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# Supporting treatment decision-making for patients with multiple myeloma post-DRd in Italy: a multi-criteria decision framework

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## Abstract

**Background** A substantial unmet medical need exists for patients with Multiple Myeloma ineligible for autologous stem cell transplantation who relapse after first-line therapy with daratumumab, lenalidomide and dexamethasone (DRd). Three therapeutic options recommended for lenalidomide-refractory patients from EHA-ESMO guidelines are approved in Europe and reimbursed in Italy: carfilzomib and dexamethasone (Kd); pomalidomide, bortezomib and dexamethasone (PVd); selinexor, bortezomib and dexamethasone (SVd). This study aimed to identify key decision criteria and their relevance for assessing these alternatives from a multi-stakeholder perspective.

**Methods** Following ISPOR good practices, we developed a multiple-criteria decision analysis framework using the Measuring Attractiveness by a Categorical-Based Evaluation Technique method. Preferences were elicited from multiple stakeholders, including hematologists, methodologists, decision-makers, and patient representatives. Decision criteria were identified through a targeted literature review, discussed in a multi-stakeholder workshop, and shortlisted with a pragmatic literature review to assess data availability for each alternative.

**Results** The final multiple-criteria decision analysis framework comprised five main criteria: acquisition cost, efficacy, organizational impact, route of administration, and safety. Within the safety criterion, we considered six sub-criteria related to six adverse events: peripheral neuropathy, diarrhoea, nausea, fatigue, anaemia, and thrombocytopenia. Efficacy emerged as the most relevant criterion by most respondents, with a median weight of 38.1%, followed by the safety criterion (26.8% median weight), with peripheral neuropathy being the most relevant safety sub-criterion (34.9%). Based on elicited preferences, SVd was ranked as the most valuable therapy with a global score of 72, followed by PVd (44) and Kd (26), on account of its clinical efficacy. No significant differences in preferences were observed across different stakeholder groups.

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**Conclusions** This study provides valuable insights into the post-DRd treatment landscape for Multiple Myeloma, supporting decision-making from an Italian multi-stakeholder perspective.

**Keywords** Multiple Myeloma, MCDA, Italy, DRd, Kd, PVd, SVd, Preference study

## Background

Multiple Myeloma (MM) is a rare hematological tumor affecting B lymphocytes and is the second-most commonly diagnosed hematological malignancy in Europe [1]. In Italy, MM accounts for 1.5% of all diagnosed tumors, with an annual incidence of approximately 5,700 cases [2] and a median age at diagnosis of 68 years [3]. From a clinical perspective, MM represents a significant burden due to its chronic nature and complex treatment pathways [1, 3].

Although the therapeutic advancements over the past two decades have considerably improved the survival rates of MM patients [4], autologous stem cell transplantation (ASCT) remains the main treatment option contributing to long-term survival, leading to an overall survival greater than 10 years [5]. For newly diagnosed MM patients not eligible for ASCT, the standard of care in first line (1L) is currently represented by the combination daratumumab plus lenalidomide and dexamethasone (DRd) [1]. Recent real-world data [6] confirmed the remarkable clinical efficacy that DRd demonstrated in the MAIA trial [7–9], thus leading to significant therapeutic improvements for ASCT-ineligible patients. This therapeutic evolution has reshaped the treatment landscape, particularly in the 1L setting.

However, the introduction of DRd has also generated a substantial unmet medical need for patients who eventually relapse, leaving them with a limited number of treatment options in second line (2L) [10]. Considering the refractoriness to lenalidomide [11] and the principle of changing drug class at each relapse [1], only three 2L therapeutic options are currently authorized by the European Medicines Agency [12–14], recommended by the EHA-ESMO guidelines for lenalidomide-refractory patients post-DRd, and reimbursed in Italy [15–17]: carfilzomib and dexamethasone (Kd); pomalidomide, bortezomib and dexamethasone (PVd); selinexor, bortezomib and dexamethasone (SVd). Despite their availability, these regimens may not be always suitable for all patients, depending on factors such as their age, clinical profile, disease severity, medical background, and any existing comorbidities [11, 18, 19].

Within this context, it was deemed relevant to conduct a structured evaluation of 2L treatment options for post-DRd MM patients. The objective of this study is to assess Kd, PVd and SVd based on relevant decision-making criteria. The study relies on a Multi-Criteria Decision Analysis (MCDA) framework, which enables a scientific and systematic approach to identify key value elements among relevant criteria from a multi-stakeholder perspective and within a specific research and decision-making context.

In contexts involving multiple, potentially conflicting needs and priorities from several stakeholders, the MCDA methodology is increasingly recognized by Health Technology Assessment (HTA) agencies and industry experts as a valuable tool for drug evaluation [20, 21], with the potential of providing further support for decision-making in clinical practice. Therefore, this study contributes to the literature by applying MCDA to a real-world therapeutic dilemma, offering a structured framework to support clinical and policy decisions in MM treatment.

## Methods

The study was conducted following the methodological steps and good practices described by the ISPOR (International Society for Pharmacoeconomics and Outcomes Research) guidance on the implementation of MCDA to support healthcare decision-making: (1) identify the decision problem including stakeholder engagement, (2) select and validate the decision criteria with relevant stakeholders and measure the performance of alternatives, (3) elicit stakeholders value judgement through criteria weighting and scoring, (4) derive aggregate scores for each treatment option and conduct uncertainty analyses [22, 23]. We elicited stakeholders' preferences in terms of criteria weighting and value functions through an online survey applying MACBETH method (Measuring Attractiveness by a Categorical-Based Evaluation Technique). This is a widely recognized MCDA method recommended by ISPOR good practices that asks for qualitative judgements in pairwise comparisons, thus facilitating respondents' tasks [22–29]. In alignment with the principles and rationale of MCDA, all study phases were carried out from a multi-stakeholder perspective.

### Decision problem

In line with ISPOR good practices [22, 23], the definition of the decision problem requires the identification of objectives, relevant alternatives, and stakeholders, acknowledging constraints such as budget, time, and resources.

In terms of alternatives, from the initial list of 2L options post-DRd recommended by the 2021 EHA-ESMO guidelines [1], we excluded lenalidomide-containing and anti-CD38-containing regimens as they are unsuitable for lenalidomide/daratumumab-refractory

patients [11]. At the time of the study initiation, we considered Kd [30], PVd [31], and SVd [32] as they were the only alternatives approved at European level [12–14] and recommended by the 2021 EHA-ESMO guidelines for 2L lenalidomide-refractory patients post-DRd. At study completion, these three alternatives became the only alternatives reimbursed in Italy for these patients [15–17].

A total of 24 Italian stakeholders from various backgrounds and areas of expertise were involved in the evaluation of the three alternatives, following a continual stakeholders' engagement approach [33]. Among the 24 participants, there were 20 hematologists from the European Myeloma Network (EMN) Italy Working Group, one methodologist, two decision-makers, and one patient representative. A subgroup of these participants, which included four hematologists and the four non-clinicians, was selected to validate the decision criteria for inclusion in the MCDA and review the final results in two separate workshops.

#### Criteria selection and performance measurement

The identification of relevant criteria began with a targeted literature review through PubMed, cross-references, and targeted research. Initially we searched for studies related to MCDA applications in MM, but since only one study emerged, the search was subsequently expanded to MCDA in other hematological tumors ($N$ = 2), rare diseases ($N$ = 7), and orphan drugs ($N$ = 14). However, due to limited evidence regarding MM among the identified studies, the review was further extended to Discrete Choice Experiments (DCEs) in the same therapeutic area ($N$ = 11), given its similarities with the MCDA method [34] and its frequency in the literature [35]. Overall, the analyzed papers reported 29 different criteria. Of these criteria, we selected those mentioned in the MCDA studies related to hematological tumors and those mentioned in at least 20% of the identified studies, resulting in a preliminary list of 18 criteria. In *Supplementary Material 1*, Figure S.1 outlines these criteria and summarizes the selection process used to define the final list.

Preliminary criteria were then assessed based on the following MCDA requirements [22]: 1) comprehensively capture relevant decision-making factors under the decision problem (*completeness*), 2) avoid unnecessary or non-operational criteria which would yield equal performance for all considered alternatives (*non-redundancy*), 3) avoid having multiple criteria that measure the same factor (*non-overlap*), and 4) avoid judging one criterion based on another (*preference independence*). The main reason for exclusion of criteria from the preliminary list was redundancy, e.g. the criteria *"unmet need," "therapeutic impact," "population size," population priorities,"* and *"common goal"* were contextual to a disease setting rather than to a specific treatment alternative. For all compliant criteria ($N$ = 9), definitions were formulated to ensure consistency with ISPOR requirements for individual criteria to be *unambiguous*, *comprehensive*, *direct*, *operational*, and *understandable* [22].

On 13th September 2023, a workshop was held to decide which criteria should be included in the questionnaire and validate their attributes and definitions. A week before the workshop, participants were provided calling notes with theoretical and methodological background on the MCDA framework together with a summary of earlier steps in criteria selection, which were also presented at the beginning of the workshop.

After the workshop, we conducted a pragmatic literature review to assess data availability to define the final list of criteria and inform the performance matrix. Methodology and results of the research are described in *Supplementary Material 1*, Appendix 1. In the performance matrix, each treatment option was allocated a performance level for each criterion and sub-criterion. Then we calculated the improvements within each criterion, i.e. the gaps between the best performance level and the worst performance level, as required by the MACBETH method [28]. The perceived importance of moving from the alternative with the worst performance level to the alternative with the best performance level in each criterion can vary based on the overall relevance of the criterion, as well as on the improvement size.

#### Weighting and scoring

After defining the performance matrix, we developed an online questionnaire to elicit stakeholder preferences. The questionnaire launch was anticipated by three training sessions, held between 15th January and 9th February 2024, aimed at describing the MACBETH method to the participants and show the questionnaire structure and functionalities. On 12th March 2024, an email was sent to all stakeholders with a unique link to access the online questionnaire. Detailed instructions and practical examples were provided on the first page and were also accessible from each questionnaire page through an information button. The questionnaire was organized into four sections, described in detail in *Supplementary Material 1*, Appendix 2. Sample questions from weighting and scoring sections are illustrated by Figs. 1 and 2, respectively.

#### Results computation and examination

Answers were collected from each participant and analyzed with Microsoft Excel. Specifically, median weights for each main criterion and sub-criterion were computed based on weight distributions assigned by participants in weighting sections, to identify an overall ranking of

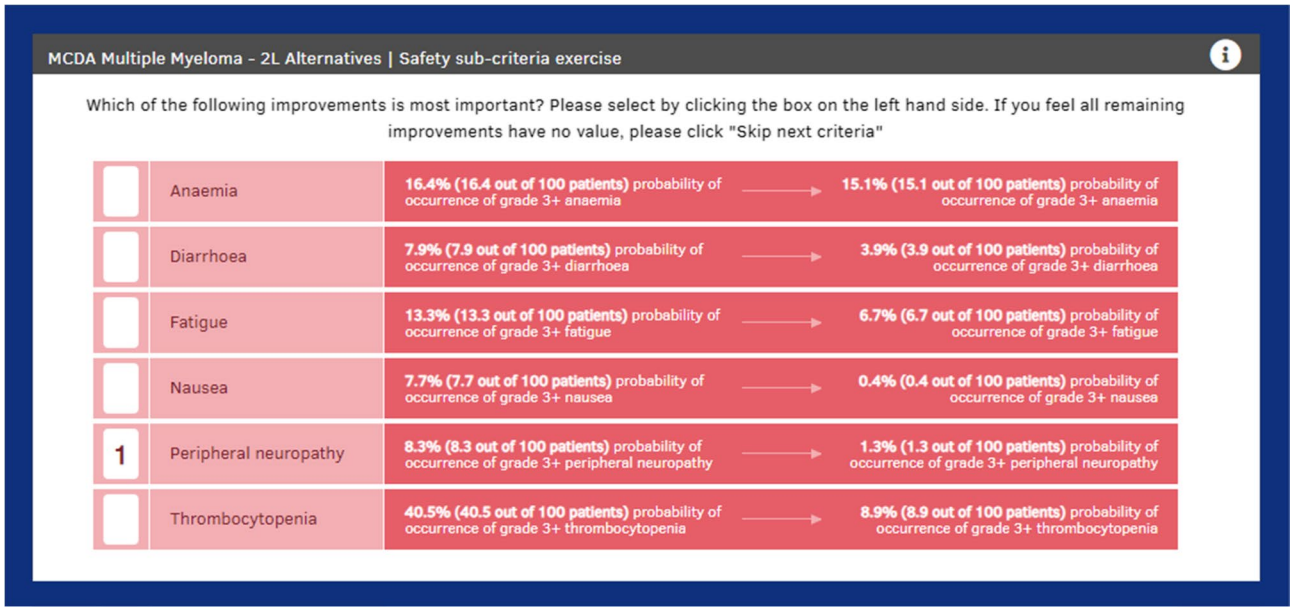


**Fig. 1** Sample question from questionnaire Sect. 1 for weighting safety sub-criteria (adverse events). At the top of the page respondents were given a task and instructions on how to perform it. In the top-right corner, the info button provided respondents the instructions needed to perform the exercise

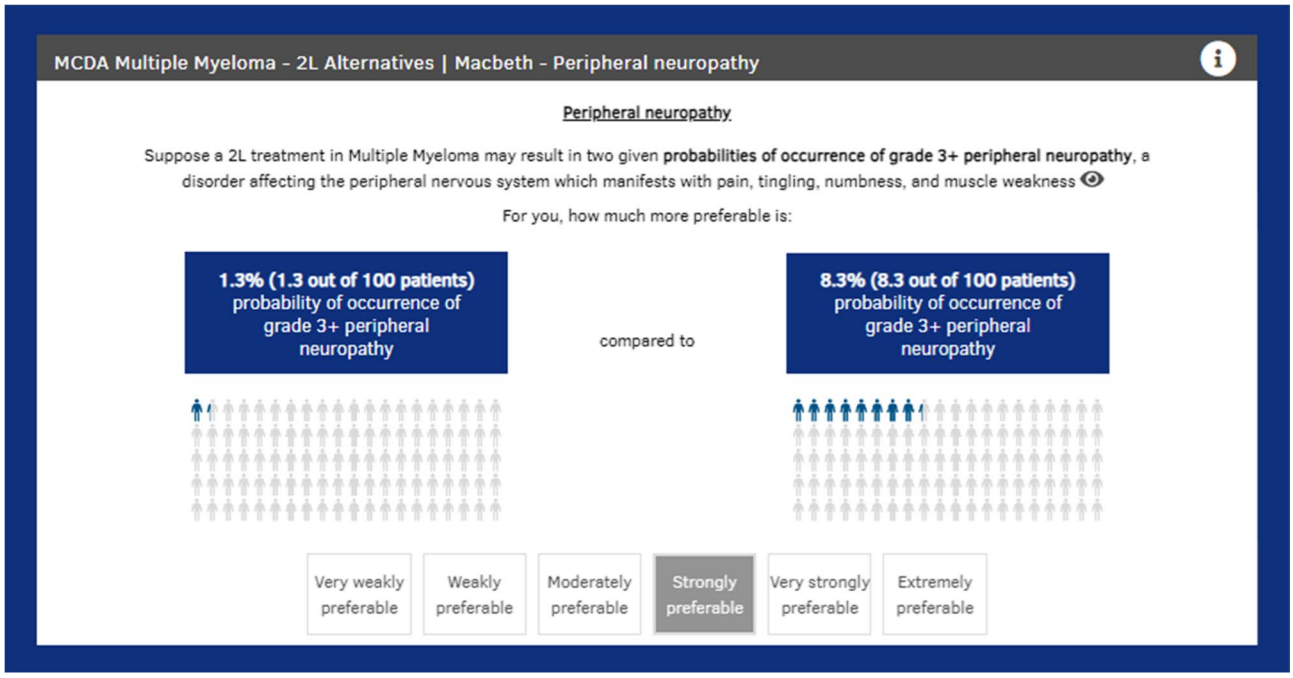


**Fig. 2** Sample question from questionnaire Sect. 2 for scoring *"peripheral neuropathy"*. In addition to a simple definition of the adverse event, respondents were also given – by clicking on the fish-eye – definitions for its grade 3 and 4 retrieved from the Common Terminology Criteria for Adverse Events (CTCAE) dictionary. To answer the question, respondents could choose among seven semantic categories. In the top-right corner, the info button recalled respondents the instructions needed to perform the exercise

criteria and sub-criteria. Next, qualitative answers from scoring sections were converted into numeric scores and value functions through the MACBETH optimization algorithm [36]. Frequencies of each value function profile were then assessed by criteria and sub-criteria. Finally, we computed both the individual and global aggregate scores of the three alternatives (Kd, PVd, and SVd), as described in *Supplementary Material 1*, Appendix 3.

As per ISPOR good practices [22, 23], uncertainty analyses were performed to test the robustness and generalizability of results. In line with previous studies implementing the MCDA methodology for drug

evaluation in Italy [37, 38], a first sensitivity analysis was conducted by stratifying results by stakeholder type (i.e., clinicians and non-clinicians). A second sensitivity analysis was then implemented by excluding criteria identified as sources of *"parameter uncertainty"* [22, 23] and accordingly increasing the weights for the remaining criteria.

On 12th July 2024, a second workshop was held to explain the methods used for weighting and scoring and the rationale behind the aggregation function, to discuss the results, to assess potential discrepancies among the participants expectations, and to gather their interpretation, possibly identifying further sensitivity analyses. A week before the workshop, participants were provided calling notes with a summary of the study phases until performance matrix development and questionnaire drafting, together with an anticipation on results regarding weighting of main criteria.

## Results

All the study phases described in the *"Criteria Selection and Performance Measurement"* section resulted in the following final list of five criteria: (1) *"efficacy"*, measured by progression-free survival (PFS) hazard ratio (HR) with respect to Vd for lenalidomide-refractory patients; (2) *"safety"*, subsequently defined by sub-criteria; (3) *"acquisition cost"*, i.e. annualized cost of combination therapy based on ex-factory prices plus wastage; (4) *"route of administration"*, i.e. combined route of administration of the molecules in the combination therapy; (5) *"organizational impact"*, which included posology schedule, variation, and setting. The *"safety"* criterion was then composed by 6 sub-criteria corresponding to the following grade 3+ adverse events, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 6.0: *"peripheral neuropathy," "diarrhoea," "nausea," "fatigue," "anemia,"* and *"thrombocytopenia"*. The safety sub-criteria were measured through the incidence rates of these adverse events derived from most recent cut-off data from the clinical trials of the three therapeutic options. Table 1 provides details on criteria and sub-criteria definitions, alternatives' performance matrix, and sources used to inform it.

All 24 participants answered the online questionnaire between 12th March and 7th May 2024. In the next sections, results are reported separately for the weighting and scoring sections of the questionnaire. Finally, the overall assessment of Kd, PVd, SVd arising from elicited preferences is illustrated.

**Table 1** Performance matrix of Kd, PVd, SVd

| Criterion | Description | Kd | PVd | SVd | Source |
|---|---|---|---|---|---|
| Efficacy | *PFS HRs with respect to Vd derived from a network meta-analysis on lenalidomide-refractory patients* | 0.80 [0.39; 1.73] | 0.66 [0.32; 1.34] | 0.52 [0.23; 1.21] | Kastritis 2023 |
| Safety | *Percentage of patients experiencing each grade 3 + adverse event at RCTs most recent data cutoff date* | | | | Nexpovio EPAR, Beksac 2024, Dimopoulos 2017 |
| | *Peripheral neuropathy* | 1.3% | 8.3% | 4.6% | |
| | *Diarrhoea* | 3.9% | 7.9% | 6.7% | |
| | *Nausea* | 1.9% | 0.4% | 7.7% | |
| | *Fatigue* | 6.7% | 9.7% | 13.3% | |
| | *Anemia* | 16.4% | 15.1% | 16.4% | |
| | *Thrombocytopenia* | 8.9% | 28.1% | 40.5% | |
| Acquisition cost | *Annualized cost of therapy based on ex-factory prices after mandatory reductions, and including wastage* | 142,559 € | 147,560 € | 116,628 € | RCTs, Italian Official Journal, Farmadati |
| Route of administration | *Combined route of administration of the molecules in the doublet/triplet combination* | Oral + IV | Oral + SC | Oral + SC | RCTs |
| Organizational impact | *Posology schedule, variation, and setting (home/hospital)* | Posology with changing dosage across treatment cycles, to be administered in the hospital setting | Posology with changing frequency of administration across treatment cycles, to be administered at home | Posology with constant frequency of administration across treatment cycles, to be administered at home | RCTs |

*K* Carfilzomib, *d* Dexamethasone, *P* Pomalidomide, *V* Bortezomib, *S* Selinexor, *PFS* Progression-Free Survival, *HRs* Hazard Ratios, *RCTs* Randomized Clinical Trials, *IV* Intravenous, *SC* Subcutaneous

### Weighting

Based on the median weights observed in Fig. 3, efficacy (38.1%, Interquartile Range [IQR]: 33.3–43.9%) and safety (26.8%, IQR: 25.5–28.7%) emerged as factors having a priority role in the context of post-DRd MM, followed by route of administration (15.1%, IQR: 10.9–18.8%), organizational impact (8.9%, IQR: 7.4–12.6%), and acquisition cost (6.4%, IQR: 4.4–10.4%). Weight distribution revealed consistency among respondent preferences for both efficacy and safety, despite the presence of few outlier weights for the latter. Overall, 20 of the 24 participants (83.3%) ranked efficacy as the most important criterion and 18 out of 24 participants (75.0%) ranked safety as the second most important criterion, emphasizing the importance of treatment effectiveness and tolerability in MM management. Instead, a lower degree of consensus emerged for route of administration, organizational impact, and acquisition cost weights, with frequently overlapping interquartile ranges (10.9–18.8%, 7.4–12.6%, and 4.4–10.4%, respectively).

No meaningful differences in weight distribution emerged between clinicians and non-clinicians. The largest differentials were observed for safety with clinicians having lower median weights than non-clinicians (26.8% vs. 29.5%), and higher median weights for route of administration (15.7% vs. 12.2%).

Relative to the safety sub-criteria, median weights indicate the following ranking (Fig. 4) of adverse events: peripheral neuropathy (34.9%, IQR: 27.2–39.3%), thrombocytopenia (16.4%, IQR: 7.4–26.0%), diarrhoea (15.2%, IQR: 7.4–16.7%), nausea (10.9%, IQR: 4.6–25.3%), fatigue (9.9%, IQR: 4.9–16.5%), and anemia (3.4%, IQR: 1.6–7.9%). Peripheral neuropathy was identified as the most important adverse event by 20 out of 24 participants (83.3%), while anemia emerged as the least important adverse event. Weights for all other adverse events were highly heterogenous with overlapping interquartile ranges.

The heterogeneity in the perceived importance of adverse events by the participants may be attributed to substantial differences across clinicians' and non-clinicians' weights. Clinicians ranked peripheral neuropathy as the most critical sub-criterion (34.9%), followed by nausea (22.2%), diarrhoea (15.6%), and thrombocytopenia (14.3%). In contrast, non-clinicians prioritized thrombocytopenia as the most important (37.3%), followed by peripheral neuropathy (35.3%), anemia (9.3%), and fatigue (4.7%). Overall, different median weights emerged among clinicians and non-clinicians for all sub-criteria except for peripheral neuropathy: 14.3% vs. 37.3% for thrombocytopenia, 15.6% vs. 1.8% for diarrhoea, 22.2% vs. 2.3% for nausea, 10.4% vs. 4.7% for fatigue, and 3.1% vs. 9.3% for anemia.

### Scoring

Figure 5 depicts the frequency of each value function profile across criteria and sub-criteria. Overall, the scoring exercise revealed a prevalence of linear preferences: participants attributed the same preference to improvements from the worst performance level to the intermediate performance level and from the intermediate performance level to the best performance level. Specifically, a linear value function represented most preferences for route of administration (62.5%), organizational impact (66.7%), acquisition cost (75.0%), and all adverse events except for nausea.

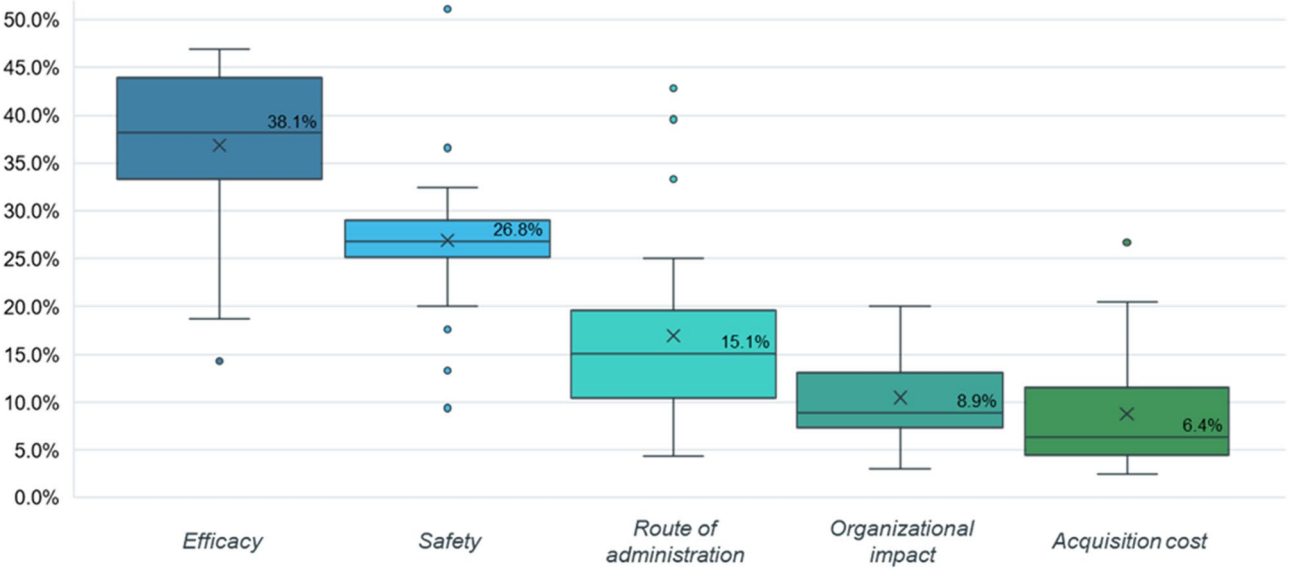


**Fig. 3** Distribution of weights of main criteria, based on 24 stakeholders' preferences. Median weights are reported on each box

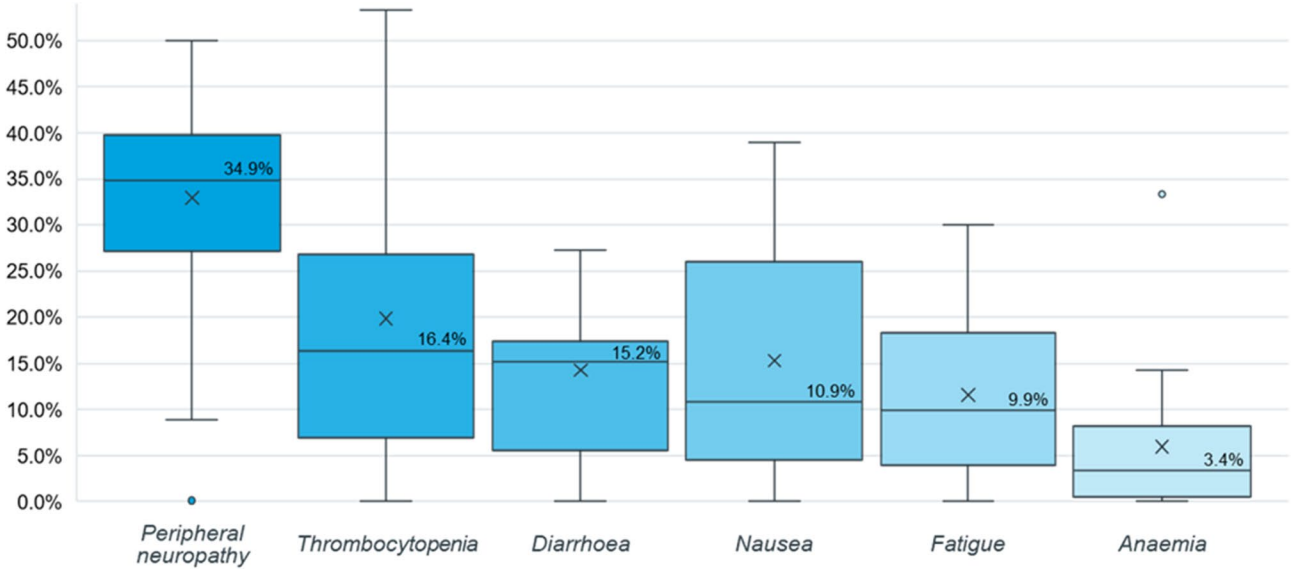


**Fig. 4** Distribution of weights of safety sub-criteria, based on 24 stakeholders' preferences. Median weights are reported on each box

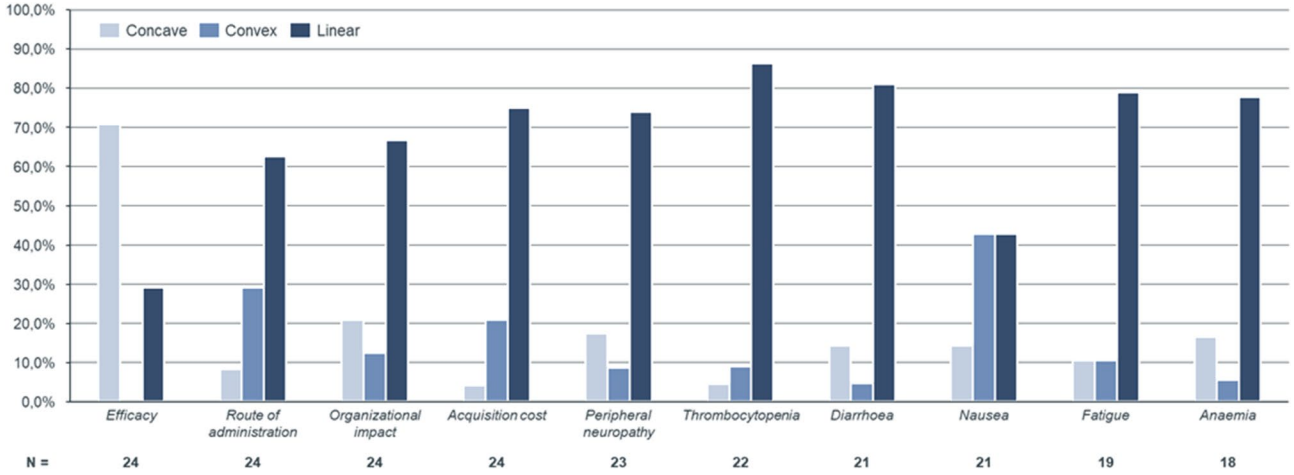


**Fig. 5** Proportion of value function profiles, by main and sub-criterion. Number of questionnaire respondents who completed the scoring exercise are reported below each criterion, as assigning a 0% weight to a safety sub-criterion implied not being asked scores

For the efficacy criterion, in terms of PFS HR vs. Vd, an improvement from 0.80 to 0.66 was valued more than an improvement from 0.66 to 0.52 by most participants (70.8%), meaning preferences were mostly concave. This result highlights that, in the setting of MM, a 2L treatment option post-DRd which increases PFS is more valuable when average PFS from existing treatments is lower. For the nausea sub-criterion, 42.9% participants valued an improvement from 7.7% to 4.0% of patients experiencing grade 3+ nausea less than an improvement from 4.0% to 0.4% (i.e., convex preferences), while another 42.9% valued improvements equally (i.e., linear preferences).

These results were consistent when stratified by clinicians' and non-clinicians' preferences. Scenario analyses only revealed a larger share of concave preferences among non-clinicians than among clinicians for the route of administration (50.0% vs. 0.0%); non clinicians attributed more importance to improvements from intravenous to subcutaneous administration than from subcutaneous to oral administration.

### Aggregate Scores

As observed in Fig. 6, the distribution of aggregate scores, computed through an additive model with participant-specific weights and scores, indicates an overall agreement as interquartile ranges for Kd, PVd, and SVd never overlap. In terms of median global scores, SVd emerged as the most valued alternative with 72.3 (IQR: 64.2–76.0), followed by PVd and Kd totaling 43.6 (IQR: 37.6–45.4) and 26.0 (IQR: 24.4–28.8), respectively. It is worth noting that the entire distribution of SVd aggregate scores lies above both PVd and Kd maximum scores; this is because

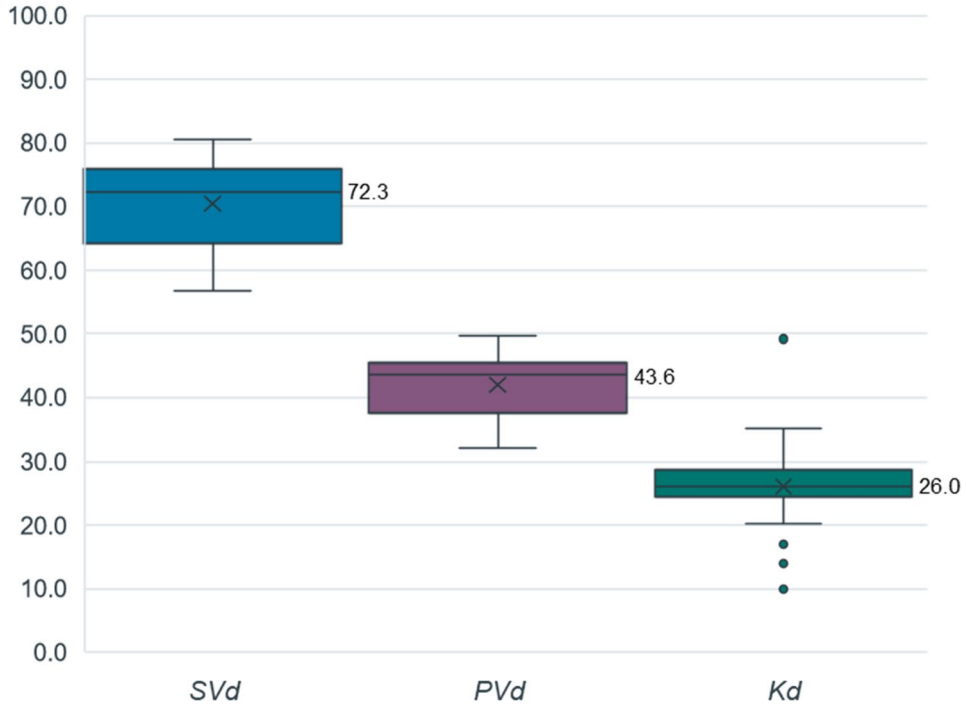


**Fig. 6** Distribution of aggregate scores of alternatives, based on 24 stakeholders' preferences. Median aggregate scores are reported beside each box

100% of participants ranked SVd first. A clear consensus also emerged regarding the relative ranking of PVd and Kd as 23 out of 24 participants (95.8%) ranked PVd > Kd; only one participant ranked Kd > PVd, attributing an outlier score of 49.2 to Kd. Moreover, 100% of clinicians had preferences compatible with SVd > PVd > Kd.

In the sensitivity analyses, the acquisition cost criterion was identified as an uncertain parameter for two reasons. First, in Italy like in other European countries, the publicly disclosed ex-factory prices – which were used to compute reference levels – do not correspond to the actual prices at which the National Health Service buys drugs, as they contain confidential and commercial discounts ranging from a few percentage points up to several tens of points [39]. Second, at the time of study, pomalidomide (i.e., one of the molecules in the combination PVd) was expected to lose its exclusivity later in 2024, leading to the market entry of more affordable equivalent versions. By removing the acquisition cost criterion, the global score of SVd reduces from 72.3 to 69.5. Conversely, by removing the acquisition cost criterion, the global score of PVd improves from 43.6 to 46.5, because PVd had the highest annualized cost among the three alternatives, and the global score of Kd improved from 26.0 to 26.5 since a larger weight was then attributed to the safety criterion.

## Discussion

The aim of this study was to identify key value elements in the treatment choice for patients with MM previously exposed to DRd and refractory to lenalidomide, by assessing the three relevant alternatives recommended by the ESMO-EHA guidelines (Kd, PVd, and SVd) [1, 11–14] and currently being reimbursed in Italy [15–17]. An MCDA framework using the MACBETH method was implemented to elicit Italian preferences from relevant stakeholder profiles, i.e. hematologists, methodologists, decision-makers, and patient representatives. In line with the methodological steps recommended by ISPOR in its MCDA good practices [22, 23], these stakeholders had a central role in the study, as they were involved throughout the entire study, expressed their preferences in the questionnaire, and were engaged in two workshops to validate methods and results. The initial workshop was conducted before the questionnaire launch during which eight stakeholders discussed the decision problem to ensure the real-world relevance of the decision criteria. In the final workshop, conducted after completion of weighting and scoring exercises by the 24 participants, these eight stakeholders also reviewed and commented on results, providing potential interpretations and implications.

In post-DRd MM, efficacy – measured by the PFS HR of each therapeutic option vs. Vd – emerged as the most important criterion, with a median weight of 38.1% (IQR: 33.3–43.9%). In the second workshop, clinicians confirmed the meaningfulness of such weight, noting that

PFS is also the primary driver for prescriptions in clinical practice. Although the PFS improvement was not statistically significant, as shown by the confidence intervals reported in the questionnaire, it was highly valued by both clinicians and non-clinicians for suggesting promising clinical prospects in terms of response to treatment. This reasoning is further supported by the scoring exercise results, where the predominance of concave preferences indicated prioritizing better health outcomes for those with poorest health status. The importance attributed to efficacy must be considered in light of the unmet medical need for post-DRd MM patients in Italy [10], who are generally elderly, with multiple comorbidities and severe disease histories [11, 18, 19].

Safety was the second most important criterion, with a median weight of 26.8% (IQR: 25.5–28.7%), but clinicians and non-clinicians diverged in weighting improvements in adverse events. As emerged during the second workshop, clinicians deemed non-hematological adverse events (peripheral neuropathy, nausea, and diarrhoea) as more relevant since they are considered harder to manage. On the other hand, due to its proposed improvement of approximately 30% points, non-clinicians considered thrombocytopenia the most important sub-criterion with a median weight of 37.3%, much higher than the median weight of 14.3% attributed by clinicians.

All remaining criteria were given minor importance, with a median weight of 15.1% for route of administration and of 8.9% for organizational impact. Despite these small weights, in the second workshop clinicians recognized that the aspect of patient management from an organizational perspective is reflected in both criteria, i.e. for example the administration setting is often a consequence of its route of administration. Therefore, in a hypothetical scenario, if route of administration was excluded from the MCDA, its weight would have been added to the weight of organization impact rather than been dispersed to the other criteria, resulting to almost a quarter of the total value spectrum.

Finally, acquisition cost was identified as the least important criterion by 62.5% of participants, with a median weight of 6.4%. The weighting exercise also revealed that non-clinicians (i.e., the cluster decision-makers belong to) assigned similar weights to the acquisition cost as clinicians. During the second workshop, stakeholders agreed on the criterion being given little importance due to the relatively small improvement of approximately €30,000 in the acquisition costs of the three alternatives, the use of ex-factory prices, and the expected loss of exclusivity of pomalidomide.

In the final ranking of alternatives, SVd was ranked first with a global score of 72.3, followed by PVd (43.6), and Kd (26.0). Moreover, 23 out of 24 participants had preferences compatible with SVd >PVd >Kd. In the second workshop, clinicians validated both the overall ranking and scores differentials. For PVd and Kd, this was based on clinical practice, whereas for SVd their judgement was grounded on their expectations arising from SVd randomized clinical trial results [32, 40] – as the treatment had not yet been reimbursed in Italy at study time.

By demonstrating the potential of a multi-stakeholder approach and considering the continuous evolution of MM treatment guidelines [41], this work underscores the feasibility and importance of maintaining active research and drug evaluation efforts within the clinical and scientific community.

Although ISPOR good practices [22, 23] were strictly followed throughout the study to ensure comprehensiveness of the decision-making process and address needs and priorities of all involved stakeholders, this study presents some limitations. First, the panel of stakeholders was mainly composed of clinicians, potentially resulting in limited representation of the needs and priorities of decision-makers and patients. This issue was addressed by assessing results by profile (i.e., clinicians vs. non-clinicians), which revealed that preferences did not differ substantially among subgroups. Second, the *"acquisition cost"* criterion was a source of parameter uncertainty [22, 23] given the confidentiality of net prices and the expected loss of exclusivity of pomalidomide, which would have occurred later in 2024. This limitation was addressed through a scenario analysis where this criterion was removed; the results of this scenario analysis were similar to the baseline results due to the low median weight associated with the acquisition cost criterion. Third, although during the first workshop patient quality of life (QoL) domain emerged as a relevant criterion, the final MCDA framework did not include it due to insufficient data retrieved through pragmatic literature review. However, although QoL is a critical component of decision-making in MM treatment – as per both clinicians [42, 43] and patients [44], during the final workshop it emerged that efficacy and safety are main drivers of QoL, and those criteria are therefore expected to partially reflect QoL. Fourth, no adverse events related to cardiotoxicity, which is a known carfilzomib side-effect [45, 46], were included among safety sub-criteria because no data on such events for SVd was available in the public domain. Nevertheless, as highlighted by clinicians during the final workshop, since SVd is expected to have lower cardiotoxicity compared to both considered alternatives, its inclusion as a sub-criterion would have confirmed the obtained ranking. Similarly, following an approach outlined in the literature [38] for measuring the safety domain, only grade 3+ treatment-related adverse events were included in the MCDA. Although no measurements for grade 1–2 ones were included, despite their potential significant impact on patient daily lives, the decision was

made to limit respondent time and cognitive burden typically required for studies with a larger number of criteria [22]. Finally, clinical criteria – namely, *"efficacy"* and *"safety"* – were assessed using clinical endpoints derived from the randomized clinical trials of the three treatment alternatives. However, these trials did not necessarily include post-DRd patients with refractoriness to both lenalidomide and daratumumab, making it challenging to generalize the results to the population of interest in this study. Although for *"efficacy"* this was partially addressed using results from a network meta-analysis focused on lenalidomide-refractory patients [47], the issue becomes more evident under the *"safety"* criterion, where alternatives are assessed through a naïve indirect comparison.

## Conclusions

To the best of the authors' knowledge, this study represents the first implementation of the MCDA methodology to assess therapeutic alternatives in post-DRd MM in Italy. This approach provides a valuable contribution to decision-making within a therapeutic area characterized by a high unmet medical need [10].

More generally, the study establishes a framework for a structured approach to evaluate and manage access, use, and prioritization of treatments in MM. This aligns with the expectations of HTA agencies and industry experts, who increasingly advocate for a multi-criteria approach in value-based drug evaluation [20, 21].

Within this framework, SVd emerged as the preferred treatment option for patients with post-DRd MM as per Italian stakeholders. While its selection was primarily driven by its clinical efficacy, the study also revealed strong consensus across different stakeholder profiles suggesting great alignment between clinical decisions and system-level priorities.

### Abbreviations

| | |
|---|---|
| MM | Multiple Myeloma |
| ASCT | Autologous stem cell transplantation |
| 1L | First line |
| DRd | Daratumumab, lenalidomide, dexamethasone |
| 2L | Second line |
| EHA-ESMO | European Hematology Association - European Society for Medical Oncology |
| Kd | Carfilzomib, dexamethasone |
| PVd | Pomalidomide, bortezomib, dexamethasone |
| SVd | Selinexor, bortezomib, dexamethasone |
| MCDA | Multi-Criteria Decision Analysis |
| HTA | Health Technology Assessment |
| ISPOR | International Society for Pharmacoeconomics and Outcomes Research |
| MACBETH | Measuring Attractiveness by a Categorical-Based Evaluation Technique |
| EMN | European Myeloma Network |
| N | Number |
| DCE | Discrete Choice Experiment |
| PFS | Progression-Free Survival |
| HR | Hazard Ratio |
| 3+ | 3 or higher |
| CTCAE | Common Terminology Criteria for Adverse Events |
| IQR | Interquartile Range |
| QoL | Quality of Life |
| RCTs | Randomized Clinical Trials |
| IV | Intravenous |
| SC | Subcutaneous |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-15083-y.

Supplementary Material 1

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### Authors' contributions

M.Cai., B.C., P.L.M., R.M., and F.F. designed the study, collected the literature, conducted both workshops, and run the analysis of questionnaire answers; M.B., F.B., G.B., P.L.C., C.G., P.M., M.R., and R.Z. participated in both workshops; M.B., A.B., F.B., S.B., G.B., P.L.C., M.Cav., A.C., L.D.P., D.D., F.D.R., C.G., F.G., M.G., N.G., V.M., P.M., M.O., F.P., M.T.P., M.R., P.T., E.Z., and R.Z. answered the questionnaire; M.Cai., B.C., P.L.M., R.M., and F.F. wrote the first manuscript draft; all authors revised the manuscript and approved the final version to be published.

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### Data availability

Results represent outcomes of IQVIA and Decision Eyes proprietary codes which cannot be publicly disclosed due to confidentiality. All other data used to build the performance matrix are either provided by public agencies, institutions, or literature contributions and are available online as appropriately cited in text.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

M.B., A.B., F.B., S.B., G.B., A.M.C., P.L.C., M.Cav., A.C., L.D.P., D.D., F.D.R., C.G., F.G., M.G., N.G., V.M., P.M., M.O., F.P., M.T.P., M.R., P.T., E.Z., and R.Z. received a professional fee to participate in the study by Menarini Stemline Italia S.r.l. At the time of project initiation and drafting of the paper, M.Cai., B.C., P.L.M., R.M., and F.F. were employed by IQVIA Italy, which receives professional service fees for a large number of activities in biopharma from a large number of sponsors, including Menarini Stemline Italia S.r.l.
M.B. has received honoraria from Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol Myers Squibb, and AbbVie; has served on the advisory boards of Janssen and GlaxoSmithKline; and has received research funding from Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol Myers Squibb, and Mundipharma. A.B. has served on the advisory boards of Janssen, Amgen, GlaxoSmithKline, and Pfizer. S.B. has received honoraria from Amgen, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Sanofi, and AbbVie; has served on the advisory boards of Bristol Myers Squibb, Janssen, Takeda, Pfizer, Stemline Therapeutics, and Oncopeptides; and has received consultancy fees from Sanofi. M.Cav. has received honoraria from Janssen, Celgene, Amgen, Bristol Myers Squibb, Takeda, AbbVie, Sanofi, and Adaptive Biotechnologies; and is a member of speakers' bureaus for Janssen and Celgene. L.D.P. has served on the advisory boards of AbbVie, Amgen, Celgene, and Janssen. F.G. has received honoraria from Amgen, Celgene, Janssen, Takeda, Bristol Myers Squibb, AbbVie, GlaxoSmithKline, and Sanofi; has served on the advisory boards of Amgen, Celgene, Janssen, Takeda, Bristol Myers Squibb, AbbVie, GlaxoSmithKline,

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## Publisher's Note