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Cost-effectiveness analysis of combination therapies involving novel agents for first/second-relapse patients with multiple myeloma: a Markov model approach with calibration techniques

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Abstract

Background As the number of randomized clinical trials (RCTs) demonstrating the survival benefits of combination therapies in previously treated multiple myeloma (MM) patients increases, it is essential to determine the most cost-effective treatment through robust economic evaluation. This study aims to assess the cost-effectiveness of combination therapies for first/second-relapse MM patients from the perspective of the Chinese healthcare system.

Methods A Markov model was developed to evaluate three combination therapy groups based on primary drugs (bortezomib, lenalidomide, and carfilzomib). The economic evaluation was conducted within each group individually, rather than across different groups. Clinical inputs for the model were derived from RCT reports, while healthcare costs were sourced from the Zhejiang Province bidding database and a retrospective analysis. Utility values were obtained through an on-site survey using the Chinese version of the EuroQoL Five-dimensional Five-level Questionnaire. One-way and probabilistic sensitivity analyses were performed to assess the robustness of the base-case results.

Results In the bortezomib group, bortezomib-dexamethasone (Vd) yielded 2.42 quality-adjusted life years (QALYs) at a cost of ¥783,775. With a willingness-to-pay (WTP) threshold of three times the 2023 per capita GDP in China (¥258,074), pomalidomide-bortezomib-dexamethasone was the most cost-effective therapy (¥86,129/QALY) in this group. In the lenalidomide group, lenalidomide-dexamethasone (Rd) resulted in 3.06 QALYs at a cost of ¥840,509. Compared to Rd, the incremental cost-effectiveness ratios (ICERs) of elotuzumab-lenalidomide-dexamethasone (¥5,095,300/QALY), ixazomib-lenalidomide-dexamethasone (¥1,605,712/QALY), carfilzomib-lenalidomide-dexamethasone (¥955,255/QALY), and daratumumab-lenalidomide-dexamethasone (¥851,933/QALY) all exceeded the WTP threshold. In the carfilzomib group, carfilzomib-dexamethasone (Kd) resulted in 3.19 QALYs at a cost of ¥1,961,624. Compared to Kd, the ICERs of daratumumab-carfilzomib-dexamethasone (¥2,250,821/QALY)

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and isatuximab-carfilzomib-dexamethasone (¥4,977,964/QALY) also exceeded the WTP. Sensitivity analyses confirmed the robustness of the base-case results.

Conclusions Although this study did not fully account for the heterogeneity of subsequent treatment regimens among first/second-relapse MM patients, it highlights that the substantial financial burden associated with combination therapies involving novel agents poses a significant challenge in justifying their economic value.

Multiple myeloma (MM) is a hematological malignancy characterized by the abnormal clonal proliferation of plasma cells. In 2016, the age-standardized incidence rate of MM worldwide was approximately 2.1 per 100,000 persons [1]. Over the past decade, advances in MM treatment have provided more therapeutic options and significantly improved the long-term survival of MM patients [2–4]. For MM patients who received one or two treatments (referred to as first/second-relapse MM patients), numerous large-scale randomized clinical trials (RCTs) have demonstrated that combination therapies involving novel agents substantially reduce the risks of mortality and disease progression [5–8]. As a result, these therapies have been approved by regulatory authorities and incorporated into clinical guidelines [9–11]. These combinations include dual and triple drug regimens based on bortezomib, lenalidomide, or carfilzomib.

As with other malignancies, novel agents not only improve survival for MM patients but also increase the associated economic burden. To reduce the risk of progression, clinical guidelines recommend continuous antimyeloma therapy until disease progression or patient intolerance. Given the long survival period (with a median survival of 10 years in newly diagnosed MM patients), this prolonged therapy inevitably leads to high cumulative lifetime healthcare costs. Numerous studies have highlighted the significant economic burden of MM treatment [12–15]. According to 2023 statistics from the National Cancer Institute of the United States [16], the average per-patient, per-cycle medical service cost for MM treatment ranked highest among all cancers at $28,524, while the average per-patient, per-cycle cost of oral prescription drugs for MM treatment ranked second at $26,443. A study by Chinese authors, using the National Basic Medical Insurance for Urban Employee and Resident Databases (2012–2016) to analyze MM patients' medical costs [17], estimated the average annual cost of MM treatment in 2016 to be ¥73,767. Given the increasing availability of novel antimyeloma drugs in China, annual treatment costs for MM patients in the country are expected to rise further.

Given the high economic burden of MM, previous studies have evaluated the cost-effectiveness of combination therapies involving novel agents in MM patients across various healthcare systems, including those in Singapore, the United States, the United Kingdom, and Canada [18–23]. These studies demonstrated that adding daratumumab to Vd or Rd regimens was not cost-effective. Furthermore, the addition of other novel agents, such as selinexor or ixazomib, did not appear cost-effective. However, few similar studies have been conducted within the Chinese context. It is important to note that China's healthcare system differs significantly from those in the aforementioned developed countries, making it inappropriate to directly apply their findings to clinical practice in China. Therefore, this study aims to evaluate the cost-effectiveness of three combination therapy groups based on primary drugs (bortezomib, lenalidomide, and carfilzomib) for first/second-relapse MM patients from the perspective of the Chinese healthcare system.

Methods

Patients and intervention

To collect clinical trial evidence on combination therapies for first/second-relapse MM patients from both domestic and international sources, we conducted a systematic literature review (SLR) in accordance with the Cochrane Handbook and the PRISMA statement. The specific research protocol for the SLR has been registered on the PROSPERO website (registration number 320006). Publication data were collected from January 1, 2010, to October 1, 2023. For detailed steps and results of the SLR, please refer to the supplementary material.

This study aims to identify and evaluate combination strategies that have been validated for safety and efficacy through phase II or III RCTs and recommended by authoritative clinical guidelines [24, 25]. The main eligibility criteria for the SLR were as follows: 1) MM subjects must have undergone one or two prior treatments; 2) the study must be a phase II or III RCT; and 3) the combination therapies investigated in the RCTs should include at least one of the prespecified novel agents: bortezomib, lenalidomide, carfilzomib, ixazomib, thalidomide, pomalidomide, daratumumab, elotuzumab, selinexor, venetoclax, vorinostat, or pembrolizumab. Based on this, we identified 13 RCTs and 15 combination therapies for first/second-relapse MM patients through the SLR.

To group the identified combination therapies, we assumed that patients in clinical trials were

homogeneous if the control treatments were the same, regardless of the intervention treatments. Thus, three groups of combination therapies were defined based on the control strategies used in the RCTs: the bortezomib group, the carfilzomib group, and the lenalidomide group. In the bortezomib group, the control treatment was bortezomib-dexamethasone; in the lenalidomide group, it was lenalidomide-dexamethasone; and in the carfilzomib group, it was carfilzomib-dexamethasone. This categorization aimed to manage heterogeneity factors such as treatment history, lines of treatment received, and individual health conditions, which could significantly influence the selection of treatment regimens and patient survival. As shown in Table S2, the patient characteristics within each group were closely similar. The economic evaluation was conducted within each group individually rather than across groups.

Treatments in the bortezomib group are appropriate for first/second-relapse MM patients who exhibit sensitivity to bortezomib. This category comprises six therapies [7, 9, 26–29]:

- bortezomib-dexamethasone (Vd);
- daratumumab-bortezomib-dexamethasone (DVd);
- selinexor-bortezomib-dexamethasone (SVd);
- pomalidomide-bortezomib-dexamethasone (PVd);
- carfilzomib-dexamethasone (Kd); and
- panobinostat-bortezomib-dexamethasone (PanVd).

Treatments in the lenalidomide group are appropriate for first/second-relapse MM patients who demonstrate sensitivity to lenalidomide. This group encompasses five therapies [6, 8, 11, 30–32]:

- lenalidomide-dexamethasone (Rd);
- elotuzumab-lenalidomide-dexamethasone (ERd);
- carfilzomib-lenalidomide-dexamethasone (KRd);
- ixazomib-lenalidomide-dexamethasone (IxaRd); and
- daratumumab-lenalidomide-dexamethasone (DRd).

Treatments in the carfilzomib group are appropriate for first/second-relapse MM patients who exhibit sensitivity to carfilzomib. This group includes three therapies [5, 10, 33, 34]:

- carfilzomib-dexamethasone (Kd);
- daratumumab-carfilzomib-dexamethasone (DKd); and
- isatuximab-carfilzomib-dexamethasone (IsaKd).

Model construction

We constructed a Markov model to compare combination therapies within each group (Fig. 1). The model comprised four states: initial treatment, subsequent treatment, last treatment, and death. Patients initially received a combination therapy and entered the initial treatment state. They could either remain in this state if they maintained PFS or transition to the subsequent treatment state upon disease progression. Similarly, patients in the subsequent treatment state could either remain there or progress to the last treatment state. In the last treatment state, patients could either remain if they continued to survive or transition to the death state if they succumbed to the disease.

We used TreeAge Pro Healthcare (TreeAge Pro version 2022, Williamstown, MA) to create our model and R (version 4.2.2) software to perform additional statistical analyses.

Survival curves extrapolation

The state membership in our Markov model was determined using Kaplan–Meier survival curves from RCTs. Given the limited follow-up period in these trials, standard extrapolation techniques were applied to estimate survival benefits beyond the follow-up cutoff. The following steps outlines the process of fitting parametric distributions to the survival curves, using Vd as a case study.

- Initially, WebPlot Digitizer (v4.0) software was used to capture survival coordinate points from the Vd Kaplan–Meier curves of progress-free survival (PFS) and overall survival (OS) in the trials, including CASTOR [7], BELLINI [9], BOSTON [26], OPTIMISMN [27], ENDEAVOR [28], and PANORAMA1 [29];
- Subsequently, the method developed by Guyot et al. was applied to reconstruct pseudoindividual patient data from these survival coordinate points. This process generated a synthetic dataset of pooled pseudoindividual data, integrating existing RCT evidence for Vd.
- Next, the pooled pseudoindividual data were fitted to seven parametric distributions (Weibull, log-logistic, log-normal, Gompertz, exponential, gamma, and generalized Gamma). The optimal survival model was selected based on the Akaike Information Criterion and visual inspection. In this study, OS and PFS for Vd were modeled using parametric curves with Weibull and log-logistic distributions, respectively (Table 1, Fig. 2);
- Finally, to prevent a plateau in the survival curve beyond the trial data period, long-term survival was extrapolated by using the higher value between the

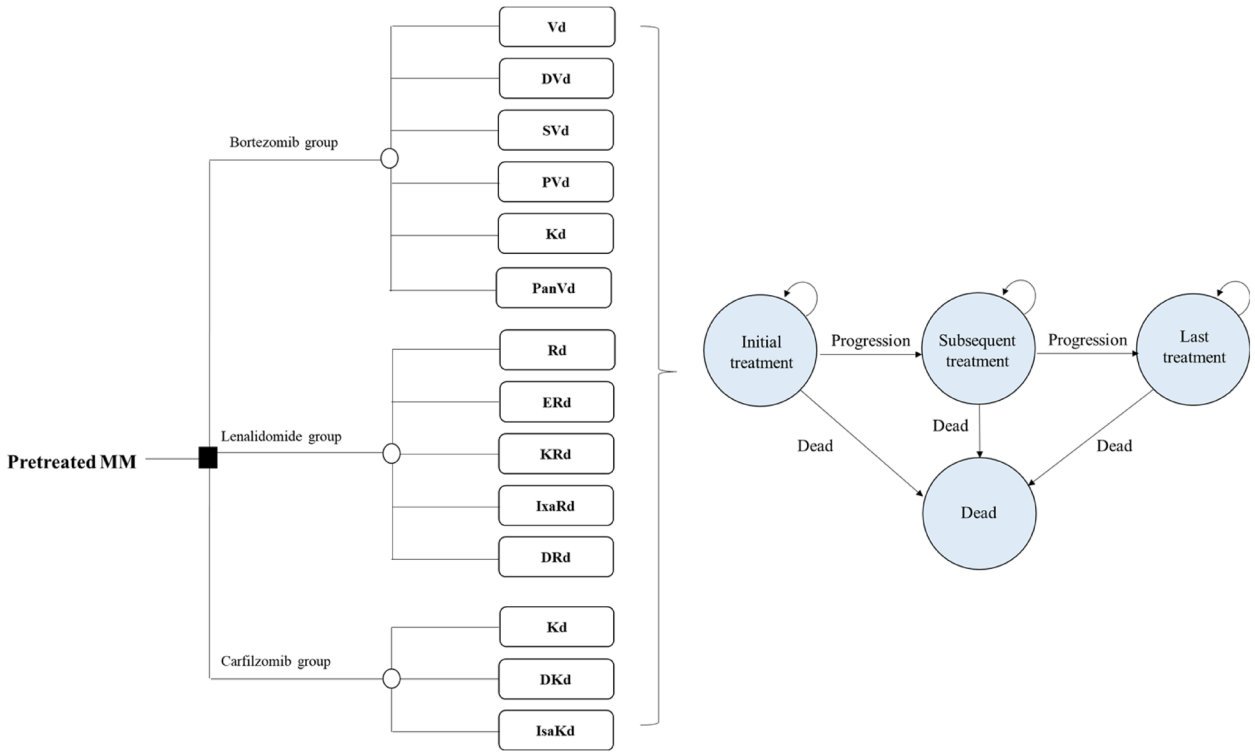

Fig. 1 Simplified diagram of Markov model. Note: Vd, bortezomib-dexamethasone; Rd, lenalidomide-dexamethasone; Kd, carfilzomib-dexamethasone; DVd, daratumumab-bortezomib-dexamethasone; SVd, selinexor-bortezomib-dexamethasone; PVd, pomalidomide-bortezomib-dexamethasone; PanVd, pomalidomide-bortezomib-dexamethasone; ERd, elotuzumab-lenalidomide-dexamethasone; DRd, daratumumab-lenalidomide-dexamethasone; KRd, carfilzomib-lenalidomide-dexamethasone; IxaRd, ixazomib-lenalidomide-dexamethasone; Kd, carfilzomib-dexamethasone; DKd, daratumumab-carfilzomib-dexamethasone; IsaKd, isatuximab-carfilzomib-dexamethasone

predicted mortality and the mortality probability derived from the Chinese lifetable [35], adjusted for a standardized mortality ratio (SMR).

Due to the limited availability of extensive follow-up studies on Chinese MM patients, our study referred to the results of a 5-year follow-up study conducted on American MM patients [36]. This study, based on the Mayo Clinic database, estimated the SMR for MM patients to be 3.94 compared to the general population, while the SMR derived from the SEER database was reported to be 5.99. Given that the MM patients in our model received adequate treatment, we selected the lower SMR of 3.94 to adjust long-term survival in our study.

Transition probabilities

For the Vd regimen in the bortezomib group, the monthly probabilities of remaining progression-free during the initial treatment phase were derived from the PFS parametric distribution for Vd. For other treatments within this group, the reported hazard ratios (HRs) with Vd as the reference were utilized to calculate the corresponding probabilities of remaining progression-free during the initial treatment phase.

Due to the unavailability or limited access to post-progression individual patient data, this study assumed that patients in the bortezomib group would receive Kd and Rd treatments equally during the subsequent treatment phase. Therefore, pooled PFS curves for Kd and Rd were used to estimate the probability of remaining progression-free in this phase. For other treatments in the bortezomib group, the average HRs for OS and PFS (with Vd as the reference) were applied to calculate the probability of remaining progression-free. Additionally, the pooled OS curve for Pd was used to determine the survival probability for all treatments during the final treatment phase.

For both the initial and subsequent treatment states, MM patients faced probabilities of remaining progression-free, experiencing death, or progressing, with the sum of these three probabilities equaling one. To account for this, a calibration technique was applied to estimate the death probabilities for both treatment states, conditioned on the probabilities of remaining progression-free. The calibration utilized the Nelder-Mead simplex

Table 1 The parameters for fitted survival curves

Strategy	Survival curve	Parameters	Source
Bortezomib group			
Vd	PFS	Log-normal: meanlog = 1.97; sdlog = 1.07	[7, 9, 26–29]
	OS	Weibull: shape = 1.10; scale = 51.11	
DVd	HR of PFS	0.31 (0.25 – 0.40)	[7, 9]
	HR of OS	0.74 (0.59 – 0.92)	
SVd	HR of PFS	0.70 (0.53 – 0.93)	[26]
	HR of OS	0.84 (0.57 – 1.23)	
PVd	HR of PFS	0.61 (0.49 – 0.77)	[27]
	HR of OS	0.98 (0.73 – 1.32)	
Kd	HR of PFS	0.53 (0.44 – 0.60)	[28]
	HR of OS	0.79 (0.65 – 0.96)	
PanVd	HR of PFS	0.63 (0.52 – 0.76)	[29]
	HR of OS	0.87 (0.69 – 1.10)	
Lenalidomide group			
Rd	PFS	Gompertz: shape = −0.011; sdlog = 0.049	[6, 8, 11, 30–32]
	OS	Log-normal: meanlog = 3.77; sdlog = 1.29	
ERD	HR of PFS	0.72 (0.60 – 0.87)	[8, 11]
	HR of OS	0.82 (0.68 – 1.00)	
KRd	HR of PFS	0.66 (0.55 – 0.78)	[30]
	HR of OS	0.79 (0.67 – 0.94)	
IxaRd	HR of PFS	0.74 (0.59 – 0.94)	[31]
	HR of OS	0.94 (0.78 – 1.12)	
DRd	HR of PFS	0.44 (0.35 – 0.55)	[6]
	HR of OS	0.73 (0.58 – 0.91)	
Carfilzomib group			
Kd	PFS	Log-normal: meanlog = 2.72; sdlog = 1.48	[5, 10, 33, 34]
	OS	Exponential: rate = 0.01513	
DKd	HR of PFS	0.59 (0.45 – 0.78)	[5, 10]
	HR of OS	0.78 (0.62 – 0.94)	
IsaKd	HR of PFS	0.58 (0.42 – 0.79)	[33, 34]
	HR of OS	0.78 (0.61 – 0.95)	
Pd	OS	Gamma: shape = 1.2023, 0.04114	

Vd bortezomib-dexamethasone, *Rd* lenalidomide-dexamethasone, *Kd* carfilzomib-dexamethasone, *DVd* daratumumab-bortezomib-dexamethasone, *SVd* selinexor-bortezomib-dexamethasone, *PVd* pomalidomide-bortezomib-dexamethasone, *PanVd* pomalidomide-bortezomib-dexamethasone, *ERd* elotuzumab-lenalidomide-dexamethasone, *DRd* daratumumab-lenalidomide-dexamethasone, *KRd* carfilzomib-lenalidomide-dexamethasone, *IxaRd* ixazomib-lenalidomide-dexamethasone, *Kd* carfilzomib-dexamethasone, *DKd* daratumumab-carfilzomib-dexamethasone, *IsaKd* isatuximab-carfilzomib-dexamethasone

optimization method to ensure that the modeled OS closely matched the reported OS for each combination therapy.

For the carfilzomib and lenalidomide groups, the process of estimating monthly transition probabilities was similar to that used for the bortezomib group. Specifically, for the carfilzomib group, the pooled PFS curve of Vd and Rd was used to determine the monthly probabilities of remaining progression-free during the subsequent treatment phase, while for the lenalidomide group, the pooled PFS curve of Vd and Kd was used for this estimation.

This study utilized PFS2 data, defined as the time from randomized assignment to progression on the next line of therapy, and externally sourced OS data [37] to conduct both internal and external validation of the entire Markov model. The validation results demonstrated that the model-predicted PFS2 closely aligned with the RCT-reported PFS2 results at 12 and 36 months, with minimal differences at 60 months (Table 2). The model-predicted OS for the combination therapies in this study was expected to be lower than the OS for second-line therapies but higher than the OS for third-line therapies observed in external studies. Since the OS reported

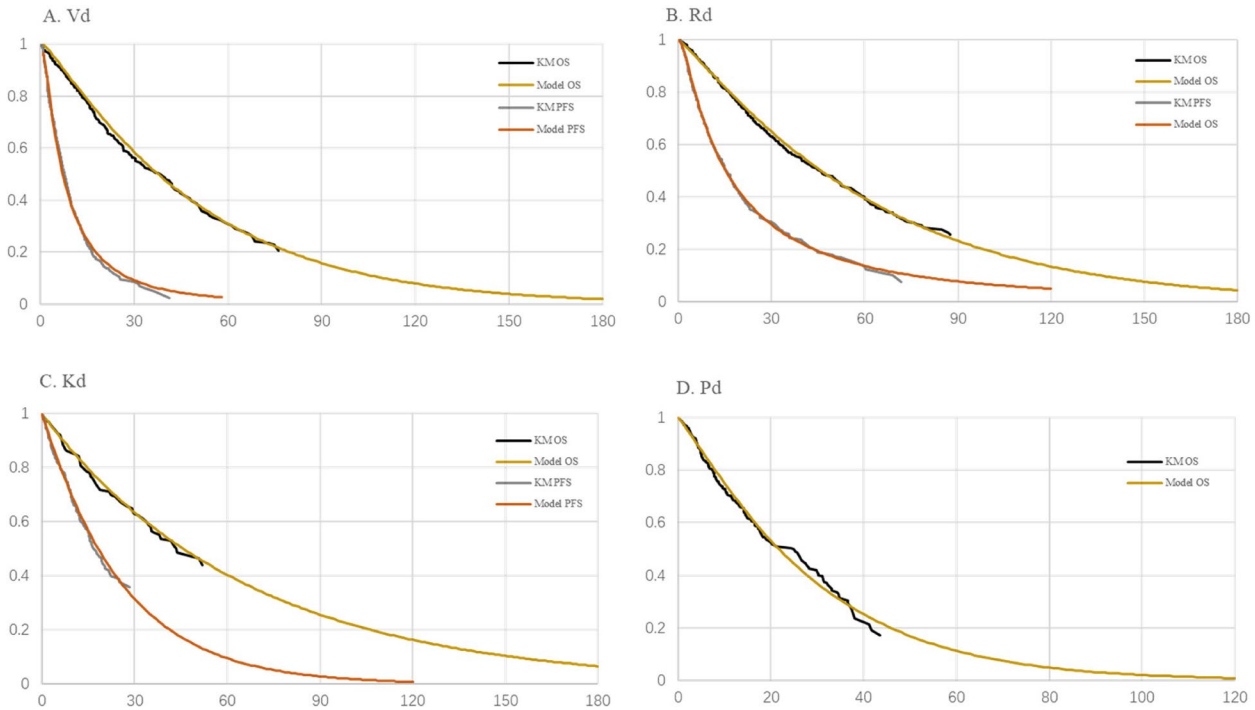

Fig. 2 Modeled survival curves of Vd, Rd, Kd, and Pd

by Goel U et al. [37] reflects the average effectiveness of all available therapies, minor discrepancies between the model-predicted and observed OS for certain therapies may be attributed to the specific clinical efficacy of each treatment strategy.

Cost estimation

In this study, direct medical costs were evaluated from the perspective of the Chinese healthcare system. These costs included treatment costs (drug acquisition and administration), costs associated with unplanned events (adverse events and progression), routine follow-up care costs, and terminal care costs (Table 3). All costs were adjusted for inflation using the Chinese Consumer Price Index and reported in 2023 Chinese Yuan.

The procurement prices of different drugs were obtained from the Zhejiang Province bidding database. For drugs with varying prices across different manufacturers, the average procurement price was calculated and used to estimate the acquisition cost of treatment regimens. For drugs not yet available in the Chinese market, such as panobinostat, elotuzumab, and isatuximab, prices were based on the listed prices in the US market (1 USD = 7.05 CNY in 2023). The US-listed prices for these drugs were sourced from the study by Dolph M et al. [38], which analyzed the US budget impact of several antimyeloma regimens for pretreated MM patients. To estimate the monthly acquisition costs for combination therapies, dosing regimens were extracted from RCT reports. A standard senior citizen (≥ 65 years of age) with a body surface area of 1.7 m^2 and a weight of 65 kg, as per the Fifth National Physical Fitness and Health Report, was used to calculate the dosage for MM patients. Given the varying durations of each treatment cycle across different therapies, treatment costs were standardized into a monthly model cycle cost for each therapy (Table S4).

Patients with MM may discontinue treatments due to adverse events (AEs), making it crucial to account for the impact of such discontinuations on treatment costs over extended periods. It is assumed that treatment discontinuation due to AEs occurs within the first 12 months of the initial treatment phase. Additionally, the monthly probability of discontinuation is assumed to follow an exponential distribution. The discontinuation rate is estimated based on the percentage of treatment discontinuation reported in relevant RCTs (Table 3). In the absence of specific data, the average discontinuation rates observed at the 12th month for combination therapies during the initial treatment phase were also applied to subsequent and final treatment states.

A retrospective analysis was conducted on the costs associated with drug administration, subsequent treatment, last treatment, and follow-up at several general hospitals in Zhejiang Province from January 2021 to

Table 2 Model validation based on clinical and external data

Survival curves	12 months	36 months	60 months
PFS2			
Modeled Vd	71.2%	21.9%	6.3%
Observed Vd	68.6%	21.7%	8.2%
Modeled DVd	84.7%	51.3%	32.5%
Observed DVd	83.4%	50.7%	37.1%
Modeled PVd	74.3%	46.1%	-
Observed PVd	71.4%	45.3%	-
Modeled Kd	81.3%	47.2%	-
Observed Kd	83.2%	48.3%	-
Modeled IsaKd	85.1%	56.8%	-
Observed IsaKd	86.1%	57.7%	-
OS			
Modeled Vd	83.30%	51.80%	30.10%
Modeled DVd	88.00%	63.10%	44.00%
Modeled SVd	85.70%	57.50%	37.40%
Modeled PVd	83.60%	52.50%	32.20%
Modeled Kd	86.50%	59.40%	40.00%
Modeled Rd	85.50%	58.90%	39.30%
Modeled ERd	88.00%	64.80%	46.50%
Modeled DRd	89.20%	67.90%	50.60%
Modeled KRd	88.30%	65.80%	47.90%
Modeled IxaRd	86.30%	60.80%	41.60%
Modeled Kd	83.40%	58.00%	40.40%
Modeled DKd	86.70%	65.20%	49.10%
Modeled IsaKd	86.80%	65.40%	49.30%
External OS with one prior lines	90.20%	66.30%	49.20%
External OS with two prior lines	82.10%	58.10%	40.80%

Vd bortezomib-dexamethasone, *Rd* lenalidomide-dexamethasone, *Kd* carfilzomib-dexamethasone, *DVd* daratumumab-bortezomib-dexamethasone, *SVd* selinexor-bortezomib-dexamethasone, *PVd* pomalidomide-bortezomib-dexamethasone, *PanVd* pomalidomide-bortezomib-dexamethasone, *ERd* elotuzumab-lenalidomide-dexamethasone, *DRd* daratumumab-lenalidomide-dexamethasone, *KRd* carfilzomib-lenalidomide-dexamethasone, *IxaRd* ixazomib-lenalidomide-dexamethasone, *Kd* carfilzomib-dexamethasone, *DKd* daratumumab-carfilzomib-dexamethasone, *IsaKd* isatuximab-carfilzomib-dexamethasone

Table 3 Input parameters of costs, ¥

Parameters	Value	Range	Source
Average Acquisition price of drugs, mg			
Bortezomib	349	279—419	Collected by authors
Carfilzomib	98	78—118	Collected by authors
Ixazomib	1,319	1,055—1,583	Collected by authors
Lenalidomide	2.0	1.8—2.2	Collected by authors
Pomalidomide	66	53—79	Collected by authors
Daratumumab	20	16—24	Collected by authors
Selinexor	59	47—71	Collected by authors
Assumed price of drugs based on listed price in US market, mg			
Panobinostat	1,599	1,279—1,919	[38]
Elotuzumab	54	43—65	[38]
Isatuximab	58	46—70	[38]
IV administration	6	5—7	Collected by authors
SC administration	3	2—4	Collected by authors
Costs for AEs (grade ≥ 3) management			
Neutropenia	36,465	29,172—43,758	Collected by authors
Anemia	20,780	16,624—24,936	Collected by authors
Thrombocytopenia	20,136	16,109—24,163	Collected by authors
Pneumonia	14,983	11,986—17,980	Collected by authors
Follow-up costs, monthly			
First year	1,186	949—1423	Collected by authors
Second and third year	593	474—712	Collected by authors
Fourth and fifth year	297	238—356	Collected by authors
Subsequent treatment costs, monthly			
Bortezomib group	35,857	23,722—35,584	Collected by authors
Lenalidomide group	32,755	28,686—43,028	Collected by authors
Carfilzomib group	29,653	26,204—39,306	Collected by authors
Last treatment costs, monthly	39,048	31,238—46,858	Collected by authors
Hospice, monthly	21,424	17,139—25,709	[40]

October 2023. The analysis included data from 1,196 patients with MM who had experienced first or second relapse, and 9,857 corresponding records. Given the sensitivity to drugs, subsequent treatment costs may vary across the three groups following disease progression. For instance, the likelihood of selecting bortezomib-based therapies significantly decreases for patients in the bortezomib group after progression. Therefore, we also considered the patients' prior treatment history when collecting cost data after disease progression (Table S7). The average monthly costs for subsequent treatment in the bortezomib, lenalidomide, and carfilzomib groups were ¥35,857, ¥32,755, and ¥29,653, respectively. Last treatment costs were assumed to be the same across the three groups. The average monthly treatment cost of ¥39,048 for patients undergoing four or more lines of treatment was used to estimate the monthly costs during the last treatment phase in this model. Patients were assumed to receive routine follow-up visits during the initial treatment phase. According to the "Guidelines for the Diagnosis and Management of Multiple Myeloma in China (2022 Revision)," MM patients should undergo follow-up visits every three months during the first year after achieving remission; every six months during the second and third years; and annually during the fourth and fifth years. These visits typically involve a physician consultation, standard laboratory tests, and physical examinations. Since the costs of subsequent and last treatments already include follow-up expenses, it is unnecessary to separately account for follow-up costs.

Consistent with previous studies [18–20], this study considered the costs associated with major severe AEs of grade ≥ 3, including neutropenia, anemia, pneumonia, and thrombocytopenia. The costs for these AEs were obtained from the Zhejiang Province Diagnosis-Related Group-based Database. Following the methodology used in a NICE study [39], the costs of severe AEs were incorporated as one-time costs at the initiation of treatment, based on their probability of occurrence. The costs of end-of-life care were estimated using data from Li et al. [40], which reported that the monthly costs for end-of-life treatment of cancer patients amounted to ¥21,424 during the final six months of life. These costs were excluded if patients continued to receive antimyeloma treatment before death.

Utility estimation

Compared to the general population, patients with MM experience varying degrees of reduced health utility due to disease progression. Therefore, measuring the health utility of MM patients is crucial for this economic evaluation. This study conducted an on-site questionnaire survey to assess the health utility of patients with relapsed/refractory MM using the Chinese version of the EuroQoL Five-Dimensional Five-Level Questionnaire (registration ID: 57,140) [41]. The survey targeted both outpatient and inpatient patients diagnosed with relapsed/refractory MM, employing a convenience sampling method for distributing the questionnaires. From February 2021 to December 2023, a total of 558 valid questionnaires were collected from several general hospitals in Zhejiang Province.

Using the utility value scoring system based on the health preferences of the mainland Chinese population [42], health utility values for MM patients were derived from quality-of-life surveys. For second-line treatment, the utility values were 0.796 with disease remission and 0.690 with disease progression (Table S9). For third-line treatment, the values were 0.762 with remission and 0.652 with progression. For fourth-line and subsequent treatments, the values were 0.686 with remission and 0.548 with progression.

To input the collected utility data into the Markov model, several assumptions were made. First, it was assumed that patients within the same treatment line and disease state have identical health utility values. Specifically, MM patients were assigned utility values associated with disease progression for the first eight cycles and utility values associated with disease remission for cycles after the eighth within the same state. In the RCTs evaluating combination therapies, it was observed that approximately half of the patients had previously received one line of treatment, while the other half had undergone two or more lines of treatment. Consequently, this study assumed that the utility values for the initial treatment state were represented as a weighted average of 50% second-line treatment and 50% third-line treatment utility values. Similarly, the utility values for the subsequent treatment state were determined as a weighted average of 50% third-line treatment and 50% fourth-line treatment utility values, while the utility values for the last treatment were based on fourth-line or later treatment utility values. The assigned health utility values for the Markov states are presented in Table 4.

Main outcomes

The primary outcomes evaluated in this study included life years (LYs), discounted lifetime costs, discounted quality-adjusted life years (QALYs), and the incremental cost-effectiveness ratio (ICER). The model was simulated in monthly cycles over a total duration of 240 cycles. By the end of the 240th cycle, the number of remaining patients was expected to fall below 5%, indicating that the simulation had effectively captured the patients' full lifetime. To account for time preferences, an annual discount rate of 5% was applied to both costs and QALYs, in accordance with the 2021 China Guidelines for Pharmacoeconomic Evaluations. In the absence of an explicit willingness-to-pay (WTP) threshold in China, the study adhered to WHO recommendations for economic evaluations in developing countries, which suggest using a WTP threshold of 1 to 3 times the per capita GDP [43]. For oncology economic evaluations, a threshold of 3 times the per capita GDP is commonly employed. Accordingly, this study adopted a cost-effectiveness threshold of 3 times the per capita GDP (¥258,074) for the base-case analysis.

Sensitivity analysis

We conducted a one-way sensitivity analysis to assess the robustness of the base-case results. In this analysis, parameters were independently varied within a plausible range, determined either by published data or by the 95% confidence interval (CI). In cases where such data were unavailable, values were varied by ± 20% of the corresponding base-case value. Additionally, price threshold analysis was performed to identify the price point at which a combination therapy involving the novel agent would become cost-effective compared to the optimal strategy identified in the base-case analysis.

Probabilistic sensitivity analyses (PSA) were conducted to account for the joint uncertainties in the input parameter values, with 10,000 simultaneous samples drawn from the uncertainty distributions of all inputs. Gamma distributions were applied to costs, while beta distributions were used for utilities and probabilities. The method

Table 4 Other key input parameters

Parameters	Value	Range	Source
Discontinuation rate due to AEs in initial treatment			
Vd	15.58%	12.46%—18.69%	[7, 9, 26–29]
DVd	17.92%	14.34%—21.50%	[7, 9]
SVd	20.44%	16.35%—24.53%	[26]
PVd	9.52%	7.61%—11.42%	[27]
Kd	15.88%	12.71%—19.06%	[28]
PanVd	31.15%	24.92%—37.38%	[29]
Rd	13.87%	11.10%—16.65%	[6, 8, 11, 30, 31]
ERd	11.89%	9.51%—14.27%	[8, 11]
KRd	11.33%	9.07%—13.60%	[30]
IxaRd	9.80%	7.84%—11.76%	[31]
DRd	11.90%	9.52%—14.28%	[6]
Kd	19.28%	15.42%—23.13%	[5, 10, 33, 34]
DKd	25.26%	20.21%—30.31%	[5, 10]
IsaKd	13.28%	10.62%—15.94%	[33, 34]
Probability of background death	Chinese lifetable		[35]
Standard mortality rate	3.94	3.15 – 4.73	[36]
Model starting age			
Bortezomib group	65	60 – 70	[7, 9, 26–29]
Lenalidomide group	65	60 – 70	[6, 8, 11, 30, 31]
Carfilzomib group	64	60—70	[5, 10, 33, 34]
Utility			
Initial treatment during first 8 cycles	0.67	0.54 – 0.80	Collected by authors
Initial treatment after 8 cycles	0.78	0.62 – 0.94	Collected by authors
Subsequent treatment during first 8 cycles	0.60	0.48 – 0.72	Collected by authors
Subsequent treatment after 8 cycles	0.72	0.58 – 0.86	Collected by authors
Last treatment during first 8 cycles	0.55	0.44 – 0.66	Collected by authors
Last treatment after 8 cycles	0.69	– 0.83	Collected by authors

Vd bortezomib-dexamethasone, *Rd* lenalidomide-dexamethasone, *Kd* carfilzomib-dexamethasone, *DVd* daratumumab-bortezomib-dexamethasone, *SVd* selinexor-bortezomib-dexamethasone, *PVd* pomalidomide-bortezomib-dexamethasone, *PanVd* pomalidomide-bortezomib-dexamethasone, *ERd* elotuzumab-lenalidomide-dexamethasone, *DRd* daratumumab-lenalidomide-dexamethasone, *KRd* carfilzomib-lenalidomide-dexamethasone, *IxaRd* ixazomib-lenalidomide-dexamethasone, *Kd* carfilzomib-dexamethasone, *DKd* daratumumab-carfilzomib-dexamethasone, *IsaKd* isatuximab-carfilzomib-dexamethasone

proposed by John K. Lin [44] was employed to generate 1,000 sets of death probabilities derived from model calibration for the PSA, utilizing the 95% confidence interval (CI) of the HR for OS. To assess the likelihood of each strategy being cost-effective at a specific willingness-to-pay (WTP) threshold, we counted the number of times the incremental cost-effectiveness ratio (ICER) fell below the specified threshold across the 10,000 iterations.

Given the significant accumulation of lifetime healthcare costs associated with extended treatment durations, this study conducted a scenario analysis to evaluate the cost-effectiveness of shorter treatment cycles. According to a study by Antonio Palumbo et al. [45], the HRs for PFS and OS with continuous therapy, compared to fixed-duration therapy (12 months), were 0.47 and 0.69, respectively. In the scenario analysis, we assumed a treatment duration of 12 cycles in the initial treatment state and used data from Antonio Palumbo et al. to derive the probabilities of remaining progression-free and surviving after 12 cycles.

Results

Base case analysis

The modelled costs and effectiveness of combination therapies over a lifetime horizon are shown in Fig. 3. The cumulative costs and QALYs curves initially rose rapidly, followed by a slower rate of increase. At the 12-month mark, the cumulative costs and QALYs for each combination therapy were as follows: for the bortezomib group, 74% to 90% of the total costs and 74% to 81% of the total QALYs; for the lenalidomide group, 57% to 77% of the total costs and 68% to 75% of the total QALYs; and for the carfilzomib group, 74% to 76% of the total costs and 65% to 71% of the total QALYs. Furthermore, there was

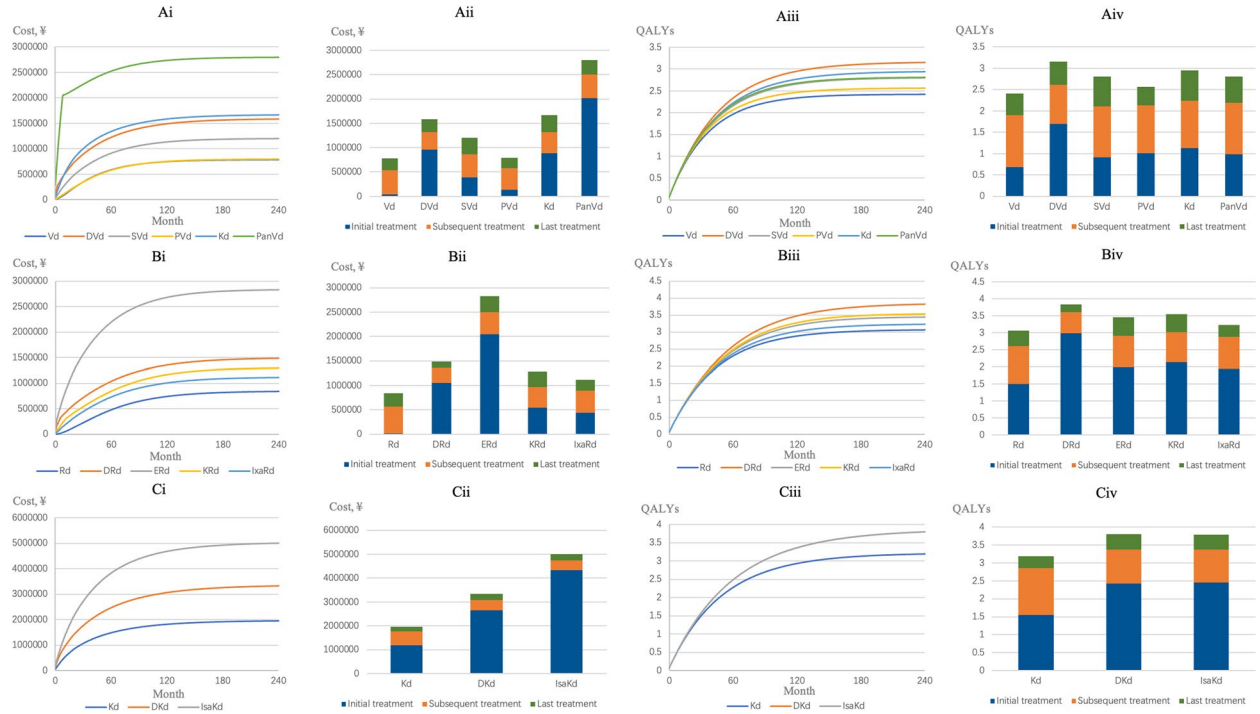

Fig. 3 Modelled costs and effectiveness for combination therapies. Ai: cumulative costs in bortezomib group, Aii: costs associated with different states in the bortezomib group, Aiii: cumulative QALYs in bortezomib group, Aiv: costs associated with different states in the bortezomib group; Bi: cumulative costs in lenalidomide group, Bii: costs associated with different states in the lenalidomide group, Biii: cumulative QALYs in lenalidomide group, Biv: costs associated with different states in the lenalidomide group; Ci: cumulative costs in carfilzomib group, Cii: costs associated with different states in the carfilzomib group, Ciii: cumulative QALYs in carfilzomib group, Civ: costs associated with different states in the carfilzomib group

significant variation in costs and QALYs during the initial treatment state across the combination therapies, whereas the costs and QALYs during subsequent and last treatment states remained relatively consistent. Therefore, the differences in costs and QALYs during the initial treatment state were the main drivers of the overall variation in total costs and total QALYs among the therapies.

The values of undiscounted LYs, discounted costs, and QALYs over the lifetime horizon are presented in Table 5. Generally, Vd, Rd, and Kd exhibited the lowest LYs and QALYs and incurred the lowest costs within their respective groups.

In the bortezomib group, the LYs gained ranged from 4.01 to 5.33, and the QALYs gained ranged from 2.42 to 3.15. Among the combination therapies, DVd demonstrated the most favorable survival outcomes in both LYs and QALYs. Vd had the lowest lifetime cost of ¥783,775, while PanVd incurred the highest lifetime cost of ¥2,801,773. The ICERs compared to Vd were ¥86,129 for PVd, ¥1,101,782 for SVd, ¥1,096,310 for DVd, ¥1,697,602 for Kd, and ¥5,174,354 for PanVd per QALY. Therefore, under the WTP threshold of ¥258,074, PVd was considered the most cost-effective therapy in the bortezomib group, while PanVd was the least cost-effective.

In the lenalidomide group, the LYs gained ranged from 5.13 to 6.38, and the QALYs gained ranged from 3.06 to 3.82. Among the treatments, DRd showed the most favorable survival outcomes in terms of both LYs and QALYs. Rd had the lowest lifetime cost at ¥840,509, while ERd had the highest lifetime cost at ¥2,827,676. Compared to Rd, the ICERs for IxaRd, KRd, DRd, and ERd were ¥1,605,712, ¥955,255, ¥851,933, and ¥5,095,300 per QALY, respectively. Thus, Rd was the most cost-effective therapy in the lenalidomide group, while ERd was the least cost-effective.

In the carfilzomib group, Kd generated 5.42 LYs and 3.19 QALYs, with lifetime costs of ¥1,961,624. Compared with Kd, DKd increased QALYs by 0.61 and costs by ¥1,373,001, resulting in an ICER of ¥2,250,821 per QALY. IsaKd increased QALYs by 0.61 compared with Kd but at an additional cost of ¥3,036,558, yielding an ICER of ¥4,977,964 per QALY. Therefore, Kd was the most cost-effective treatment in the carfilzomib group, while IsaKd was the least cost-effective.

Table 5 The result of base-case analysis over lifetime horizon

Strategies	LYs	QALY	Incremental QALY	Costs, ¥	Incremental Costs, ¥	ICER, ¥/QALY	Rank by Cost-effectiveness
Bortezomib Group							
Vd	4.01	2.42	Ref	783,775	Ref	Ref	2
PVd	4.22	2.56	0.14	795,833	12,058	86,129	1
SVd	4.79	2.80	0.38	1,202,452	418,677	1,101,782	3
DVd	5.33	3.15	0.73	1,584,081	800,306	1,096,310	4
Kd	5.05	2.94	0.52	1,666,528	882,753	1,697,602	5
PanVd	4.75	2.81	0.39	2,801,773	2,017,998	5,174,354	6
Lenalidomide Group							
Rd	5.13	3.06	Ref	840,509	Ref	Ref	1
IxaRd	5.39	3.23	0.17	1,113,480	272,971	1,605,712	2
KRd	6.00	3.53	0.47	1,289,479	448,970	955,255	3
DRd	6.38	3.82	0.76	1,487,978	647,469	851,933	4
ERd	5.86	3.45	0.39	2,827,676	1,987,167	5,095,300	5
Carfilzomib Group							
Kd	5.42	3.19	Ref	1,961,624	Ref	Ref	1
DKd	6.63	3.80	0.61	3,334,625	1,373,001	2,250,821	2
IsaKd	6.63	3.80	0.61	4,998,182	3,036,558	4,977,964	3

Vd bortezomib-dexamethasone, *Rd* lenalidomide-dexamethasone, *Kd* carfilzomib-dexamethasone, *DVd* daratumumab-bortezomib-dexamethasone, *SVd* selinexor-bortezomib-dexamethasone, *PVd* pomalidomide-bortezomib-dexamethasone, *PanVd* pomalidomide-bortezomib-dexamethasone, *ERd* elotuzumab-lenalidomide-dexamethasone, *DRd* daratumumab-lenalidomide-dexamethasone, *KRd* carfilzomib-lenalidomide-dexamethasone, *IxaRd* ixazomib-lenalidomide-dexamethasone, *Kd* carfilzomib-dexamethasone, *DKd* daratumumab-carfilzomib-dexamethasone, *IsaKd* isatuximab-carfilzomib-dexamethasone

Sensitivity analysis

In the one-way sensitivity analysis, the factors that had a significant impact on the estimated ICERs included the discount rate, the price of novel agents, and the utilities of progression-free survival during both initial and subsequent treatments. Notably, variations in each parameter did not alter the cost-effectiveness profile in the base-case results. According to the price threshold analysis, compared to PVd in the bortezomib group (Table S10), a 73.3% reduction in the price of daratumumab made DVd cost-effective, an 87.2% reduction in the price of carfilzomib made Kd cost-effective, and a 98.1% reduction in the cost of panobinostat made PanVd cost-effective. However, even with a 100% reduction in the price of the considered novel agents, neither combination therapies in the lenalidomide group nor in the carfilzomib group could achieve cost-effectiveness. For the PSA, the cost-effectiveness probability of PVd was 50% at a WTP of ¥75,505, and then it increased to 100%. Additionally, Rd and Kd almost reached a 100% probability under a WTP ranging from 0 to 6 times the per capita GDP in their respective groups (Fig. 4), indicating the robustness of the base-case analysis results.

According to the scenario analysis with a fixed treatment duration of 12 months for combination therapies in the initial treatment state (Table 6), the lifetime healthcare costs associated with each treatment decreased to varying extents, with the most significant reduction observed in the carfilzomib group. Concurrently, the QALYs associated with each treatment also declined, indicating potential trade-offs between cost savings and health outcomes. Despite these changes, the cost-effectiveness results within each group remained consistent. Specifically, PVd in the bortezomib group, Rd in the lenalidomide group, and Kd in the carfilzomib group remained the most cost-effective treatments.

Discussion

Over the past decade, the approval of novel antimyeloma agents and continuous updates to clinical recommendations for combination therapies have led to improved long-term survival for patients with MM. However, this also presents challenges for clinical decision-making in MM treatment, particularly in choosing combination therapies that maximize patient survival benefits while effectively controlling healthcare costs. Therefore, we conducted a cost-effectiveness analysis of combination therapies involving novel agents for first/second-relapse MM patients over a lifetime horizon, aiming to identify treatment options that offer good value for money. In this study, the selection of combination therapies for evaluation was guided by a systematic literature review

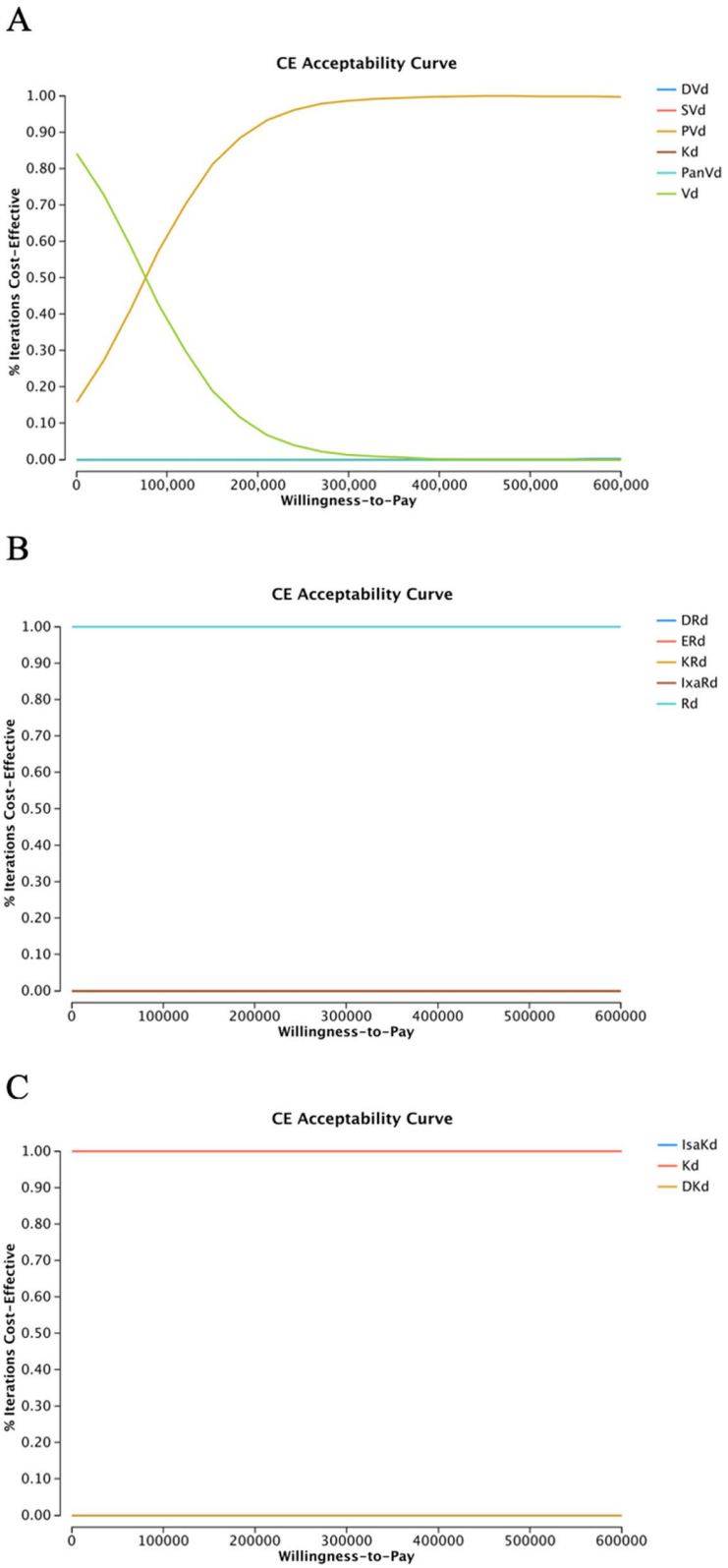

Fig. 4 Cost-effectiveness acceptability curves

Table 6 The result of scenario analysis (12-month treatment duration) over lifetime horizon

Strategies	LYs	QALY	Incremental QALY	Cost, ¥	Incremental Costs, ¥	ICER, ¥/QALY
Bortezomib Group						
Vd	3.72	2.23	Ref	747,026	Ref	Ref
PVd	3.93	2.33	0.10	725,352	−21,674	A.D
SVd	4.42	2.62	0.39	908,078	161,052	412,954
DVd	4.97	2.93	0.70	1,022,211	275,185	393,121
Kd	4.71	2.74	0.51	1,150,666	403,640	791,451
PanVd	4.42	2.60	0.37	2,636,796	1,889,770	5,107,486
Lenalidomide Group						
Rd	4.83	2.82	Ref	783,318	Ref	Ref
IxaRd	5.13	2.87	0.05	999,134	215,816	4,316,320
KRd	5.37	3.17	0.35	1,049,942	266,624	761,783
DRd	6.27	3.41	0.59	9,863,567	9,080,249	15,390,253
ERd	5.74	3.09	0.27	1,673,607	890,289	3,297,367
Carfilzomib Group						
Kd	5.14	2.86	Ref	879,879	Ref	Ref
DKd	6.29	3.44	0.58	1,348,696	468,817	808,305
IsaKd	6.30	3.45	0.59	1,772,247	892,368	1,512,488

Vd bortezomib-dexamethasone, *Rd* lenalidomide-dexamethasone, *Kd* carfilzomib-dexamethasone, *DVd* daratumumab-bortezomib-dexamethasone, *SVd* selinexor-bortezomib-dexamethasone, *PVd* pomalidomide-bortezomib-dexamethasone, *PanVd* pomalidomide-bortezomib-dexamethasone, *ERd* elotuzumab-lenalidomide-dexamethasone, *DRd* daratumumab-lenalidomide-dexamethasone, *KRd* carfilzomib-lenalidomide-dexamethasone, *IxaRd* ixazomib-lenalidomide-dexamethasone, *Kd* carfilzomib-dexamethasone, *DKd* daratumumab-carfilzomib-dexamethasone, *IsaKd* isatuximab-carfilzomib-dexamethasone, *A.D.* Absolute Dominant

and the latest clinical treatment guidelines. RCT data and calibration techniques were used to determine state membership in the Markov model. Cost parameters were informed by a retrospective analysis of real-world hospital medical data, while utility parameters were obtained through a cross-sectional survey on quality of life. As a result, the findings of this study can serve as decision-making references for various stakeholders within the Chinese context, including patients, families, healthcare providers, and government insurance agencies.

For patients with first/second-relapse MM, the selection of clinical treatments often requires careful consideration of individual patient conditions and drug sensitivities. In recent years, extensive RCTs have been conducted to explore various combination therapies for MM. In this study, based on the treatment regimens from the control arms of RCTs, all treatment strategies were categorized into three distinct groups, with economic evaluations conducted only within each group. This approach not only controls the heterogeneity of MM patients but also facilitates comparisons of treatment strategies within each group. In contrast, the study by Michael Dolph et al. integrated all treatment strategies into a single decision analysis model to perform cost-effectiveness analysis in patients with relapsed/refractory MM [20], which may undermine the reliability of the assessment results. For instance, directly comparing combination therapies for advanced MM with those for early-stage MM may lack clinical relevance. Furthermore, our study evaluated novel agents that are not yet marketed in China but are approved in the US and recommended by the National Comprehensive Cancer Network Guidelines for Multiple Myeloma, with the goal of assessing their economic value upon potential entry into the Chinese market.

Pater KK et al. developed a Markov model with six health states to simulate the treatment trajectory from first-line to fourth-line therapies in MM patients [19]. This model estimated the probability of remaining progression-free using parameterized PFS curves and calculated the probability of death based on both background mortality and adverse event-related mortality. Another study by Canada's Health Technology Agency (CHTA) used an individual-level model to simulate treatment trajectories from first-line to fourth-line therapies in MM patients, deriving transition probabilities from a real-world database [21]. In these two studies, the first approach did not incorporate OS data from RCTs to inform state membership, while the second approach relied on extensive real-world patient data to generate survival distributions. Building upon these methodologies, our study developed a Markov model with four health states to simulate a three-line treatment trajectory for first/second-relapse MM patients. The model framework to exclude the four-line treatment trajectory was based on the limited membership observed in the

fourth-line treatment state, which had minimal impact on model outcomes. A critical aspect of our study involved parameterizing survival curves to accurately determine state membership. The NICE DSU Technical Support Document 14 identified two key issues for survival analysis in economic evaluations [46]: first, the risk of a prolonged, flattened tail (right-skewed survival curve) when extrapolating survival data, and second, the necessity of performing a proportional hazards (PH) test when using HR to derive clinical efficacy. To address these issues, we employed the SMR to adjust the mortality rate for the general population, thereby establishing the background mortality rate for MM patients and mitigating the risk of long-term tailing. Furthermore, the results of the PH test confirmed that the PH assumption was valid for the majority of survival curves derived from the RCTs.

Our study suggests that triple-drug therapies provide only marginal QALY benefits compared to traditional dual-drug therapies, while significantly increasing treatment costs, thus challenging their cost-effectiveness. In the bortezomib group, DVd resulted in a modest increase of 0.74 QALYs compared to Vd, and ERd showed a slight increase of 0.60 QALYs compared to Rd. Similarly, both DKd and IsaKd demonstrated an increase of 0.61 QALYs compared to Kd. These modest QALY gains were primarily driven by the introduction of costly novel agents. Specifically, in this study, the monthly treatment costs for daratumumab (¥22,330 per cycle), selinexor (¥25,243), carfilzomib (¥14,392 per cycle), and ixazomib (¥16,597) were substantial. With prolonged treatment periods and continuous administration, the addition of these novel agents substantially increased overall treatment costs. Our findings align with those of previous studies. A study by Sen Wang et al. [47], from the perspective of the U.S. healthcare system, found that adding daratumumab to Rd and Vd regimens was not cost-effective. Similarly, studies by Dolph M et al. [22] and Patel KK et al. [18] indicated that SVd was not cost-effective compared to Vd in the U.S. healthcare context. A study by Jiang Qin et al. [48], evaluating the cost-effectiveness of DVd versus Vd in Chinese patients with relapsed and refractory MM, found an ICER of ¥631,164 per QALY for DVd, suggesting it was not cost-effective. Notably, due to the availability of only a generic version of pomalidomide in China, the treatment cost for pomalidomide is relatively low (¥5,317 per month). As a result, the lifetime cost of PVd treatment is only ¥12,058 higher than that of Vd, making PVd a cost-effective option.

It is important to recognize that while the cost-effectiveness analysis in this study suggests that some newer therapies may incur higher costs, these therapies could also offer significant clinical benefits, including improvements in survival outcomes and quality of life for patients. Additionally, the findings are limited by the inherent challenges of incorporating biological and dynamic risk factors from clinical trial data. Factors such as patient heterogeneity and the evolving nature of the disease are difficult to fully capture within the modeling framework and were not entirely addressed in this analysis. As a result, the findings may not be directly generalizable to the broader population of patients with relapsed/refractory multiple myeloma.

The results of the sensitivity analysis reinforced the robustness of the base-case findings. The price threshold analysis revealed that only three out of the ten treatments would become cost-effective if the price of novel agents were reduced by more than 70%. Even with a 100% price reduction for novel agents, the remaining treatments would still fail to achieve cost-effectiveness. Similarly, the study by CHTA [21] demonstrated that a price reduction of over 90% for daratumumab was required for the DVd regimen to be considered cost-effective. In the scenario analysis where the treatment duration in the initial treatment state was shortened to 12 months, the cost-effectiveness results remained consistent with the base-case analysis. These findings underscore the substantial costs associated with MM combination therapies that incorporate novel agents, highlighting that these costs are disproportionate to the survival benefits they offer.

Our study has several limitations. First, although we applied calibration methods to align the model's OS with the data observed in RCTs, the estimation of state membership relied on key assumptions that may not fully represent clinical practice. For example, our model assumed that patients would receive Vd, Rd, or Kd in subsequent treatment states, and Pd in the final treatment state. Furthermore, we used average HRs for OS and PFS across each combination therapy to adjust for differences in the probabilities of remaining progression-free in subsequent treatment states. However, clinical decision-making is often more complex, as the selection of subsequent treatments is influenced by multiple factors such as prior therapies, economic considerations, and patient health status. Despite these complexities, making reasonable assumptions was necessary to determine state membership, particularly given the limited available data.

Second, a key assumption in this study was patient homogeneity, based on the similarity of treatments in the control group. However, this assumption does not fully capture the various sources of heterogeneity between studies, such as genetic variations, differences in prognosis, and variations in study timing. Although this assumption was made to simplify the analysis, the failure to account for these factors may influence the interpretation and generalizability of the findings.

Third, the utility data for remission states in this study combined both partial and complete remission, as investigators encountered challenges in accurately distinguishing between the two based on questionnaire data and electronic medical records. However, aggregating the remission utility data into a single average may not fully reflect the distinct cost-effectiveness profiles associated with partial and complete remission, potentially limiting the precision of the results.

Fourth, accurately modeling the costs associated with multi-agent treatment regimens requires precise information on treatment discontinuations unrelated to disease progression. For instance, a notable number of patients in the DKd and Kd arms of the CANDOR trial discontinued carfilzomib, which significantly affects overall treatment costs due to its high acquisition cost. In this study, we assumed that discontinuations due to AEs occurred exclusively within the first 12 months of treatment. However, in the absence of individual patient data, the uncertainty regarding the temporal pattern of discontinuation complicates the accurate estimation of treatment costs, introducing potential bias into the cost-effectiveness analysis.

Fifth, due to budgetary and logistical constraints, the collection of cost and utility data for this study was limited to the Zhejiang Province region. As a result, the study's findings reflect the diagnostic and treatment patterns, as well as the healthcare costs associated with MM, specific to Zhejiang Province. Given that Zhejiang is one of China's most economically developed regions, the cost estimates in this study are likely higher than the national average. Therefore, caution should be taken when generalizing these findings to other regions or applying them to the country as a whole.

Finally, the survival curves for combination therapies were fitted based on data from foreign RCTs. Given the disparity in healthcare standards between domestic and foreign settings, particularly the limited accessibility to novel antimyeloma agents in China, this study may overestimate the clinical effectiveness during the subsequent and final treatment states in the Chinese context.

Conclusion

The findings of this economic evaluation indicate that, from the perspective of the Chinese healthcare system, the PVd regimen is the most cost-effective option for first/second-relapse MM patients who are sensitive to bortezomib. Similarly, the Rd regimen is the most cost-effective choice for those sensitive to lenalidomide, while the Kd regimen offers the most cost-effective option for patients sensitive to carfilzomib. Although the heterogeneity of subsequent treatment regimens was not thoroughly addressed, our study suggests that the healthcare costs of MM treatments are substantial and disproportionate to the survival benefits provided by combination therapies involving novel agents, raising significant concerns about the justification of their economic value in clinical practice.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13561-025-00611-0.

Supplementary Material 1.

Code availability

Available upon request.

Authors' contributions

Wu and Tang developed the economic model, performed the analyses and reviewed the data. Wu, Tang, Yang and Wang collected the data. Wu, Wang and Zhao interpreted the results and drafted the manuscript. All authors reviewed the data, interpreted the results and revised the manuscript. Gao and Dong supervised the whole study.

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Data availability

Data can be made available upon reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate

This research, involving the collection of cost and health utility data in MM patients, was approved by the Institutional Review Board of the School of Public Health, Zhejiang University (ZGL202008-1) and conducted in accordance with the Declaration of Helsinki. Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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