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Research paper

An Italian Delphi consensus on the current and future burden and clinical management of lenalidomide-refractory multiple myeloma

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ABSTRACT

Background: Refractoriness to lenalidomide in patients treated for multiple myeloma (MM) is increasing. Exploring opinions of experts on the burden of lenalidomide-refractory MM and on current and future therapeutic options is critical for optimizing care in this setting.
Methods: From January to July 2024, we conducted a modified Delphi study involving 12 haematologists in Italy. The project followed the best practices for Delphi studies, including anonymity, iteration, controlled feedback, definition and analysis of consensus.
Results: Two rounds were required to complete the Delphi process. Participation of clinicians was complete. Experts agreed that more than 80% of Italian patients starting second-line therapy are expected to be refractory to lenalidomide in 2026. Full consensus emerged (100% of panellists) that the main clinical unmet needs in this patient setting are the approval and access to novel (immuno)therapies with new mechanisms of action. More than two-thirds of panellists also agreed, in principle, to the use of T-cell redirecting therapies, including CAR-T and bispecific antibodies, from the second-line of treatment onwards. No clear patient characteristics emerged to drive therapeutic options in specific subgroups of subjects with lenalidomide-refractory MM.
Conclusions: This Delphi consensus study reported a major clinical unmet need of newly available and accessible therapeutic options for lenalidomide-refractory MM, already starting from the second-line of treatment.

1. Introduction

Multiple myeloma (MM) is a haematological malignancy characterized by the accumulation of monoclonal plasma cells within the bone marrow [1]. MM represents approximately 1% of all malignancies, with almost 190,000 new cases diagnosed worldwide in 2022 and a uniformly increasing trend in incidence [2,3].

Substantial improvements were achieved during the last decades in the treatment of MM, through the development of novel, effective therapies such as proteasome inhibitors, immunomodulatory drugs and monoclonal antibodies, and through their implementation in combined treatment regimens [4,5]. Lenalidomide, a second-generation immunomodulatory drug, is a treatment mainstay for MM in the front-line and relapsed refractory settings, either as monotherapy or in combination with other drugs [6–9]. Generic lenalidomide, available in Italy since 2022, showed comparable response rates and safety profile as original lenalidomide [10]. An increasing proportion of MM patients treated with lenalidomide or lenalidomide-based regimens becomes refractory to this drug [1,11], and their management in everyday clinical practice represents an emerging therapeutic challenge [12–14]. Recent data from Italy indicate that about two-thirds of MM patients who started frontline treatment from 2021 onwards, and experienced disease relapse, are lenalidomide refractory, and this proportion will increase rapidly in the near future [14]. A systematic review of

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Real-World studies found worse treatment outcomes in lenalidomide refractory MM patients with a high number of earlier lines of treatment as well as in those who were refractory to several drug classes [15].

In consideration of the great heterogeneity in treatment strategies for MM across countries [16], driven by different healthcare systems, time to access and reimbursement of emerging therapies, and indications for their use based on local clinical practice guidelines, the management of lenalidomide-refractory MM presents relevant territorial variations, and should thus be evaluated at both a national and international level. Further, the therapeutic scenario of MM is continuously evolving and new key therapies for lenalidomide-refractory MM patients, including CAR T-cell therapy and bispecific antibodies, have emerged [17,18], with different availabilities between countries [19].

Exploring opinions of experts on the frequency of lenalidomide-refractory MM in the near future, propensity to use current treatments and expectations towards new therapeutic options is critical for optimizing care in this setting. With the aim to provide a structured synthesis of views of haematologists in Italy on these and other interrelated topics, we conducted an online, modified Delphi study focused on the current and future burden and clinical management of lenalidomide-refractory MM since the second line of therapy. Treatments considered in the Delphi were those already available in early 2024, when the study was started, and expected to get reimbursement over the next 2 years, until 2026.

2. Materials and methods

We invited 12 nationally and internationally recognized clinical experts of MM, from different geographical areas of Italy and from a variety of hospital settings, to reach an agreement on various issues related to the management of lenalidomide-refractory disease through an online consensus process. The project began in January 2024 and was overseen by an expert in Delphi methodology (P.Ma.) and a biostatistician (C.G.) with previous experience in the field [20,21]. The interactive analysis adhered to established guidelines for determining consensus in Delphi studies, and we documented the methods, whole process and outcomes of the investigation using the recently developed ACCORD reporting guidelines [22,23]. The study protocol was not registered in advance. The project followed best practices for Delphi studies, including anonymity of panellists, iterative rounds, controlled feedback, definition of consensus criteria and analysis of consensus [24]. The ACCORD checklist is provided in Supplementary Table 1. Fig. 1 outlines the sequential phases and overall workflow of the project, that is also hereby described in detail.

2.1. Literature Review

The project started with a comprehensive, non-systematic review of studies of RRMM, that was conducted in January 2024. The main goals of the bibliographic review were to provide an up-to-date overview of the recent/current landscape of treatment (i.e., most frequently used treatment combinations and sequencies) in lenalidomide-refractory MM, with specific focus on the Italian setting, and to pinpoint controversial or understudied aspects of the disease that could be suitable for inclusion in the Delphi survey. Different search strategies and combinations of terms were adopted for each study aim. These were used to explore the available literature through PubMed/Medline, Google Scholar and the Cochrane Library. Thus, the terms included in the search strings were “relapsed refractory multiple myeloma” or “RRMM” or “lenalidomide-refractory MM” combined, in turn, with “Real-World treatment”, “treatment sequence”, “unmet needs”, etc. For selected aims, e.g. for the review of frequently used treatment sequences, an additional term for “Italy” was included. Given the rapidly changing disease scenario and since the interest was focused on recent developments, the search was restricted to the last decade (i.e., 2015–2024). Relevant studies were selected, and the key findings identified were summarized, presented and discussed with the Executive Committee during the kick-off meeting.

2.2. Knowledge Gaps

The literature review helped to identify and define the gaps of knowledge in this disease setting. After the review, five main research areas were selected for inclusion in the Delphi survey: 1) Definition of lenalidomide-refractory MM; 2) Frequencies of lenalidomide-refractory MM, both in the recent past (year 2023) and expected in the near future (until year 2026); 3) Propensity to use second-line lenalidomide-sparing treatments that were available at that time for the management of lenalidomide-refractory MM; 4) Unmet needs of patients with lenalidomide-refractory MM; 5) Propensity to use novel treatments for lenalidomide-refractory MM that were expected to get reimbursement between 2024 and 2026. These latter treatments were identified at a kick-off meeting (see details reported below) and included CAR-T cell therapy and bispecific antibodies targeting BCMA and GPRC5D. Second-line lenalidomide-sparing regimens available in Italy in 2024 included the following: daratumumab, pomalidomide and dexamethasone (DPd); pomalidomide, bortezomib and dexamethasone (PVd); isatuximab, carfilzomib and dexamethasone (IsaKd); selinexor, bortezomib, and dexamethasone (SVd); carfilzomib and dexamethasone (Kd). Daratumumab, carfilzomib and dexamethasone (DKd) was not reimbursed, although EMA-approved. None of the novel treatment options reported above were reimbursed in January 2024. Notably, at that time, results of the DREAMM-7 and DREAMM-8 studies were not yet available [25,26], and thus belantamab mafodotin in combination with either bortezomib and dexamethasone (BVd) or pomalidomide and dexamethasone (BPd) were not included among the novel treatment options. A sixth relevant area of investigation emerged after discussing the results of the first Delphi iteration and was included in the second round, i.e.: 6) Main characteristics of patients making them candidate to selected treatments for lenalidomide-refractory MM.

2.3. Executive Committee

A multidisciplinary Executive Committee, comprising three haematologists (M.C., P.C., P.Mu.), one expert of the Delphi method (P.Ma.) and one biostatistician (C.G.) was formed, with the aims to define research objectives, conduct the project and overview its findings.

A first, virtual kick-off meeting of the Executive Committee was held on 6th February 2024. During this meeting, the main results of the literature review were presented and the topics to be included in the Delphi study were discussed. A preliminary set of questions was also outlined. In order to verify the expertise in the disease and thus the eligibility of each potential panellist, the Executive Committee agreed as inclusion criterium in the Delphi panel that any participating clinician had to diagnose/treat at least 250 patients with MM during the previous 5 years. Executive Committee members did not take part in the voting rounds of the Delphi process.

Subsequent tasks of the Executive Committee were to review and approve the final questionnaires for the Delphi iterations, to overview the corresponding results and to discuss and interpret the key findings of the Delphi study. To achieve the latter aim, a final virtual meeting of the Executive Committee was organized at the end of the whole process, on 17th October 2024.

2.4. Development of Questionnaires

The questionnaires were designed to achieve the highest level of agreement among the panellists, through a quantitative approach [27]. After identifying specific topics for exploration and creating a questionnaire (in Italian language), we employed an iterative process to refine the research questions. A preliminary item aimed to assess the panellists' expertise and eligibility, according to the inclusion criterium

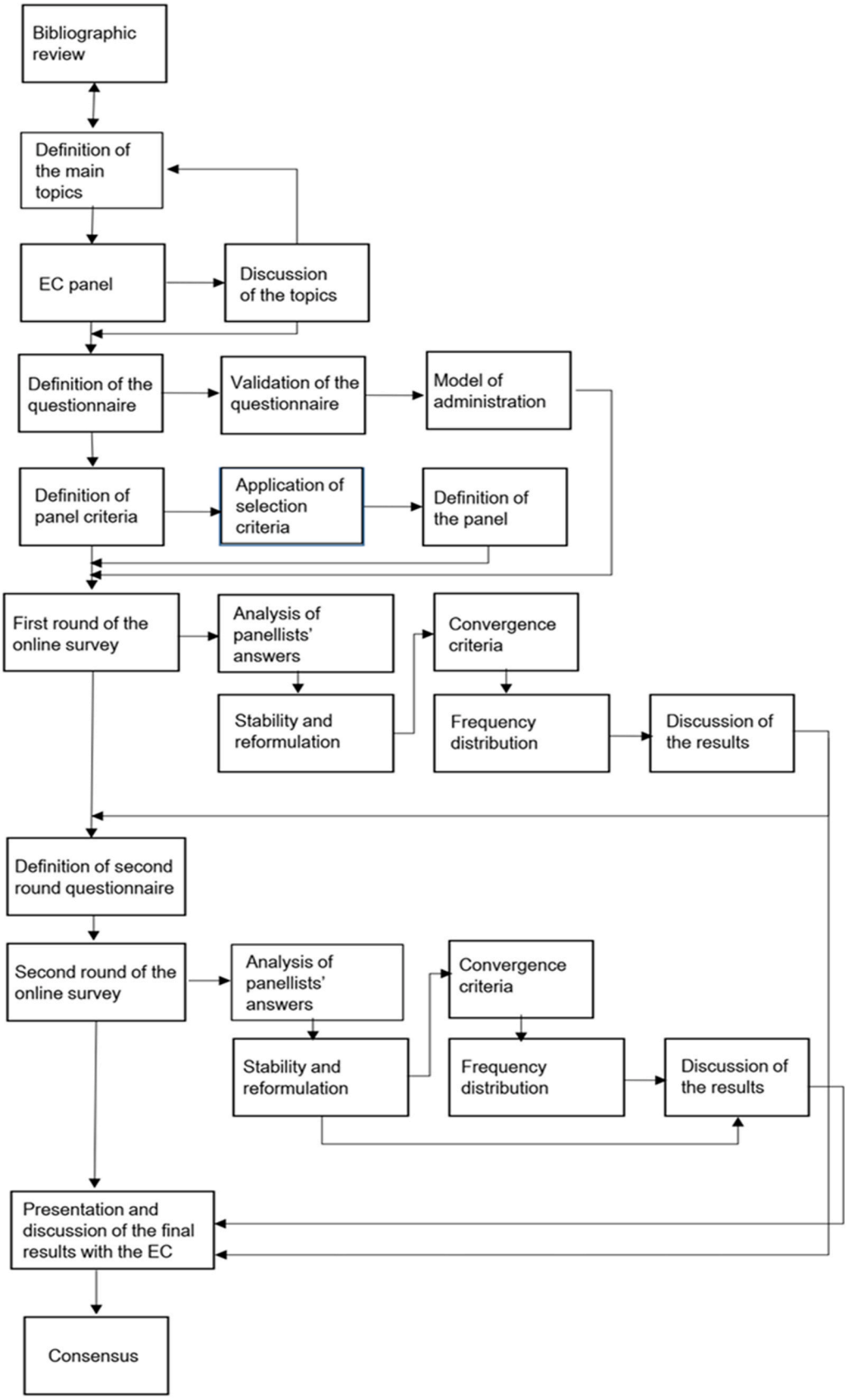

Fig. 1. Workflow of subsequent phases of the project EC: Executive Committee.

defined by the Executive Committee (reported above), was included to qualify for the Delphi project. Then, a variable number of items was entered in the questionnaire for each predefined research area, in a mix of open-ended questions, multiple-choice questions, and statements on specific topics. With reference to the statements, panellists were asked to indicate their agreement or disagreement using either a binary "yes"/"no" response or a 4-point Likert scale as "fully disagree," "partially disagree," "partially agree," or "fully agree." Responses indicating "full" or "partial" agreement (or disagreement) were grouped together in the analysis to obtain binary responses and assess consensus levels. Several questions/statements included an additional open-ended field for panellists to provide potential comments. The questionnaire of the second Delphi round included some additional items that emerged as relevant after the discussion of the results of the first iteration.

Validation of the survey questionnaires involved a qualitative review of both their facade and content [28]. Facade validity was assessed by examining the questionnaires' elements to determine their suitability for non-experts. Content validity was evaluated through an expert analysis to ensure comprehensive coverage of each research area. A member of the Executive Committee (C.G.) was involved in pilot testing of the questionnaires.

2.5. Expert panel

A panel of 12 clinical specialists of MM, operating in haematological Departments and Units of various referral centres and hospitals distributed in Northern, Central and Southern Italy, was identified and invited to participate. All invited clinicians were haematologists recognized for their expertise in MM diagnosis and management, they met the predefined inclusion criterium, and completed the whole Delphi process of two rounds. Panellists were provided a reimbursement fee for the time spent to respond to the Delphi questionnaires.

Selected information on the study centre of the panellists (e.g., geographic area, type of hospital, number of MM patients treated, etc.), but not on socio-demographic characteristics of each participant, was collected.

2.6. Consensus

In each round of the Delphi, consensus was determined by the percentage of agreement among panellists. The convergence criterion for consensus was pre-established and based on results stability, set at a threshold of two-thirds of response frequency. Each questionnaire item was classified using the following Focus Level [29]: A) Strong agreement among respondents ($\geq$67%). No reconsideration needed in the next Delphi round; B) Moderate-to-high response variability. Requires reconsideration in the next Delphi round; C) Frequent "I do not know" answers (>33%). Requires reconsideration in the next Delphi round.

For Focus Level "A", agreement between 67% and 99% of panellists was considered a "majority," while 100% agreement was defined as "full consensus". Items demonstrating high agreement, meeting the Focus Level "A" criteria, were immediately accepted and excluded from subsequent iterations [30].

2.7. Delphi rounds

An initial email introducing the project and inviting participation was sent to all potential Delphi panellists on April 8, 2024. On the same day, a few hours later, an email with a link to the first e-Delphi round questionnaire was sent. The questionnaire, administered through SurveyMonkey®, was accessible from April 8 to April 17, 2024. After examining the first round responses, a second round questionnaire was prepared (using the same methods and criteria of the first round) and was sent to the panellists on June 25, 2024, being accessible until July 7, 2024.

The goal of each Delphi round was to achieve expert consensus on the proposed topics. The consistency of answers between the two iterations was generally high, indicating reliable statement definitions. Focus Level "A" was achieved for most questionnaire items in the second round, leading to the termination of iterations and the conclusion of the Delphi process. A few items of the sixth area of analysis (i.e., patients' characteristics in relation to candidacy to selected treatments for lenalidomide-refractory MM) had Focus Level "B", but were not explored further in a third round because a high heterogeneity of answers was akin to a lack of clear-cut characteristics associated to a treatment.

2.8. Ethical considerations

This study is a survey of clinicians of MM, contributing with their expertise and beliefs. No sensitive data were collected and no patient was involved in the study. Therefore, the study does not fall among those requiring ethical approval in Italy (Determine AIFA: 8th August 2024, https://www.gazzettaufficiale.it/eli/id/2024/08/20/24A04320/sg; 20th March 2008, https://www.gazzettaufficiale.it/eli/id/2008/03/31/08A02109/sg). All the panellists were informed by electronic means of the aims of the research before initiating the survey, both in a contact e-mail and in a preliminary page of the survey.

3. Results

Table 1 reports consensus results for specific items included in the Delphi study, according to different research areas investigated. During the first Delphi round, the majority of panellists (75%) agreed that the IMWG definition of lenalidomide-refractory disease is satisfactory and does not require any modification. Also, all questions related to the recent (i.e., in 2023) and expected (i.e., in 2026) proportions of patients with lenalidomide-refractory MM achieved an agreement during the first iteration. Overall, according to the majority of experts more than 80% of ASCT-eligible patients, and from 60% to 90% of ASCT-ineligible patients, were lenalidomide-refractory at the time of starting second-line therapy in year 2023. Further, according to the majority of panellists, at that time almost all patients in third, fourth or later-lines of therapy were lenalidomide-refractory. The proportions of lenalidomide-refractory patients expected to receive their second-line of therapy in year 2026 were > 90% and > 80% in the ASCT and non-ASCT settings, respectively. Overall, panellists agreed that the preferred second-line treatments for a broad population of lenalidomide-refractory MM patients were the PVd regimen for those ASCT-ineligible (agreed by 91% of experts), and IsaKd and DPd for ASCT-eligible patients (full consensus of experts). In the second Delphi round, full consensus emerged on the needs of lenalidomide-refractory MM patients to receive novel treatments with new mechanisms of action. With reference to T-cell redirecting therapies, most panellists would be favourable to the use of CAR-T cell therapy (92% agreement) after the first relapse [31], while 83% agreement was found on the use of bispecific antibodies in the same line of therapy, provided that results from ongoing phase 3 studies - not yet available – supported this choice. Accordingly, in the second iteration most of panellists (92%) agreed to state that in the near future T-cell redirecting therapies are likely to be the most frequently used second-line treatment strategies for lenalidomide-refractory MM patients who are eligible to receive them.

Fig. 2 shows consensus findings on selected characteristics of patients, including age, presence of comorbidities, cytogenetic risk and extra-medullary disease, that could make them candidate to receive already available second-line treatment regimens non including lenalidomide (ASCT-ineligible patients: Panel A; ASCT-eligible patients: Panel B) or novel treatments, independent of treatment line (Panel C). Among ASCT-ineligible patients with lenalidomide-refractory MM, the majority of panellists agreed that IsaKd as second-line therapy might be considered for non-frail patients without cardiovascular comorbidities and/or with pre-existing peripheral neuropathy, and that, by the opposite, PVd

Table 1
Key research areas and list of specific items included in the Delphi study, with agreement level among panellists.

Research area / Specific item	Most frequent answer[a]	Agreement level	# Round of agreement
Definition of patient with lenalidomide-refractory disease			
✓ In line with the IMWG definition, a patient has lenalidomide-refractory disease if he/she has had disease relapse/progression during lenalidomide treatment or within 60 days of the last dose administered. Based on your clinical experience, would you propose any changes to this definition?	No	Majority, 75%	1
Frequency of lenalidomide-refractory MM: recent (2023) and future (2026) scenarios			
✓ In your opinion, in 2023, which proportion of ASCT patients had lenalidomide-refractory disease at starting second-line treatment?	More than 80%	Majority, 67%	1
✓ In your opinion, in 2026, which proportion of ASCT patients will have lenalidomide-refractory disease at starting second-line treatment?	More than 90%	Majority, 83%	1
✓ In your opinion, in 2023, which proportion of non-ASCT patients had lenalidomide-refractory disease at starting second-line treatment?	Between 60% and 90%	Majority, 75%	1
✓ In your opinion, in 2026, which proportion of non-ASCT patients will have lenalidomide-refractory disease at starting second-line treatment?	More than 80%	Majority, 83%	1
✓ In your opinion, in 2023, which proportion of patients had lenalidomide-refractory disease at starting third-line treatment?	All patients	Majority, 67%	1
✓ In your opinion, in 2026, which proportion of patients will have lenalidomide-refractory disease at starting third-line treatment?	All patients	Majority, 67%	1
✓ In your opinion, in 2023, which proportion of patients had lenalidomide-refractory disease at starting fourth- or higher-line treatment?	All patients	Majority, 67%	1
✓ In your opinion, in 2026, which proportion of patients will have lenalidomide-refractory disease at starting fourth- or higher-line treatment?	All patients	Majority, 83%	1
Propensity towards current second-line therapeutic regimens			
✓ In ASCT patients with lenalidomide-refractory MM, the most suitable options for second-line treatment are currently IsaKd and DPd	-	Consensus, 100%	2
✓ In non-ASCT patients with lenalidomide-refractory MM, which second-line therapeutic regimens currently represent the most suitable options?	PVd	Majority, 91%	1
Unmet needs			
✓ The most important unmet needs in patients with lenalidomide-refractory MM are: i) the availability of new therapeutic options ii) the approval and availability of immunotherapy and non-immunotherapy treatments whose efficacy and safety have already been tested	-	Consensus, 100%	2
Novel treatments			
✓ Considering the evolving therapeutic scenario in MM over the next 3 years, it is expected that, in the near future, bispecific antibodies and CAR-T therapy will be the most frequently used treatments in patients with lenalidomide-refractory disease from the second-line of therapy onwards	-	Majority, 92%	2
✓ Ideally, if a CAR-T therapy was available in the setting of patients with lenalidomide-refractory MM, in which line of treatment would you be most inclined to use this therapy?	Second-line	Majority, 92%	1
✓ Ideally, if a therapy based on bispecific antibodies was available in the setting of patients with lenalidomide-refractory MM, in which line of treatment would you be most inclined to use this therapy?	Second-line	Majority, 83%	1

ASCT: autologous stem cell transplantation; CAR-T: Chimeric antigen receptor T-cell; DPd: daratumumab, pomalidomide and dexamethasone; IMWG: International Myeloma Working Group; IsaKd: isatuximab, carfilzomib and dexamethasone; MM: multiple myeloma; PVd: pomalidomide, bortezomib and dexamethasone

[a] The main reply is reported for multiple choice or open-ended questions, while statements did not require any reply.

is the most appropriate for those without neuropathy and/or with cardiovascular comorbidities. There was full consensus that the use of IsaKd is independent of the cytogenetic risk of the patient. Among ASCT-eligible patients, the majority of panellists agreed that each of available regimens, including IsaKd, DaraPd, PVd and SVd, could be used regardless of the cytogenetic profile and/or the presence of extramedullary disease. Panellists agreed that also in this setting the choice between carfilzomib- and bortezomib-based triplets was driven by the presence or absence of cardiovascular comorbidity and peripheral neuropathy. No agreement was, on the other hand, reached on the most suitable age class of patients to be candidate to each regimen. With reference to novel treatments considered, i.e., CAR-T therapy, anti-BCMA and anti-GPRC5D bispecific antibodies, no specific indication emerged on candidate patients, i.e., either agreement emerged that patients could be candidate to these treatments independently of the characteristics examined (particularly for cytogenetic risk and presence of extra-medullary disease), or a high heterogeneity of replies was found and thus no agreement on clear-cut patients' characteristics associated to novel treatments was achieved.

4. Discussion

The expert panel, consistently with previous indications from a few other high-income countries [13,32], agreed that most relapsed Italian

A

	Isa-Kd	Dara-Pd	PVd	SVd
Age	Patients aged 60-70 years	Patients are candidate to this therapy independently of their age	*High heterogeneity of answers across age categories*	Patients are candidate to this therapy independently of their age
Presence of comorbidities	Patients without cardiovascular comorbidities	*High heterogeneity of answers across different comorbidities*	Patients without neuropathy	*High heterogeneity of answers across different comorbidities*
Cytogenetic risk	Patients are candidate to this therapy independently of their cytogenetic risk	Patients are candidate to this therapy independently of their cytogenetic risk	Patients are candidate to this therapy independently of their cytogenetic risk	Patients are candidate to this therapy independently of their cytogenetic risk
Extra-medullary disease	Patients are candidate to this therapy independently of having extra-medullary disease	Patients are candidate to this therapy independently of having extra-medullary disease	*High heterogeneity of answers on extra-medullary disease*	Patients are candidate to this therapy independently of having extra-medullary disease

B

	Isa-Kd	Dara-Pd	PVd	SVd
Age	*High heterogeneity of answers across age categories*	*High heterogeneity of answers across age categories*	*High heterogeneity of answers across age categories*	*High heterogeneity of answers across age categories*
Presence of comorbidities	Patients without cardiovascular comorbidities	*High heterogeneity of answers across different comorbidities*	*High heterogeneity of answers across different comorbidities*	Patients are candidate to this therapy independently of their comorbidities
Cytogenetic risk	Patients are candidate to this therapy independently of their cytogenetic risk	Patients are candidate to this therapy independently of their cytogenetic risk	Patients are candidate to this therapy independently of their cytogenetic risk	Patients are candidate to this therapy independently of their cytogenetic risk
Extra-medullary disease	Patients are candidate to this therapy independently of having extra-medullary disease	Patients are candidate to this therapy independently of having extra-medullary disease	Patients are candidate to this therapy independently of having extra-medullary disease	Patients are candidate to this therapy independently of having extra-medullary disease

C

	CAR-T therapy	Bispecific antibodies anti-BCMA	Bispecific antibodies anti-GPRC5D
Age	*High heterogeneity of answers across age categories*	*High heterogeneity of answers across age categories*	Patients are candidate to this therapy independently of their age
Presence of comorbidities	*High heterogeneity of answers across different comorbidities*	*High heterogeneity of answers across different comorbidities*	Patients are candidate to this therapy independently of their comorbidities
Cytogenetic risk	Patients are candidate to this therapy independently of their cytogenetic risk	Patients are candidate to this therapy independently of their cytogenetic risk	Patients are candidate to this therapy independently of their cytogenetic risk
Extra-medullary disease	Patients are candidate to this therapy independently of having extra-medullary disease	Patients are candidate to this therapy independently of having extra-medullary disease	Patients are candidate to this therapy independently of having extra-medullary disease

(caption on next page)

Fig. 2. Eligibility of lenalidomide-refractory patients to receive already reimbursed second-line lenalidomide sparing regimens (Panel A: ASCT-ineligible patients; Panel B: ASCT-eligible patients) or novel treatments, regardless of treatment line (Panel C), according to experts evaluations based on several key characteristics. [a] ASCT: autologous stem cell transplantation; BCMA: B-cell maturation antigen; CAR-T: Chimeric antigen receptor T-cell; Dara-Pd: daratumumab, pomalidomide and dexamethasone; GPCR5D: G protein-coupled receptor 5D; Isa-Kd: isatuximab, carfilzomib and dexamethasone; MM: multiple myeloma; PVd: pomalidomide, bortezomib and dexamethasone; SVd: Selinexor, bortezomib, and dexamethasone [a] The level of agreement is shown by colour. Yellow: no agreement (less than 8 out of 12 [<66.7%] of panellists agreed on the characteristic); light green: moderate agreement (8 or 9 out of 12 panellists agreed); midtone green: high agreement (10 or 11 out of 12 panellists agreed); dark green: full consensus (all 12 panellists agreed).

MM patients are now refractory to lenalidomide. The panel expected an additional surge in the proportion of refractory cases during the period 2024–2026 in patients starting second-line treatment, while all patients starting third or subsequent lines were already considered to be lenalidomide-refractory. These findings are likely explained by the increasing availability of quadruplet regimens for newly diagnosed MM (and associated long-term exposure to lenalidomide), and are in line with those of a recent Real-World study from Italy that reported a rapid increase in early refractoriness to lenalidomide over time [14]. Patients with lenalidomide-refractory MM have suboptimal disease outcomes [15]. In this study, the availability of novel therapeutic options emerged as a key unmet need in this patient setting, and the favourable opinion of experts to use CAR-T and bispecific antibodies since the second-line of treatment reflects the challenging management of these patients.

Different treatment options, with corresponding strengths and weaknesses, are available in second-line of therapy for patients refractory to lenalidomide [33]. According to the 2021 ESMO and IMWG guidelines, also depending on the prior regimen used, the main viable alternatives include PVd, DKd, IsaKd, SVd and daratumumab, bortezomib, and dexamethasone (DVd) [9,11]. The DPd regimen was marginally considered in the above guidelines since findings of the phase III APOLLO trial have been released recently, after the publication of the ESMO and IMWG recommendations [34]. Consistently with the guidelines and based on the increasing use of daratumumab, lenalidomide and dexamethasone (DRd) until disease progression as upfront therapy for ASCT-ineligible patients, the majority of experts agreed that, overall, PVd is the preferred option as second-line treatment for these latter patients, while IsaKd and DPd are most suitable in ASCT-eligible patients. DPd was deemed appropriate independently of age, and may therefore be a suitable option also for patients with pre-existing neurological toxicity. Consensus results from Italy on therapeutic options for lenalidomide-refractory MM are relevant, considering that national guidelines date back to a few years ago [35,36] - in the framework of a continuously evolving treatment landscape. For completeness, the recent guidelines from the European Hematology Association (EHA) and European Myeloma Network (EMN), released after the conduction of this Delphi study, supported treatment with cilta-cel – when available – in eligible patients with lenalidomide-refractory MM not previously treated with, or with disease sensitive to, anti-CD38 antibodies. Other favourite options were DKd, IsaKd, and BPd, followed by BVd, DPd and SVd [37]. In patients with MM refractory to both lenalidomide and daratumumab, cilta-cel and BPd were the favourite treatment options.

When it comes to the appropriate treatment regimen in each single patient with lenalidomide-refractory MM, the choice is complex [38]. This is also reflected in Real-World studies, that showed that a plethora of regimens and treatment sequences have been used in MM in Italy over the last decade [14,16,39]. On the basis of patient- and/or disease-related characteristics, a specific treatment regimen may be prioritized or, in contrast, may not be advised [40,41]. In our study, beyond a few known unfavourable features hindering the use of specific drugs, e.g., patients with cardiovascular comorbidities are not candidate to the use of IsaKd because of the risk of cardiac toxicities associated with carfilzomib [42] (particularly in already frail non-ASCT patients, thus driving the preferences towards PVd), no absolute criteria emerged to drive the regimen choice in subgroups of lenalidomide-refractory MM cases. This was, in particular, true for innovative treatment options including CAR-T therapy, anti-BCMA and anti GPRC5D bispecific antibodies. According to the experts' opinions, lenalidomide-refractory MM patients are candidate to these novel treatments independently of their cytogenetic risk or presence of extra-medullary disease. It should be stressed, however, that evidence-based data on the efficacy and safety of CAR-T and bispecific antibodies are now increasingly being released, particularly across patient subgroups, and these findings may reflect preliminary opinions, rather than strong beliefs, of the experts.

Limits of this Delphi survey are those typical of consensus studies [43]. Such analyses are, in fact, based on opinions of experts rather than on original clinical data, and their level of evidence is thus low. For a few topics explored, particularly those related to incoming new treatments, many uncertainties remain due to the limited quantitative information available to date, and in a few cases an agreement between experts on these topics could not be achieved. Furthermore, the therapeutic scenario for MM is continuously evolving and thus the regimens and novel therapies included in this Delphi may not be fully up-to-date and/or in line with other high-income countries. In particular, as reported above, findings from the DREAMM-7 and DREAMM-8 studies [25,26,44] were not yet available in the early phases of our study, and combination therapy with BVd was therefore not considered in the questionnaire, particularly in the section on patient characteristics associated to eligibility to different treatment regimens. All participating haematologists were from Italy, and our findings are primarily applicable to the Italian setting. However, several topics explored were wide and relevant at an international level.

In an overall MM scenario headed towards a rapid increase in the proportion of both triple-class exposed and double-refractory patients, this Delphi consensus study of haematological experts reported a major clinical unmet need of newly available and accessible therapeutic options for lenalidomide-refractory MM, already starting from the second-line of treatment. More than 80% of patients starting second-line therapy, in fact, either after ASCT or not, are expected to be refractory to lenalidomide in Italy by 2026. As regards currently available treatments in patients starting second-line therapy, Italian experts were, in general, inclined towards the use of IsaKd and DPd in ASCT patients and towards PVd in non-ASCT patients. Most clinicians were in principle favourable to the (future) use of novel, incoming immunotherapies in the same patient setting (i.e., second-line therapy), while no clear patient characteristics emerged to drive their use in specific subgroups of subjects.

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CRediT authorship contribution statement

Paolo Corradini: Writing – review & editing, Validation, Supervision, Investigation. **Michele Cavo:** Writing – review & editing, Validation, Supervision, Investigation. **Pellegrino Musto:** Writing – review & editing, Validation, Supervision, Investigation. **Carlotta Galeone:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Paolo Mariani:** Writing – review & editing, Methodology, Formal analysis. **Federica Resci:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of Competing Interest

Competing Interests: M. Cavo has received honoraria and has served in a consulting/advisory role for Amgen, AbbVie, Bristol-Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Menarini Stemline, Pfizer, and Sanofi. P. Corradini has served as speaker and/or advisory board for: AbbVie, Amgen, BeOne, BMS, Daiichi Sankyo, Eli Lilly, Gilead/Kite, GSK, Incyte, Janssen, Jazz Pharma, Novartis, Pfizer, Roche, Sanofi, SOBI, Takeda; and has received travel accommodations from AbbVie, Amgen, BMS, Gilead/Kite, Janssen, Novartis, Roche, Takeda, BeOne. P. Musto has received honoraria for lectures and/or participation to advisory board memberships, including travels and hotel accommodations, with: Abbvie, Alexion, Amgen, Astellas, Astra-Zeneca, Bei-Gene, Bristol-Myers Squibb, Daichi-Sankyo, Eli-Lilly, Gilead, Glaxo-Smith-Kline, Grifols, Incyte, Johnson & Johnson, Jazz, Kyowa Kirin, Menarini-Stemline, Otsuka, Novartis, Pfizer, Roche, Sanofi, Servier, Sobi, and Takeda. F. Resci is an employee of Johnson & Johnson, Italy. C. Galeone and P. Mariani have nothing to disclose.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.leukres.2026.108230.

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