treatment given alongside daratumumab. For example, DaraCyBorDex in the 1L produces costs of $585,117 per patient whereas

DaraLenDex costs $673,129. Likewise, as patients are not retreated with the same drug, what therapy is given alongside daratumumab will dictate what treatment options remain available for patients should they require a subsequent line of therapy. Strategies that use daratumumab in the second-line setting generated between 4.88 to 5.30 QALYs (approximately 6.29 to 6.80 LYs). Relative to strategies which used daratumumab in the first line, these strategies also generated lower costs to the health system with lifetime costs being on average $300,000 less per patient. Strategies that did not use daratumumab generated the smallest health outcomes, between 4.71 and 5.19 QALYs (approximately 6.09 to 6.69 LYs). On average, these strategies also generated the lowest costs to the health system.

These broad conclusions were robust across all the conducted scenario analyses with the size of the incremental QALY benefit varying but overall ranking of treatments remaining largely unchanged. For example, a daratumumab-based regimen in the first-line setting remained the most efficacious strategy across all scenarios with the incremental QALYs relative to the next most effective strategy ranging from 0.33 to 0.63. It should be noted that costs and health benefit are highly correlated for most treatment sequences. If a treatment is more effective then this means the patient will remain on that therapy for a longer period as most therapies, apart from some bortezomib and carfilzomib regimens, are given until progression or unacceptable toxicity. This means that in cases where a treatment is more efficacious drug costs are also higher.

When considering the cost-effectiveness of daratumumab, using public list prices, the ICER of strategies which included daratumumab in the first line, compared to when daratumumab is used in the second line exceeded $500,000 per QALY gained. The ICER of strategies which included daratumumab in the second line relative to strategies which included it in the fourth line/no lines exceeded $300,000 per QALY gained. Price reductions would be required for use of daratumumab in the first line to represent a cost-effective use of health care resources at willingness-to-pay thresholds up to $500,000 per QALY gained. As daratumumab appears in most strategies, price reductions reduce the cost of all strategies which include daratumumab. This increases the price reduction required to achieve cost-effectiveness in the first-line setting. If the price of daratumumab is decreased, then the cost of using it in the first line decreases but so does its use in the second line and so forth. For illustrative purposes, at a willingness-to-pay threshold of $50,000 per QALY gained and assuming full list price for all other drugs, lifetime costs associated with daratumumab would need to be below $56,000 (90% price reduction) for the strategy (1L:DaraCyBorDex, 2L: LenDex, 3L: PomBorDex, 4L: CarDex) to be deemed cost-effective relative to all other strategies. It is noted these price reductions are illustrative only as there are confidential price agreements for many drugs in the analysis, such as carfilzomib and isatuximab, and a $50,000 willingness-to-pay threshold is assumed. Second this may represent the upper limit of the price reduction as scenario analyses have shown the efficacy of daratumumab may have been underestimated. The impact of daratumumab price reductions on total costs is shown in Table 29. Reducing the price of daratumumab has the largest impact on total costs for strategies which utilizes in the first-line setting. If the price of daratumumab is reduced by 90% then the total cost of the strategy DaraCyBorDex,LenDex,PomBorDex,CarDex is actually lower than the strategy “LenBorDex,DaraBorDex,PomBorDex,CarDex.” This is because patients spend longer on daratumumab in this treatment pathway than any other therapy, so this strategy is impacted more by daratumumab price

reductions. With a 90% price reduction DaraCyBorDex,LenDex,PomBorDex,CarDex remains approximately $50,000 more per patient than CyBorDex,LenDex,PomDex,DaraBorDex.

Table 29: Impact of Daratumumab Price Reductions on Total Costs

Sequence	Total costs (list prices)	Total costs (50% price reduction for daratumumab)[a]	Total costs (90% price reduction for daratumumab)[a]
CyBorDex,LenDex,PomDex,DaraBorDex	$372,577	$333,148	$275,080
LenBorDex,DaraBorDex,PomBorDex,CarDex	$537,263	$447,478	$359,181
DaraCyBorDex,LenDex,PomBorDex,CarDex	$795,676	$554,373	$328,592

CarDex = carfilzomib and dexamethasone; CarLenDex = carfilzomib, lenalidomide, and dexamethasone; CyBorDex = cyclophosphamide, bortezomib, and dexamethasone; DaraBorDex = daratumumab, bortezomib, and dexamethasone; DaraCyBorDex = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; DaraLenDex = daratumumab, lenalidomide, and dexamethasone; DaraMphBorPred = daratumumab, melphalan, bortezomib, and dexamethasone; IsaPomDex = isatuximab, pomalidomide, and bortezomib; LenDex = lenalidomide and dexamethasone; LenBorDex = lenalidomide, bortezomib, and dexamethasone; PomBorDex = pomalidomide; bortezomib and dexamethasone; PomDex = pomalidomide and bortezomib.

[a]List prices are assumed for all other drugs.

Note: Bold text indicates where daratumumab appears in the treatment pathway.

Regarding other treatments evaluated in this analysis, outside of daratumumab, there was limited evidence generated from the NMA that showed 1 treatment being substantially more effective than another in the relapsed setting. For all strategies which utilized 4 treatment lines a regimen was not given twice. This meant that if a patient failed lenalidomide for example they would not receive a regimen which included lenalidomide in subsequent lines. Due to this, the choice of next therapy is determined by what treatments have not been utilized in prior lines. Regarding the cost of other treatment regimens LenDex, CyBorDex and, LenBorDex were the lowest cost regimens to administer, costing on average $60,000 less per year than carfilzomib and daratumumab-based regimens. Strategies which utilized LenDex, CyBorDex and LenBorDex in first- or second-line setting were associated with substantially lower costs. Of the remaining therapies, regimens which utilized pomalidomide (PomDex, IsaPomDex, PomBorDex) were substantially more costly than other treatment regimens. Strategies which utilized PomDex in earlier lines incurred higher costs and given the incremental benefit was potentially lower than other strategies these strategies tended to be dominated (produced lower health benefits at a higher cost). From this, the following general conclusions can be extracted from the model in the relapsed setting. Prior therapies will dictate which options remain for later lines. Evidence on incremental differences between therapies is limited. Given some therapies (such as pomalidomide) have a higher cost (using list prices), there is limited evidence to support their use in earlier lines from a health economic perspective.

Although the model is informed by the best available evidence from both a NMA and real-world evidence in Canada, uncertainty remains when looking at specific treatment strategies. This is due to uncertainty in the underlying evidence base, such as the lack of direct comparison between the backbone regimens (i.e., CyBorDex vs. Rd), and wide confidence intervals around effect estimates. Likewise, there are no trials just conducted in the second line. This requires assumptions as to how relative treatment efficacy may change as we progress down treatment lines. Studies in the relapsed setting were also not restricted to patients who are transplant ineligible, which may influence the relative efficacy between therapies. Finally, the type

of therapy the patient failed on in a prior line may also have an impact as to the efficacy of future treatment lines. As part of this analysis, attempts were made to answer these questions using real-world evidence from CMRG, however there was an insufficient degree of granularity to adjust for even known confounders. Outcomes from such an analysis would present a different set of limitations than the ones derived through the NMA.

Given the rapid evolution of treatments in the MM space there are some new treatment strategies that are not considered in this analysis. These include isatuximab given in combination with carfilzomib and dexamethasone; selinexor given in combination with bortezomib, and CAR T. At public list prices, all these therapies are associated with higher costs than all the reviewed therapies in this review except for IsaPomDex.

Finally, given the lack of robust data, this analysis does not explicitly consider differing safety profiles between treatments. Safety likely impacts time on therapy which has been accounted for in this analysis, but the quality-of-life impact and medical costs associated with treating AEs has not. Although there are noted side effects associated with certain treatments the degree to which these are incrementally different is uncertain. It is likely however that by not accounting for the quality-of-life impact associated with AEs that the benefit of strategies which use more invasive therapies, such as IV, has been overestimated. Given these limitations only broad conclusions from this analysis have been drawn as opposed to the recommendation of a specific line of therapy. These broad conclusions are:

- Sequences which include daratumumab in the first- or second-line setting are the most effective. Price reductions on the list price are required to ensure the use of daratumumab in the first or second line represents good value. The exact price reduction required to achieve cost-effectiveness will be influenced by the combination therapy daratumumab is considered in, any negotiated prices available for other therapies, the decision-makers willingness-to-pay threshold.
- Evidence for the optimal sequence of therapies after the first line is uncertain. The choice of the optimal sequence will depend on what therapies are used in the first line as this will restrict which options remain in later lines. There is a large cost disparity between some therapies in the relapsed setting with regimens including pomalidomide having the highest cost.

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ISSN: 2563-6596

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.