SYSTEMATIC REVIEW

A Systematic Review of Modeling Approaches to Evaluate Treatments for Relapsed Refractory Multiple Myeloma: Critical Review and Considerations for Future Health Economic Models

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Abstract

Background and Objective Multiple myeloma is a rare incurable hematological cancer in which most patients relapse or become refractory to treatment. This systematic literature review aimed to critically review the existing economic models used in economic evaluations of systemic treatments for relapsed/refractory multiple myeloma and to summarize how the models addressed differences in the line of therapy and exposure to prior treatment.

Methods Following a pre-approved protocol, literature searches were conducted on 17 February, 2023, in relevant databases for models published since 2014. Additionally, key health technology assessment agency websites were manually searched for models published as part of submission dossiers since 2018. Reported information related to model conceptualization, structure, uncertainty, validation, and transparency were extracted into a pre-defined extraction sheet.

Results In total, 49 models assessing a wide range of interventions across multiple lines of therapy were included. Only five models specific to heavily pre-treated patients and/or those who were refractory to multiple treatment classes were identified. Most models followed a conventional simple methodology, such as partitioned survival ($n = 28$) or Markov models ($n = 9$). All included models evaluated specific interventions rather than the whole treatment sequence. Where subsequent therapies were included in the model, these were generally only considered from a cost and resource use perspective. The models generally used overall and progression-free survival as model inputs, although data were often immature. Sensitivity analyses were frequently reported ($n = 41$) whereas validation was only considered in less than half ($n = 19$) of the models.

Conclusions Published economic models in relapsed/refractory multiple myeloma rarely followed an individual patient approach, mainly owing to the higher need for complex data assumptions compared with simpler modeling approaches. As many patients experience disease progression on multiple treatment lines, there is a growing need for modeling complex treatment strategies, leading to more sophisticated approaches in the future. Maintaining transparency, high reporting standards, and thorough analyses of uncertainty are crucial to support these advancements.

1 Background

Multiple myeloma (MM) is a rare incurable hematological cancer that forms in plasma cells, a type of white blood cell that produces antibodies [1]. As malignant plasma cells accumulate in the bone marrow, they eventually lead to bone destruction and marrow failure. In 2020, more than 176,000 new cases of MM (~ 0.9% of all new cancer cases) and 117,000 deaths due to MM (~ 1.2% of all cancer deaths) were recorded globally according to data from the Global Cancer Statistics initiative of the World Health Organization [2]. Multiple myeloma accounts for 1.8% of all new cancers and 13% of hematologic cancers in the USA [1, 3]. Similar overall trends have been observed in the European Union (approximately 36,000 new cases in 2020 with an age-adjusted standardized incidence rate of 7.5 cases per 100,000), although the incidence of disease differed considerably (range: 2.7 per 100,000 in Bulgaria to 10.9 per 100,000 in Denmark) across the member states [4].

The cause of MM is not fully known. The disease disproportionately affects people over the age of 60 years and men, [5], as well as Black individuals and African American individuals, who are more than twice as likely to be diagnosed with MM than White individuals (estimated 15.9 vs 6.9 cases, respectively, per 100,000) in the USA in 2019 [6]. Disease prognosis remains poor, with a 5-year relative survival rate of less than 60% in the USA [3]. Most patients

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Extended author information available on the last page of the article

Key Points

This review examined how existing health economic models (i.e., tools to demonstrate the monetary value of a new treatment and its impact on a healthcare system) are used to evaluate drugs for relapsed/refractory multiple myeloma; in particular, it evaluated challenges associated with key methodological concepts, including conceptualization, model structure, uncertainty analyses, model validation, and transparency; and how health economic models addressed differences in the line of therapy and exposure to prior treatment.

Published economic models in relapsed/refractory multiple myeloma mostly adhere to conventional methodology, such as cohort partitioned survival or Markov models, as opposed to more complex, individual patient model types due to the higher data requirements associated with the latter. Less than half of the models included a step to verify the results, potentially reflecting the variance in validation reporting between health technology assessment submissions and journal articles, where journals typically offered a more comprehensive coverage.

with MM eventually relapse and/or become refractory to treatment (RRMM) [7]; therefore, treatment goals aim to prolong survival and maximize quality of life by alleviating symptoms, controlling disease progression, and minimizing adverse events.

In the last decade, the treatment of MM has improved dramatically with the introduction of agents such as second-generation proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and monoclonal antibodies (mAbs) [8]. In recent years, other novel agents have received marketing authorization, including a chimeric antigen receptor T-cell (CAR-T) targeting B-cell maturation antigen immunotherapy, idecabtagene vicleucel, which was approved by the US Food and Drug Administration in 2021 for adults with RRMM after four or more lines of therapy (including a PI, an IMiD, and an anti-CD38) [9]. The choice of second-line or later-line treatment for RRMM generally depends on the exposure and response to first-line agents and varies among organizations and jurisdictions. Recommended first-line treatment options include lenalidomide-based, bortezomib-based and/or daratumumab-based regimens. In patients who are eligible for transplant, first-line induction treatment is followed by

autologous stem cell transplantation and lenalidomide or bortezomib maintenance therapy [7, 10–12].

As the therapeutic landscape in RRMM continues to evolve, decision-analytic models play a cornerstone role in the economic evaluations of treatments to inform decision makers, payers, and stakeholders about whether new treatments should be adopted and reimbursed and whether existing regimens remain as an efficient use of healthcare resources [13]. The aim of this research was two-fold: (1) to critically review the existing health economic models used in economic evaluations of systemic treatments for RRMM to better understand their methodological challenges and rigor and (2) to summarize how health economic models addressed differences in the line of therapy and exposure to prior treatment. To achieve these objectives, a systematic literature review (SLR) was conducted to comprehensively summarize the available information on decision-analytic models used in economic evaluations of systemic treatments for patients with RRMM. In addition, the critical review of the economic evaluations was based on five aspects as recommended by Caro [14]: conceptualization, model structure, uncertainty analyses, model validation, and transparency.

2 Methods

The SLR was conducted in accordance with the reporting requirements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15] guidance and general methodological requirements outlined in the Cochrane Handbook for Systematic Reviews of Interventions [16].

2.1 Literature Sources

Literature searches were performed on 17 February, 2023, in MEDLINE and MEDLINE In-Process, Embase, National Health Service Economic Evaluations Database, EconLit, Database of Abstracts of Reviews of Effects, the Health Technology Assessment (HTA) database (via International Network of Agencies for HTA), and the Cost-Effectiveness Analysis Registry as part of a wider SLR of economic evidence. The bibliographies of any identified SLRs published since 2020 were reviewed to ensure that all relevant studies were captured.

Additionally, manual searches were conducted to identify any economic models that were only published as part of submission dossiers to key HTA agencies (Canadian Agency for Drugs and Technologies in Health [CADTH]/pan-Canadian Oncology Drug Review, National Institute for Health and Care Excellence [NICE] in England, Australian Pharmaceutical Benefits Advisory Committee [PBAC], and Scottish

Table 1 Population, Interventions, Comparisons, Outcomes, and Study (PICOS) design selection criteria

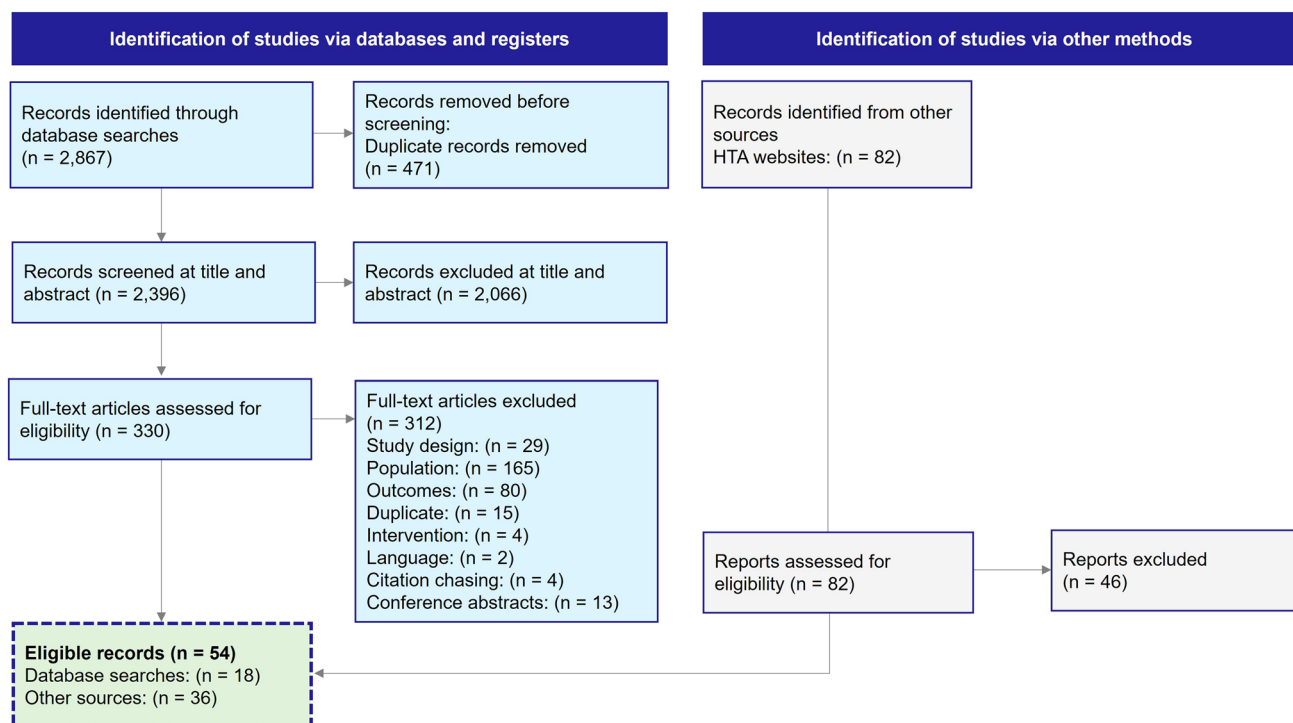| Inclusion	Exclusion
Population	
Adults with RRMM	Untreated MM (i.e., first-line treatment setting)
	Any other population
Interventions/comparators	
Any	Economic evaluations exclusively for diagnostic testing or patient management strategies
Outcomes	
Model conceptualization	Any other outcome
Model structure	
Uncertainty assessment	
Validation	
Transparency	
Study design and publication type	
Economic evaluations (cost-effectiveness, cost-utility, cost consequence, cost-minimization, and cost-benefit analysis)	Clinical trials
	Non-SLRs
SLRs/NMAs (to be hand searched for relevant studies)	Conference abstracts
	Budget impact analysis
	Non-human studies
	Pharmacodynamic studies
	Preclinical studies
	Case reports
	Commentaries, editorials, and letters
	Consensus reports
	Observational RWE studies
Additional limits	
Date of publication	
Full texts since 2014	Full-text references published prior to 2014
HTA submissions since 2018	HTA submissions published prior to 2018
Language	
English	Non-English articles

HTA health technology assessment, *MM* multiple myeloma, *NMA* network meta-analysis, *RRMM* relapsed/refractory multiple myeloma, *RWE* real-world evidence, *SLR* systematic literature review

Medicines Consortium [SMC]) and a US-based non-profit organization (Institute for Clinical and Economic Review) that produces clinical and cost-effectiveness reports for use by multiple stakeholders. A full list of literature database search sources is presented in Table 1 of the Electronic Supplementary Material (ESM).

Database searches were restricted to journal articles published since 2014. Bortezomib, lenalidomide, and daratumumab were first approved to treat MM in the first-line setting in 2008 [17], 2015 [18], and 2018 [19], respectively, and thus studies published before 2014 were unlikely to include significant numbers of patients who received these treatments in the first-line setting. Similarly, manual HTA searches were restricted to dossiers (first submissions) published since 2018 given the time needed from enrolling patients into a clinical trial to HTA submission. The full search strategies can be found in the ESM.

2.2 Study Selection and Screening

The selection of relevant economic models followed predefined criteria using the Population, Interventions, Comparisons, Outcomes, and Study (PICOS) design framework as outlined in Table 1. The target population comprised adults with RRMM irrespective of the treatment previously received or line of therapy. Any systemic pharmacological intervention aimed at managing the disease was considered and no restrictions were placed on included comparators. Outcomes of interest included economic model conceptualization, structure, uncertainty elaboration, validation, and transparency to align with the recommendations in Caro [14]. Only full economic evaluations (i.e., cost-effectiveness analysis, cost-utility analysis, cost-minimization analysis, and cost-benefit analysis) published in full-text articles and first submission documents were considered for inclusion. Budget impact and cost analyses were excluded. Conference abstracts were not considered given the limited information on the economic

Identification of studies via databases and registers

Records identified through database searches (n = 2,867) → Records removed before screening: Duplicate records removed (n = 471)

Records screened at title and abstract (n = 2,396) → Records excluded at title and abstract (n = 2,066)

Full-text articles assessed for eligibility (n = 330) → Full-text articles excluded (n = 312)
Study design: (n = 29)
Population: (n = 165)
Outcomes: (n = 80)
Duplicate: (n = 15)
Intervention: (n = 4)
Language: (n = 2)
Citation chasing: (n = 4)
Conference abstracts: (n = 13)

Eligible records (n = 54)
Database searches: (n = 18)
Other sources: (n = 36)

Identification of studies via other methods

Records identified from other sources
HTA websites: (n = 82)

Reports assessed for eligibility (n = 82) → Reports excluded (n = 46)

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram. *HTA* health technology assessment

model structure and methods provided. No geographical restrictions were applied to literature database searches. Only English-language publications and HTA dossiers were included.

Screening of articles identified through the literature database searches was conducted by two independent reviewers at both the title/abstract and full-text levels. Any discrepancies were resolved by a third, more senior reviewer. Manual searches of HTA submission dossiers were conducted by one reviewer, with a second reviewer validating the search approach and results.

2.3 Data Extraction

Data from the included models were extracted by one reviewer with full data validation by a second reviewer using pre-designed data extraction sheets. Extracted data variables were related to the five core model elements highlighted by Caro [14]: conceptualization, structure, uncertainty, validation, and transparency. Patient and treatment/comparator characteristics, data sources and inputs, and assumptions were also systematically extracted. To avoid double counting, we connected related (multiple) publications by mapping identified models for the same treatment, treatment line, and country as well as re-submissions to the same HTA agency.

3 Results

The database searches returned 2867 records, of which 2396 records were screened at the title/abstract level following the removal of duplicates; 330 full-text articles were screened, of which 312 were excluded. In total, 18 full-text articles published in peer-reviewed journals were eligible from the literature and an additional 36 records were identified via HTA websites, resulting in 54 records (49 primary publications representing unique models and five related publications) included in the SLR (see Fig. 1). The evidence summary refers to the 49 primary publications hereafter.

3.1 Overview of General Model Characteristics

3.1.1 Treatments Evaluated in the Included Models

Most models included patients across multiple lines of treatment; seven models were in second line only [20–26], 27 models were second-line or later-line therapies [27–53], and 14 models were in patients who had received three or more lines of treatment previously [54–67]. One model in heavily pre-treated patients did not specify the treatment line setting, but the clinical trial data used for the model suggested that patients had received a median of five prior treatments [68]. Overall, information on relapse and refractoriness to prior therapy was limited; most models

referred to the population as RRMM without specifying the exact line of therapy or exposure to prior therapy. From those publications providing more information on this area, one model each was in patients who were triple-class refractory [33], triple-class exposed [56], triple-refractory or penta-refractory [64], triple-/quad-/penta-refractory [67], and second-line, lenalidomide-refractory [39]. Baseline demographics of the clinical studies utilized were presented in 17 models [20, 22, 28–30, 36, 37, 39–41, 44, 55, 58–60, 62, 67].

Of the 49 models evaluated, seven [25, 29, 37, 43, 45, 51, 67] evaluated the cost effectiveness of multiple interventions, while the remainder focused on a single agent or treatment combination versus comparator treatment(s). The models evaluated a wide range of treatments and combination regimens, many of which contained a PI, an IMiD, and an mAb. Bortezomib-based ($n = 26$) [20, 22, 23, 25–27, 30, 32, 34, 36–40, 42–46, 48, 49, 51, 52, 59–61] or lenalidomide-based regimens (n=17) [27, 28, 30, 31, 35, 37, 38, 40, 43–46, 49, 51, 62, 66, 67] were the most common reference treatments across the models. Sixteen models evaluated the cost effectiveness of treatments including an mAb, such as daratumumab, elotuzumab, or isatuximab [22, 23, 25, 29, 35–37, 41, 45, 47, 51, 53, 58, 60, 61, 63]. Thirty-nine models assessed a combination including a PI, such as bortezomib, carfilzomib, and ixazomib [21–32, 34–41, 43–46, 48–52, 62, 66]. This number was mainly driven by bortezomib-based regimens, which have become a cornerstone of MM treatment. Lenalidomide-based and pomalidomide-based treatments (both of which are IMiDs) were evaluated in 27 models [20, 21, 24, 28, 29, 31, 35, 37–39, 42–45, 47, 49, 52–55, 58–60, 62, 63, 66, 68]. Chimeric antigen receptor T-cell therapy was evaluated in two models only [56, 67]. This may reflect the recent approval of these therapies since 2021 by the US Food and Drug Administration [69–71], which are generally reserved for patients who have received multiple prior lines of treatment.

3.1.2 Model Outcomes

Health benefits were primarily reported in terms of quality-adjusted life-years (QALYs). Forty-two models reported incremental cost-effectiveness ratios (ICERs) per QALY [20–22, 25–48, 51, 54–62, 64–68] and 31 models reported ICERs per life-year gained [20, 22, 28–32, 35–44, 48, 54–57, 59–62, 64–68]. Nine models (of note, all of which were included in submissions to the PBAC in line with requirements for presenting cost data and cost implications to the Australian health budget [72]) reported total costs and additional costs per course and patient as a result of introducing a new treatment [23, 24, 48–50, 52, 53, 63, 65]. As some model publications reported more than one type of outcome, the sum of the models reported above is higher

than the total number of unique 49 models included in this SLR.

3.1.3 Model Settings and Perspectives

The vast majority of the models examined a population from a certain country, such as Australia (14, mostly driven by a high number of PBAC submissions) [23–26, 48–53, 63–66] the USA (12 models) [27, 29–34, 36, 37, 57, 67, 68], the UK (UK; eight out of 11 from England [22, 42–44, 59–62] and the other three from Scotland [45–47]), and Canada (five models) [38–41, 58]. One model each examined a population from Singapore [35], Czech Republic [28], Chile [20], Sweden [54], South Africa [21], and France [55]. Among all identified models, only one reported and compared the results across populations from multiple countries (i.e., from Canada and France) [56].

The majority of analyses in the identified models used a public healthcare payer perspective ($n = 35$) [20, 22–26, 29, 33, 35, 37–53, 58–63, 65, 66, 73], followed by eight models using a payer perspective without further definition [27, 28, 31, 32, 34, 36, 67, 68]. Two models used a commercial healthcare payer perspective [30, 57], three were from a societal perspective [21, 54, 56], and one model did not report the perspective [55].

A summary of the characteristics of models published in peer-reviewed journals and those included in HTA submissions is given in Tables 2 and 3, respectively. Characteristics of each identified model according to the recommended core model elements by Caro [14] are presented in the following sections.

3.2 Conceptualization

Six of the 18 models published in a peer-reviewed journal described the intended audience, including health policy makers, payers, and other stakeholders [21, 27, 29, 35, 37, 56]. All of the models included in submissions to CADTH, NICE, PBAC, and SMC were intended for HTA reimbursement. The model included in the Institute for Clinical and Economic Review assessment report was intended for multiple stakeholders and healthcare decision makers in the USA given the remit of this organization [67].

Most models were cohort level ($n = 46$) [20–32, 34–41, 43–53, 55–68] and three were individual patient level [33, 42, 54]. All models were developed for a single application (i.e., assessing the added cost and clinical benefit of a certain technology at a single point in the treatment pathway). Multiple applications may include, for example, "whole disease models," where the scope of the economic evaluation is more extensive and covers more than one decision point in the disease pathway; no model captured such considerations. A summary of conceptualization items of models published

Table 2 Model characteristics: peer-reviewed articles (19 articles)

Study, year	Perspective	Country/sponsor	Base-case population	Treatment line	Interventions	Comparators	Analyses type	Model outcomes
Aceituno et al. (2018) [20]	Public payer	Chile/Tecnofarma S.A.	Adults with RRMM not eligible for transplantation and previously treated	2L	Rd	Vd	CUA and CEA	Costs, LYs, QALYs, ICER
Borg et al. (2016) [54]	Societal	Sweden/Celgene, Kista, Sweden through IHE and BresMed	Adults with previously treated RRMM	3L+	Pd	High-dose d	CUA	Costs, LYs, QALYs, ICER
Cai et al. (2019) [27]	Payer	USA/Fujian Provincial Department of Science and Technology of the People's Republic of China and National Natural Science Foundation of China	Adults with previously treated RRMM	2L+	Vd	IRd, Rd, VTd	CUA	Costs, QALYs, ICER
Campioni et al. (2020) [28]	Payer	Czech Republic/NR	Adults with relapsed MM	2L+	KRd	Rd	CUA	Costs, LYs, QALYs, ICER
Carlson et al. (2018) [29]	Healthcare payer	USA/Institute for Clinical and Economic Review	Adults with previously treated RRMM	2L/3L	Rd, IRd, ERd, KRd, PanVd, DVd, DRd	NR	CUA	Costs, LYs, QALYs, ICER
Dolph et al. (2021) [30]	Commercial payer	USA/Karyopharm Therapeutics	Adults with previously treated RRMM	2L/3L+	XVd (low-dose dexamethasone)	Main: Vd. Additional comparators for exploratory analysis: DPd, DRd, Rd, PVd, EPd, KPd, DVd	CUA and CEA	Costs, LYs, evLYs, QALYs, ICER
Gueneau et al. (2018) [55]	NR	France/NR	Adults with RRMM who have received at least 2 prior anti-myeloma therapies	3L+	Pd	P	CEA	Costs, LYs, ICER
Jakubowiak et al. (2016) [31]	Payer	USA/Amgen	Adults with relapsed MM	2L+	KRd	Rd	CUA	Costs, LYs, QALYs, ICER
Jakubowiak et al. (2017) [32]	Payer	USA/Amgen	Adults with previously treated RRMM	2L+	Kd	Vd	CUA	Costs, LYs, PF LYs, QALYs, ICER
Kapinos et al. (2023) [33]	Healthcare payer	USA/none	Adults with triple-class refractory MM	2L+	Belamaf	Ide-cel, Cilta-cel	CUA	QALYs, ICER

Table 2 (continued)

Study, year	Perspective	Country/sponsor	Base-case population	Treatment line	Interventions	Comparators	Analyses type	Model outcomes
Karampampa et al. (2023) [56]	Societal	Canada and France/Bristol Myers Squibb	Adults with triple-class exposed MM	4L+	Ide-cel	Conventional care	CUA and CEA	Costs, LYs, QALYs, ICER
Matsela et al. (2022) [21]	Societal	South Africa/none	Adults with previously treated RRMM	2L	VRd	d	CUA	Costs, QALYs, ICER
Nikolaou et al. (2021) [57]	Commercial payer	USA/GlaxoSmithKline	Adults with RRMM who have received at least 4 prior anti-myeloma therapies	5L+	Belamaf	Xd	CUA and CEA	Costs, LYs (PF LY, PP LY), QALYs (PF QALY, PP QALY), ICER
Patel et al. (2021) [34]	Payer	USA/American Society of Hematology Physician-Scientist Career Development Award; Frederick A. DeLuca Foundation	Adults with previously treated RRMM	2L+	XVd	Vd	CUA	Costs, QALYs, ICER
Pelligra et al. (2017) [68]	Payer	USA/Celgene	Adults with heavily pre-treated RRMM	NR	Pd	D monotherapy K monotherapy	CUA	Costs, LYs, QALYs, ICER
Wong et al. (2021) [35]	Public payer	Singapore/none	Adults with previously treated RRMM	2L+	DRd	Rd	CUA	Costs, PF LYs, LYs, QALYs, ICER
Zeng et al. (2020) [36]	Payer	USA/none	Adults with previously treated RRMM	2L+	DVd	Vd	CUA and CEA	Costs, LYs, QALYs, ICER
Zhang et al. (2018) [37]	Healthcare payer	USA/none	Adults with previously treated RRMM	2L+	DVd DRd	Vd Rd	CUA	Costs, LYs, QALYs, ICER

2L second line, *2L+* second line and later, *3L* third line, *3L+* third line and later, *4L+* fourth line and later, *5L+* fifth line and later, *belamaf* belantamab-mafodotin, *CEA* cost-effectiveness analysis, *cilta-cel* ciltacabtagene autoleucel, *CUA* cost-utility analysis, *d* dexamethasone, *DPd* daratumumab plus pomalidomide and dexamethasone, *DRd* daratumumab plus lenalidomide and dexamethasone, *DVd* daratumumab plus bortezomib and dexamethasone, *EPd* elotuzumab plus pomalidomide and dexamethasone, *ERd* elotuzumab plus lenalidomide and dexamethasone, *evLY* equal value life year, *ICER* incremental cost-effectiveness ratio, *ide-cel* idecabtagene vicleucel, *IHE* The Swedish Institute for Health Economics, *IRd* ixazomib plus lenalidomide and dexamethasone, *KPd* carfilzomib plus pomalidomide and dexamethasone, *KRd* carfilzomib plus lenalidomide and dexamethasone, *LY* life-year, *MM* multiple myeloma, *NR* not reported, *P* pomalidomide, *PanVd* panobinostat plus bortezomib and dexamethasone, *Pd* pomalidomide plus dexamethasone, *PF* progression free, *PP* post-progression, *PVd* pomalidomide plus bortezomib and dexamethasone, *QALY* quality-adjusted life-year, *Rd* lenalidomide and dexamethasone, *RRMM* relapsed/refractory multiple myeloma, *V* bortezomib, *Vd* bortezomib and dexamethasone, *VTd* bortezomib plus thalidomide and dexamethasone, *XVd* selinexor plus bortezomib and dexamethasone

in peer-reviewed journals and included in HTA submissions is reported in Tables 4 and 5, respectively.

3.3 Model Structure

Partitioned survival models (PSMs) are frequently used in oncology [74, 75]. This modeling approach determines health-state membership based on the within-trial relationship between survival curves that are non-mutually exclusive. In a typical three health-state PSM, progression-free survival (PFS) and overall survival (OS) curves directly determine the proportion of patients who remain alive in the progression-free and the overall proportion of alive patients, respectively, while the proportion of patients with non-fatal progression is based on the difference between the two curves. Overall survival and PFS are projected independently, and transition probabilities are not required to establish the distribution of patients across the health states over time [74, 75]. In state transition models (e.g., Markov, semi-Markov), the distribution of patients across health states is determined based on transition probabilities that depend on the current health state, and, in the case of semi-Markov models, also on time [75, 76]. In discrete event simulation models, the simulated patients experience events at specific (i.e., discrete) timepoints and the consequences of each event (costs and health benefits or harms) are processed as the events occur [77, 78].

3.3.1 Cohort vs Individual Patient Approach

Following the classification provided by Caro [14], this review classified models into two main modeling approaches, deterministic and stochastic. Stochastic models incorporate randomness or uncertainty to simulate different possible scenarios and their associated outcomes and determine individual trajectories under varying conditions such as disease progression and patient characteristics, which is referred to as an individual patient approach or an individual-level approach hereafter. For example, Monte Carlo Markov Chain (MCMC) microsimulation models allow hypothetical individuals within hypothetical populations to transition to different states included in the model structure. By contrast, deterministic models consider the entire cohort based on fixed parameters and assumptions and do not involve randomness, which is referred to as a cohort-level approach in this review. The cohort-level approach includes, for example, decision trees, PSMs, and Markov models; although probabilistic analyses are usually conducted within these approaches to assess parameter uncertainty [79, 80].

Of the 49 models, three were individual-level models, two were discrete event simulation models [42, 54], and one was an MCMC microsimulation model [33]. Among the 46 cohort-level models, 27 employed a PSM structure [22, 25, 28–32, 35, 38–41, 43–48, 52, 56–58, 60–62, 64, 66], six were Markov models [20, 21, 33, 34, 36, 59], two were semi-Markov models [37, 65], and one model combined a decision node and a PSM [67]. Structure was not explicitly reported for ten models [23, 24, 26, 49–51, 53, 55, 63, 68].

3.3.2 Justification and Description of Model Structure

Overall, there was a lack of justification on the model structure chosen. The rationale was available in eight out of 49 reports[20, 22, 44, 56, 60, 62, 64, 67]. Of those, six were PSMs [22, 44, 56, 60, 62, 64], one combined a decision-node and PSM structure [67] and one was a Markov model [20]. The use of PSMs was mainly justified as being a common approach that was consistent with other models and/or appraisals in RRMM and had been widely used and accepted in economic evaluation studies in the same or similar settings in oncology [22, 44, 60]. Other reasonings provided in those models included being the best use given data availability [22, 44, 60, 64] and limited assumptions needed [44, 60], as well as the rationale that these models provided a better fit to OS and PFS data from clinical trials [60, 62]. The only combined model (a decision node and PSM) justified the selection of the decision node component by stating it better reflected the model purpose of describing costs and outcomes associated with the preparation for receiving CAR-T therapy [67]. The Markov structure was argued to be appropriate when disease conceptualization necessitated a long-term perspective and entailed transitions between distinct health states [20].

Among eight out of 49 included models, one publication described a model that combined a decision node and PSM structure [67], which was developed to investigate various CAR-T therapies. In this model, the decision node covered the initiation of the CAR-T therapy process by including all patients eligible for CAR-T who had received leukapheresis. Following the initiation of leukapheresis, patients would either continue to a T-cell infusion or would discontinue because of other reasons such as progressed disease, adverse events, manufacturing failures, or death before receiving the infusion. Patients who discontinued treatment because of reasons other than death receive a basket of treatments appropriate for triple-refractory or quad-refractory patients. The PSM structure was designed to capture long-term costs and benefits related to various treatments and covered three health states, two of which represented the response status (i.e., alive and responding to treatment; alive and not responding to treatment) and an absorbing death health state. Responding patients continued with the current treatment, while non-responders transitioned to progressed disease and received the basket of subsequent treatments. In addition, different costs and utility values were applied to distinguish

Table 3 Model characteristics: health technology assessment submissions (31 submissions)

Study (year)	Perspective	Country/sponsor	Base-case population	Treatment line	Interventions	Comparators	Analyses type	Model outcomes
CADTH PC0164-000 (2019) [38]	Publicly funded healthcare payer	Canada/Takeda	Adults with RRMM who have received at least 1 prior therapy	2L+	IRd	Rd KRd DRd DVd Other comparators included in scenario analyses of 2L+ population only: Pd Kd	CUA	Costs, QALYs, LYs, ICER
CADTH PC0165-000 (2019) [39]	Publicly funded healthcare payer	Canada/Celgene	Adults with RRMM who have received at least 1 prior treatment regimen including lenalidomide	2L+	PVd	Vd Other comparators included in scenario analysis of lenalidomide-exposed patients with RRMM: Vd DVd Kd VCd	CUA	Costs, QALYs, LYs, ICER
CADTH PC0220-000 (2021) [58]	Publicly funded healthcare payer	Canada/Sanofi	Adults with RRMM who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor	3L+	IsaPd	Pd	CUA	Costs, QALYs, ICER
CADTH PC0256-000 (2022) [41]	Publicly funded healthcare payer	Canada/Sanofi	Adults with RRMM who have received 1 to 3 prior lines of therapy	2L+	IsaKd	Kd	CUA	Costs, QALYs, LYs, ICER

Table 3 (continued)

Study (year)	Perspective	Country/sponsor	Base-case population	Treatment line	Interventions	Comparators	Analyses type	Model outcomes
CADTH PC0276-000 (2022) [40]	Publicly funded healthcare payer	Canada/FORUS Therapeutics	Adults with RRMM who have received at least 1 prior therapy	2L+	XVd	Vd VCd DRd DVd KCd Kd KRd PVd Rd SOC comprising an equally weighted average of Vd, PVd, KCd, Kd, VCd, DVd, DRd, Rd, and KRd	CUA	Costs, QALYs, LYs, ICER
Institute for Clinical and Economic Review (ide-cel, cilta-cel, belamaf assessment) (2021) [67]	Healthcare payer	USA/government grants and non-profit foundations	Adults with heavily pre-treated MM beginning at age 60 years who were eligible for CAR-T therapy and who had undergone leukapheresis	4L+	Ide-cel Cilta-cel Belamaf	Market basket combining: KCd, PCd, IPd, EPd, IRd, and the combination of bendamustine, prednisone, dexamethasone, cyclophosphamide, etoposide, and cisplatin	CUA and CEA	Costs, QALYs, LYs, ICER
NICE TA171 (2019) [42]	UK NHS and PSS	UK/Celgene	Adults with RRMM who have received at least 1 prior therapy	2L+	Rd	For people who have received only one prior therapy: V monotherapy For people in whom bortezomib is contraindicated, people who have received two or more prior therapies, and people who have received prior thalidomide (only one prior therapy or two or more prior therapies): d monotherapy	CUA	Costs, QALYs, LYs, ICER

Table 3 (continued)

Study (year)	Perspective	Country/sponsor	Base-case population	Treatment line	Interventions	Comparators	Analyses type	Model outcomes
NICE TA573 (2019) [22]	UK NHS and PSS	UK/Janssen	Adults with RRMM who have received 1 prior line of therapy	2L	DVd	Vd Kd	CUA	Costs, QALYs, LYs, ICER
NICE TA586 (2019) [59]	UK NHS and PSS	UK/Celgene	Adults with RRMM contraindicated to thalidomide whose disease progressed after bortezomib (and who are not eligible for SCT)	3L	Rd	MP V	CUA	Costs, QALYs, LYs, ICER
NICE TA657 (2020) [43]	UK NHS and PSS	UK/Amgen	Adults with RRMM who have received at least 1 prior therapy	2L+	KRd Kd	For KRd: Rd For Kd: Vd	CUA	Costs, QALYs, LYs, ICER
NICE TA658 (2020) [60]	UK NHS and PSS	UK/Sanofi	Adults with RRMM who have received 3 prior therapies, including lenalidomide and a proteasome inhibitor, and whose disease progressed on the last therapy	4L	IsaPd	Pd PanVd	CUA	Costs, QALYs, LYs, ICER
NICE TA695 (2021) [44]	UK NHS and PSS	UK/Amgen	Adults with RRMM who have received at least 1 prior therapy	2L+	KRd	Rd DVd	CUA	Costs, QALYs, LYs, ICER
NICE TA783 (2022) [61]	UK NHS and PSS	UK/Janssen	Adults with RRMM who have received 3 previous treatments including a PI and an IMiD	4L	D monotherapy	Pd PanVd	CUA	Costs, QALYs, LYs, ICER
NICE TA870 (2023) [62]	UK NHS and PSS	UK/Takeda	Adults with RRMM who have received 2 or 3 lines of therapy	3L+	IRd	Rd	CUA	Costs, QALYs, LYs, ICER

Table 3 (continued)

Study (year)	Perspective	Country/sponsor	Base-case population	Treatment line	Interventions	Comparators	Analyses type	Model outcomes
PBAC 5.02 July 2021, Darzalex [23]	Australian healthcare payer	Australia/Janssen	Adults with RRMM who have received 1 prior line of therapy	2L	DVd	DVd (different dosage)	CMA	Costs
PBAC 5.04 November 2020, Empliciti [63]	Australian healthcare payer	Australia/Bristol Myers Squibb	Adults with RRMM	3L	ERd	Kd	CMA	Costs
PBAC 5.07 July 2021, Xpovio [48] Resubmission: PBAC 7.07 November 2022, Xpovio [98] Resubmission: PBAC 7.10 March 2022, Xpovio [99]	Australian healthcare payer	Australia/Antengene Pty Ltd	Adults with RRMM who have received at least 1 prior therapy	2L+	XVd	Vd Kd	CUA, CEA and CMA	Costs, LY, QALYs, ICER
PBAC 5.07 November 2020, Ninlaro [49]	Australian healthcare payer	Australia/Takeda	Adults with RRMM who have experienced disease progression with at least 1 prior therapy	2L+	IRd	Kd Rd DVd	CMA	Costs
PBAC 5.08 July 2021, Xpovio [64] Resubmission: PBAC 7.09 March 2022, Xpovio [100]	Australian healthcare payer	Australia/Antengene Pty Ltd	Adults with RRMM who have received at least 4 prior therapies and whose disease is refractory to at least 2 PIs, at least 2 IMiDs, and an anti-CD38 monoclonal antibody	4L/5L	Xd	Combination of d, C, etoposide, and cisplatin	CUA and CEA	Costs, LY, QALYs, ICER

Table 3 (continued)

Study (year)	Perspective	Country/sponsor	Base-case population	Treatment line	Interventions	Comparators	Analyses type	Model outcomes
PBAC 5.09 July 2019, Aplidin [65] Resubmission: PBAC 7.06 March 2020, Aplidin [101]	Australian healthcare payer	Australia/Specialised Therapeutics Pharma Pty Ltd	Adults with RRMM who have received at least 3 prior treatments, including both a PI and an IMiD, or failure of 2 prior treatments if contraindicated or intolerant to a PI and an IMiD	3L/4L	Plitidepsin + d	3L: Pd 4L: d monotherapy	CUA (4L) and CMA (3L)	3L: total costs and cost breakdown 4L: costs, QALYs, LYs, ICER
PBAC 6.08 July 2019, Pomalyst [24] Resubmission: PBAC 7.13 November 2019, Pomalyst [73]	Australian healthcare payer	Australia/Celgene	Adults with RRMM who have undergone or are ineligible for a SCT, and who have received at least 1 prior treatment regimen including lenalidomide for at least 2 consecutive cycles	2L	PVd	Kd	CMA	Costs
PBAC 6.08 July 2020, Kyprolis [50]	Australian healthcare payer	Australia/Amgen	Adults with RRMM who have received at least 1 prior therapy	2L+	Kd	Kd (different dosage)	CMA	Costs
PBAC 7.01 November 2019, Darzalex [25]	Australian healthcare payer	Australia/Janssen	Adults with RRMM who have received 1 prior line of therapy	2L	Regimens including D and V	V-based regimens Kd	CUA	Costs, QALYs, ICER
PBAC 7.03 March 2019, Darzalex [51]	Australian healthcare payer	Australia/Janssen	DVd: adults with RRMM after at least 1 prior therapy D monotherapy: adults with RRMM after at least 3 prior lines of therapy which included a PI and IMiD, or who are refractory to both a PI and IMiD	2L+	DVd D monotherapy	For DVd: Vd, Kd, VCd, Rd D monotherapy: no specific comparator	CUA	Costs, QALYs, ICER

Table 3 (continued)

Study (year)	Perspective	Country/sponsor	Base-case population	Treatment line	Interventions	Comparators	Analyses type	Model outcomes
PBAC 7.03 March 2022, Kyprolis [52]	Australian healthcare payer	Australia/Amgen	Adults with RRMM who have received at least 1 prior therapy	2L+	KRd	Kd Eld PVd	CMA	Costs
PBAC 7.05 July 2021, Emplicit [53]	Australian healthcare payer	Australia/Bristol Myers Squibb	Adults with RRMM	2L+	ERd	Kd	CMA	Costs
PBAC 7.06 March 2022, Ninlaro [66]	Australian healthcare payer	Australia/Takeda	Adults with RRMM who have received at least 2 prior therapies	3L+	IRd	Rd Kd ERd	CUA and CEA	Costs, LYs, QALYs, ICER
PBAC 7.11 July 2020, Darzalex [26]	Australian healthcare payer	Australia/Janssen	Adults with 2L RRMM	2L	DVd	Vd	CUA	Costs, QALYs, ICER
SMC 2180 (2019) [45]	NHS Scotland	UK/Janssen	Adults with RRMM who have received at least 1 prior therapy	2L+	DRd or DVd	Kd Rd Vd	CUA	Costs, QALYs, ICER
SMC 2290 (2020) [46]	NHS Scotland	UK/Amgen	Adults with RRMM who had received 1 to 3 prior therapies	2L+	K monotherapy	Rd DVd	CUA	Costs, QALYs, ICER
SMC 2303 (2021) [47]	NHS Scotland	UK/Sanofi	Adults with RRMM who have received at least 2 prior therapies including lenalidomide and a PI and have demonstrated disease progression on the last therapy	2L+	IsaPd	Pd D monotherapy	CUA	Costs, QALYs, ICER

2L second line, 2L+ second line and later, 3L third line, 3L+ third line and later, 4L+ fourth line and later, 5L+ fifth line and later, belamaf belantamab-mafodotin, C cyclophosphamide, CAR-T chimeric antigen receptor T-cell, CEA cost-effectiveness analysis, cilta-cel ciltacabtagene autoleucel, CMA cost-minimization analysis, CUA cost-utility analysis, d dexamethasone, DPd daratumumab plus pomalidomide and dexamethasone, DRd daratumumab plus lenalidomide and dexamethasone, DVd daratumumab plus bortezomib and dexamethasone, Eld elotuzumab in combination with lenalidomide and dexamethasone, EPd elotuzumab plus pomalidomide and dexamethasone, ERd elotuzumab plus lenalidomide and dexamethasone, ICER incremental cost-effectiveness ratio, ide-cel idecabtagene vicleucel, IMiD immunomodulatory drug, IRd ixazomib plus lenalidomide and dexamethasone, IsaKd isatuximab plus carfilzomib and dexamethasone, IsaPd isatuximab plus pomalidomide plus dexamethasone, Kd carfilzomib + dexamethasone, KRd carfilzomib plus lenalidomide and dexamethasone, LY life-year, MM multiple myeloma, NHS National Health Service, NICE National Institute for Health and Care Excellence, P pomalidomide, PanVd panobinostat plus bortezomib and dexamethasone, PBAC Pharmaceutical Benefits Advisory Committee, Pd pomalidomide plus dexamethasone, PI proteasome inhibitor, PSS Personal Social Services, PVd pomalidomide plus bortezomib and dexamethasone, QALY quality-adjusted life-year, Rd lenalidomide and dexamethasone, RRMM relapsed/refractory multiple myeloma, SCT stem cell transplantation, SMC Scottish Medicines Consortium, TA technology appraisal, V bortezomib, VCd bortezomib plus cyclophosphamide and dexamethasone, Vd bortezomib and dexamethasone, VTd bortezomib plus thalidomide and dexamethasone, Xd selinexor plus dexamethasone, XVd selinexor plus bortezomib and dexamethasone

Table 4 Model conceptualization: peer-reviewed articles (19 articles)

Study (year)	Objective	Audience	Intended use	Cohort vs individual patient approach
Aceituno et al. (2018) [20]	To estimate the incremental cost-effectiveness ratio of lenalidomide in combination with dexamethasone versus bortezomib in combination with dexamethasone for the second-line treatment of patients with multiple myeloma who have received previous treatment with bortezomib, from the perspective of the Chilean National Health Service	NR	NR	Cohort
Borg et al. (2016 [54]	To evaluate the cost effectiveness of P as an add-on to best supportive care in patients with RRMM in Sweden	NR	NR	Individual
Cai et al. (2019) [27]	To evaluate the cost effectiveness of treatment plans involving different combinations of isatuximab, R, and V in Chinese patients with RRMM after the full assessment on national drug price negotiations, which provide the basis for RRMM clinical and medical insurance decision making	Chinese doctors and medical insurance decision makers	NR	Cohort
Campioni et al. (2020 [28]	To estimate the real-world cost effectiveness of K in combination with Rd compared with Rd for the treatment of RRMM after one to three prior therapies	NR	NR	Cohort
Carlson et al. (2018 [29]	To assess the comparative clinical and economic outcomes for drugs used to treat patients with RRMM in the second or third line of therapy from a US health system perspective	MM stakeholders	NR	Cohort
Dolph et al. (2021 [30]	To evaluate the cost effectiveness of XVd vs Vd in previously treated MM from a US commercial perspective	NR	NR	Cohort
Gueneau et al. (2018 [55]	To investigate the efficacy, safety, and cost of a Pd regimen in patients with RRMM	NR	NR	Cohort
Jakubowiak et al. (2016 [31]	To demonstrate the economic value of K from a US payer perspective by comparing KRd with Rd using the direct head-to-head comparative data from the ASPIRE trial	NR	NR	Cohort
Jakubowiak et al. (2017 [32]	To report the economic value of Kd56 from a US payer perspective	NR	NR	Cohort
Kapinos et al. (2023 [33]	To compare the expected costs per QALYs gained among a hypothetical cohort of patients with triple-class refractory MM who are treated with one of three treatments: (1) ide-cel, (2) cilta-cel, and (3) belamaf	NR	NR	To conduct a preliminary cost-effectiveness analysis comparing ide-cel and cilta-cel with a CAR-T comparator market basket as well as comparing belamaf with its own comparator market basket

Table 4 (continued)

Study (year)	Objective	Audience	Intended use	Cohort vs individual patient approach
Karampampa et al. (2023) [56]	To develop a cost-effectiveness analysis for ide-cel vs conventional care for the treatment of patients with TCE RRMM who have demonstrated disease progression on their last therapy. To assess the comparative economic and clinical value of ide-cel in a broader RRMM context	Healthcare providers and payers	NR	Cohort
Matsela et al. (2022) [21]	To conduct a cost-utility analysis of d compared with V-based and R-based regimens for the second-line treatment of MM from a South African public health perspective	NEMLC	To inform the decision-making process of NEMLC	Cohort
Nikolaou et al. (2021) [57]	To evaluate the cost effectiveness of belamaf from a US commercial payer's perspective, compared indirectly with Xd, for adults with RRMM who have received four or more prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb (alone or in combination)	NR	NR	Cohort
Patel et al. (2021 [34]	To evaluate if the use of once-weekly SVd for patients with RRMM is a cost-effective treatment strategy compared to the use of twice-weekly Vd under current pricing	NR	To demonstrate selinexor has the potential to lead to significant cumulative healthcare expenditure	Cohort
Pelligra et al. (2017 [68]	To assess the clinical and economic implications of treatment with Pd vs daratumumab and vs K in heavily pretreated patients with RRMM	NR	NR	Cohort
Wong et al. (2021 [35]	To evaluate the cost effectiveness of DRd relative to Rd for the treatment of patients with RRMM who have received at least one prior therapy	Policymakers	To inform funding decisions from the Singapore perspective	Cohort
Zeng et al. (2020 [36]	To re-evaluate the cost effectiveness of the addition of daratumumab to Vd on the basis of the latest updated analysis of data from the CASTOR study	NR	To re-evaluate the cost effectiveness of the addition of daratumumab to Vd on the basis of the latest updated analysis of data from CASTOR	Cohort
Zhang et al. (2018) [37]	To determine the cost effectiveness from a US healthcare payer perspective of the addition of daratumumab to traditional doublet regimens (DRd and DVd) compared with doublet regimens (Rd or Vd) alone for patients with RRMM who received at least prior therapy	Decision-makers	NR	Cohort

belamaf belantamab-mafodotin, *CAR-T* chimeric antigen receptor T-cell, *cilta-cel* ciltacabtagene autoleucel, *d* dexamethasone, *DRd* daratumumab plus lenalidomide and dexamethasone, *DVd* daratumumab plus bortezomib and dexamethasone, *ide-cel* idecabtagene vicleucel, *IMiD* immunomodulatory drug, *K* carfilzomib, *Kd56* carfilzomib 56 mg/m^2 and dexamethasone, *KRd* carfilzomib plus lenalidomide and dexamethasone, *mAb* monoclonal antibody, *MM* multiple myeloma, *NEMLC* National Essential Medicines List Committee, *NR* not reported, *P* pomalidomide, *Pd* pomalidomide plus dexamethasone, *PI* proteasome inhibitor, *QALY* quality-adjusted life-year, *R* lenalidomide, *Rd* lenalidomide and dexamethasone, *RRMM* relapsed/refractory multiple myeloma, *SVd* selinexor plus bortezomib and dexamethasone, *TCE* triple-class exposed, *V* bortezomib, *Vd* bortezomib and dexamethasone, *Xd* selinexor plus dexamethasone, *XVd* selinexor plus bortezomib and dexamethasone

Table 5 Model conceptualization: health technology assessment submissions (31 submissions)

Study	Objective	Audience	Intended use	Cohort vs individual patient approach
CADTH PC0164-000 (2019) [38]	To examine the cost effectiveness of ixazomib in combination with lenalidomide and dexamethasone for patients with MM who have received at least one prior therapy	pCODR Expert Review Committee	To support reimbursement decisions	Cohort
CADTH PC0165-000 (2019) [39]	To evaluate the cost and benefit related to pomalidomide in combination with dexamethasone and bortezomib for treatment of adult patients with RRMM who have received at least one prior treatment regimen including lenalidomide	pCODR Expert Review Committee	To support reimbursement decisions	Cohort
CADTH PC0220-000 (2021) [58]	To compare isatuximab in combination with pomalidomide + dexamethasone to pomalidomide + dexamethasone for patients with RRMM who have received two or more prior therapies, including lenalidomide and a proteasome inhibitor	pCODR Expert Review Committee	To support reimbursement decisions	Cohort
CADTH PC0256-000 (2022) [41]	To assess the cost and benefit of isatuximab in combination with pomalidomide and dexamethasone, for the treatment of patients with RRMM who have received 1 to 3 prior lines of therapy	pCODR Expert Review Committee	To support reimbursement decisions	Cohort
CADTH PC0276-000 (2022) [40]	To assess the cost effectiveness of XVd compared with Vd, PVd, KCd, Kd, CyBorD, DVd, DRd, Rd, KRd, and standard of care, which was assumed to comprise an equally weighted average of Vd, PVd, KCd, Kd, CyBorD, DVd, DRd, Rd, and KRd	pCODR Expert Review Committee	To support reimbursement decisions	Cohort
Institute of Clinical and Economic Review (ide-cel, cilta-cel, belamaf assessment) (2021) [67]	To assess the lifetime cost effectiveness of ide-cel, cilta-cel, and belamaf as compared to relevant comparator treatments	Decision makers and other interested stakeholders	To support reimbursement decisions	Cohort
NICE TA171 (2019) [42]	To demonstrate the cost effectiveness of lenalidomide plus dexamethasone over dexamethasone only for patients with RRMM whose disease has relapsed after treatment with bortezomib	TAC	To support reimbursement decisions	Individual
NICE TA573 (2019) [22]	To assess the cost effectiveness of daratumumab in combination with bortezomib as 2L treatment for RRMM in the UK	TAC	To support reimbursement decisions	Cohort
NICE TA586 (2019)[59]	To demonstrate the effectiveness and cost effectiveness of lenalidomide for the treatment of MM in people who have received at least one prior therapy with bortezomib	TAC	To support reimbursement decisions	Cohort
NICE TA657 (2020) [43]	To evaluate the cost and benefit of carfilzomib for previously treated MM	TAC	To support reimbursement decisions	Cohort

Table 5 (continued)

Study	Objective	Audience	Intended use	Cohort vs individual patient approach
NICE TA658 (2020) [60]	To evaluate the clinical and cost effectiveness of isatuximab, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with RRMM who have received at least 2 lines of prior therapies including lenalidomide and a proteasome inhibitor	TAC	To support reimbursement decisions	Cohort
NICE TA695 (2021) [44]	To evaluate the use of carfilzomib, in combination with lenalidomide and dexamethasone as 2L treatment only, in patients who received prior bortezomib in the first-line setting	TAC	To support reimbursement decisions	Cohort
NICE TA783 (2022) [61]	To evaluate the cost and benefits of daratumumab monotherapy as 4th line treatment for adult patients with MM who have received 3 lines of therapy in the UK	TAC	To support reimbursement decisions	Cohort
NICE TA870 (2023) [62]	To evaluate the cost and benefits and the request for reimbursement of ixazomib in combination with lenalidomide and dexamethasone for the treatment of adult patients with MM who have received 2 or 3 lines of therapy in England	TAC	To support reimbursement decisions	Cohort
PBAC 5.02 July 2021, Darzalex [23]	To assess daratumumab subcutaneous flat dosing regimen, in combination with bortezomib and dexamethasone, for the treatment of second-line MM	PBAC	To support reimbursement decisions	Cohort
PBAC 5.04 November 2020, Empliciti [63]	To assess elotuzumab in combination with lenalidomide and dexamethasone for the treatment of RRMM	PBAC	To support reimbursement decisions	Cohort
PBAC 5.07 July 2021, Xpovio [48] Resubmission: PBAC 7.07 November 2022, Xpovio [98] Resubmission: PBAC 7.10 March 2022, Xpovio [99]	To assess selinexor in combination with bortezomib and dexamethasone for the treatment of RRMM	PBAC	To support reimbursement decisions	Cohort
PBAC 5.07 November 2020, Ninlaro [49]	To assess ixazomib in combination with lenalidomide and dexamethasone for the treatment of RRMM	PBAC	To support reimbursement decisions	Cohort
PBAC 5.08 July 2021, Xpovio [64] Resubmission: PBAC 7.09 March 2022, Xpovio [100]	To assess the cost and benefit of selinexor in combination with dexamethasone for the treatment of adult patients with triple class refractory and penta-refractory MM	PBAC	To support reimbursement decisions	Cohort

Table 5 (continued)

Study	Objective	Audience	Intended use	Cohort vs individual patient approach
PBAC 5.09 July 2019, Aplidin [65] Resubmission: PBAC 7.06 March 2020, Aplidin [101]	To evaluate the cost and benefit of plitidepsin in treatment for patients with RRMM who have received at least three prior treatment regimens, including both a proteasome inhibitor and an immunomodulator, or failure of two prior treatments if contraindicated or intolerant to a proteasome inhibitor and an immunomodulator	PBAC	To support reimbursement decisions	Cohort
PBAC 6.08 July 2019, Pomalyst [24] Resubmission: PBAC 7.13 November 2019, Pomalyst [73]	To examine the costs of pomalidomide in combination with bortezomib and dexamethasone for the treatment of patients with RRMM who have undergone or are ineligible for a stem cell transplant, and who have received at least one prior treatment regimen including lenalidomide for at least two consecutive cycles	PBAC	To support reimbursement decisions	Cohort
PBAC 6.08 July 2020, Kyprolis [50]	To assess the addition of a 70-mg/m^2 once-weekly dosing regimen to the current 56-mg/m^2 twice-weekly dosing regimen for carfilzomib for use in combination with dexamethasone in patients with RRMM	PBAC	To support reimbursement decisions	Cohort
PBAC 7.01 November 2019, Darzalex [25]	To assess daratumumab in combination with bortezomib and dexamethasone in patients with RRMM who have received one prior therapy only (i.e., patients who have relapsed or are refractory following first-line treatment for newly diagnosed MM, and hereafter referred to as second-line treatment)	PBAC	To support reimbursement decisions	Cohort
PBAC 7.03 March 2019, Darzalex [51]	To assess daratumumab in combination with bortezomib and dexamethasone for patients with RRMM who had failed at least one prior therapy and as monotherapy for highly treatment-experienced patients or patients refractory after at least three prior lines including a proteasome inhibitor and an immunomodulatory or who are refractory to both	PBAC	To support reimbursement decisions	Cohort
PBAC 7.03 March 2022, Kyprolis [52]	To assess carfilzomib in combination with lenalidomide and dexamethasone for the treatment of RRMM	PBAC	To support reimbursement decisions	Cohort
PBAC 7.05 July 2021, Emplicit [53]	To assess the cost and benefit of elotuzumab in combination with lenalidomide and dexamethasone in treating RRMM	PBAC	To support reimbursement decisions	Cohort

Table 5 (continued)

Study	Objective	Audience	Intended use	Cohort vs individual patient approach
PBAC 7.06 March 2022, Ninlaro [66]	To assess the cost and benefit of ixazomib in combination with lenalidomide and dexamethasone for the treatment of RRMM after at least two prior therapies	PBAC	To support reimbursement decisions	Cohort
PBAC 7.11 July 2020, Darzalex [26]	To evaluate the costs and effectiveness of daratumumab plus bortezomib and dexamethasone as a second-line treatment for patients with MM	PBAC	To support reimbursement decisions	Cohort
SMC 2180 (2019) [45]	To assess daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with MM who have received at least one prior therapy	NDC	To support reimbursement decisions	Cohort
SMC 2290 (2020) [46]	To assess carfilzomib in combination with lenalidomide and dexamethasone for the treatment of adult patients with MM who have received at least one prior therapy	NDC	To support reimbursement decisions	Cohort
SMC 2303 (2021) [47]	To evaluate isatuximab in combination with pomalidomide and dexamethasone within a subgroup of the licensed indication (adult patients with RRMM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy	NDC	To support reimbursement decisions	Cohort

2L second line, *belamaf* belantamab-mafodotin, *CADTH* Canadian Agency for Drugs and Technologies in Health, *cilta-cel* ciltacabtagene autoleucel, *CyBorD* cyclophosphamide, bortezomib, and dexamethasone, *DRd* daratumumab plus lenalidomide and dexamethasone, *DVd* daratumumab plus bortezomib and dexamethasone, *ide-cel* idecabtagene vicleucel, *KCd* carfilzomib, cyclophosphamide, and dexamethasone, *Kd* carfilzomib and dexamethasone, *KRd* carfilzomib plus lenalidomide and dexamethasone, *MM* multiple myeloma, *NDC* New Drugs Committee, *NICE* National Institute for Health and Care Excellence, *PBAC* Pharmaceutical Benefits Advisory Committee, *pCODR* pan-Canadian Oncology Drug Review, *PVd* pomalidomide plus bortezomib and dexamethasone, *Rd* lenalidomide and dexamethasone, *RRMM* relapsed/refractory multiple myeloma, *SMC* Scottish Medicines Consortium, *TA* technology appraisal, *TAC* technology appraisal committee, *Vd* bortezomib and dexamethasone, *XVd* selinexor plus bortezomib and dexamethasone

on treatment and off treatment in the corresponding health state.

Thirty-seven of the 46 cohort-level models reported on specific health states: 22 employed a three-health-state model [21, 25, 27–29, 35–39, 43, 46–48, 52, 56, 58, 62, 64, 66–68], nine used four health states [20, 30, 32, 41, 44, 57, 60, 61, 65], and six used five health states [22, 31, 34, 40, 45, 59]. Progression free, progressive disease, and death were the most common health states. Where more than three health states were employed, progression free and/or progressive disease were usually split into sub-categories of patients who were on or off treatment.

One of the three individual-patient level models (i.e., a discrete event simulation) [54] modeled a patient's course through three health states including stable disease, progressive disease, and death, while the other discrete-event simulation model, based on patient characteristics and treatment, calculated time to progression and post-progression survival, which were then added to calculate OS [42]. The model choice in the latter model was justified as an appropriate approach to capture the clinical history and variation in efficacy between patients, and that this structure did not require a half-cycle correction. However, the Evidence Review Group (ERG) was not convinced with the justification for the extra complexity of a discrete event simulation model, especially when the model only examined one course of the drug and did not track patients through a sequence of treatments. Additionally, another critique was that a half-cycle correction could be easily implemented in other simpler structures such as Markov models, while the marginal benefit of incorporating precise event timing into discrete-time modeling would be negligible given the model's overarching uncertainties [42]. An MCMC microsimulation model [33] generated both duration on treatment and survival estimates at the patient level from trial data using the PFS and OS curves and simulated subjects across different health states including complete response, minimal response, no response, and progressive disease. The authors stated that the model structure was chosen to extend the preliminary analysis from the Institute for Clinical and Economic Review. In this model, the initial analysis compared idecabtagene vicleucel and ciltacabtagene autoleucel, with a basket of relevant comparator regimens. It also investigated costs and QALYs related to belantamab-mafodotin versus its own comparator market basket, without comparing the three treatments with each other directly. By using the MCMC approach, the analysis generated a hypothetical cohort of patients with RRMM who were treated with one of the three treatments of interest, which enabled direct comparisons across their costs and outcomes.

3.3.3 Cycle Length

Sixteen models each used a monthly (or 28-day) cycle length [20, 21, 28, 31–34, 37, 43, 44, 46, 51, 56, 59, 67, 68] or a 1-week cycle length [22, 29, 30, 35, 38, 40, 41, 45, 48, 57, 60–62, 64–66]. Two models used a cycle length of 3 weeks (21 days) [36, 39]. One of the two discrete-event simulation models mentioned that the concept of a model cycle length was not applicable as it was a continuous time model [42]. The remaining models did not provide this information.

Ten models explicitly consider a half-cycle correction (five from those with a monthly cycle [37, 44, 56, 59, 68], four with a weekly cycle [22, 29, 35, 62], and one with a 3-week cycle [36]). No other information related to this, including the methods used for a half-cycle correction, was reported by the other models.

3.3.4 Time Horizon

The time horizon used across the models varied. Almost half of the models (*n* = 22) specifically stated that a lifetime horizon was used in the model, with a range between 15 and 40 years [21, 22, 28–30, 33, 34, 36, 39, 41, 42, 44–47, 54, 56, 58–60, 62, 67]. Eight models used a time horizon of 20–30 years [20, 25, 31, 32, 38, 40, 51, 66], and ten used a time horizon of 15 years or less [26, 27, 35, 37, 48, 57, 61, 64, 65, 68].

Where used, the lifetime horizon was justified as suitable and sufficient to capture all potential long-term costs and benefits related to treatments and economic and clinical impacts of RRMM as this is an incurable disease that requires lifelong treatment. In three models, a time horizon at a certain duration was selected where almost all patients would have died (i.e., survival is around 1–2%), which was also deemed to be a lifetime horizon [42, 57, 62].

3.3.5 Clinical Inputs

In most instances, clinical inputs were not discussed in detail. Instead, only trial names and, if applicable, indirect treatment comparison (ITC) methods were mentioned. Most of the clinical efficacy data were provided by ITCs (*n* = 33), including network meta-analyses, matching-adjusted indirect comparisons, or simulated treatment comparisons [20–23, 27–31, 33, 38–46, 48, 50, 52, 53, 56, 57, 59, 61–65, 67, 68]; individual clinical trials provided clinical model inputs in 11 cases [23, 26, 32, 34–36, 54, 55, 58, 60, 66].

Health utilities were sourced directly from clinical trials (*n* = 12) [22, 25, 41, 44–48, 60, 62, 64, 68] or from the existing literature in the absence of utility data collected in the clinical trials (*n* = 12) [20, 21, 27, 29, 33–37, 40, 42, 59]. Eleven models used a mixed approach combining both clinical trial data and literature sources [28, 30–32,

39, 43, 54, 56, 57, 65, 67], while the remaining 14 models did not provide this information [23, 26, 38, 49–53, 55, 58, 61, 63, 66]. Cost inputs were generally from country-specific published sources such as public, academic, or non-governmental reference cost lists. Where reported, healthcare resource use (HCRU) inputs were obtained from the published literature or previous HTA submissions (n = 8) [22, 28, 30, 31, 57, 60, 67, 68], specific trials or observational studies (n=5) [20, 21, 28, 35, 60], expert elicitation (n = 4) [21, 31, 42, 60], or were based on the study authors' data and assumptions (n = 2) [34, 54].

Among the 41 models reporting the type of clinical efficacy data used, 39 models used both PFS and OS data [20–22, 25–37, 39–41, 43–48, 51, 54, 56–62, 64–68], while one model each reported using OS [55] or PFS data [38] only. Time to discontinuation was incorporated in 19 models [22, 25, 28, 31, 32, 39, 41, 44, 46–48, 51, 57, 60–62, 64–66]. Response status was used as a secondary clinical outcome in ten models, of which the objective response rate was used in nine of them [22, 30, 34–36, 40, 46, 60, 64], whereas various response outcomes were used in one model [33].

As OS and PFS data from clinical trials are not typically reported over a lifetime, these endpoints required long-term extrapolation when the time horizon of the economic model was longer than the trial follow-up period. Given that prolonging survival constitutes one of the primary objectives for treatments targeting patients with RRMM, precise estimations of survival advantages hold significant importance. Typically, the identified models determined their fitness of parametric distributions to the observed PFS and OS data from trials and the long-term extrapolations based on various factors, including goodness-of-fit statistics (such as Akaike or Bayesian information criterion), visual assessment of goodness of fit to the observed Kaplan–Meier data, and clinical plausibility of the long-term extrapolations [22, 28, 30, 32, 34, 35, 41, 43, 44, 46, 54, 56, 57, 60, 61, 68]. While it was stated in some models that no long-term data were available to assess the clinical plausibility of long-term extrapolations [34, 35, 60], for some models, decisions were validated with clinical experts [22, 32, 38, 41, 44, 47, 61] to assess the clinical plausibility or evaluate against different trials or real-world evidence [31, 43, 44, 61, 62, 64]. For example, real-world data from registry and observational data were used to derive the probability of survival beyond the trial follow-up [31, 44, 62, 64], or were leveraged to validate generalizability of the trial data [61]. Different trials with the same treatments were utilized to adjust the efficacy of the treatment (i.e., compared PFS and OS outcomes across trials using matching-adjusted indirect comparison methodology before fitting on the matched data) [43].

3.3.6 Subsequent Therapies

Considerations around subsequent therapies were specifically mentioned in 28 models [20, 22, 27, 28, 30–37, 39–42, 44, 45, 47, 56, 57, 59–62, 66–68]. However, limited information was available in terms of how this was incorporated in the models. Subsequent treatments were mostly modeled for patients entering the progressive disease state (n = 13) [22, 28, 32, 34–36, 44, 47, 56, 57, 60, 62, 67], while two models assumed subsequent therapies only for patients who discontinued their initial treatments irrespective of disease progression [30, 40]. Given the wide range of treatment regimens and combinations available for patients with RRMM [7, 10–12], the most common approach to considering subsequent treatment lines was to use a weighted basket of treatments (n = 15) [22, 30, 33, 34, 36, 37, 40–42, 57, 59, 60, 66–68], while three models reported the specific treatments modelled [39, 44, 47]. The remaining ten models mentioning subsequent treatments did not provide further clarity on how this information was captured [20, 27, 28, 31, 32, 35, 45, 56, 61, 62].

Approaches used to consider the efficacy of subsequent treatments were briefly mentioned in some HTA submissions, such as the two-stage methodology with re-censoring [62, 66] or the inverse probability of censoring weights methodology [22] to adjust OS data and to align the included subsequent therapies with routine clinical practice in the country of interest. Jakubowiak et al. stated that OS data from the ASPIRE trial was used to incorporate efficacy data from subsequent therapy implicitly, however, the authors did not report the method used [31]. Costs related to subsequent treatments were either applied per cycle (n = 11) [20, 22, 28, 30–32, 37, 44, 57, 59, 68] or as one-off cost (n = 5) [40, 41, 56, 60, 62]. The most common approach to considering costs related to subsequent treatment lines was to use a basket of treatments with a distribution of subsequent treatments according to market share and treatment patterns (n = 15) [22, 30, 33, 34, 36, 37, 40–42, 57, 59, 60, 66–68]. The relevant inputs such as doses, proportion of patients receiving these treatments, treatment duration, or market share/prescribing distribution were obtained from the same clinical trials that provided clinical inputs or observational studies in 18 models [22, 28, 30, 31, 34, 36, 37, 39–41, 44, 45, 47, 60–62, 66, 67] and clinical experts in four models [20, 32, 35, 57]; a combination of both sources was used in one model [56] and the manufacturer's unpublished data (i.e., subsequent treatment distributions derived from market share data) was used in another model [68].

3.3.7 Handling of HCRU Data

Of the 20 models that reported how HCRU data were incorporated, either in the main text or as supplementary

material, 14 described both related unit costs and frequencies [20–22, 28, 30, 31, 35, 42, 54, 56, 57, 60, 67, 68], five reported only cost data [27, 36, 37, 44, 62], and one included only frequency data [34]. The most common approach to incorporating HCRU data was the calculation of per-cycle costs for each health state using frequency data and unit costs for those resources that were incurred more than once during the time horizon, as reported in 16 models [21, 22, 27–30, 32, 34–37, 44, 60, 62, 67, 68]. Four models only reported the annual cost based on average frequency per year without specifying how this average cost was applied in the patient flow [31, 42, 54, 68]. A summary of the structure-specific items of models published in peer-reviewed journals and included in HTA submissions is reported in Tables 6 and 7, respectively.

3.4 Uncertainty

All but eight models [23, 24, 38, 42, 45, 50, 53, 55] reported conducting different sensitivity analyses, including deterministic sensitivity analyses (DSAs), probabilistic sensitivity analyses (PSAs) and scenario analyses. Among the 18 models published in peer-reviewed journals, 12 reported DSAs, PSAs, and scenario analyses [28–32, 34, 35, 37, 54, 56, 57, 68], and four reported DSAs and PSAs only [20, 27, 33, 36]. One model reported DSAs and scenario analyses [21], while the remaining model did not report any sensitivity analyses [55].

Among the 31 models published as part of the HTA submissions, nine reported all three types of sensitivity analyses [22, 41, 43, 44, 59–62, 67], and three models reported DSAs and scenario analyses [46, 47, 65]. Eleven models reported scenario analyses only [25, 26, 39, 40, 48, 49, 51, 52, 63, 64, 66]. One model reported a DSA [58]. The remaining seven models did not report any sensitivity analyses [23, 24, 38, 42, 45, 50, 53].

3.4.1 Structural Uncertainty (Scenario) Testing

The most common aspects tested in scenario analyses were parametric distributions modeling for OS, PFS, and time to discontinuation (n = 22) [22, 25, 26, 28, 29, 31, 32, 41, 44, 46–48, 57, 59–62, 64–68], followed by time horizons (n = 22) [22, 25, 26, 28, 29, 31, 32, 41, 42, 44, 46–48, 57, 60–62, 64–68], utility values (n = 17) [22, 28–32, 34, 35, 41, 44, 46, 48, 56, 57, 60, 65, 68], annual discount rates for cost and benefits (n = 11) [22, 28, 30–32, 41, 44, 57, 60, 66, 68], treatment prices [e.g., discount applied to treatment prices] (n = 9) [22, 32, 37, 44, 59, 60, 62, 66, 68], treatment duration and discontinuation (n = 8) [44, 46, 49, 52, 54, 60, 63, 64], wastage assumptions (n = 8) [22, 31, 32, 41, 44, 60, 65, 68], assumptions related to subsequent treatments (n = 6) [22, 44, 47, 60–62], cost categories included (n = 6) [28, 30, 31, 44, 57, 67], dose-intensity assumptions (n = 6) [22, 31, 32, 48, 49, 63], assumptions related to lines of treatment (n = 6) [29–32, 34, 59], and different perspectives (n = 2) [54, 67].

The most frequently included parameters in DSAs were costs including of treatment and administration, health state utility and utility decrements, efficacy variables such as hazard ratios and curve fit, treatment durations, adverse event rates, HCRU frequency, and discount rates. Among those parameters, the most influential were efficacy, costs, and utility inputs.

In those models in which justifications were provided on the range used in the DSA, the majority was based on 95% confidence intervals identified in the literature or trial data when available [20, 22, 28–32, 34, 37, 43, 56, 60]. In the absence of data on confidence intervals, the variation ranged from ±10% [28, 30, 56] to 20% [20, 22, 27, 31, 32, 35–37, 61], 25% [60], or 50% [21, 34] of the mean.

Regarding PSAs, most models (n = 14) generated 1000 simulations [20, 22, 27, 30–33, 36, 37, 40, 41, 56, 57, 68]. Probability sensitivity analysis outputs were evaluated by averaging outcomes from multiple simulations for a higher number of iterations such as 4000 [29], 5000 [28, 62, 67], 10,000 [34, 44, 61], and 15,000 [35]. Because of the high number of parameters considered in the PSA, this information was rarely reported in detail across the models.

One of the discrete-event simulation models included a stochastic sensitivity analysis of the base case with regard to age and time spent in each health state [54]. This sensitivity analysis was similar to a PSA, although it only varied a few parameters (e.g., the mean time in stable and progressive disease in each treatment arm and by age), while all other model parameters were held constant. A summary of the methods used to address uncertainty for models published in peer-reviewed journals and included in HTA submissions is reported in Tables 8 and 9, respectively.

3.5 Model Validation

Five types of validation methods were identified across the models, including face validity, internal validity, external validity, cross validity, and predictive validity. Nineteen models reported at least one type of validation [20, 22, 28–32, 35–37, 43, 44, 54, 56, 57, 60, 62, 67, 68]. There were considerable differences in the reporting of validation between models published in peer-reviewed journals and those included in HTA submissions. Thirteen of the 18 models published in journals [20, 28–32, 35–37, 54, 56, 57, 68] provided this information, compared with six of 31 HTA submissions (including five NICE submissions and one Institute for Clinical and Economic Review submission) [22, 43, 44, 60, 62, 67].

Table 6 Model structure: peer-reviewed articles (19 articles)

Study (year)	Model structure	Health states	Structure justification	Time horizon	Cycle length	Source of clinical inputs	Source of utility and disutility values	Source of HCRU inputs
Aceituno et al. (2018) [20]	Markov model	1. Progression free (on treatment) 2. Progression free (off treatment) 3. Progressive disease 4. Death	Markov structure was argued to be appropriate when disease conceptualization necessitated a long-term perspective and entails transitions between distinct health states	25 years	4 weeks	Clinical trials and retrospective study	Literature	Clinical trials
Borg et al. (2016) [54]	Simple discrete event simulation model	3 events 1. Stable disease 2. Progressive disease 3. Death	NR	Lifetime	NR	Clinical trials	Clinical trials, literature	Literature
Cai et al. (2019) [27]	Markov model	1. Progression free 2. Progressive disease 3. Death	NR	10 years	NR	NMA	Literature	RWE
Campioni et al. (2020) [28]	PSM	1. Progression free 2. Progressive disease 3. Death	NR	Lifetime (40 years)	4 weeks	Clinical trials and real-world data	Clinical trials, literature	Literature
Carlson et al. (2018) [29]	PSM	1. Progression free 2. Progressive disease 3. Death	NR	Lifetime	1 week	NMA	Literature	NR
Dolph et al. (2021) [30]	PSM	1. Progression free (on treatment) 2. Progression free (off treatment) 3. Progressive disease 4. Death	NR	Lifetime (40 years)	1 week	Clinical trials, NMA	Clinical trials, literature	Literature
Gueneau et al. (2018) [55]	NR	NR	NR	NR	NR	Clinical trials	NR	NR

Table 6 (continued)

Study (year)	Model structure	Health states	Structure justification	Time horizon	Cycle length	Source of clinical inputs	Source of utility and disutility values	Source of HCRU inputs
Jakubowiak et al. (2016) [31]	PSM	1. Progression free (on treatment) 2. Progression free (off treatment) 3. Progressive disease 4. Subsequent lines 5. Best supportive care 6. Death	NR	30 years	4 weeks	Clinical trials and real-world data	Clinical trials, literature	Literature
Jakubowiak et al. (2017) [32]	PSM	1. Progression free (on treatment) 2. Progression free (off treatment) 3. Progressive disease 4. Death	NR	30 years	4 weeks	Clinical trials	Clinical trials, literature	NR
Kapinos et al. (2023) [33]	Monte Carlo Markov Chain	For CAR-T: 1. Complete response 2. Minimal response 3. No response 4. Progressive disease For belamaf: 1. Complete response 2. Minimal response 3. Progressive disease Within each state, patients could either die or survive	NR	Lifetime	Monthly	Clinical trials[a]	Literature	NR
Karampampa et al. (2023) [56]	PSM	1. Progression free 2. Progressive disease 3. Death	In line with previous economic evaluations and health technology assessments of treatments for RRMM	Lifetime (15 years)	Monthly	Clinical trials and real-world data	Clinical trials, literature	Clinical expert opinion

Table 6 (continued)

Study (year)	Model structure	Health states	Structure justification	Time horizon	Cycle length	Source of clinical inputs	Source of utility and disutility values	Source of HCRU inputs
Matsela et al. (2022) [21]	Markov model	1. Progression free 2. Progressive disease 3. Death	NR	Lifetime (15 years)	4 weeks	Clinical trials, NMA	Literature	Literature
Nikolaou et al. (2021) [57]	PSM	1. Progression free (on treatment) 2. Progression free (off treatment) 3. Progressive disease 4. Death	NR	10 years	1 week	Clinical trials, MAIC	Clinical trials, literature	Clinical expert opinion
Patel et al. (2021) [34]	Markov model (treatment sequencing)	1. Second-line treatment (either SVd or Vd) 2. Third-line treatment 3. Fourth-line treatment 4. Best supportive care 5. Death	NR	Lifetime	Monthly	Clinical trials	Literature	Literature
Pelligra et al. (2017) [68]	NR	1. Progression free 2. Progressive disease 3. Death	NR	3 years	4 weeks	Clinical trials and MAIC	Clinical trial and mixed-effect model	Literature
Wong et al. (2021) [35]	PSM	1. Progression free 2. Progressive disease 3. Death	NR	10 years	1 week	Clinical trials	Literature	Clinical trials, literature
Zeng et al. (2020) [36]	Markov model	1. Stable disease 2. Progressive disease 3. Death	NR	Lifetime	3 weeks	Clinical trials	Literature	NR
Zhang et al. (2018) [37]	Semi-Markov model	1. Progression free 2. Progressive disease 3. Death	NR	10 years	4 weeks	Clinical trials[a]	Literature	NR

belamaf belantamab-mafodotin, *CAR-T* chimeric antigen receptor T-cell, *HCRU* healthcare resource use, *MAIC* matching-adjusted indirect comparison, *NMA* network meta-analysis, *NR* not reported, *PSM* partitioned survival model, *RRMM* relapsed/refractory multiple myeloma, *RWE* real-world evidence, *SVd* selinexor plus bortezomib and dexamethasone, *Vd* bortezomib and dexamethasone

[a]Models that provided more than one clinical trial as sources for clinical inputs but did not provide any further information regarding how these sources were incorporated in the calculations

Table 7 Model structure: health technology assessment submissions (31 submissions)

Study (year)	Model structure	Health states	Structure justification	Time horizon	Cycle length	Source of clinical inputs	Source of utility and disutility values	Source of HCRU inputs
CADTH PC0164-000 (2019) [38]	PSM	1. Progression free 2. Progressive disease 3. Death	NR	25 years	1 week	Clinical trials, NMA	NR	NR
CADTH PC0165-000 (2019) [39]	PSM	1. Progression free 2. Progressive disease 3. Death	NR	Lifetime (25 years)	3 weeks	Clinical trials, NMA, MAIC	Clinical trials, literature	NR
CADTH PC0220-000 (2021) [58]	PSM	1. Progression free 2. Progressive disease 3. Death	NR	Lifetime (20 years)	NR	Clinical trials	NR	NR
CADTH PC0256-000 (2022) [41]	PSM	1. Progression free (on treatment) 2. Progression free (off treatment) 3. Progressive disease 4. Death	NR	Lifetime (37 years)	1 week	Clinical trials, NMA, MAIC	Clinical trials	Clinical expert opinion
CADTH PC0276-000 (2022) [40]	PSM	1. Progression free (on treatment) 2. Progression free (off treatment) 3. Progressive disease (on treatment) 4. Progressive disease (off treatment) 5. Death	NR	20 years	1 week	Clinical trials, NMA	Literature	Clinical expert opinion, literature

Table 7 (continued)

Study (year)	Model structure	Health states	Structure justification	Time horizon	Cycle length	Source of clinical inputs	Source of utility and disutility values	Source of HCRU inputs
Institute for Clinical and Economic Review (ide-cel, cilta-cel, belamaf assessment) (2021) [67]	Decision-node and PSM	1. Decision node: continue with treatment after leukapheresis 2. Discontinue treatment (before infusion but after leukapheresis) because of disease progression, adverse events, or manufacturing failures 3. Death before receiving the infusion. PSM: 1. Progression free 2. Not responding to treatment 3. Death	The initial decision node better fits the purpose of the model, which is to reflect costs and outcomes following the initiation of the CAR-T therapy process	Lifetime	Monthly	Clinical trials, meta-analysis	Clinical trials, literature	Literature
NICE TA171 (2019) [42]	Discreet-event simulation model	NR	NR	Lifetime (30 years)	Not applicable (continuous time model)	Clinical trials, meta-analysis	Literature	NHS Reference Cost sheet, data on file, HES data
NICE TA573 (2019) [22]	PSM	1. Progression free (on treatment) 2. Progression free (off treatment) 3. Progressive disease (on treatment) 4. Progressive disease (off treatment) 5. Death	Best use of available data, minimum amount of assumptions and captures the novel mechanism of action of daratumumab	Lifetime (30 years)	1 week	Clinical trials, NMA	Clinical trials	NHS Reference Cost sheet, literature

Table 7 (continued)

Study (year)	Model structure	Health states	Structure justification	Time horizon	Cycle length	Source of clinical inputs	Source of utility and disutility values	Source of HCRU inputs
NICE TA586 (2019) [59]	Markov model	1. Progression free (on treatment) 2. Progression free (off treatment) 3. Progressive disease (on treatment) 4. Progressive disease (off treatment) 5. Death	NR	Lifetime (25 years)	4 weeks	Clinical trials, literature, meta-analysis	Literature	NR
NICE TA657 (2020) [43]	PSM	1. Progression free 2. Progressive disease 3. Death	NR	NR	4 weeks	Clinical trials, MAIC	Clinical trials, literature	NR
NICE TA658 (2020) [60]	PSM	1. Progression free (on treatment) 2. Progression free (off treatment) 3. Progressive disease 4. Death	The main advantage of the PSM approach vs the Markov approach is that it provides a much closer fit to the actual PFS and OS data (that is, Kaplan–Meier curves) as observed in the clinical trials	Lifetime (15 years)	1 week	Clinical trials	Clinical trials	NHS Reference cost sheet, clinical expert opinion, literature

Table 7 (continued)

Study (year)	Model structure	Health states	Structure justification	Time horizon	Cycle length	Source of clinical inputs	Source of utility and disutility values	Source of HCRU inputs
NICE TA695 (2021) [44]	PSM	1. Progression free (on treatment) 2. Progression free (off treatment) 3. Progressive disease 4. Death	Best use of available data, minimal assumptions, captures key clinical outcomes measured in the ASPIRE study and those of most relevance to patients and clinicians and is consistent with the majority of previous appraisals in RRMM allowing comparison of outcomes	Lifetime (40 years)	4 weeks	Clinical trials, registry data, MAIC	Clinical trials	NHS Reference Cost sheet and data on file
NICE TA783 (2022) [61]	PSM	1. Progression free (on treatment) 2. Progression free (off treatment) 3. Progressive disease 4. Death	NR	15 years	1 week	Clinical trials, registry data, MAIC	NR	NR

Table 7 (continued)

Study (year)	Model structure	Health states	Structure justification	Time horizon	Cycle length	Source of clinical inputs	Source of utility and disutility values	Source of HCRU inputs
NICE TA870 (2023) [62]	PSM	1. Progression free 2. Progressive disease 3. Death	A PSM considers estimates for each clinical endpoint separately and, as such, maintains consistency between the endpoints used in the CEA and the published clinical data. This approach also enables external data sources to be incorporated into the model for each of the clinical endpoints	Lifetime (25 years)	1 week	Clinical trials, real-world data	Clinical trials	NHS Reference Cost sheet
PBAC 5.02 July 2021, Darzalex [23]	NR	NR	NR	NR	NR	Clinical trials	NR	NR
PBAC 5.04 November 2020, Empliciti [63]	NR	NR	NR	NR	NR	Clinical trials, ITC	NR	NR
PBAC 5.07 July 2021, Xpovio [48] Resubmission: PBAC 7.07 November 2022, Xpovio [98] Resubmission: PBAC 7.10 March 2022, Xpovio [99]	PSM	1. Progression free 2. Progressive disease 3. Death	NR	15 years	1 week	Clinical trials, ITC	Clinical trials	NR
PBAC 5.07 November 2020, Ninlaro [49]	NR	NR	NR	NR	NR	Clinical trials, naïve ITC	NR	NR

Table 7 (continued)

Study (year)	Model structure	Health states	Structure justification	Time horizon	Cycle length	Source of clinical inputs	Source of utility and disutility values	Source of HCRU inputs
PBAC 5.08 July 2021, Xpovio [64] Resubmission: PBAC 7.09 March 2022, Xpovio [100]	PSM	1. Progression free 2. Progressive disease 3. Death	PSMs rely on the within-trial relationship between non-mutually exclusive survival curves to determine health state membership	7 years	1 week	Clinical trials, non-matched ITC	Clinical trials	NR
PBAC 5.09 July 2019, Aplidin [65] Resubmission: PBAC 7.06 March 2020, Aplidin [101]	Semi-Markov model	1. Progression free (on treatment) 2. Progression free (off treatment) 3. Progressive disease 4. Death	NR	7 years	1 week	Clinical trials, ITC (standard Bucher method)	Clinical trials, literature	NR
PBAC 6.08 July 2019, Pomalyst [24] Resubmission: PBAC 7.13 November 2019, Pomalyst [73]	NR	NR	NR	NR	NR	Clinical trials[a]	NR	NR
PBAC 6.08 July 2020, Kyprolis [50]	NR	NR	NR	NR	NR	Clinical trials, naïve ITC	NR	NR
PBAC 7.01 November 2019, Darzalex [25]	PSM	1. Progression free 2. Progressive disease 3. Death	NR	20 years	NR	Clinical trials[a]	Clinical trials	NR
PBAC 7.03 March 2019, Darzalex [51]	NR	NR	NR	20 years	Monthly	Clinical trials[a]	NR	NR
PBAC 7.03 March 2022, Kyprolis [52]	PSM	1. Progression free 2. Progressive disease 3. Death	NR	NR	NR	Clinical trials, naïve ITC	NR	NR
PBAC 7.05 July 2021, Emplicit [53]	NR	NR	NR	NR	NR	Clinical trials, ITC	NR	NR

Table 7 (continued)

Study (year)	Model structure	Health states	Structure justification	Time horizon	Cycle length	Source of clinical inputs	Source of utility and disutility values	Source of HCRU inputs
PBAC 7.06 March 2022, Ninlaro [66]	PSM	1. Progression free 2. Progressive disease 3. Death	NR	20 years	1 week	Clinical trials	NR	NR
PBAC 7.11 July 2020, Darzalex [26]	NR	NR	NR	15 years	NR	Clinical trials	NR	NR
SMC 2180 (2019) [45]	PSM	1. Progression free (on treatment) 2. Progression free (off treatment) 3. Progressive disease (on treatment) 4. Progressive disease (off treatment) 5. Death	NR	Lifetime (30 years)	1 week	Clinical trials, multivariate regression analysis	Clinical trials	Clinical expert opinion, prior NICE submission
SMC 2290 (2020) [46]	PSM	1. Progression free 2. Progressive disease 3. Death	NR	Lifetime (40 years)	4 weeks	Clinical trials, MAIC, meta-regression analysis	Clinical trials	Literature
SMC 2303 (2021) [47]	PSM	1. Progression free 2. Progressive disease 3. Death	NR	Lifetime (20 years)	NR	Clinical trials, MAIC	Clinical trials	NR

belamaf belantamab-mafodotin, *CADTH* Canadian Agency for Drugs and Technologies in Health, *CAR-T* chimeric antigen receptor T-cell, *CEA* cost-effectiveness analysis, *cilta-cel* ciltacabtagene autoleucel, *HCRU* healthcare resource use, *HES* Hospital Episode Statistics, *ide-cel* idecabtagene vicleucel, *ITC* indirect treatment comparison, *MAIC* matching-adjusted indirect comparison, *NHS* National Health Service, *NICE* National Institute for Health and Care Excellence, *NMA* network meta-analysis, *NR* not reported, *OS* overall survival, *PBAC* Pharmaceutical Benefits Advisory Committee, *PFS* progression-free survival, *PSM* partitioned survival model, *RRMM* relapsed/refractory multiple myeloma, *SMC* Scottish Medicines Consortium, *TA* technology appraisal

[a] Models that provided more than one clinical trial as sources for clinical inputs but did not provide any further information regarding how these sources were incorporated in the calculations

Table 8 Model uncertainty and validation: peer-reviewed articles (19 articles)

Study (year)	Sensitivity analyses reported	Face validity	Verification of internal validity	Cross validity	External validity	Predictive validity
Aceituno et al. (2018) [20]	PSA, DSA	NR	NR	NR	All model inputs validated by two hematologists with extensive experience in the treatment of multiple myeloma in Chile	NR
Borg et al. (2016) [54]	PSA, DSA, scenarios	NR	NR	NR	Validated through the submission and the reimbursement application for pomalidomide in Sweden	NR
Cai et al. (2019) [27]	PSA, DSA	NR	NR	NR	NR	NR
Campioni et al. (2020) [28]	PSA, DSA, scenarios	NR	NR	NR	In a recent retrospective analysis of long-term PFS and OS data of Rd patients in the RMG registry, the median PFS and OS values are very closely in line with the predictions of our model	NR
Carlson et al. (2018) [29]	PSA, DSA, scenarios	For curve fitting and drug cost estimates (compared against an analysis performed by Potluri et al. 2015)	NR	NR	NR	NR
Dolph et al. (2021) [30]	PSA, DSA, scenarios	Clinical and health economic expert guidance throughout the development of the model	Quality-control validation using a cost-effectiveness model verification checklist	Cross-validation performed via an assessment of observed PFS and OS outcomes, against which model outputs were compared	Systematic examination of calculations and VBA coding accuracy by external reviewers; results and model approaches compared with previously published relevant economic analyses; validation of external data sources	NR
Gueneau et al. (2018) [55]	NR	NR	NR	NR	NR	NR

Table 8 (continued)

Study (year)	Sensitivity analyses reported	Face validity	Verification of internal validity	Cross validity	External validity	Predictive validity
Jakubowiak et al. (2016) [31]	PSA, DSA, scenarios	NR	NR	NR	Comparing the estimated total survival for Rd based on the K-GEM to that estimated in a life-time CE model from the UK NHS perspective	NR
Jakubowiak et al. (2017) [32]	PSA, DSA, scenarios	NR	Using data from a well-conducted phase III randomized trial that showed superiority of Kd56 over Vd in PFS and OS and the estimation of long-term survival for the Vd arm from matched registry patients	NR	Using SEER registry data to validate results	NR
Kapinos et al. (2023) [33]	PSA, DSA	NR	NR	NR	NR	NR
Karampampa et al. (2023) [56]	PSA, DSA, scenarios	NR	NR	NR	Validated for long-term estimates of OS and PFS with standard parametric models by clinical experts	NR
Matsela et al. (2022) [21]	DSA, scenarios	NR	NR	NR	NR	NR
Nikolaou et al. (2021) [57]	PSA, DSA, scenarios	Conceptual validity through critical literature review and validated by two key opinion leaders	The model was validated according to the AdViSHE checklist by an independent modeling expert	NR	NR	NR
Patel et al. (2021) [34]	PSA, DSA, scenarios	NR	NR	NR	NR	NR
Pelligra et al. (2017) [68]	PSA, DSA, scenarios	The results of the model were compared with what was expected for each input	Model validation and verification was undertaken using the AdViSHE checklist. The conceptual model was reviewed by health economists and clinicians at Celgene	NR	Validation of the results by comparing the health outcomes for Pd to a recent CE study published in a similar population and comparing the cost results to a study of patients with RRMM in the USA	NR

Table 8 (continued)

Study (year)	Sensitivity analyses reported	Face validity	Verification of internal validity	Cross validity	External validity	Predictive validity
Wong et al. (2021) [35]	PSA, DSA, scenarios	NR	NR	NR	NR	Validity of the chosen distributions by comparing the extrapolated outcomes with the updated survival analysis based on the latest follow-up data and comparing the extrapolated hazard estimates with the observed hazard estimates based on the Kaplan–Meier curves
Zeng et al. (2020) [36]	PSA, DSA	The Weibull survival model that was selected matched the PFS curves of the trial satisfactorily. In this evaluation, the uncertainty of PFS estimation was verified adequately by the sensitivity analyses	NR	NR	NR	NR
Zhang et al. (2018) [37]	PSA, DSA, scenarios	NR	NR	NR	NR	The estimated rate of PFS at 1 or 2 years according to the model were compared to the clinical results of the RCTs

AdViSHE Assessment of the Validation Status of Health-Economic Decision Models, *CE* cost-effectiveness, *DSA* determinied sensitivity analysis, *K-GEM* Kyprolis Global Economic Model, *NHS* National Health Service, *NR* not reported, *OS* overall survival, *Pd* pomalidomide plus dexamethasone, *PFS* progression-free survival, *PSA* probabilistic sensitivity analysis, *RCT* randomized controlled trial, *Rd* lenalidomide and dexamethasone, *RMG* Registry of Monoclonal Gammopathies, *SEER* Surveillance, Epidemiology, and End Result, *VBA* Visual Basic for Applications, *Vd* bortezomib and dexamethasone

One type of validation was reported for ten models [20, 28, 29, 31, 35–37, 43, 54, 56], five models reported using two types [22, 32, 57, 60, 62], and three models were validated with three methods [44, 67, 68]. One model reported four validation types [30], and zero reported using all five methods.

The most common validation method used was external validity (*n* = 14) [20, 22, 28, 30–32, 43, 44, 54, 56, 60, 62, 67, 68], followed by verification of internal validity (*n* = 8) [22, 30, 32, 44, 57, 60, 67, 68], face validity (*n* = 8) [29, 30, 36, 44, 57, 62, 67, 68], predictive validity (*n* = 2) [35, 37], and cross validity (*n* = 1) [30]. Of the eight models with internal validation, three specifically mentioned that validation had been performed by an independent group of experts [57, 60, 67]. A summary of the validation methods used for models published in peer-reviewed journals and included in HTA submissions is reported in Tables 8 and 9, respectively.

3.6 Transparency

Among the 49 models, three did not report the sponsor or funding source [28, 33, 55] and four reported not receiving any funding [21, 35–37]. Most of the models were industry sponsored (*n* = 38), which was mainly driven by the high number of HTA submissions included [20, 22–26, 30–32, 38–54, 56–66, 68]. Four models received grants or funding from governments, non-government or not-for-profit organizations, or academic institutions [27, 29, 34, 67].

All 18 peer-reviewed publications provided a plain language non-technical summary within the main text [20, 21, 27–37, 54–57, 68], while a detailed technical documentation was available for six models [30–32, 56, 57, 68]. One model published in a peer-reviewed journal was available for review upon request [33].

Among the 31 HTA submissions, five CADTH submissions and the Institute for Clinical and Economic Review submission provided a dedicated non-technical summary of the model [38–41, 58, 67]. The NICE company submissions generally focus on a detailed technical documentation; therefore, non-technical summaries are likely available from companion documentation produced by NICE (e.g., committee slides or summaries). All NICE and PBAC submissions included a detailed technical documentation of the model, although commercially sensitive information was redacted in publicly available submission documents [22–26, 42–44, 48–53, 59–66]. Limited information on the model was available for the SMC submissions [45–47]. Models were not available for review from any of the HTA submissions.

Microsoft Excel® (Redmond, WA, USA) was the most common software used to implement the models (*n* = 11) [30, 31, 35, 39, 41, 44, 57, 60, 62, 64, 68]. Five models used

TreeAge (Williamstown, MA, USA) [21, 27, 34, 36, 37], three models used R [34, 36, 37]. The remaining studies did not state the software used to implement the models. A summary of the transparency elements for models published in peer-reviewed journals and included in HTA submissions is provided in Tables 10 and 11, respectively.

3.7 Models in Heavily Pre-Treated Patients with RRMM

Heavily pre-treated patients who are refractory to different treatment classes have limited treatment options and thus a high disease burden. The introduction of novel treatments to address these unmet needs is also associated with unique modeling challenges to demonstrate the cost effectiveness of new therapies. This may include higher heterogeneity in patient populations across trials included in the ITC because of differences in prior treatments; the need to consider the whole treatment sequence rather than modeling the current treatment line only because prior treatment may impact the choice of subsequent treatment; and insufficient data for robust extrapolations owing to data from fewer patients being available in later treatment lines. For these reasons, we separately present information from models for this population.

Five of the 49 models included in this review were specifically in patients who were refractory to at least one treatment class: lenalidomide refractory [39], triple-class refractory [33], triple-class exposed [56], triple-refractory or penta-refractory [64], and triple-/quad-/penta-refractory [67].

All models involved cost-utility analyses reporting ICERs per QALY, with three models also including a cost-effectiveness analysis component of ICER per life-year gained [56, 64, 67]. Four models used a healthcare payer perspective [33, 39, 64, 67] and one a societal perspective, accounting for absenteeism from work or school and productivity losses [56]. All but one model were cohort level, covering three PSMs with three health states [39, 56, 64], and a model with three health states combining both decision node and PSM aspects [67, 81]. Last, the individual-patient level model also included three health states [33].

Four models used a lifetime horizon [33, 39, 56, 67], while one model used a 7-year horizon driven by prior PBAC decisions for a shorter time horizon in later-line or last-line treatment settings and the associated shorter median OS [64]. Three models considered a 4-week cycle length [33, 56, 67], and one model each had a 3-week [39] and 1-week [64] cycle length. Clinical data and utilities were generally sourced from clinical trials or previously published literature.

Table 9 Model uncertainty and validation: health technology assessment submissions (31 submissions)

Study	Sensitivity analyses reported	Face validity	Verification of internal validity	Cross-validity	External validity	Predictive validity
CADTH PC0164-000 (2019) [38]	NR	NR	NR	NR	NR	NR
CADTH PC0165-000 (2019) [39]	Scenarios	NR	NR	NR	NR	NR
CADTH PC0220-000 (2021) [58]	DSA	NR	NR	NR	NR	NR
CADTH PC0256-000 (2022) [41]	DSA, PSA, scenarios	NR	NR	NR	NR	NR
CADTH PC0276-000 (2022) [40]	Scenarios	NR	NR	NR	NR	NR
Institute for Clinical and Economic Review (ide-cel, cilta-cel, belamaf assessment) (2021) [67]	DSA, PSA, scenarios	Model input parameters were varied to evaluate face validity of changes in results	Validation of the model by independent modelers	NR	Literature review findings	NR
NICE TA171 (2019) [42]	NR	NR	NR	NR	NR	NR
NICE TA573 (2019) [22]	DSA, PSA, scenarios	NR	Validation of the model structure, calculations, and inputs	NR	Multiple advisory boards	NR
NICE TA586 (2019) [59]	DSA, PSA, scenarios	NR	NR	NR	NR	NR
NICE TA657 (2020) [43]	DSA, PSA, scenarios	NR	NR	NR	Feedback from clinical experts	NR
NICE TA658 (2020) [60]	DSA, PSA, scenarios	NR	Validation by an independent group	NR	Feedback from clinical and economic modeling experts	NR
NICE TA695 (2021) [44]	DSA, PSA, scenarios	Validation against trial and literature data	Internal validation	NR	Advisory board	NR
NICE TA783 (2022) [61]	DSA, PSA, scenarios	NR	NR	NR	NR	NR
NICE TA870 (2023) [62]	DSA, PSA, scenarios	Validation against trial and RWE data	NR	NR	Advisory board	NR
PBAC 5.02 July 2021, Darzalex [23]	NR	NR	NR	NR	NR	NR
PBAC 5.04 November 2020, Empliciti [63]	Scenarios	NR	NR	NR	NR	NR
PBAC 5.07 July 2021, Xpovio [48] Resubmission: PBAC 7.07 November 2022, Xpovio [98] Resubmission: PBAC 7.10 March 2022, Xpovio [99]	Scenarios	NR	NR	NR	NR	NR
PBAC 5.07 November 2020, Ninlaro [49]	Scenarios	NR	NR	NR	NR	NR
PBAC 5.08 July 2021, Xpovio [64] Resubmission: PBAC 7.09 March 2022, Xpovio [100]	Scenarios	NR	NR	NR	NR	NR

Table 9 (continued)

Study	Sensitivity analyses reported	Face validity	Verification of internal validity	Cross-validity	External validity	Predictive validity
PBAC 5.09 July 2019, Aplidin [65] Resubmission: PBAC 7.06 March 2020, Aplidin [101]	DSA, scenarios	NR	NR	NR	NR	NR
PBAC 6.08 July 2019, Pomalyst [24] Resubmission: PBAC 7.13 November 2019, Pomalyst [73]	NR	NR	NR	NR	NR	NR
PBAC 6.08 July 2020, Kyprolis [50]	NR	NR	NR	NR	NR	NR
PBAC 7.01 November 2019, Darzalex [25]	Scenarios	NR	NR	NR	NR	NR
PBAC 7.03 March 2019, Darzalex [51]	Scenarios	NR	NR	NR	NR	NR
PBAC 7.03 March 2022, Kyprolis [52]	Scenarios	NR	NR	NR	NR	NR
PBAC 7.05 July 2021, Emplicit [53]	NR	NR	NR	NR	NR	NR
PBAC 7.06 March 2022, Ninlaro [66]	Scenarios	NR	NR	NR	NR	NR
PBAC 7.11 July 2020, Darzalex [26]	Scenarios	NR	NR	NR	NR	NR
SMC 2180 (2019) [45]	NR	NR	NR	NR	NR	NR
SMC 2290 (2020) [46]	DSA, scenarios	NR	NR	NR	NR	NR
SMC 2303 (2021) [47]	DSA, scenarios	NR	NR	NR	NR	NR

belamaf belantamab-mafodotin, *CADTH* Canadian Agency for Drugs and Technologies in Health, *cilta-cel* ciltacabtagene autoleucel, *DSA* deterministic sensitivity analysis, *ide-cel* idecabtagene vicleucel, *NICE* National Institute for Health and Care Excellence, *NR* not reported, *PBAC* Pharmaceutical Benefits Advisory Committee, *PSA* probabilistic sensitivity analysis, *RWE* real-world evidence, *SMC* Scottish Medicines Consortium, *TA* technology appraisal

Two models addressed uncertainty through the use of DSAs, PSAs, and scenario analyses [56, 67], one model considered both DSAs and PSAs [33], and the remaining two models used scenario analyses only [39, 64]. One model reported three validation methods (face, internal, and external) [67], while another model reported external validation only [56]. The other three models did not report this information [33, 39, 64].

Four models [39, 56, 64, 67] were industry sponsored. The last model did not provide this information [33]. Plain language summaries were available for four models [33, 39, 56, 67], while detailed technical documentation was available for three models [33, 56, 64]. Only one model was available for an external review upon request [33]. Two models provided information on the software used, which was Microsoft Excel® in both cases [39, 64].

4 Discussion

This SLR provides an up-to-date summary and critique of RRMM health economic models, using a systematic approach and a wide evidence base (published peer-reviewed literature and HTA submissions), filling an evidentiary gap in this indication. Three previously published SLRs of economic models in MM focused mainly on describing factors impacting the cost-effectiveness results [82–84]. The most recently published SLR by Choon-Quinones et al. [85] covered economic models of treatments and diagnostic procedures for both untreated and previously treated MM. However, the review did not comprehensively capture the model elements and modeling challenges for either population. The SLR presented here has a wider evidence scope than

Table 10 Model transparency: peer-reviewed articles (19 articles)

Study (year)	Sponsor type	Plain-language summary availability	Technical documentation availability	Model available to review and use/ replicate	Software
Aceituno et al. (2018) [20]	Industry	Yes	NR	NR	NR
Borg et al. (2016) [54]	Industry	Yes	NR	NR	NR
Cai et al. (2019) [27]	Government	Yes	NR	NR	TreeAge 2015
Campioni et al. (2020) [28]	NR	Yes	NR	NR	NR
Carlson et al. (2018) [29]	Nonprofit	Yes	NR	NR	NR
Dolph et al. (2021) [30]	Industry	Yes	Yes	NR	Microsoft Excel
Gueneau et al. (2018) [55]	NR	Yes	NR	NR	NR
Jakubowiak et al. (2016) [31]	Industry	Yes	NR	NR	Microsoft Excel
Jakubowiak et al. (2017) [32]	Industry	Yes	Yes	NR	NR
Kapinos et al. (2023) [33]	NR	Yes	Yes	Yes (upon request)	NR
Karampampa et al. (2023) [56]	Industry	Yes	Yes	NR	NR
Matsela et al. (2022) [21]	None	Yes	NR	NR	TreeAge Pro Healthcare 2021
Nikolaou et al. (2021) [57]	Industry	Yes	Yes	NR	Microsoft Excel
Patel et al. (2021) [34]	Nonprofit	Yes	NR	NR	TreeAge Pro, R, and STATA
Pelligra et al. (2017) [68]	Industry	Yes	Yes	NR	Microsoft Excel
Wong et al. (2021) [35]	None	Yes	NR	NR	Microsoft Excel
Zeng et al. (2020) [36]	None	Yes	NR	NR	TreeAge Pro 2018 and R software version 3.5.0
Zhang et al. (2018) [37]	None	Yes	NR	NR	TreeAge Pro 2017 and R software version 3.3.1

NR not reported

previously published SLRs as a result of searching related evidence through additional literature database sources and HTA agencies; including all types of economic evaluations (such as cost-minimization analyses previously used by HTA agencies, such as NICE [86, 87] and PBAC [72], to assess novel health technologies); and providing a detailed summary and critique of the methodology adopted by each included model (i.e., beyond a description by line of treatment and geography, based on the recognized recommendations outlined by Caro [14]).

The key issues identified in the development of economic models in RRMM were: (1) how to accurately incorporate trial data and extrapolate to a lifetime horizon; (2) how to model comparators without head-to-head evidence; (3) how to correctly model the costs and efficacy of subsequent treatment lines; (4) how to handle efficacy data from trials in which the subsequent treatment mix did not match that of the target population; (5) how to handle patient-level or subgroup-level heterogeneity in efficacy data; (6) how to accurately capture robust health benefit data and the impact of treatment on patient quality of life when there is a lack of such data from clinical trials; and (6) how to handle structural and parameter uncertainty.

In studies and HTA submissions reporting the clinical efficacy information used, OS and PFS were the primary model inputs; other model inputs, such as response status,

were used as secondary clinical outcomes. The majority of models faced challenges because of immature OS and PFS data from the clinical trials informing clinical efficacy inputs, thus necessitating long-term extrapolations and the respective validation of the clinical plausibility of such extrapolations. When assessing the survival benefit of treatments, extrapolation beyond the duration of clinical trials is crucial for estimating mean survival gains and assessing the long-term cost effectiveness. Although several survival extrapolation curves are available, selection of the appropriate curve requires careful consideration as different survival curves could lead to variations in estimates and uncertainty [88, 89]. While clinical plausibility assessments via expert elicitation or external validation using trial or real-world data are accepted by payers, biases may still arise from the former because of the rigor employed in eliciting expert knowledge or wider social pressures impacting expert opinion. In addition, changes to clinical practice may impact the appropriateness of data sources for external validation. Future models considering extrapolation beyond trial duration should attempt a systematic approach to avoid these potential drawbacks [87].

Similar to observations in other oncology indications [90], Markov models and PSMs were the most common approach in economic models for RRMM. All but three [33, 42, 54] of the economic models included in this SLR

Table 11 Model transparency: health technology assessment submissions (31 submissions)

Study	Sponsor type	Plain-language summary availability	Technical documentation availability	Model available to review and use/ replicate	Software
CADTH PC0164-000 (2019) [38]	Industry	Yes	No	No	NR
CADTH PC0165-000 (2019) [39]	Industry	Yes	No	No	Microsoft Excel
CADTH PC0220-000 (2021) [58]	Industry	Yes	No	No	NR
CADTH PC0256-000 (2022) [41]	Industry	Yes	No	No	Microsoft Excel
CADTH PC0276-000 (2022) [40]	Industry	Yes	No	No	NR
Institute for Clinical and Economic Review (ide-cel, cilta-cel, belamaf assessment) (2021) [67]	Government and non-profit organizations	Yes	No	No	NR
NICE TA171 (2019) [42]	Industry	No	Yes	No	NR
NICE TA573 (2019) [22]	Industry	No	Yes	No	NR
NICE TA586 (2019) [59]	Industry	No	Yes	No	NR
NICE TA657 (2020) [43]	Industry	No	Yes	No	NR
NICE TA658 (2020) [60]	Industry	No	Yes	No	Microsoft Excel
NICE TA695 (2021) [44]	Industry	No	Yes	No	Microsoft Excel
NICE TA783 (2022) [61]	Industry	No	Yes	No	NR
NICE TA870 (2023) [62]	Industry	No	Yes	No	Microsoft Excel
PBAC 5.02 July 2021, Darzalex [23]	Industry	No	Yes	No	NR
PBAC 5.04 November 2020, Empliciti [63]	Industry	No	Yes	No	NR
PBAC 5.07 July 2021, Xpovio [48] Resubmission: PBAC 7.07 November 2022, Xpovio [98] Resubmission: PBAC 7.10 March 2022, Xpovio [99]	Industry	No	Yes	No	NR
PBAC 5.07 November 2020, Ninlaro [49]	Industry	No	Yes	No	NR
PBAC 5.08 July 2021, Xpovio [64] Resubmission: PBAC 7.09 March 2022, Xpovio [100]	Industry	No	Yes	No	Microsoft Excel
PBAC 5.09 July 2019, Aplidin [65] Resubmission: PBAC 7.06 March 2020, Aplidin [101]	Industry	No	Yes	No	NR
PBAC 6.08 July 2019, Pomalyst [24] Resubmission: PBAC 7.13 November 2019, Pomalyst [73]	Industry	No	Yes	No	NR
PBAC 6.08 July 2020, Kyprolis [50]	Industry	No	Yes	No	NR
PBAC 7.01 November 2019, Darzalex [25]	Industry	No	Yes	No	NR
PBAC 7.03 March 2019, Darzalex [51]	Industry	No	Yes	No	NR
PBAC 7.03 March 2022, Kyprolis [52]	Industry	No	Yes	No	NR
PBAC 7.05 July 2021, Emplicit [53]	Industry	No	Yes	No	NR
PBAC 7.06 March 2022, Ninlaro [66]	Industry	No	Yes	No	NR
PBAC 7.11 July 2020, Darzalex [26]	Industry	No	Yes	No	NR
SMC 2180 (2019) [45]	Industry	No	No	No	NR
SMC 2290 (2020) [46]	Industry	No	No	No	NR
SMC 2303 (2021) [47]	Industry	No	No	No	NR

belamaf belantamab-mafodotin, *CADTH* Canadian Agency for Drugs and Technologies in Health, *cilta-cel* ciltacabtagene autoleucel, *ide-cel* idecabtagene vicleucel, *NICE* National Institute for Health and Care Excellence, *NR* not reported, *PBAC* Pharmaceutical Benefits Advisory Committee, *SMC* Scottish Medicines Consortium, *TA* technology appraisal

used a cohort-level approach. More than half of the models using a cohort-level approach employed a PSM structure to allow direct use of the PFS and OS data from clinical trials (with an additional long-term extrapolation) within a simple model structure. Cohort-level Markov and semi-Markov structures were also used, typically to allow for the inclusion of subsequent treatment lines and health states, especially with a distinction between on-treatment and off-treatment within the conventional pre-progression and post-progression health states [34, 59]. The International Society for Pharmacoeconomics and Outcomes Research advocates for the use of state-transition models when disease conceptualization spans a long time horizon and encompasses transitions between diverse health states, or if the simulation of multiple consecutive treatment lines is required [91]. Individual-patient level simulation was not widely used across models included in the SLR; however, where it was used, it allowed modelers to capture heterogeneity amongst the patient population in terms of different response categories (e.g., complete response, partial response/minimal response, no response), patient characteristics, and treatment pathways (i.e., prior treatment, current treatment, and comparator choice) [33, 54].

The PSM structure maintains enduring popularity, with no apparent trend towards an alternative. Of note, in its updated guidance on economic modeling [92], CADTH recently recommended against the use of PSM for long-term extrapolations, irrespective of disease area, owing to the importance of considering causal relationships between the probability of events and time, health status, and treatment. The PSM structure is no longer preferred by CADTH as it relies on an assumption of independence between the OS and PFS curves and does not integrate the likelihood of events and their evolution over time, along with changes in patient conditions, which could hinder CADTH or other external parties from conducting a robust and thorough assessment of the evidence. The preferred approach of CADTH is therefore one that appropriately accounts for the causal relationships between the probability of events and time-varying parameters. It is possible that this pattern may initiate a transition away from PSMs. However, it remains conceivable that PSMs could continue to be used for HTA submissions in other jurisdictions, concurrently developing economic models with structures, such as Markov models, tailored to the requirements of CADTH. As novel and innovative medications receive approval for RRMM, the focus of decision-making may transition from economic evaluations of individual treatment regimens to assessments of treatment sequences. This shift necessitates the consideration of alternative modeling approaches to accurately capture these sequences, whether it involves evaluating a single regimen within a treatment sequence or analyzing sequences of regimens as a whole.

Among included models for which there was an absence of sufficient direct head-to-head comparisons of relevant treatment regimens, clinical model inputs were typically sourced from ITCs. However, no information was available on how these clinical sources were initially identified (e.g., whether an SLR had been conducted). When ITCs were employed, information regarding the comparability of studies and feasibility of conducting such analyses were generally limited, including references to related publications that may elaborate on these analyses and their assumptions (e.g., selection of ITC methodology, and differences in trial and population comparability) [93].

Appropriately including the efficacy and costs of subsequent therapies is a key aspect of modeling therapies for which there is one or more potential subsequent treatment available. However, information on how subsequent therapies were considered in the economic models included in this review was generally limited. Where such information was reported, models generally referred to a basket of available treatments rather than individual treatment regimens [22, 30, 33, 34, 36, 37, 40–42, 57, 59, 60, 66–68] and only considered the impact of subsequent treatments from a cost and HCRU perspective; the assumption in these models is that the impact of subsequent treatments on clinical outcomes is captured in the OS data used to inform the clinical efficacy inputs. Furthermore, costing of subsequent treatments was mostly done on a per-cycle basis, based on treatment duration and the proportion of patients receiving later lines, or was applied as a one-off cost either at the time of initial treatment discontinuation or post-progression. It should be noted that the four-state PSM (progression-free on treatment, progression-free off treatment, progressed disease, and death), as opposed to the conventional PSM (progression-free, progressed disease, and death), can capture time on and off treatment more appropriately and reflect additional nuances in disease progression or treatment response [22, 30–32, 40, 41, 44, 45, 57, 60, 61].

In some cases, it was found that the subsequent treatment mix in the clinical trial did not match the therapies approved in the country of the target population of the economic model. Furthermore, the impact of subsequent treatment on clinical outcomes was only infrequently addressed and, as mentioned above, typically assumed to be captured by the OS data. Three studies reported that OS was adjusted using the two-stage methodology with re-censoring [62, 66] or using inverse probability of censoring weights methodology [22] to more accurately predict the treatment effect expected in routine clinical practice or the expected treatment effect if no differences in the distribution of subsequent treatments between treatment arms had been present. An SLR by Sullivan et al. suggested that insufficient reporting regarding the implementation of the methods used

for treatment switching amplifies uncertainty surrounding outcomes, potentially diminishing the adoption of these techniques by decision makers [94]. The NICE TSD provides comprehensive guidance on treatment switching, covering aspects such as timing of switching, clinical evidence (i.e., from clinical trials, real-world studies, or SLRs), patient preferences, cost effectiveness comparing switching treatments versus continuation of current therapy, and healthcare resource implications [95]. Future economic models should be developed with the capability to assess outcomes in scenarios using the observed data from clinical trials (i.e., without adjustments for subsequent treatments) as well as adjusting for subsequent treatments to better reflect those used in routine clinical practice in the country and setting of interest and, if appropriate, real-world effectiveness. These analyses can help address uncertainty around the impact of subsequent treatments on the model outcomes, which would be of relevance, and is often required, during HTA submissions.

In general, there were no discernable differences between the model structures utilized across various lines of treatment. However, one model for a CAR-T cell therapy included a decision node to model the CAR-T cell therapy pre-treatment process in order to determine which patients would be receiving this therapy, moving then to a PSM structure to assess the long-term clinical and economic outcomes of the CAR-T cell therapy [67]. Across the included economic models, a wide range of interventions were included. Most models were in second-line or third-line settings, yet there was limited information on the relapsed/refractory status following prior therapy. This review identified few models in later-line settings or those explicitly in patients who were refractory to specific previous therapies [33, 39, 56, 64, 67], which may be indicative of the limited treatment options available to these patients and potentially a lack of standardized clinical practice. Furthermore, all models evaluated specific interventions rather than the whole treatment sequence, which may introduce a higher degree of uncertainty due to differences in prior treatments across the trials.

Modeling treatment sequencing likely requires model structures that are more complex than typical cohort-level approaches, such as PSMs, for several reasons. First, the choice of subsequent treatments is heavily impacted by prior treatment lines and the type of treatment (e.g., IMiD, PI, mAb) under which a patient has experienced disease progression. Second, efficacy outcomes are likely to differ across treatments in the overall sequence of multiple treatment lines, resulting in complex calculations of the cumulative effect of multiple treatments in a sequence and across different sequences. This is also likely to introduce heterogeneity into the model given differences in patient populations and study designs across the sources for clinical inputs. Third, treatment-free intervals between lines of treatments, if they do occur, may also affect clinical outcomes. There are therefore considerable limitations to using a PSM structure to model treatment sequences in the absence of clinical trials that have been specifically designed to capture the cumulative effect of treatment sequences in OS and PFS. As more therapies enter the treatment landscape, decision problems may increasingly shift from selecting the most cost-effective treatment within a specific line of therapy to determining the optimal treatment sequence.

Where health utilities could be derived from the clinical trials informing the efficacy and safety inputs of the economic model, such inputs were generally considered suitable for the models. This approach was in line with, for example, current NICE methods that consider the mapping of patient-level data from clinical trials to utility values appropriate [87]. However, some records raised concerns regarding the lack of generalizability of clinical trial data to a wider population, particularly data from small trials. There was no common approach across models regarding the use of treatment-specific utilities/disutilities. In addition, some challenges remain regarding the requirement for geography or country-specific preference weights (i.e., tariffs) to derive health utilities from the health-related quality-of-life data from clinical trials or sourcing utility data from the published literature, especially in HTA submissions. While some HTA agencies accept health utilities from different countries, other HTA agencies are stricter and may not accept utility data derived from tariffs from a country other than the one considered in the model [96].

The presence of structural uncertainty can significantly influence the results of cost-effectiveness models. Whilst parameter uncertainty was addressed in almost all models reviewed (i.e., using PSAs, DSAs, or both), structural uncertainty (i.e., using a scenario analysis) was less commonly assessed. Assumptions such as drug wastage, subsequent treatments, treatment lines, and perspective were tested in some models, but not all. Given the growing treatment landscape, testing assumptions around both the cost and efficacy of subsequent lines of therapy is likely to become more important over time.

The results of this SLR should be viewed considering specific limitations related to selection criteria (search dates, language, and selected HTA bodies). First, evidence searches were restricted to the preceding 10 years for models published in peer-reviewed journals and the preceding 5 years for HTA submissions. However, the publication period restriction in the search was justified by aligning with current treatment pathways, which generally consider daratumumab-based, lenalidomide-based, or bortezomib-based regimens in the first-line treatment setting. Although economic models frequently evaluate treatments that have not yet sufficiently penetrated the market, models published

before 2014 would not include a sufficient number of patients with RRMM who aligned with current clinical practice. From a purely methodological point of view, however, this may have resulted in economic models that describe some relevant technical model aspects having been missed. Second, the restriction to English-language publications may limit the generalizability of findings to other settings, local languages, or HTA decision makers. However, most pivotal/first economic models for a treatment of interest are typically published in English and only subsequent local adaptations may be published in other languages. Therefore, key model aspects are likely to have been captured in this review as part of the pivotal/first economic model. Third, potential double counting of models may have occurred if insufficient information was available to connect related publications. Given the objective of this review was to describe the methodology and challenges of existing economic models in RRMM, any such double counting is unlikely to impact the overall review findings. Finally, journal word restrictions or dossier templates and publication policies by HTA agencies may have impacted the breadth of information on modeling methods provided. Data availability in HTA documents may have also been subject to redaction of commercially sensitive material. While ensuring data confidentiality, further efforts to promote transparency of the evidence and decision-making processes could increase the level of modeling detail provided and thus support the appropriate development of future models in the same diseases. Recently, NICE, CADTH, and the Institute for Clinical and Economic Review have published a joint statement on changes in how confidential information about health technologies is handled to streamline processes and increase transparency, thus hopefully impacting future submissions and the level of public information available [97].

5 Conclusions

Most health economic models in RRMM lacked sufficient information on the patient population with regard to the treatment-line setting, incorporation of clinical inputs in the model, consideration of subsequent therapy and its impact on health outcomes, and structural parameter uncertainty.

This systematic review highlighted that, in line with other oncology indications, most models followed a conventional approach, such as PSM or Markov models. This was mainly driven by the lower data requirements needed for these modeling approaches compared with more complex, individual-patient level model types. However, as more patients experience disease progression following multiple lines of treatment, there is expected to be a growing need to appropriately model more complex treatment strategies, including longer treatment sequences with more complex subsequent treatment mixes. This, added to more complex analyses to overcome trial and indirect comparison challenges, as well as guidance from at least one HTA agency highlighting the limitations of PSMs, may lead to a trend towards more complex modeling approaches in the future. More extensive data requirements would accompany any such development. Transparency remains fundamental, requiring high reporting standards, and a comprehensive analysis of structural and parameter uncertainty.

Declarations

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