Adjusting for subsequent therapies in the TOURMALINE-MM1 study shows clinically meaningful improvement in overall survival with addition of ixazomib to lenalidomide and dexamethasone

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Running title: Impact of subsequent therapy on OS with IRd in MM

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HC, JD, RL contributed to the conception and design of the study. HC contributed to the collection of data. KR, NJB, SKK, AK, HC, BW, JD, RL, PGR, PM contributed to the analysis and interpretation of data. KR, AK, HC, RL drafted the manuscript. KR, NJB, SKK, AK, HC, BW, JD, RL, PGR, PM performed a critical review of the paper for important intellectual content. AK, BW contributed to the statistical analysis. HC provided study materials or patients. JD contributed to obtain funding. HC provided administrative, technical, or logistic support. HC, JD supervised the work. All authors approved the final version of the manuscript.

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**Data sharing statement.**

The datasets, including the redacted study protocol, redacted statistical analysis plan, and
individual participants’ data supporting the results reported in this article, will be made available
within three months from initial request to researchers who provide a methodologically sound
proposal. The data will be provided after its de-identification, in compliance with applicable
privacy laws, data protection and requirements for consent and anonymization.
Abstract

TOURMALINE-MM1, the only blinded randomized study in patients with relapsed and/or refractory multiple myeloma (RRMM; ≥1 prior therapy) in the last 10 years, investigated ixazomib+lenalidomide+dexamethasone (IRd) versus lenalidomide+dexamethasone (Rd). Final overall survival (OS) data were based on a median follow-up of 85 months. In RRMM trials where patients have had 1-3 relapses after initial treatment, a high proportion receive subsequent therapy. Application of salvage therapies in blinded trials and newer modes of therapy can increasingly complicate the interpretation of OS. This analysis explores the impact of subsequent therapies on OS outcomes in TOURMALINE-MM1.

The inverse probability of censoring weights (IPCW) method, marginal structural model (MSM), and rank preserving structural failure time model (RPSFTM) were utilized to adjust for confounding on OS, introduced by subsequent therapies. Analyses were conducted for the intent-to-treat (ITT) population and ≥2 prior lines subgroup.

Unadjusted hazard ratio (HR) for IRd versus Rd was 0.94 (95% confidence interval [CI]: 0.78-1.13) in the ITT population. After adjusting for the impact of subsequent therapies by the RPSFTM method, estimated HR for IRd versus Rd in the ITT population was 0.89 (95% CI: 0.74-1.07). Adjusting with IPCW and MSM methods also showed an improvement in HR, favoring IRd. IRd may be particularly beneficial in patients with ≥2 prior lines of therapy (IPCW and MSM HR=0.52, 95% CI: 0.30-0.88; RPSFTM HR=0.68, 95% CI: 0.51-0.91).

These analyses highlight the growing challenge of demonstrating OS benefit in multiple myeloma patients and the importance of assessing confounding introduced by subsequent therapies when interpreting OS.
Introduction

The improvement in overall survival (OS) in patients with multiple myeloma (MM) has been associated with the introduction of multiple, active novel agents over the past decade.\(^1\) Consequently, interpretation of OS has become increasingly confounded by the use of these novel agents, and their availability as experimental treatment arms in clinical trials, in subsequent therapy lines.\(^2\) OS is an important endpoint in MM clinical trials and provides an excellent indicator of efficacy; however, currently randomized trials do not control for subsequent therapies.\(^3\) It is difficult to isolate the true survival benefit of a specific line of therapy in newly diagnosed MM or early relapsed and/or refractory MM (RRMM) due to the confounding caused by initiating subsequent lines of anti-cancer treatment.\(^4\) All patients will ultimately relapse and receive multiple lines of therapy, therefore patients become refractory to different agents/classes of drug at various points throughout their disease course.\(^5\) Each therapy line includes a different combination of chemotherapy agents of different drug classes; for MM these typically include a proteasome inhibitor (PI), immunomodulatory drug, corticosteroid, and in recent years anti-CD38 monoclonal antibodies have been approved for use in these combinations.\(^6\) A number of novel alternative therapeutic options became clinically available during the TOURMALINE-MM1 study course, namely daratumumab, which is now a widely used drug for MM.\(^7\) This means a given studied intervention may be administered to a placebo patient at a later recurrence and thus confer benefit to OS. In contrast, a patient may be treated with an agent they are already refractory to during a later line of therapy; however, due to study blinding the administering clinician is unaware, thus conferring an OS disadvantage. The availability of an increasingly wider range of novel drugs adds to this confounding by providing more therapy options, often with alternative mechanisms of action, which provide further
survival benefits for patients. Without controlling for subsequent therapies, OS should be regarded as the reflection of continued improvement in MM therapy and a continued assessment of safety instead of a long-term measure of the efficacy of a particular drug combination versus another drug combination. Albeit more efficacious drug combinations administered throughout the disease course will therefore contribute to an overall longer OS.

As an example, the recent DETERMINATION study of lenalidomide + bortezomib + dexamethasone (RVd) followed by autologous stem cell transplant (ASCT) versus RVd alone in patients with symptomatic myeloma failed to demonstrate OS improvement, despite a 21.3-month improvement in promising progression-free survival (PFS) outcomes, with the impact of novel therapies as well competing risk contributing to the marked difference in clinical benefit parameters seen. The TOURMALINE-MM1 clinical study (NCT01564537) compared ixazomib + lenalidomide + dexamethasone (IRd) with lenalidomide + dexamethasone (Rd) in patients with RRMM after at least one line of prior therapy. The IRd combination showed a statistically significant and clinically meaningful PFS benefit over Rd, leading to its approval for the treatment of patients with MM who have received ≥1 prior therapy. Final OS data from TOURMALINE-MM1, based on a median follow-up of 85 months (median of 18 treatment cycles for IRd and 16 for Rd), showed a small, non-significant, improvement in median survival with IRd (median OS: IRd=53.6 months and Rd=51.6 months; hazard ratio [HR]=0.939, P = 0.495). Improved HRs were observed in pre-defined subgroups, notably in patients with ≥2 prior therapies. Subsequent therapies were received by 71.7% and 69.9% of patients in the IRd and Rd arms, respectively. The impact of these improved options and resultant better outcomes for patients with RRMM are evident from the observed extended OS in the Rd arm of the TOURMALINE-MM1 clinical trial; the median OS (51.6 months) is the longest observed
across any historical Rd arm from large clinical trials to date in the RRMM population.\textsuperscript{11-14} In contrast, the median OS observed in the Rd arms of four comparable historical clinical trials ranged between 20.3 months and 40.4 months.\textsuperscript{11,12,15,16}

We have previously outlined how subsequent therapy impacted intent-to-treat (ITT) OS outcomes in the TOURMALINE-MM1 trial.\textsuperscript{2} The double-blind nature of the study caused imbalances between arms in terms of subsequent therapy. Compared with the IRd arm, patients in the Rd group received a higher number of subsequent therapies, and also received subsequent PIs, daratumumab, and other agents more frequently.\textsuperscript{2} In this subsequent evaluation, we have conducted a range of novel statistical analyses to examine the impact of subsequent therapies on OS in the TOURMALINE-MM1 study, in the overall patient population and by line of therapy. Both IRd and Rd are approved for the treatment of RRMM in many geographies after $\geq$2 prior lines and hence the results for this subgroup will be useful for clinical practice. In these analyses, we attempt to isolate the impact of IRd compared with Rd on OS from the impact of subsequent therapies.
Methods

Patients and study design

The details of the study design for TOURMALINE-MM1 have been previously published elsewhere.\textsuperscript{2,8,17} To summarize, TOURMALINE-MM1 was a phase III, randomized, double-blind, controlled clinical trial designed to assess the efficacy of IRd versus Rd in patients with RRMM (i.e., ≥1 prior therapy). Patients were randomly assigned to IRd or Rd, stratified by number of prior therapies (1 vs. 2 or 3), previous proteasome inhibitor (PI) exposure (exposed vs. naïve), and International Staging System (ISS) disease stage (I or II vs. III).\textsuperscript{2}

The trial was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and appropriate regulatory requirements. Local ethics committees or institutional review boards approved the protocol, which is available at https://www.nejm.org/doi/suppl/10.1056/NEJMoa1516282/suppl_file/nejmoa1516282_protocol.pdf. All patients provided written informed consent.

Statistical analyses

The following analyses of TOURMALINE-MM1 clinical trial data were conducted with the ITT population and the subgroups of patients who had received ≥1 and ≥2 prior lines of therapy. Analyses were conducted in SAS version 9.0. All subgroup analyses used stratified Cox Proportional hazard models to estimate HRs and stratified log-rank test to obtain $P$ values. Unless mentioned otherwise, survival curves were generated using the Kaplan-Meier method. To remove the effect of subsequent therapies from OS outcomes and quantify causal survival benefit of IRd over Rd, the inverse probability of censoring weighted (IPCW), marginal structural models (MSM), and the rank preserving structural failure time models (RPSFTM)
methods were used. In the ITT population, IPCW and MSM were pre-specified analyses and RPSFTM was an *ad hoc* analysis, while for the subgroup of patients who had received ≥2 prior treatment lines, all three analyses were *post-hoc*. For all analyses, stratification factors were aligned with randomization stratification factors. More detail on the IPCW, MSM and RPSFTM methods are provided in the Supplementary Material.
Results

In TOURMALINE-MM1, a total of 722 patients were enrolled; patients were randomly assigned to IRd (n=360) or Rd (n=362) per the stratification factors. In the IRd and Rd arms, 62/27/11% and 60/31/9% of patients had received 1/2/3 prior therapies, respectively; 69% and 70% had prior PI exposure, and 63/25/12% and 64/24/12% had ISS disease stage I/II/III disease. There were fewer lines of subsequent therapy received in the IRd arm versus the Rd arm (median 2 vs. 3 in the ITT population). Most of the subsequent therapies received were balanced across treatment arms in the ITT population, including lenalidomide (IRd: 29%; Rd: 28%) and dexamethasone (IRd: 87%; Rd: 91%). A slightly lower proportion of patients in the ITT population received subsequent ASCT in the IRd versus Rd arms (4% vs. 10%) and this was also observed in the ≥2 prior lines of therapy subgroup (<1% vs. 10%; Table 1). A slight imbalance was seen for patients receiving a subsequent PI therapy in the IRd versus Rd arms (ITT: 72% vs. 77%; ≥2 prior lines: 64% vs. 69%, Table 1); for patients receiving subsequent carfilzomib in the ITT population (IRd: 27%; Rd: 33%) and the ≥2 prior lines subgroup (IRd: 25%; Rd: 28%; Table 1), the Rd arm had a greater survival benefit (ITT HR=1.08, 95% confidence interval [CI] 0.71-1.62 and ≥2 prior lines subgroup HR=1.20, 95% CI 0.62-2.34). Notably, there was a clear imbalance in the proportion of patients receiving subsequent daratumumab (IRd: 25%; Rd: 34%). The same phenomenon was observed in the ≥2 prior lines of therapy subgroup (IRd: 18%; Rd: 33%; Table 1). Thus, among patients who received daratumumab as a subsequent therapy, it was evident that compared with the IRd arm, patients in the Rd arm derived a larger benefit in survival (ITT HR=1.15, 95% CI: 0.73-1.81 and ≥2 prior lines subgroup HR=1.48, 95% CI: 0.69-3.19). This is likely due to patients in the Rd arm...
receiving daratumumab earlier than in the IRd arm in the follow-up of TOURMALINE-MM1 (Figure 1).

Table 2 provides the adjusted OS results from different methods for the ITT population and the ≥2 prior lines subgroup. When adjusting for the confounding due to subsequent therapies, all methods indicated a trend towards a survival benefit for patients in the IRd arm compared with the Rd arm (HR=≤1). As previously reported for the ITT population, the estimated HR was 0.70 (95% confidence interval [CI]: 0.48-1.03, \( P = 0.071 \); Figure 2) using the IPCW method, and 0.68 (95% CI: 0.46-1.00, \( P = 0.054 \)) using the MSM method, compared with an unadjusted HR of 0.939. The estimated HR using the RPSFTM method was consistent with these findings (HR=0.89, 95% CI: 0.74-1.07, \( P = 0.202 \); Figure 3). Estimated HRs for the ≥2 prior lines of therapy subgroup after adjustment were 0.52 (95% CI: 0.30-0.88, \( P = 0.016 \); Table 2) for IPCW and MSM, and 0.68 (95% CI: 0.51-0.91, \( P = 0.008 \); Table 2) for RPSFTM, compared with an unadjusted HR of 0.85 (95% CI: 0.64-1.11 \( P = 0.232 \); Table 2).

A small, non-significant, difference in favor of Rd was observed when analyzing time from subsequent therapy to death between the IRd and Rd arms (Figure 4; HR=1.08, 95% CI: 0.88-1.33). This was exaggerated further in the ≥2 prior lines of therapy subgroup (HR=1.14, 95% CI: 0.82-1.59).
Discussion

Recently published data from the TOURMALINE-MM1 clinical trial indicated a numerically favorable trend in OS with IRd versus Rd, although there was no statistically significant difference in final OS between the two treatment arms. However, the impact of subsequent therapies on survival outcomes was not investigated; this is a major limitation in assessment of OS in patients with likely long life expectancy. In these analyses, we elaborated on the methods and results for the ITT population and showed how subsequent therapies impacted outcomes in the ≥2 prior line subgroup. The IPCW, MSM, and RPSFTM methods were implemented to effectively reduce bias from subsequent therapies and estimate the “true” OS benefit received by adding ixazomib to the Rd combination in the presence of confounding.

The results indicate that the unadjusted survival data from TOURMALINE-MM1 are confounded by imbalances in the number and type of subsequent therapies between the treatment arms. IPCW, MSM, and RPSFTM all minimized estimation bias by switching and adjusting for confounding resulting from subsequent therapy when comparing survival outcomes. By applying these three commonly used approaches, all adjusted HRs using causal inference methods utilized in this analysis were reduced, demonstrating a trend towards favoring IRd versus Rd in terms of OS, concluding that the TOURMALINE-MM1 OS results were confounded by subsequent therapy. In particular, adjusting for confounding in the ≥2 prior lines of therapy subgroup demonstrated a substantial OS benefit with IRd versus Rd. Though the degree of benefit was different as per the different methods, the consistent direction of the results indicates that the IRd combination may have a meaningful positive OS impact in this patient population.

The greater number of lines of subsequent therapy received in the Rd arm versus the IRd arm was driven by earlier progression of patients in the Rd arm, allowing them more opportunity for
subsequent therapies across the follow-up time from TOURMALINE-MM1. Importantly, this phenomenon allowed patients in the Rd arm to receive effective monoclonal antibody-based subsequent therapies that became available during the study course. Therefore, this allowed patients in the Rd arm to have better OS outcomes than expected. Patients in the IRd arm could have also ultimately received subsequent therapies as a result of experiencing a longer OS.

The imbalance in the number of patients who received subsequent daratumumab is particularly important as daratumumab has a completely different mechanism of action that patients would not have been exposed to in prior therapies, and which has been shown to be highly efficacious for this patient population.\textsuperscript{11,18,19} TOURMALINE-MM1 enrolled patients between August 2012 and May 2014. The median time to progression was 21.4 \textit{versus} 15.7 months in the IRd and Rd groups, respectively.\textsuperscript{8} Daratumumab was a newly available and highly active drug that was approved in November 2015,\textsuperscript{7} which likely coincided with the time that a number of TOURMALINE-MM1 patients, particularly those in the Rd arm, developed a need for subsequent therapies. The availability of daratumumab improved the salvage capability in the Rd arm substantially, driving post-discontinuation survival outcomes in these patients.

As previously reported, approximately 70\% of patients in each arm had received prior therapy with a PI at baseline, and in patients who went on to receive a PI as next-line therapy after IRd or Rd, analysis of OS favored the Rd arm (HR=1.04, 95\% CI: 0.78-1.40).\textsuperscript{2} Furthermore, this outcome was observed in patients who subsequently received the PI carfilzomib in the ITT population (HR=1.08, 95\% CI 0.71-1.62) and the \geq 2 prior line subgroup (HR=1.20, 95\% CI 0.62-2.34). Patients progressing on Rd had a PI-free interval or may still have been PI-naïve; therefore, these patients were more likely to have remained PI-sensitive and benefitted from PI-based subsequent therapy. However, for patients progressing on IRd, subsequent PI-based
therapy was potentially their third exposure to a PI. Therefore, they were likely to have become PI-refractory, and PI-based next-line therapy would potentially have been less effective, as well as being inconsistent with clinical guidelines. Thus the high use of PIs as next line of therapy in the TOURMALINE-MM1 IRd arm (47%) may have specifically affected OS outcomes, preventing the PFS advantage seen in the IRd arm from translating into OS benefit.

Per the study design, patients and clinicians remained blinded throughout subsequent therapy. However, unblinding was permitted to properly treat an adverse event or other safety issue, and for the treating physician to choose subsequent therapy. As previously reported, this led to a minority of instances where clinicians were unblinded (21/360 vs. 37/362 in the IRd and Rd arms, respectively). Clinicians who were unblinded at discontinuation of IRd tended to treat patients at the next line with a treatment that included a drug with a different mechanism of action (76% of unblinded IRd patients received a non-PI based next-line therapy), whereas clinicians who were unblinded at discontinuation of Rd tended to treat patients at the next line with a PI-containing regimen (81% of unblinded Rd patients received PI-containing next-line therapy). This contrasted with clinicians who remained blinded – there was a 50:50 split in PI versus no PI next-line regimens across both treatment arms.

Other similar trials in the past decade were either open-label/unblinded or unblinded after first interim analysis. In a real-world setting, the type of prior therapy received by the patient is important when choosing the next best option. Blinding is a feature of a controlled clinical trial and does not represent real-world practice. Based on these findings and clinical expectations, it is less likely that a patient discontinuing IRd in the real-world would proceed to another PI in the next line of therapy.
A small, non-significant difference favoring Rd was observed when analyzing time from subsequent therapy to death between the IRd and Rd arms in both the overall population and the ≥2 prior lines of therapy subgroup. These findings were unexpected, as we anticipated the study arms would perform similarly after receiving subsequent therapies. However, the imbalances in the number and type of subsequent therapies in the two arms likely drove the additional benefit received by patients in the Rd arm during the trial follow-up. Given the salvage therapies available in the modern era of MM treatment, and the introduction of many new therapies that became available for treatment of RRMM shortly following completion of enrollment to TOURMALINE-MM1,16,21,25-27 it is increasingly difficult to demonstrate OS improvement. This was exemplified in the results from the recent DETERMINATION study, in which RVd followed by ASCT failed to show a significant improvement in OS compared with RVd alone, despite a 21.3-month improvement in PFS.³ Nevertheless, contrasting data demonstrating OS improvements in patients with RRMM have been reported in ELOQUENT-2, ASPIRE, and POLLUX.¹¹,¹⁴,¹⁵ Of note; however, these were open-label studies. Furthermore, in the phase 3 ELOQUENT-2 study of elotuzumab-lenalidomide-dexamethasone (ERd) versus Rd, no more than 10% of patients with prior lenalidomide therapy were permitted to be enrolled, thus decreasing the proportion of patients likely to be lenalidomide-refractory.¹⁵ In addition, as daratumumab was not FDA-approved until 2015, it was not as readily available at the time of the ELOQUENT-2 study; only 9% and 12% of patients in the respective ERd and Rd groups received subsequent daratumumab therapy, which could be one reason for the reported OS differences between treatment groups in the study.

This was a post-hoc study conducted in a setting where an OS benefit was not reported in the ITT population and as such is a key limitation of the study. Additional limitations of these
analyses relate to the assumptions underpinning the statistical methodologies. The IPCW and MSM analyses assume “no unmeasured confounders” which cannot be tested. This is a known limitation of the method. We used a large set of covariates to predict the treatment switch and found most of the covariates were eliminated after model selection (please see the Supplementary Material for a list of the baseline covariates). All these covariates were also pre-specified to avoid any post-study bias. The IPCW/MSM methodology requires that the patients who received a subsequent therapy are censored at receipt of therapy; n=65 events in the IRd arm and n=55 events in the Rd arm remained after censoring. Therefore, 84% of the patients were censored, which is very close to the 90% censoring Latimer et al.\textsuperscript{28} indicated to be the cut-off when the IPCW method is not reliable.\textsuperscript{28} The RPSFTM does not require the “no unmeasured confounders” assumption. However, it is subject to two key assumptions: (1) patients in the IRd arm continued to derive similar benefit until death/censor post-study treatment discontinuation as when they were on-treatment, and (2) patients in the Rd arm post-discontinuation derived the same survival benefit as patients in the IRd arm. While these limitations cannot be overcome methodologically, it is important to recognize that all methods indicated confounding in the same direction and hence the results from the methods cannot be ignored. Indeed, in a recent appraisal by UK’s National Institute for Health and Care Excellence (NICE), these methods were used to adjust OS in TOURMALINE-MM1 for confounding due to subsequent therapy to better reflect clinical practice in the UK, and it was concluded by NICE that IRd “likely improves overall survival” based on these analyses.\textsuperscript{29}

These analyses look at the impact of removing the effect of all active subsequent therapies. We did not look at country-specific scenarios where only certain subsequent therapies may be available, owing to extremely different and complex pathways across different countries.
In conclusion, the analyses presented here provide statistical evidence in relation to the potential for confounding in survival results from subsequent therapies and blinded trial designs in incurable malignancies. Although the methods are underpinned by strong assumptions, all approaches resulted in an improvement in the HR for IRd versus Rd and remain relevant in informing clinical decisions. In addition, adjusted OS results indicated a possible clinically and statistically meaningful OS benefit with IRd treatment compared with Rd treatment among MM patients with ≥2 prior lines of therapy. While these results are encouraging, it is important to note that these data are relevant to patients not lenalidomide-refractory at relapse. Furthermore, many MM patients do not reach subsequent therapy or have access to the latest novel drugs; the analyses highlighted here are important for informing clinical practice in the RRMM setting, while in turn helping translate these findings to real world practice and further improving patient outcomes.30
References


17. clinicaltrials.gov. A Phase 3 Study Comparing Oral Ixazomib Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With
Relapsed and/or Refractory Multiple Myeloma. ClinicalTrials.gov Identifier: NCT01564537. 


### Tables

**Table 1.** Subsequent therapies received in $\geq 5\%$ of patients in either arm in TOURMALINE-MM1 (≥2 prior lines).

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<tr>
<th>Antineoplastic therapy reported</th>
<th>IRd n=149</th>
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<td>n (%)</td>
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<tr>
<td>Bendamustine</td>
<td>14 (13)</td>
<td>21 (23)</td>
<td>35 (18)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>2 (2)</td>
<td>5 (5)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>10 (10)</td>
<td>14 (15)</td>
<td>24 (12)</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>9 (9)</td>
<td>12 (13)</td>
<td>21 (11)</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>10 (10)</td>
<td>14 (15)</td>
<td>24 (12)</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>9 (9)</td>
<td>12 (13)</td>
<td>21 (11)</td>
</tr>
<tr>
<td>Histone deacetylase inhibitors</td>
<td>5 (5)</td>
<td>5 (5)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>5 (5)</td>
<td>5 (5)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Topoisomerase inhibitors</td>
<td>4 (4)</td>
<td>8 (9)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Etoposide</td>
<td>3 (3)</td>
<td>6 (6)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>36 (34)</td>
<td>42 (45)</td>
<td>78 (39)</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>19 (18)</td>
<td>31 (33)</td>
<td>50 (25)</td>
</tr>
<tr>
<td>All other therapeutic products</td>
<td>3 (3)</td>
<td>8 (9)</td>
<td>11 (6)</td>
</tr>
<tr>
<td>Elotuzumab</td>
<td>3 (3)</td>
<td>7 (8)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Autologous stem cell transplant</td>
<td>1 (&lt;1)</td>
<td>9 (10)</td>
<td>10 (5)</td>
</tr>
</tbody>
</table>

IRd: ixazomib + lenalidomide + dexamethasone; Rd: lenalidomide + dexamethasone.
Table 2. Unadjusted and adjusted results for ITT population and ≥2 prior lines subgroup.

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>Median OS IRd (months)</th>
<th>Median OS Rd (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ITT (≥1 prior lines)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.939 (0.784-1.125)</td>
<td>0.495</td>
<td>53.6</td>
<td>51.6</td>
</tr>
<tr>
<td>IPCW</td>
<td>0.70 (0.48-1.02)</td>
<td>0.067</td>
<td>NE</td>
<td>86.9</td>
</tr>
<tr>
<td>MSM</td>
<td>0.67 (0.45-1.00)</td>
<td>0.051</td>
<td>Method does not provide median</td>
<td></td>
</tr>
<tr>
<td>RPSFTM</td>
<td>0.89 (0.74-1.07)</td>
<td>0.202</td>
<td>53.6</td>
<td>48.8</td>
</tr>
</tbody>
</table>

| ≥2 prior lines subgroup |                      |          |                        |                       |
| Unadjusted             | 0.85 (0.64-1.11)    | 0.232    | 53.0                   | 43.0                  |
| IPCW                  | 0.53 (0.31-0.91)    | 0.021    | 88.6                   | NE                    |
| MSM                   | 0.52 (0.30-0.89)    | 0.018    | Method does not provide median |                       |
| RPSFTM                | 0.68 (0.51-0.91)    | 0.008    | 53.0                   | 39.6                  |

ITT (≥1 prior lines) data (except RPSFTM method) and ≥2 prior lines unadjusted data previously reported by Richardson PG et al. J Clin Oncol. 2021;39(22):2430-2422 and reproduced with permission from the first author, Dr Paul Richardson.²

CI: confidence interval; HR: hazard ratio; IPCW: inverse probability of censoring weights; IRd: ixazomib + lenalidomide + dexamethasone; ITT: intent-to-treat; MSM: marginal structural model; NE: not evaluable; OS: overall survival; Rd: lenalidomide + dexamethasone; RPSFTM: rank preserving survival failure time model.
**Figure legends**

**Figure 1.** Starting year for subsequent daratumumab.

IRd: ixazomib + lenalidomide + dexamethasone; Rd: lenalidomide + dexamethasone.

**Figure 2.** Time from randomization to death as per IPCW method when patients who took a subsequent therapy were censored the day before (ITT population).

HR, 95% CI and \( P \) value for HR previously reported by Richardson PG *et al.* J Clin Oncol. 2021;39(22):2430-2422 and reproduced with permission from the first author, Dr Paul Richardson.²

CI: confidence interval; HR: hazard ratio; IPCW: inverse probability of censoring weights; IRd: ixazomib + lenalidomide + dexamethasone; ITT: intent-to-treat; Rd: lenalidomide + dexamethasone.

**Figure 3.** Time from randomization to death as per RPSFTM method (ITT population).

CI: confidence interval; HR: hazard ratio; IRd: ixazomib + lenalidomide + dexamethasone; ITT: intent-to-treat; Rd: lenalidomide + dexamethasone; RPSFTM: rank preserving structural failure time model.

**Figure 4.** Time from subsequent therapy to death (ITT population).

CI: confidence interval; HR: hazard ratio; IRd: ixazomib + lenalidomide + dexamethasone; ITT: intent-to-treat; Rd: lenalidomide + dexamethasone.
No. at risk

IRd  |  360  |  342  |  319  |  298  |  276  |  256  |  233  |  218  |  206  |  193  |  182  |  160  |  149  |  137  |  126  |  115  |  99   |  53   |  15   |  0

Rd   |  362  |  346  |  322  |  296  |  274  |  249  |  225  |  210  |  200  |  182  |  167  |  156  |  138  |  121  |  110  |  96   |  64   |  28   |  0

Probability of survival

Time (months) from randomization

Median, months  |  IRd   |  Rd   |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>53.6</td>
<td>48.8</td>
<td></td>
</tr>
</tbody>
</table>

Events, n       | 240    | 243   |

HR (95% CI)      | 0.89 (0.74-1.07) |

Log-rank P value | 0.202  |
Supplementary Material

Inverse probability of censoring weights (IPCW)\textsuperscript{1,2}

The IPCW method artificially censors switchers (i.e., patients receiving subsequent therapies) at the time of treatment switch, and then weights each patient’s contribution to the estimation based on the patient’s propensity for switching to subsequent therapy, predicted by baseline and time-dependent covariates. Estimates obtained using this pseudo population then have causal interpretation free of the impact of the subsequent therapy. The IPCW are estimated using logistic models on the whole dataset with the binary outcome of censoring at the time of switching to a subsequent therapy (0 if not censored, 1 if censored) as the response, and study treatment and baseline/time-varying characteristics as covariates.\textsuperscript{3} Individual logistic regression models (for both numerator and denominator of the inverse censoring weight) started with all pre-specified covariates, which included both the time-fixed and time-varying covariates: region (North America vs. others), age (<75 vs. \geq 75), race (white vs. non-white), Eastern Cooperative Oncology Group score (0 or 1 vs. 2), relapse and/or refractory (relapsed vs. refractory vs. relapsed and refractory), type of myeloma (IgA vs. other), percentage of plasma cells (\leq 30 vs. >30; missing), presence of extramedullary plasmacytomas (yes vs. no), presence of lytic bone lesions (yes vs. no), cytogenetic abnormalities (high risk vs. others), prior lenalidomide (yes vs. no), prior thalidomide (yes vs. no), prior proteasome inhibitor (yes vs. no), number of line therapies (1 vs. 2 or 3), baseline hemoglobin, baseline platelets, creatinine clearance (median), albumin (median), lactate dehydrogenase (median), \beta 2 microglobulin (median), and corrected calcium (median); duration of exposure, disease progression status at each study visit, hemoglobin value at each study visit and progression/relapse, platelets value at each study visit and progression/relapse, M-protein value at progression/relapse, type of subsequent therapy with proteasome inhibitor, types of subsequent
therapy with immunomodulatory drugs. Each logistic model was shrunk until no covariate in the
model had a $P$ value more than 0.1. Covariates remaining in any of the individual models were
retained in all the logistic models. Stabilized weights were used for the analyses. A stratified
weighted Cox model was used to estimate the hazard ratio (HR), and the Chi-squared test was used
to generate the $P$ value for treatment effect. The Cox model results were used to generate the
survival curves.

**Marginal structural model (MSM)**

A logistic model on the whole data from both arms with a switch to a subsequent therapy (0 if not
switched, 1 if switched) as the response, and study treatment and pre-specified baseline/time-
varying characteristics as covariates was used to calculate the inverse probability of treatment
switching weight (IPTW). Separately, to adjust for possible bias caused by informative censoring,
a logistic model on the whole data from both arms with censoring (0 if not censored, 1 if censored)
as the response, and study treatment and baseline/time-varying characteristics as covariates was
used to calculate the IPCW. Afterwards, IPTW and IPCW were multiplied for each patient at each
observed timepoint to get the combined inverse probability weight for each patient. Like the IPCW
method, individual logistic regression model building started with all covariates, and was shrunk
until no covariate in the model had a $P$ value more than 0.1. Stabilized weights were re-scaled
using a similar approach as described for the IPCW method.

A stratified Weighted Cox model that has treatment, indictor function for the switch to subsequent
therapy, and an interaction of the previous two variables was used to estimate the HR. Chi-squared
test for HR=1 as the null hypothesis was used to generate the $P$ value.
Rank preserving structural failure time model (RPSFTM)\textsuperscript{3,5}

The RPSFTM method adjusts the survival times for the switchers using an acceleration factor (calculated through g-estimation) such that they represent the predicted survival time had the patient not switched and received subsequent therapies. As there was no protocol-defined crossover in this study, we followed a similar implementation approach as in the “treatment group” approach described in the literature.\textsuperscript{6-8} Following this we assumed that:

1. Patients in the IRd arm continued to derive similar benefit until death/censor post study treatment discontinuation as when they were on-treatment, and
2. Patients in the Rd arm post discontinuation derived the same survival benefit as patients in the IRd arm (common treatment effect assumption).

Based on the above assumptions, the acceleration factor was estimated and then used to estimate the counterfactual survival time from subsequent therapy to death/censor and thus overall counterfactual survival time if patients would not have switched to a subsequent therapy for patients in the Rd arm. Recensoring is applied as explained in Latimer \textit{et al.}\textsuperscript{9} where the recensoring cut-off was the longest survival time in this study. A stratified Cox proportional hazards model was used to estimate the HR, and a stratified log-rank test was used to generate the \textit{P} value, by using randomization stratification factors. The Kaplan-Meier estimates for counterfactual survival time were used to generate the survival curves.
References


