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## ORIGINAL PAPER

# Time-to-event surrogate end-points in multiple myeloma randomised trials from 2005 to 2019: A surrogacy analysis

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## Summary

Use of surrogate end-points such as progression-free survival (PFS) and other time-to-event (TTE) end-points is common in multiple myeloma (MM) clinical trials. This systematic review characterises all published randomised controlled trials (RCTs) in MM using PFS or other TTE end-points between 2005 and 2019 and assesses strength of surrogacy of PFS for overall survival (OS). The association between OS hazard ratios (HRs) and PFS HRs was evaluated with linear regression, and the coefficient of determination with Pearson's correlation. We identified 88 RCTs of which 67 (76%) used PFS as the primary/co-primary end-point. One trial indicated whether progression was biochemical or clinical. Of the variance in OS, 39% was due to variance in PFS. Correlation between PFS and OS was weak (0.62, 95% confidence interval [CI] 0.38–0.78). In newly diagnosed MM, 43% of the variance in OS was due to changes in PFS. The correlation between PFS and OS was weak (0.65, 95% CI 0.30–0.84). In relapsed/refractory MM, 58% of the variance in OS was due to changes in PFS. Correlation between PFS and OS was medium (0.76, 95% CI 0.42–0.91). We demonstrate that PFS and progression characteristics are characterised poorly in MM trials and that PFS is a poor surrogate for OS in MM.

## KEY WORDS

end-point, multiple myeloma, overall survival, progression-free survival, randomised controlled trial

## INTRODUCTION

The use of end-points other than overall survival (OS) in oncological randomised controlled trials (RCTs) can, under some conditions, reduce the cost and duration of studies.<sup>1</sup> However, the validity of these alternative end-points is not consistently proven in most malignancies, including multiple myeloma (MM), and therefore their widespread use is of concern.<sup>2</sup>

Drugs approved by regulatory authorities for MM on the basis of surrogate end-points in Europe and the United States over the last 15 years include carfilzomib, ixazomib, thalidomide, lenalidomide, pomalidomide, liposomal doxorubicin, panobinostat, daratumumab, isatuximab, elotuzumab,<sup>3</sup> selinexor, belantamab mafodotin, ciltacabtagene autoleucel, and idecabtagene vicleucel.<sup>4–6</sup> Some of these agents have gone on to demonstrate an OS benefit in confirmatory registration trials.<sup>7,8</sup>

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Buyse et al.<sup>9</sup> have defined two criteria for surrogacy. The first concerns a relationship at the trial level – asking if interventions that improve the surrogate also improve survival. The second criteria asks, adjusting for treatment, if achievement of the surrogate has prognostic value for an individual. In our paper we focus on the former. Although the latter is vital, it is not clear if it is necessary for regulatory decision making. Meanwhile, the United States Food and Drug Administration (FDA) itself has stated that trial level validity is the standard to which they aspire and has conducted several papers assessing that.<sup>10</sup> Progression-free survival (PFS) has been accepted by regulatory authorities as a valid end-point for registrational clinical trials in MM. Previous analysis of surrogacy of PFS for OS conducted by industry, as well as an older independently conducted analysis, has shown a positive association between treatment effects on PFS and OS.<sup>11–13</sup> As an example, an analysis conducted by industry evaluated 21 randomised MM trials that reported hazard ratios (HRs) for both PFS and OS, the correlation coefficient, which is a measure of linear correlation between two variables, was 0.82 between the HR of PFS and OS. The coefficient of determination, which is the proportion of the variance in the dependent variable that is explained by the independent variable was 0.67. Given that several recent MM trials have demonstrated discordance between PFS and OS,<sup>14,15</sup> there is a need for an independently conducted updated surrogacy analysis of PFS and OS.

Progression in MM may occur clinically (with the appearance of, e.g., new lytic lesions or extramedullary disease) or biochemically, with a rise of a monoclonal protein. As clinical progression may be more prognostically relevant than asymptomatic biochemical progression,<sup>16,17</sup> it is important for clinical trials to include the nature of progression as part of their results. For all randomised trials that used a primary or co-primary time-to-event end-point such as PFS, event-free survival (EFS) and time to progression (TTP), we assessed whether progression was reported as a biochemical progression or a clinical progression and whether a benefit in PFS translated to an OS benefit upon extended follow-up. We also performed a surrogacy analysis of PFS for OS in these trials to evaluate the strength of surrogacy.

## METHODS

### Search strategy

Three databases were searched (MEDLINE/PubMed, Embase, and Cochrane Registry of Controlled Trials) for all RCTs in MM from 2005 to 2019. The search was last performed on 1 April 2020, and data for this study were analysed on 30 December 2021. Examples of search strategies using the aforementioned databases are highlighted in the supplement. The ‘snowballing’ procedure was performed by searching reference lists of included studies and relevant review articles. Major conference proceedings (American Society of Clinical Oncology, American Society

of Haematology, European Haematology Association) were also reviewed. Two independent reviewers (G.R.M., K.K.) screened all studies, and any conflict was resolved through mutual discussion. This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.<sup>18</sup>

### Inclusion and exclusion criteria

Our search strategy was restricted to all randomised trials (phase II or phase III) that were published in manuscript or abstract form from 1 January 2005 to 30 December 2019. All other studies including editorials, case reports, case series, review articles, case-controls, retrospective/prospective cohorts, and single-arm studies were excluded. The search strategy was not restricted to language. We initially searched for all RCTs that had a primary analysis result reported even if the trial was still in progress. Descriptive abstracts of methodology without any results were not included. Trials included for final analysis (listed in Supplement) in our study were randomised trials that used time-to-event end-points (PFS or OS) as their primary or co-primary end-point. Trials included for surrogacy analysis were only phase III trials, because of the underpowered nature of phase II trials to assess OS differences. Two authors (G.R.M. and K.K.) performed and verified all data extraction as part of a previous research project that examined and characterised end-points used in MM trials.<sup>19</sup> We identified the following characteristics of studies: phase of study (Phase II/III), line of therapy being treated (relapsed/refractory or front-line) and location of study (enrolment limited to the United States vs. enrolment in multiple countries).

### Definitions

Definitions of response rates (RRs), PFS, TTP and EFS were as per the respective studies, with the International Myeloma Working Group (IMWG) criteria<sup>20</sup> or the Blade Criteria commonly used.<sup>21</sup>

### Statistical analysis

The primary objective of this study were twofold. Firstly, to evaluate the proportion of RCTs using time-to-event end-points that reported whether progression was biochemical and/or clinical. Secondly, our objective was to evaluate the strength of surrogacy of PFS to OS for those RCTs that used PFS or OS as a primary or co-primary end-point. Other outcomes included the proportion of RCTs that applied independent review for the assessment of the primary outcome and the proportion of trials that reported an OS advantage. We used an unadjusted linear regression to evaluate the association between the OS HR and PFS HR for studies

reporting time-concurrent numbers, or for studies reporting OS at a later follow-up, and to calculate the coefficient of determination ( $R^2$ ). We also calculated Pearson's correlation coefficients and 95% confidence intervals (CIs) for the correlation coefficients. R statistical software (version 3.6.2) was used for this analysis. We classified the strength of association as weak ( $r \leq 0.7$ ), medium ( $r > 0.7$  to  $r < 0.85$ ), and strong ( $r \geq 0.85$ ) based on a guidance document<sup>22</sup> and a systematic review<sup>23</sup> (Table 1). We calculated  $R^2$  and correlation coefficients for all studies combined, studies limited to newly diagnosed MM, and studies limited to relapsed/refractory MM. The regression was weighted by sample size and a sensitivity analysis by which outliers were removed was performed. The studies used for the regression analysis were phase III trials with PFS or OS as either a primary or co-primary end-point that reported both PFS and OS at the same time, or if not reporting OS numbers at primary publication, those that reported OS at follow-up. The most recent HR for OS was used, whenever applicable. Studies that did not meet these criteria, either by not reporting the HR for PFS and/or OS or by not having reached maturity for OS or PFS HR calculation, were not included in the linear regression. Only studies that clearly stated which established criteria were used for assessment of response and progression were included in the surrogacy analysis.

## RESULTS

The initial search strategy yielded 1171 results (Figure 1). After searching conference proceedings and excluding duplicates or studies not meeting inclusion criteria, 151 discrete RCTs were included. Amongst these 151 randomised trials, 44 (29%) used RRs as a primary end-point, and 19 (13%) used other primary end-points (such as measurable residual disease [MRD] negativity, transplant/collection-related outcomes, symptom measures, proportion proceeding to transplant etc). When substratified for only those trials that were primarily evaluating time-to-event end-points, a total of 88 studies were identified, of which 67 had PFS as either a primary or co-primary end-point. A total of 41 studies included HRs for both PFS and OS, allowing for regression analysis. Table 2 highlights characteristics of included studies and Table 3 (provided in Appendix S1) highlights details of each of the 41 studies individually that were included in the surrogacy analysis.

**TABLE 1** Proof of validity of surrogate end-points and correlation ( $r$ ) limits in oncology, adapted from the Institute for Quality and Efficiency in health Care<sup>23</sup>

Correlation ( $r$ )	Proof of validity
$r \geq 0.85$ (strong correlation)	Validity can be inferred
$r > 0.7$ to $r < 0.85$ (medium correlation)	Unclear validity
$r \leq 0.7$ (weak correlation)	Lack of validity can be inferred

## Reporting of PFS

We found only one study that described whether progression events were biochemical or clinical.<sup>24</sup> Two additional studies reported time-to-first skeletal event,<sup>25</sup> and renal impairment reversal<sup>26</sup> respectively but did not clearly differentiate between biochemical and clinical progression. Most RCTs defined response and progression according to established international criteria, such as European Society for Blood and Marrow Transplantation (EBMT)/Blade criteria, IMWG criteria, and International Uniform Response Criteria for MM<sup>27</sup> with 22 (25%), 41 (47%) and 13 (15%) RCTs using these criteria respectively. These criteria include both biochemical and clinical parameters, with the remaining 12 studies using other criteria or not clearly describing the criteria used.

A total of 38 of the 88 (43%) studies reported using independent review of efficacy data, whereas 14 (16%) studies reported using investigator-based review of efficacy. The remaining 36 studies (41%) were a mix of algorithm-based review, blinded investigator review, and unreported review methods. A total of five studies reported efficacy findings (6%) according to both investigator and independent review.

## Overall survival reporting

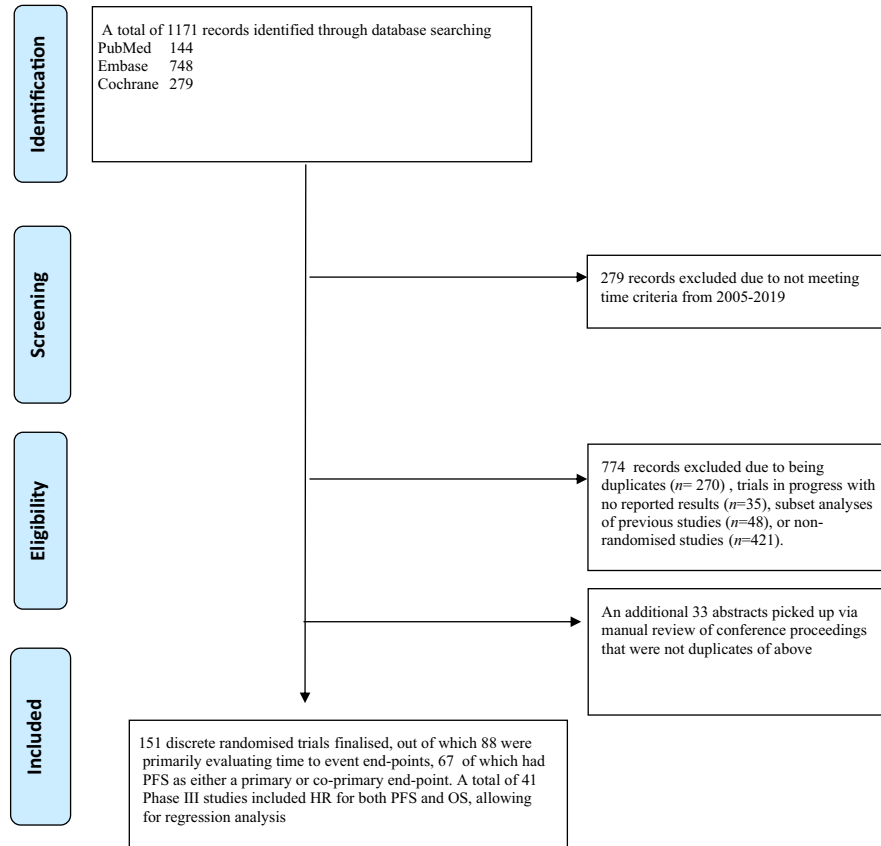
A total of 81 studies reported data on OS. At the most recent follow-up of included studies where OS data were obtained, 23 out of 81 (28%) trials showed significant improvement in OS at either first publication or at most-recent follow-up. Six trials (7%) showed improvement in OS at follow-up but did not show an improvement at primary analysis.<sup>28–33</sup> One study failed to show improvement in OS at follow-up but demonstrated an OS benefit at primary analysis.<sup>34</sup> There were three studies (4%) that showed a decrement to OS.<sup>15,35,36</sup> The remaining 48 (59%) studies showed no significant OS benefit (or decrement) at primary analysis or on the most recent follow-up.

## Progression-free survival as a surrogate for OS

Amongst the 41 studies where correlation could be assessed, the  $R^2$  from the regression model suggested that amongst the variance in OS, 39% was explained by PFS (Figure 2). The correlation between PFS and OS was 0.62 (95% CI 0.38–0.78), indicating a weak association of PFS with OS (Figure 2A). When excluding two outliers, the variance in OS due to PFS was 40%, with a correlation of 0.63 (95% CI 0.40–0.79) (Figure 2B).

For newly diagnosed MM ( $n = 21$ ) studies, 43% of the variance in OS was due to changes in PFS. The correlation between PFS and OS was 0.65 (95% CI 0.30–0.84) indicating a weak association of PFS with OS (Figure 2C).

For studies of relapsed/refractory MM ( $n = 16$ ), 58% of the variance in OS was due to changes in PFS. The correlation between PFS and OS was 0.76 (95% CI 0.42–0.91), indicating a medium association of PFS with OS (Figure 2D).



**FIGURE 1** Flow diagram depicting our search strategy and study inclusion. HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

**TABLE 2** Characteristics of included randomised trials reporting on overall survival and progression-free survival in multiple myeloma (2005–2019;  $N = 88$ )

Characteristic	Number of studies (%)
Phase II	23 (26.1)
Phase III	65 (73.9)
Pharmaceutical studies	37 (42.0)
Front-line or consolidation after front-line	44 (50.0)
Relapsed/refractory	35 (39.8)
Maintenance	9 (10.2)
Enrolled in multiple countries	51 (57.9)
Time-to-event end-point as primary end-point	
Progression-free survival	67 (76.1)
Time to progression	13 (14.7)
Event-free survival	7 (8.1)
Other	1 (1.1)

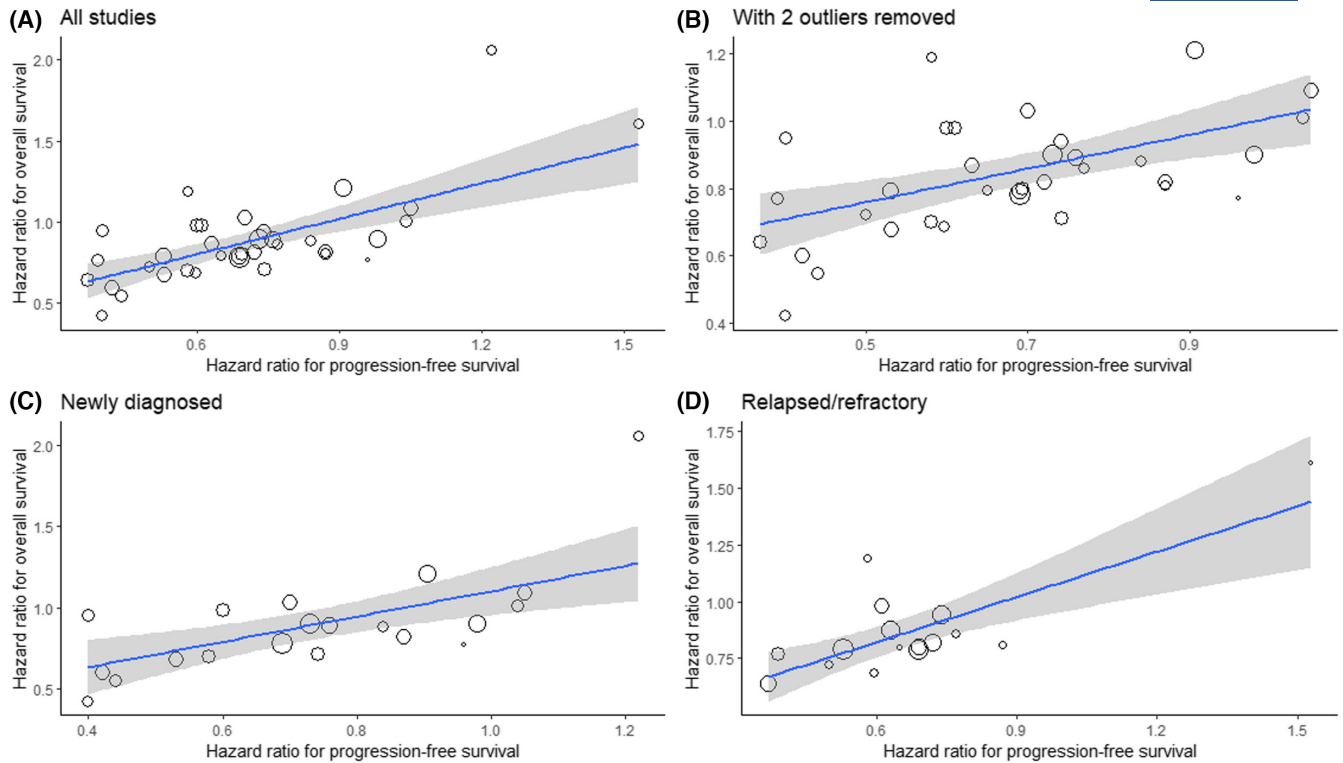
## DISCUSSION

Our study demonstrates that for MM, differences in PFS do not reliably predict differences in OS, and that PFS is not a valid surrogate for OS. There was a weak correlation

between PFS and OS in the newly diagnosed setting, and a medium correlation in the relapsed/refractory setting. As efforts are underway to establish MRD as a surrogate for PFS, these findings are especially relevant, as a proven surrogacy between MRD and PFS, while expediting drug approval, may not result in those approvals necessarily translating into patients living longer.<sup>37</sup> Furthermore, although the distinction between clinical and biochemical PFS is relevant from a prognostic and practical standpoint, the nature of disease progression is almost never reported in MM clinical trials. Although PFS is a frequently used approved end-point for regulatory purposes,<sup>19</sup> and it is undeniable that outcomes in MM have improved dramatically for patients, the results of this analysis highlight the limitations of currently used surrogate outcomes.

The use of surrogate end-points in MM stems from a desire to deliver results in a timely manner and to make new drugs rapidly available to patients. In the newly diagnosed setting, waiting for an OS advantage may indeed take a very long time. However, for multiply relapsed disease with limited survival, OS remains a practical end-point. Furthermore, OS remains the best way to determine whether combining drugs is more beneficial than sequencing them, a pressing question in MM.

It is important to reiterate that our results differ from prior analysis of surrogacy.<sup>11–13</sup> The analysis by Cartier et al.<sup>11</sup> of surrogacy of PFS for OS showed higher correlations



**FIGURE 2** Linear regression plots for overall survival (OS) and progression-free survival (PFS) hazard ratios in randomised trials reporting on OS and PFS in multiple myeloma (MM). Linear regression plots for (A) all studies, (B) all studies with two outliers removed, (C) newly diagnosed MM and (D) relapsed/refractory MM.

than those we observed. Our independently conducted analysis includes more recent studies where changes in PFS have not correlated to changes in OS.<sup>15</sup> It is notable that the study by Cartier et al.<sup>11</sup> was funded by industry, included far fewer RCTs (21 vs. 41) and included studies only up to December 2013. It included fewer studies in the relapsed/refractory setting (three vs. 16). Seven out of 21 studies (33%) in that analysis neither used PFS nor OS as primary end-point, and one phase II study was also included in that study. Of those seven studies two used TTP, two used EFS and the three remaining studies used response-based end-points. The median follow-up was on average 20 months longer in our surrogacy analysis (38 vs. 58 months). Seventeen studies utilised immunomodulatory drugs alone or in some combination, either with transplant, proteasome inhibitors, cytotoxics or interferon. One study's HRs were included twice, one from primary publication and one from a follow-up publication.<sup>38,39</sup> The more contemporary and larger series of RCTs included in the present analysis should therefore raise serious questions about the role of PFS in our field, despite the practical limitations of using OS as an end-point.

It is also worth noting that correlations between PFS and OS vary by disease type, setting and class of agent.<sup>23,40</sup> Our analysis concerns PFS for newly diagnosed disease and for relapsed/refractory disease and involves existing classes of drugs such as proteasome inhibitors, anti-CD38 monoclonal antibodies, alkylators and immunomodulatory drugs. As no randomised trials have yet reported for other agents such as bispecific agents and chimeric antigen receptor therapy, our

results may not be applicable to those settings. However, our analysis is directly applicable to the FDA's use of PFS as regulatory end-point.

Although a post hoc analysis of two randomised phase III trials has shown that symptomatic (clinical) progression (as opposed to biochemical progression) may predict worse OS, poor characterisation of progression details in reported clinical trials prevents use of morbid progression as a meaningful end-point.<sup>41</sup> A recent retrospective analysis of patients with biochemical versus clinical progression shows that patients with clinical progression have worse OS,<sup>17</sup> highlighting the importance of reporting of progression outcomes in clinical studies. At the same time, these preliminary results are prognostic analyses and not formal studies of surrogacy, which ask if the change in a surrogate seen across trials of novel agents can faithfully predict changes in clinically meaningful end-points.

The German based Institute for Quality and Efficiency in Health Care (IQWiG), a Health Technology Assessment institute, provides guidance on surrogate end-point use in oncology.<sup>42</sup> Correlation of a surrogate end-point with a clinically meaningful end-point (such as OS)  $<0.7$  is considered a weak correlation and shows a lack of validity of the surrogate. We demonstrate that PFS (especially for newly diagnosed MM) falls below this threshold, and hence remains an unproven/uncertain surrogate for OS.

Although we recognise that OS may not be a practical end-point in many settings, and PFS is a more convenient regulatory end-point, we urge caution. In the updated

results of the BELLINI trial (ClinicalTrials.gov Identifier: NCT02755597), PFS was significantly improved with the investigational agent, but the drug led to an increase in mortality.<sup>43</sup> Similarly, in the OCEAN trial (ClinicalTrials.gov Identifier: NCT03151811), despite a PFS advantage in the melflufen treatment arm, a decrement in OS was observed.<sup>44</sup> There is a possibility that by leaning too much on unvalidated surrogate end-points we harm our patients.

There have been recent attempts to establish MRD as a surrogate for PFS in MM.<sup>45,46</sup> We argue that, given the current drawbacks in the reporting of PFS and its limited status as a validated surrogate end-point, efforts ought to be made to evaluate MRD as a surrogate end-point only for OS. Even if surrogacy between PFS and MRD is established, it may not predict meaningful outcomes for patients, as it would only prove that MRD is a surrogate for an end-point that is in itself not a reliable surrogate for OS. However, we recognise that if MRD was to be established as a robust surrogate for OS, this indeed could help expedite approval of beneficial drugs. We also recognise that attempts to 'cure' MM may indeed hinge on novel therapeutic strategies applied early in the disease course using surrogate measures of disease to dictate intensity of therapy, and that relying on OS to evaluate the efficacy of those interventions (although ideal), may not be practically feasible. Nevertheless, responsible discourse about the limitations of surrogates should be encouraged and use of OS when it is highly practical (such as in heavily relapsed disease) should be preferred and sought by regulatory authorities.

Unless further granularity on surrogate end-points is provided, and surrogacy adequately proven, the magnitude of clinical benefit of drugs approved cannot be accurately ascertained, and decisions on prioritising where resources should be allocated cannot effectively be made. By having more information on how progression is delayed, both the benefit and total cost of treatment can better be assessed. This could lead to better and more effective decision-making by regulatory agencies, by insurance companies, and when deciding on government subsidisation of drugs.

This study has some limitations. We do not have access to patient-level data, and trial summary statistics are utilised in aggregate. As such we could not perform a bivariate copula distribution and we also could not analyse rank correlation between PFS and OS at pre-specified time-points. More than half of the studies formed the input for the surrogacy analysis but we cannot approximate the effect of the unknown HRs from the remaining studies on our results. Furthermore, a heterogeneous group of patients were included in this study, spanning various time eras, various treatments with different mechanisms of action, and various disease states. The strength of surrogacy may vary for each of these unique situations. We did analyse the strength of surrogacy individually for certain scenarios (such as newly diagnosed vs. relapsed/refractory) in an effort to correct this heterogeneity. We postulate that differences in the robustness of surrogacy between newly diagnosed and relapsed/refractory setting are due to the receipt of post-protocol therapy, with effective

therapy at relapse leading to a decreased translation of a positive PFS result to a positive OS result. However, it should be emphasised that the onus for additional novel interventions for newly diagnosed disease should be to improve survival even if effective therapies are given later upon progression.<sup>47</sup> In other words, the evidence should show that meaningful outcomes such as OS (and not just surrogates) improve when effective drugs are moved into earlier lines of therapy. The analysis of varying strength of surrogacy by setting is counterbalanced by thin data. Salami slicing of conditions can lead to situations where only two or three trials are examined for surrogacy; this would result in sizable uncertainty. Given that our surrogacy analysis includes a variety of drug classes, the level of certainty regarding PFS as a poor surrogate for OS, might not be true for all classes of drugs. Moreover, further follow-up time might change the strength of correlation when HRs are updated. A last limitation of our study is that although three databases were searched, it is conceivable that some trials may have been missed.

In summary, this systematic review and surrogacy analysis of randomised MM trials between 2005 and 2019 underscores the need for more comprehensive reporting of progression characteristics in order to establish the magnitude of clinical benefit to our patients. While acknowledging the tremendous improvements in outcomes in patients with MM with the current framework of trials, we highlight that differences in PFS do not reliably predict differences in OS, and we urge caution in attempts to establish surrogacy of other outcomes such as MRD with PFS.

#### AUTHOR CONTRIBUTIONS

Ghulam Rehman Mohyuddin and Aaron Goodman conceived the idea. Ghulam Rehman Mohyuddin and Kelly Koehn performed a literature review, verified and collected the initial data. Tommy Etekal collected additional data, performed statistical analysis and wrote the first draft of the paper. Samer Al Hadidi, Katherine Berger, Christopher Booth, Douglas W. Sborov, Brian McClune and Vinay Prasad provided critical input on the methodology of the study and reviewed the manuscript. Alyson Haslam conducted statistical analysis pertaining to surrogacy and provided manuscript review. All authors approved the final version of the manuscript.

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#### CONFLICT OF INTEREST

Aaron Goodman reports consulting for Seattle Genetics and EUSA Pharma. Vinay Prasad reports receiving royalties from his books, funding from the Laura and John Arnold Foundation; honoraria for Grand Rounds and lectures from several universities, medical centres, non-profit groups, and professional societies; serving as a writer for Medscape; and making the podcast Plenary Session, which has Patreon

backers, outside the submitted work. Douglas W. Sborov reports consulting for Janssen, GlaxoSmithKline, Legend Biotech, Amgen, Celgene, Sanofi and SkylineDX. The other authors report no conflict of interest.

## DATA AVAILABILITY STATEMENT

The dataset from which data was analysed is available upon reasonable request to the corresponding author.

## PATIENT CONSENT STATEMENT


No patient-level data have been used.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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