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Publication Date

2024-10-04

DOI

10.1016/j.critrevonc.2024.104529

Peer reviewed

Critical Reviews in Oncology / Hematology 204 (2024) 104529

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Outcomes in randomized controlled trials of therapeutic interventions for multiple myeloma: A systematic review

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ARTICLE INFO

Keywords:
Multiple myeloma
Systematic review
Regression
Outcomes research

ABSTRACT

Purpose: Many clinical trials of therapeutic interventions for multiple myeloma do not use patient important outcomes and rely on the use of surrogate endpoints. The aim of this systematic review was to depict the landscape of randomized controlled trials in myeloma research and compile the endpoints utilized.
Methods: We searched Embase, PubMed, and the Cochrane Library for randomized controlled trials in myeloma published in English up to October 2023. We included trials exploring efficacy of therapeutic modalities for myeloma itself or supportive care interventions.
Results: A total of 2181 records, reporting data from 624 trials (448 comparing anti-myeloma treatments and 176 comparing supportive interventions) were deemed eligible. The most common primary outcome reported was disease response, followed by progression free survival (PFS) and overall survival (OS). Across all trials, 119 (19.1 %) used OS as the primary endpoint, while 316 (50.6 %) listed it as a secondary endpoint. Quality of life was less commonly prioritized, featured as primary endpoint only in seven studies (1.1 %) and as secondary endpoint in 115 studies (18.4 %). Studies funded by the pharmaceutical industry were more likely (Odds Ratio [OR] 3.85, 95 % CI 2.41–6.35) to use PFS as primary outcome. Similarly, studies with authors that had conflicts of interest with the funding source were more likely (OR 4.57, 95 % CI 2.72–7.92) to use PFS as the primary outcome.
Conclusion: While randomized controlled trials for multiple myeloma predominantly rely on surrogate endpoints, particularly PFS, the importance of OS as an outcome should not be overlooked.

1. Introduction

Significant advancements have been made in the management of multiple myeloma over the years. This progress is marked by the approval of numerous new drugs and a notable improvement in patient outcomes. The evolution in treatment strategies is largely attributed to an increased understanding of the disease, coupled with a surge in clinical trials focusing on treatment of myeloma. Such trials have paved the way for enhanced patient survival rates, instilling hope for a potential cure for a disease currently deemed incurable (Kumar et al., 2014, 2008; Kyle and Rajkumar, 2008).

Despite these advances, multiple myeloma remains the second most common hematologic malignancy, impacting a significant number of people. Many patients undergo prolonged treatment phases, which can be challenging. The disease's impact can be profound, with some patients requiring extended hospital stays, receiving numerous medications, or suffering from severe bone complications, including fractures, which can be painful and can limit daily activities (Rizzo et al., 2014).

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https://doi.org/10.1016/j.critrevonc.2024.104529
Received 30 August 2024; Received in revised form 30 September 2024; Accepted 1 October 2024
Available online 4 October 2024

Therapeutic strategies for multiple myeloma encompass a vast range of interventions. Antimyeloma regimens aim to induce disease remission and extend survival. These pharmaceutical interventions, as well as procedures like autologous stem cell transplantation, control the disease and initial patient symptoms. Supportive interventions do not target myeloma cells but help control multiple myeloma complications including bone disease, infections, and pain or facilitate the collection of stem cells for transplantation. While the primary antimyeloma drugs target disease progression and aim to extend life, the supplemental therapies aim to ensure enhanced quality of life by managing symptoms and complications that arise from this complex malignancy.

Regulatory bodies, such as the FDA and EMA, albeit recognizing the importance of overall survival (OS) as a clinical trial endpoint for approval of an anticancer drug, often do not require documentation of hard clinical outcomes to prove efficacy (European Medicines Agency, Committee for Medicinal Products for Human Use CHMP (2023); FDA Briefing Document, 2024; U.S. Department of Health and Human Services, 2018). Instead, surrogate outcomes such as response and progression free survival (PFS), even when their correlation with overall survival might be weak in many circumstances, are considered sufficient to secure approval, even in advanced stages of diseases like myeloma (Etekal et al., 2023; Kim and Prasad, 2016). Surrogate outcomes, by their very nature, may hold little relevance and may not be intuitively grasped by patients unless explicitly informed of their significance (Anderson et al., 2007; Booth et al., 2023; Etekal et al., 2023; Gyawali and Prasad, 2017). Consequently, important outcomes like OS, which is perceived as time-consuming to capture (Holstein et al., 2019) -even though this has been challenged by some researchers (Chen et al., 2019)- might be overlooked. The same holds true for quality of life and other patient important outcomes which have only recently gained attention (Laane et al., 2023; U.S. Department of Health and Human Services, 2021).

Prioritization of clinically important outcomes by patients, clinicians and researchers is often discordant. This systematic review is the first part of an ongoing multi-staged research project, aimed at exploring the alignment or disagreement among the views of different myeloma stakeholders. The outcomes used in myeloma clinical trials were assessed through the present systematic review, while patients' and clinicians' priorities are being evaluated through a mixed-methods study including interviews and surveys.

The aim of this systematic review was to develop comprehensive evidence map of randomized controlled trials in patients with multiple myeloma, capturing their scope, characteristics, and endpoints utilized. Our primary goal was to extract the primary endpoints of eligible studies. Additionally, we captured secondary outcomes and explored the potential associations between outcomes and specific trial characteristics.

2. Methods

We adhere to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study protocol is available at https://doi.org/10.17605/OSF.IO/MXK8T.

2.1. Search methods for identification of studies

We searched PubMed, Embase, and the Cochrane Library, for randomized controlled trials of interventions in patients with myeloma published in English up to October 2023. We developed and used a comprehensive search strategy that incorporated free-text terms related to multiple myeloma, along with relevant MeSH terms, and applied filters specifically for randomized controlled trials. The complete search strategy for each database is available at the appendix. Additionally, we searched Clinicaltrials.gov for completed studies reporting results.

2.2. Eligibility criteria

We included randomized controlled trials assessing any therapeutic intervention in patients with multiple myeloma used either as antimyeloma treatment (drugs and their combinations, or hematopoietic cell transplantation) or as supportive care intervention for myeloma complications, treatment adverse events, or bone marrow transplantation. We excluded Phase 1 studies as they primarily assess drug safety and often involve healthy volunteers, study protocols, and studies with a population other than solely patients with myeloma (for example studies including patients with both myeloma and lymphoma). Studies in patients with smoldering myeloma (according to Internation Myeloma Working Group [IMWG] criteria (Rajkumar et al., 2014)) were also included. Due to the change in the definition of myeloma, patients who were previously classified as stage I or asymptomatic myeloma according to the former classification (Kyle et al., 2003), are now categorized as smoldering myeloma.

2.3. Data collection and analysis

2.3.1. Selection of studies

After removing duplicates, the search records were uploaded to an online software (DistillerSR®) to facilitate study selection. Pairs of reviewers independently assessed potentially eligible articles, initially by reading the title and abstract, followed by a full-text review. Any disagreements were resolved through discussions among the reviewers. Post full-text review, all reports of the same study, as identified by shared attributes like the trial identifier in Clinicaltrials.gov (NCT), authors' names, and title, were collated into a single record.

2.3.2. Data extraction and management

We extracted data on study participants (number of participants, age, sex, race, transplant eligibility, and disease phase, namely newly diagnosed myeloma, relapsed, or smoldering), type of interventions utilized (antimyeloma treatment regimen, specific drugs under investigation, and other interventions), and study characteristics (study's location, initiation year, blinding, phase, funding, and authors' potential conflicts of interest) using predesigned online forms within DistillerSR®. For studies incorporating multiple sequential randomization phases, data were extracted separately for each comparison. We extracted all primary and secondary endpoints from eligible studies. We also extracted data on instruments utilized to assess quality of life and determined the direction of effect by examining the presence of statistical significance for either the sole or all primary outcomes. Presence of authors' conflicts of interest were recorded based on the study's funding source. For studies funded by pharmaceutical industries, we extracted the number of authors with financial or occupational affiliations with the funding source. In the absence of pharmaceutical industry funding, conflicts of interest were recorded as absent, provided that disclosure of conflicts was explicitly reported by all authors. We did not differentiate between types of conflicts of interest (research funding or personal payments etc.) and did not distinguish conflicts based on the position of the author.

2.3.3. Assessment of risk of bias

We did not assess risk of bias in included studies as this was beyond the primary aim of this review, which was to map all outcomes studied in myeloma trials.

2.3.4. Data synthesis

Results are presented descriptively. We used frequencies and proportions to describe categorical data, and median or mean values for continuous data. We explored potential associations between studies sponsored by the pharmaceutical industry, the described outcomes and the study results (whether statistically significant or not for the primary outcome). We hypothesized a priori that the primary endpoints as well as the results of a study may vary, depending on funding source, study

initiation date, and investigator conflict of interest. We used logistic regression analysis for the categorical outcomes, to detect any association between pharmaceutical industry sponsorship and the three most frequently observed study outcomes. Additionally, we investigated the potential correlation between study funding and the nature of results (positive/negative, meaning statistically significant results for the primary outcome or not) using logistic regression for the dichotomous outcome of interest. Lastly, a trend analysis was conducted to assess how the type of study outcomes evolved over time. In all analyses a p-value of less than 0.05 was considered statistically significant and all reported p-values were two-tailed. Regression results were expressed as an Odds Ratio (OR), 95 % CI and a P value. All calculations were performed in R studio software Version: 2023.12.1+402. (RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/).

3. Results

3.1. Search results

The study selection process is summarized in Fig. 1. Our initial search yielded 29,736 records. Following removal of duplicates, 25,072 records were imported into DistillerSR®. After screening at title and abstract, 4675 records were assessed at full-text level. Following full-text screening, we cross-referenced eligible records using NCT identifier, authors, and titles, and collated records referring to the same study. As a result, a total of 624 studies which encompassed 2181 publications were included in the systematic review. Of these, 34 studies involved multiple randomizations, leading to separate data extraction for each randomization.

3.1.1. All studies

The 624 studies included a total of 131,255 patients. The median duration of follow-up was 26.1 months (minimum 0.2 months and maximum 624 months). Supplementary figure 1 presents the number of studies conducted over time, noting a marked increase post-2000, while supplementary figure 2 shows studies' sample sizes. Based on 477 studies (76.4 %) that provided relevant data, 61,243 patients (55.9 %) were men. Among the 143 studies (22.9 %) that reported data on participants' race, 35,089 (80.6 %) were white, 2414 (5.5 %) black, 101 (0.2 %) Hispanic, 3497 (8.0 %) Asian and 1822 (4.2 %) were of other or unknown race.

A total of 276 (44.2 %) studies were conducted in Europe, 164 (26.3 %) in North America, 98 (15.7 %) were multinational, 58 (9.4 %) were in Asia, seven (1.1 %) were based in South America, four (0.6 %) were conducted in Africa and seven (1.1 %) in Australia.

262 studies (42,0 %) received at least some funding from the pharmaceutical industry (that might be just providing study drug free of charge). In contrast, 171 studies (27.4 %) did not specify any funding source. Notably, after the year 2000, the proportion of studies backed at least partly by pharmaceutical industry was 58.1 %, while the fraction of studies not disclosing funding dropped to 16.5 %. A total of 304 studies

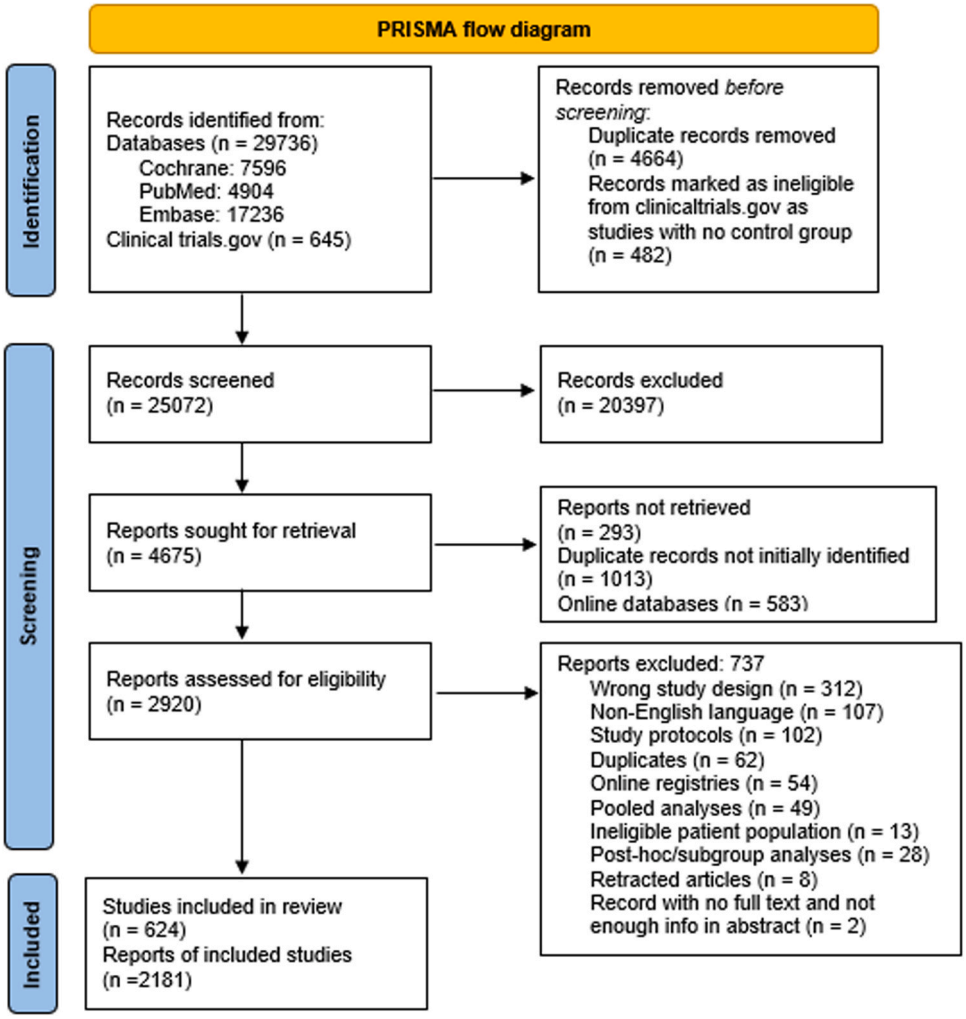

Fig. 1. Flow diagram of study selection process.

(48.7 %) did not provide information on disclosures on conflicts of interest, whereas 194 (31.1 %) acknowledged some form of conflict between the authors and the funding source.

The most common endpoint assessed was treatment response. A total of 119 studies (19.1 %) identified overall survival as their primary endpoint, while 316 (50,6 %) listed it as a secondary endpoint. Quality of life was less commonly prioritized, being featured as a primary endpoint in seven studies (1.1 %) and as a secondary endpoint in 115 studies (18.4 %). Among the studies that used OS as the primary outcome, only 26 (21.8 %) yielded statistically significant results. For those that prioritized quality of life, only five yielded positive findings.

The ten most commonly reported primary outcomes in all studies were Response (214, 34.3 %), PFS (150, 24.0 %), OS (119, 19.1 %), Adverse events (74, 11.9 %), Disease complications (49, 7.9 %), Time to progression (23, 3.7 %), Event free survival (21, 3.7 %), Number of cells (graph mobilization) (18, 2.9 %), Duration of response (12, 1.9 %) and Feasibility (11, 1.8 %) (supplementary figure 3). Amongst phase three studies (211 studies), the five most common primary outcomes were PFS (101, 47.9 %), Response (49, 23.2 %), OS (37, 17.5 %), Time to progression (16, 7.6 %), Adverse events (13, 6.2 %).

The increase in the use of progression free survival as primary outcome can be seen in the studies published in recent years in Fig. 2.

Out of the 624 studies, 448 focused on anti-myeloma therapies, while the remaining 176 addressed supportive therapies. These adjuvant treatments pertained to disease complications or other necessary interventions related to the condition but did not encompass drugs with direct anti-myeloma activity. The main study characteristics are summarized in Table 1.

3.1.2. *Anti-myeloma therapies*

Of the 448 studies comparing anti-myeloma therapies, including 110,506 patients, 109 (24.3 %) pertained to induction therapy, 80 (17.9 %) were related to maintenance therapy, 30 (6.7 %) to conditioning therapy prior to autologous transplantation, 22 (4.9 %) to consolidation therapy and eight (1.8 %) to intensification therapy. 199 (44.4 %) studies did not specify the type of treatment, often because the regimen was intended to last until disease progression, commonly seen in cases of relapsed myeloma or there was a comparison between a transplant and non-transplant approach.

Regarding the type of treatments compared in the studies with anti-myeloma treatments, we looked at the type of comparisons based on the number of drugs used in the intervention group and the control group respectively. Thus 91 (20.3 %) studies compared three drugs in the intervention group versus two in the control group. 54 (12.1 %) studies made a comparison between two drugs in the intervention against one drug in the control group, 42 (9.4 %) studies compared one drug versus no drug, 38 (8.5 %) studies compared two drugs in both the intervention and control groups, and 36 (8.0 %) studies one drug versus one (supplementary figure 4). Of note, there were also studies examining therapeutic strategies, as autologous stem cell transplantation versus drug combinations without transplant. All the comparisons between different drugs are presented in the corresponding tables (supplementary tables 1–5).

The most frequently used primary endpoint was response to treatment (complete response, partial response – CR, PR, etc.) with a rate of 45.1 % (202 studies), followed by PFS and OS with rates of 31.5 % (141 studies) and 24.8 % (111 studies) respectively. Adverse events were the fourth most frequently reported primary outcome, mentioned in 33 studies (7.4 %) and Time to progression was fifth, with 22 studies (4.9 %). In supplementary table 6 we present use of primary endpoints in myeloma trials based on disease phase. MRD (Measurable residual disease) was primary endpoint in three (0.7 %) studies, with one having statistically significant results. All of them were in the state of newly diagnosed myeloma, two of them were phase 2 studies and one phase 3. As a secondary endpoint MRD was listed in 54 studies. The most frequent secondary endpoints in the studies involving anti-myeloma treatments are shown in supplementary table 7.

Tools used to assess quality of life included general tools (in 37 trials) and combination of general and disease-specific tools (in 41 trials). The most commonly used tools were EORTC QLQ-C30 and EQ-5D-5 L, and among the myeloma-specific EORTC QLQ-MY20 and EORTC QLQ-MY24.

Finally, 220 (49.1 %) trials were negative (reporting non-statistically significant result for the primary endpoint) and 164 (36.6 %) were positive (statistically significant result for the primary endpoint). The remaining studies (many of them published before 2000) did not report p-values or confidence intervals for their statistical tests. (Additionally, several studies, particularly those from clinicaltrials.gov that terminated prematurely due to recruitment challenges, did not conduct statistical tests.)

3.1.3. *Supportive therapies*

A total of 176 studies focusing on supportive treatments for multiple myeloma were identified, encompassing 20,749 patients. Studies in this category primarily addressed specific treatments, with a predominant focus on bone disease, cell collection for autologous transplantation, infections, kidney failure, and the overall impact of patient symptoms. Supplementary figure 5 highlights the most common study topics.

The drugs or interventions that exist in this category mainly address complications, special treatments and symptomatic treatment with non-

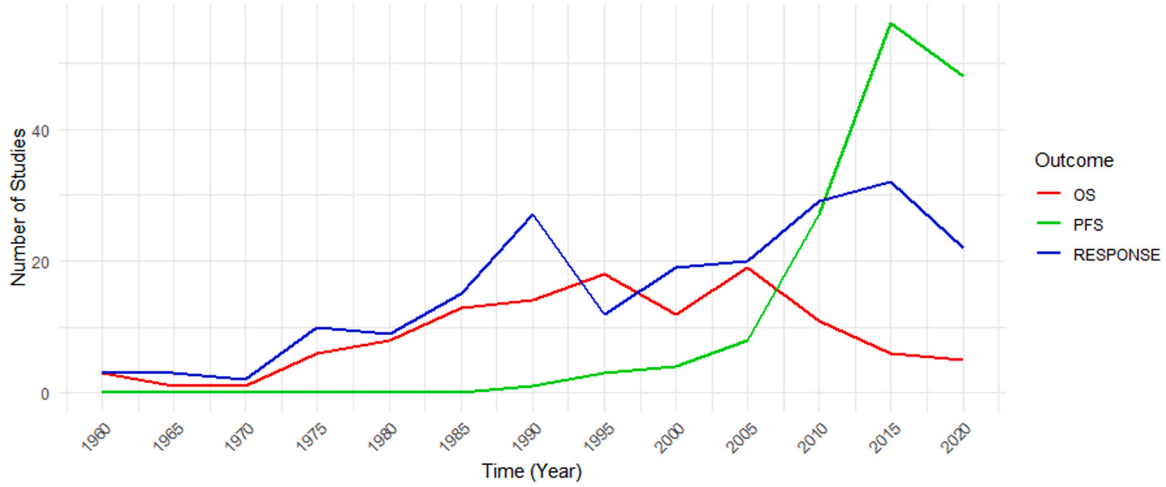

Fig. 2. Trend of primary outcomes in studies over time. PFS: Progression free survival, OS: Overall survival.

Table 1
Characteristics of included studies.

	Antimyeloma treatments (448 studies)		Supportive treatments (176 studies)	
	Treatment type, n (%)		**Study focus, n (%)**	
	Induction	109 (24.3 %)	Bone disease	42 (23.9 %)
	Consolidation	22 (4.9 %)	Symptom burden	24 (13.6 %)
	Conditioning	30 (6.7 %)	Infections and vaccine responses	23 (13.1 %)
	Intensification	8 (1.8 %)	Collection of stem cells (ASCT)	22 (12.5 %)
	Maintenance	80 (17.9 %)	Quality of life (Exercise ect.)	17 (9.7 %)
	Not specified	199 (44.4 %)	Other	
Disease phase				
o Newly Diagnosed Multiple Myeloma	264 (58.9 %)		64 (36.4 %)	
o Relapsed/ Refractory Multiple Myeloma	121 (27.0 %)		10 (5.7 %)	
o Not specified	55 (12.3 %)		98 (55.7 %)	
o Smoldering myeloma	8 (1.8 %)		4 (2.3 %)	
Transplantation eligibility				
o Transplant eligible	119 (26.6 %)		76 (43.2 %)	
o Transplant ineligible	59 (13.2 %)		2 (1.1 %)	
o Transplant eligibility not reported or both	270 (60.3 %)		98 (55.7 %)	
Study phase				
o Phase 3	184 (41.1 %)		27 (15.3 %)	
o Phase 2	98 (21.9 %)		29 (16.5 %)	
o Phase 4	1 (0.2 %)		2 (1.1 %)	
o Not reported	157 (35.0 %)		103 (58.5 %)	
o Pilot/feasibility study	8 (1.7 %)		15 (8.5 %)	
Authors conflicts of interest with funding company				
o More than half	73 (16.3 %)		9 (5.1 %)	
o Less than half	90 (20.1 %)		22 (12.5 %)	
o No conflicts	72 (16.1 %)		54 (30.7 %)	
o Not reported	213 (47.5 %)		91 (51.7 %)	
Funding				
o Pharma funded	102 (22.8 %)		32 (18.2 %)	
o Pharma + other funding	105 (23.4 %)		23 (13.1 %)	
o Not pharma funded	137 (30.6 %)		54 (30.7 %)	
o Funding not reported	104 (23.2 %)		67 (38.1 %)	

pharmacological interventions. The most commonly assessed treatments were bisphosphonates, growth factors and exercise intervention programs. Comparisons and focuses of each study can be found in detail in the corresponding table (supplementary table 6).

The five most common primary endpoints were: Disease complications in 45 studies (25.6 %), adverse events in 41 studies (23.3 %), number of cells in mobilization of stem cells in 18 studies (10.2 %), response outcomes in twelve studies (6.8 %) and feasibility of an intervention in eleven studies (6.3 %).

Further elaborating on the complications, 23 studies had primary endpoints related to bone disease, nine focused on pain management, six on renal function, four on thrombotic events and nine on infections. Adverse events when serving as the primary endpoint mainly included oral mucositis, peripheral neuropathy, anemia, and gastrointestinal disturbances (nausea, vomiting, diarrhea, constipation). Thrombosis and infections are obviously related both to the disease itself and to the treatment followed and are also mentioned in this category.

For the secondary endpoints, adverse events were again the most frequent as presented in supplementary table 2.

Sixty nine (39.2 %) studies performed a statistical test which indicated non-significant results for the primary outcome while 67 (38.1 %) studies had results statistically significant for the outcome of interest.

3.1.4. Regression analyses

The use of response outcomes had an OR 0.36, 95 % CI (0.24, 0.53) for studies not funded by pharmaceuticals. Similarly, for OS, the OR was 0.39, 95 % CI (0.24, 0.65). However, PFS is more commonly used in studies funded by the pharmaceutical industry with OR 3.85, 95 % CI (2.41, 6.35). Studies that received funding other than non-profit, were approximately 3.8 times more likely to have PFS as their primary outcome ($p < 0.001$) (Fig. 3).

Regarding the association of pharmaceutical funding and a positive or negative study outcome (statistically significant), logistic regression revealed a positive association with an OR of 1.60, 95 % CI (1.06, 2.44). Studies that had some support from pharmaceutical companies were about 1.6 times more likely to have positive results ($p=0.025$).

Also, the correlation between choice of primary outcome with the researchers' conflict of interest was examined. Response was not significantly correlated with conflicts of interest with an OR 0.69, 95 % CI (0.41, 1.16). PFS however had 4.57 times higher chance of being chosen as a primary outcome in studies where authors had conflicts with the funding source, with an OR 4.57, 95 % CI (2.72, 7.92). OS revealed no association with conflicts of interest, OR 0.81, 95 % CI (0.36, 1.89) (Fig. 3).

4. Discussion

Our systematic review of randomized controlled trials on therapeutic interventions for multiple myeloma revealed a marked preference for surrogate endpoints, PFS and response outcomes, especially in the setting of relapsed/refractory myeloma. Overall survival was underrepresented as primary outcome, and this diminished with time. Interestingly, among trials that used it as primary outcome, hence had adequate power to detect a potential effect, only a small proportion had significant results, suggesting that only few studies in myeloma have demonstrated actual survival advantage with the intervention studied. Similarly, quality of life was also underrepresented with a very small proportion of studies highlighting it as primary outcome and an even smaller proportion showing statistically significant results.

Additionally, a significant number of trials were lacking clarity on funding, and declaration of authors' conflicts of interest. We identified an association between funding by pharmaceutical companies and use of PFS as primary outcome. PFS has been shown to be an easier outcome to achieve statistically significant results, making it a favorable candidate to support applications for market approval. Moreover, there was a positive correlation between funding from pharmaceutical companies and yielding positive results. These findings resonate with the broader debate on the role of pharmaceutical industry in clinical research, underscoring the need for transparency and rigor.

Furthermore, downplaying negative results when presenting efficacy of a new drug, is common in oncology. Presenting subgroup analyses and surrogate outcomes that achieve statistical significance while the survival benefit is not detected, creates a spin in oncology trials and does not help doctors distinguish results that truly serve patients (Wayant et al., 2019). Additionally, positive results of new treatments are most likely to be published and promoted accordingly, even with marginal clinical benefits.

Our study results align with the reported decline of use of OS as the primary endpoint in multiple myeloma trials as already identified by previous studies (Mohyuddin et al., 2021b). This underscoring of overall survival and shift towards surrogate endpoints is a well-recognized reality in oncological research (Holstein et al., 2019). This preference

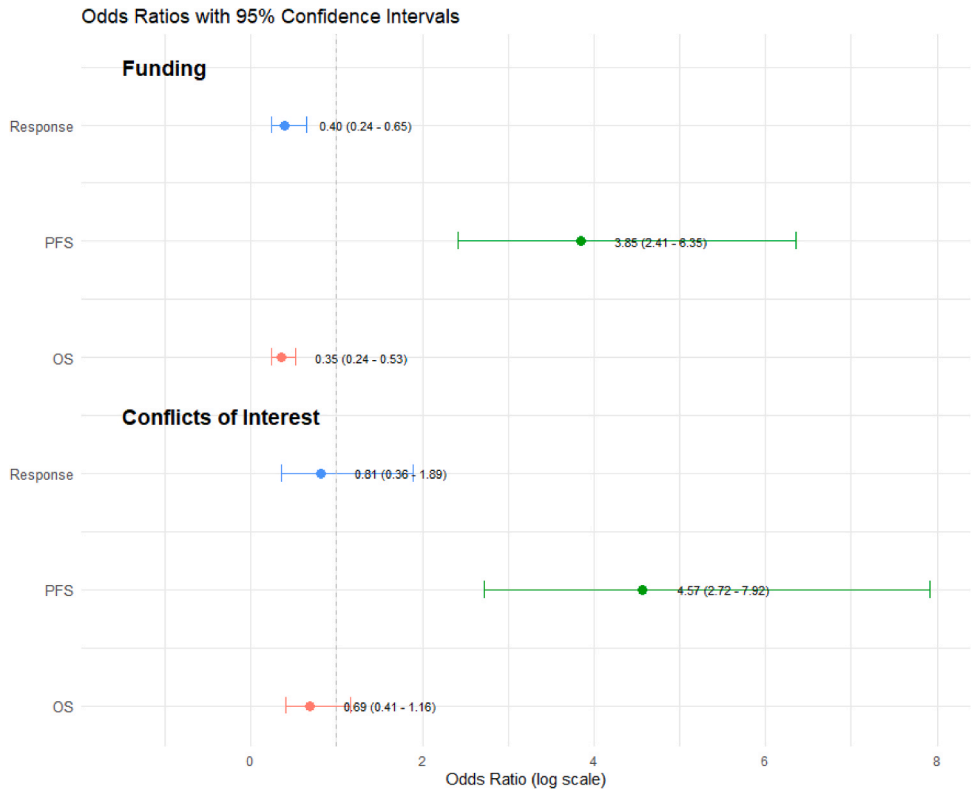

Fig. 3. Regression analysis. Primary outcome selection in relation to funding and authors' conflicts of interest. PFS: Progression free survival, OS: Overall survival.

often arises from the desire for faster results and as regulatory authorities do not demand hard clinical endpoints for drug approval, survival advantage can be neglected (Kim and Prasad, 2016). However, it raises questions about the true clinical benefit these interventions provide in terms of extending life (Anderson et al., 2007; Cliff and Mohyuddin, 2022; Gyawali and Prasad, 2017; Haslam et al., 2019).

The value of PFS as an endpoint has sparked debates, with some studies emphasizing its correlation with OS, while others question its adequacy in capturing net clinical benefits in certain therapeutic contexts (Etekal et al., 2023; Gyawali et al., 2022; Gyawali and Prasad, 2017). In the stage of relapsed/refractory multiple myeloma where survival can be measured in months, solely relying on PFS might not be practical. In newly diagnosed setting on the other hand, correlation between OS and PFS is weak (Etekal et al., 2023), although some lack of OS benefit can be a consequence of short follow-up. Depending solely on PFS could potentially lead to detrimental decisions for patients. Therefore, conducting follow-up studies to ensure survival benefit is imperative (Kumar and Rajkumar, 2019). Our study underscores the importance of careful consideration when adopting PFS, particularly considering the diverse definitions of progression in myeloma, which range from clinical manifestations to mere biochemical markers.

The issue of surrogacy also applies to response outcomes and MRD assessment which is becoming increasingly relevant to current myeloma trials. While the debate on PFS still holds, response rates and MRD are being considered as potential surrogates for PFS in studies in newly diagnosed multiple myeloma, where detecting OS is particularly challenging (Avet-Loiseau et al., 2020; Daniele et al., 2022). However response rates might not correlate well with survival (Mainou et al., 2017) and although MRD has been established as a prognostic marker, it presents challenges, such as uniform reporting between studies (Anderson et al., 2021; Derman and Jakubowiak, 2022; Munshi et al., 2020; Van Oekelen et al., 2022). After recent approval of MRD as an endpoint for accelerated drug approval in myeloma, process of new products coming to market will be faster to address patients' urgent need for novel treatments (Combined FDA and Applicants ODAC Briefing Document, 2024). Without undermining the progress made in response markers in myeloma, we echo recent calls for a sensible approach in oncology trials, prioritizing outcomes that matter most to patients (Booth et al., 2023).

Quality of life is another important parameter, often neglected in trials. Despite its importance, our review found a limited focus on quality of life as a primary endpoint. Different disease specific or generic tools are validated to assist evaluation of patients' health-related quality of life (HRQoL). However, it is not certain that they capture the symptom burden of patients with multiple myeloma in their enduring journey with the disease (Kvam et al., 2009; LeBlanc et al., 2020; Mohyuddin et al., 2022; Nielsen et al., 2019, 2017; Osborne et al., 2012; Rizzo et al., 2014; Sonneveld et al., 2013). In addition, there is a concern about continuous treatment in myeloma, and its' impact on patient burden, as "treatment-free intervals" are becoming shorter with the use of maintenance therapy and use of multiple drugs together to achieve cure (Bonello et al., 2019; Ludwig and Zojer, 2017; Palumbo et al., 2015; Rajkumar et al., 2011). Also, long-term follow-up and appropriate time points in which quality of life is measured, should be taken into account when evaluated in oncology clinical trials (Haslam et al., 2020).

An issue underscored across numerous myeloma trials is the challenge of appropriately sequencing drugs withing various combinations, alongside the absence of head-to-head comparisons. In our study a significant number of trials compared 3 versus 2 drugs, a problem reported since triplets became standard of care (Mohyuddin et al., 2021a). The simple measurement of response rates between triplets and duplets and now between quads and triple drug combinations, offers little information for clinical practice, when uncertainty persists about whether employing all drugs upfront yields superior survival outcomes compared to reserving them for relapse (Walia et al., 2023).

Another point worth noting is the country in which trials were conducted, mostly coming from Europe and North America, showing a well-recognized issue of access of anticancer drugs to every patient, even in underdeveloped countries. This extends to also lower representation of non-white patients in myeloma studies, creating a question of fairness

for patients, also noted in other oncology trials (Asher et al., 2022; Bhandari et al., 2021; Fahmawi et al., 2023; Turner et al., 2022).

Our study shares similarities with the systematic review conducted previously (Mohyuddin et al., 2021b) et al. but extends beyond by incorporating a larger number of trials, providing a comprehensive overview of the myeloma landscape over time. Additionally, we tried to explore potential associations of study outcomes and conflicts of interest, through regression analyses.

Certain limitations should be acknowledged. The heterogeneity of the included trials, different phases, variations in definitions of endpoints, and potential publication biases might have influenced our results. In particular, the change in the definition of multiple myeloma in 2014 integrated the SLiM criteria (Rajkumar et al., 2014) which defined myeloma as the phase of the disease characterized with high tumor burden but no identified organ damage yet. As a result, cases previously characterized as smoldering myeloma, are nowadays classified as myeloma and this can have an impact in study outcomes, shifting results towards positivity (Landgren and Rajkumar, 2016; Ludwig et al., 2023; Mosebach et al., 2019; Rajkumar, 2016). In our review we categorized cases previously labeled as "asymptomatic myeloma" in earlier studies as smoldering myeloma. Also, older studies used different definitions of response from those published later by the IMWG (Kumar et al., 2016).

Furthermore, we acknowledge that we categorize conflicts of interest by grouping together financial payments to authors and research payments. Additionally, we did not distinguish conflicts based on the position of the author (e.g., first, last, or middle author) due to the complexity and variability of authorship contributions across different studies. However, we acknowledge that the role and influence of specific authors could impact study outcomes, and this is an important consideration for future analyses. We recognize that conflicts of interest can exist beyond direct industry funding and could influence study outcomes regardless of the funding source. Our methodology aimed to directly assess the influence of pharmaceutical sponsorship, with the inclusion of conflicts intended to provide context on potential biases related to the funding source. Unfortunately, capturing the details of conflicts of interest is not always straightforward.

Finally, while we captured a comprehensive snapshot of MM trials at the time of the search data, the rapidly evolving landscape of MM research may lead to shifts in trends and preferences and our observations could become easily outdated.

The findings from this systematic review provided a foundational list of outcomes, which, along with outcomes identified through patient and clinician interviews, were used to create surveys for both patients and myeloma-treating doctors. These qualitative findings, combined with survey results, will be presented in a mixed-methods study aimed at understanding whether the priorities of patients and clinicians align with those traditionally used in clinical trials. This research aims to inform future trial designs to better address stakeholder priorities.

5. Conclusion

In conclusion, while surrogate endpoints like PFS and response are being used more in myeloma research, survival and quality of life of patients is being neglected. Our study underscores the need for a balanced approach, valuing patient-centered outcomes alongside clinical markers. Transparency concerning funding and conflicts of interest, independence of investigators and consideration of a holistic set of endpoints to guide questions relevant to clinical practice is needed.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

M.M.: Conceptualization, Data curation, Formal analysis, Methodology, Writing - original draft. K.T., T.M., K.M.: Data curation, Investigation. T.K.: Methodology, Writing – review and editing. I.A.: Conceptualization, Methodology. A.L.: Formal analysis, Methodology. M.P., E.T.: Supervision, Writing – review and editing. V.P.: Methodology, Validation. A.T.: Conceptualization, Methodology, Supervision, Writing – review and editing.

Declaration of Competing Interest

None of the other authors have any other conflicts of interest.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgements

M.M. is PhD candidate at Aristotle University of Thessaloniki. This work is submitted in partial fulfillment of the requirement for the PhD.

Conflict of interest disclosures

E.T. reports research support from GSK, Janssen, Takeda, and Sanofi. He declares Horonaria from Amgen, Antengene, BMS, GSK, Celgene, Janssen, Menarini/Stemline, Novartis, Sanofi, Swixx, and Takeda and advisory board participation from Amgen, BMS, GSK, Celgene, Janssen, Menarini/Stemline, Sanofi, Swixx, and Takeda. V.P. receives research funding from Arnold Ventures through a grant made to UCSF, and royalties for books and writing from Johns Hopkins Press, MedPage, and the Free Press. He declares consultancy roles with UnitedHealthcare and OptumRX; He hosts the podcasts, Plenary Session, VPZD, Sensible Medicine, writes the newsletters, Sensible Medicine, the Drug Development Letter and VP's Observations and Thoughts, and runs the YouTube channel Vinay Prasad MD MPH, which collectively earn revenue on the platforms: Patreon, YouTube and Substack. None of the other authors have any other conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2024.104529.

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