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Daratumumab-based quadruplet versus triplet induction regimens in transplant-eligible newly diagnosed multiple myeloma: a systematic review and meta-analysis

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The treatment landscape for transplant-eligible patients with newly diagnosed multiple myeloma (TE-NDMM) has evolved with the introduction of daratumumab-based quadruplet regimens. Adding daratumumab to traditional triplet regimens has demonstrated improved response rates and progression-free survival (PFS). However, the impact on long-term outcomes, particularly overall survival (OS), remains uncertain. This systematic review and meta-analysis aimed to compare the survival outcomes of these quadruplet regimens with triplets. Conducted in adherence to Cochrane Collaboration and PRISMA guidelines and registered on PROSPERO (CRD42024571946), the study involved searching PubMed, Embase, and Cochrane databases, from inception to June 2024. We included randomized clinical trials (RCT) and non-randomized controlled studies (NRCS) that compared daratumumab-based quadruplet regimens to triplets, focusing on OS and PFS, with a minimum follow-up of 18 months. The meta-analysis included 3327 TE-NDMM patients from four studies, comprising three RCT and one NRCS. Daratumumab-based regimens were administered to 1328 (40%) patients. The analysis revealed that daratumumab-based quadruplet regimens significantly improved both OS (pooled HR 0.60; 95% CI 0.48–0.75; $P < 0.00001$; $I^2 = 0\%$) and PFS (pooled HR 0.49; 95% CI 0.37–0.65; $P < 0.00001$; $I^2 = 52\%$). A per-protocol subgroup analysis comparing D-VRD to VRD further confirmed these benefits, with significant improvements in both OS (pooled HR 0.68; 95% CI 0.48–0.97; $P = 0.03$; $I^2 = 0\%$) and PFS (pooled HR 0.41; 95% CI 0.31–0.54; $P < 0.00001$; $I^2 = 0\%$). This meta-analysis consolidates evidence that daratumumab-based quadruplet regimens significantly improve OS, compared to triplet regimens for TE-NDMM patients.

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INTRODUCTION

Multiple myeloma (MM) is a complex and heterogeneous hematologic malignancy, primarily characterized by the clonal proliferation of malignant plasma cells within the bone marrow [1]. For transplant-eligible newly diagnosed multiple myeloma (TE-NDMM) patients, the choice of induction therapy plays a critical role in determining long-term outcomes. Recent advances in therapeutic strategies have focused on incorporating of novel agents to enhance the depth of response before autologous stem cell transplantation (ASCT) [2]. Among these innovations, daratumumab, a monoclonal antibody targeting CD38, has emerged as a pivotal component in frontline regimens [3].

Traditionally, the standard induction therapy is a triplet regimen combining a proteasome inhibitor (PI), an immunomodulatory agent (IMiD) and corticosteroids. However, the emergence of daratumumab-based quadruplet regimens represents a significant evolution in treatment, offering the potential for deeper responses and improved disease control, with an acceptable safety profile [4–9].

Clinical trials have shown promising outcomes with these regimens, particularly in terms of response rates, minimal residual disease (MRD) negativity and progression-free survival (PFS) [4–9]. However, the impact on long-term outcomes, particularly overall survival (OS), is still under investigation. This uncertainty underscores the need for a comprehensive evaluation of the available evidence to guide clinical decision-making.

To this end, we conducted a systematic review (SR) and meta-analysis (MA) to compare daratumumab-based quadruplet versus triplet induction regimens in the frontline treatment of TE-NDMM patients. By synthesizing data from relevant studies, we aim to provide a clearer understanding of the impact on overall survival and discuss the implications of these findings for the future landscape of MM therapy.

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METHODS

This SR and MA were performed and reported following the Cochrane Collaboration Handbook for Systematic Review of Interventions recommendations and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines [10, 11]. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42024571946).

Databases search strategy

We systematically searched PubMed, Embase, and Cochrane Library databases from inception to June 2024. The search strategy was as follows: ("myeloma" OR "multiple myeloma") AND ("daratumumab" OR "darzalex") AND ("newly diagnosed" OR "first line" OR "front line" OR "eligible" OR "induction" OR "autologous" OR "transplantation").

Eligibility criteria

Pre-specified Population, Intervention, Comparator, Outcome, Time and Study design (PICOTS) criteria were used to develop the search strategy. Included studies met the following eligibility criteria: (1) randomized clinical trials (RCT) and non-randomized controlled studies (NRCS); (2) that compared daratumumab-based quadruplet induction regimens to triplet induction regimens; (3) in TE-NDMM patients; (4) reported the outcomes of interest: OS and PFS and; (5) with a minimum follow-up of 18 months. We excluded studies that were non-controlled or with overlapping patient populations.

Selection criteria

Citations from all databases were imported into a Zotero reference manager software (Corporation for Digital Scholarship) and duplicates were removed. Two authors (JTDSF and LCO) independently screened search records to identify eligible studies, using the pre-established criteria for search, data extraction and quality assessment. Disagreements were resolved by consensus among the authors.

Data extraction

Data extracted included study characteristics (first author, year of publication, journal, study design, sample size, treatment regimens and duration of follow-up), baseline characteristics of the participants (age, sex, distribution by the International Staging System [ISS] and cytogenetic risk) and outcome data (OS and PFS).

Definition of outcomes

The primary outcome was OS, defined as the time from randomization to the date of death. We also evaluated the PFS, defined as the time from randomization to the date of the first confirmed progression or date of death, whichever occurred earlier. We quantified associations in terms of hazard ratios (HRs) and 95% confidence intervals (95% CI). If multiple publications of the same study were available, the publication with the longest available follow-up results was used to extract the summary effect.

Quality assessment

Two investigators (JTDSF and LCO) independently assessed each study's quality and risk of bias. Randomized controlled trials were appraised, using Cochrane's "Risk-of-bias tool for randomized trials Version 2" (RoB-2) [12, 13]. Meanwhile, non-randomized controlled studies were assessed, using Cochrane's "Risk of bias in non-randomized studies of interventions" (ROBINS-I) [14]. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) assessment was conducted to assess the overall certainty of the evidence for each outcome [15]. The Summary of Findings (SoF) Table was made to facilitate a clear and comprehensive presentation of the evidence [10]. Publication bias was assessed through funnel plot analysis, which examined the relationship between point estimates and study weights [16].

Statistical analysis

We pooled the treatment effects from each study to estimate HRs and their corresponding 95% CIs for time-to-event outcomes. When the reported CI differed from a 95% CI, the provided CI was converted to a 95% CI for consistency, using a calculations spreadsheet [17]. In studies where the HR were not directly reported, they were extracted from the published Kaplan-Meier curves [17]. Heterogeneity across studies was assessed, using Cochrane's Q test and I^2 statistics. A P-value of less than 0.10 was considered significant of significant heterogeneity, with I^2 values categorized as low (0–40%), moderate (30–60%), substantial (50–90%) and considerable (75–100%) heterogeneity [12]. The DerSimonian and Laird random-effects model was used. Leave-one-out sensitivity analysis were conducted to identify outliers in the MA. All P-values were two-sided, with statistical significance set at $P < 0.05$. Statistical analyses to pool HRs and generate the corresponding forest plots were conducted, using the Review Manager, version 5.4.1 (The Cochrane Collaboration, Denmark). Additionally, patient-level data of each treatment arm in each trial were reconstructed from Kaplan-Meier curves, using the IPDfromKM method [18]. Kaplan-Meier curves were digitalized with the Engauge Digitizer (version 12.1). Subsequently, the IPDfromKM Shiny app (version: 1.2.3.0, available at https://biostatistics.mdanderson.org/) was used to reconstruct the individual patient data (IPD). Finally, pooled survival curves were generated from the reconstructed IPD, along with the relevant Cox statistics, using the "coxph", "survfit", and "ggsurvplot" packages in R Statistical Software (version 4.4.1) [19].

RESULTS

Study selection

The initial search yielded 4789 results. After removing duplicates, 3502 articles were screened by title and abstract, leaving 142 potentially eligible studies for detailed review. Following the exclusion of 135 studies, seven reports from a total of four studies were included in the SR and MA (Supplementary Fig. 1).

Characteristics of studies and study population

Four studies involving 3327 TE-NDMM patients were included, comprising three randomized controlled trials (CASSIOPEIA [4–6], GRIFFIN [7, 8], and PERSEUS [9]) and one non-randomized controlled study based on real-world data [20, 21]. The publication years ranged from 2019 to 2024. Across three studies, daratumumab in combination with bortezomib, lenalidomide, and dexamethasone (D-VRD) was compared to bortezomib, lenalidomide, and dexamethasone (VRD) [8, 9, 20], while one study compared daratumumab with bortezomib, thalidomide and dexamethasone (D-VTD) to bortezomib, thalidomide, and dexamethasone (VTD) [6]. Sample sizes ranged from 207 to 1326 patients. The weighted median follow-up duration was 51.7 months, with a range from 19.1 to 88.4 months. The weighted median patient age was 60 years, 57% were male, 46% had ISS stage I, 36% had ISS stage II, 18% had ISS stage III disease and 17.5% of patients had a high-risk cytogenetic profile. The main characteristics of the included studies are reported in Table 1.

Outcome analysis

In the comparative analysis of OS and PFS, data from a total of 3327 patients were included, with 1328 patients (40%) receiving a daratumumab-based quadruplet induction regimen. Specifically, 785 patients (24%) were treated with D-VRD, while 543 patients (16%) received D-VTD. The remaining 1999 patients (60%) were administered a triplet regimen, with 1457 patients (44%) receiving VRD and 542 patients (16%) receiving VTD.

Among the four studies evaluating the addition of daratumumab to backbone regimens, the HRs for PFS, using the most recent follow-up data, were 0.61 (95% CI, 0.52–0.72) in the CASSIOPEIA study [6], 0.45 (95% CI, 0.21–0.95) in the GRIFFIN study [8], 0.42 (95% CI, 0.30–0.59) in the PERSEUS study [9], and 0.34 (91% CI, 0.2–0.67) in the study by Joseph et al. [20]. Since the Joseph et al. study reported its results with a 91% CI, the interval was converted to a 95% CI (0.17–0.68) for consistency [17]. All these findings were statistically significant.

Regarding OS, the HR for quadruplet therapy was 0.55 (95% CI, 0.42–0.73) in the CASSIOPEIA study [6], 0.90 (95% CI, 0.31–2.56) in the GRIFFIN study [8], and 0.53 (91% CI, 0.3–0.96) in the Joseph

et al. study, which was again converted to a 95% CI (0.27–1.04) [20]. In the PERSEUS study, the HR for D-VRD was reported as 0.73; however, the confidence intervals (CIs) were not directly provided. In this manner, the 95% CI was extracted from the published Kaplan-Meier curves (95% CI, 0.47–1.14) [9, 22]. Among these studies, only the CASSIOPEIA trial demonstrated a statistically significant improvement in OS with a 95% CI. Regarding postprotocol therapies, only the CASSIOPEIA trial presented these data, documenting that 68% of patients in the observation group (VTd plus observation) received an anti-CD38–based regimen as their first subsequent therapy [6].

Pooled analyses of OS and PFS

In this MA, we evaluated the impact of daratumumab-based quadruplet regimens, compared to triplet regimens, on OS and PFS.

For OS, our analysis demonstrated that quadruplet regimens incorporating daratumumab resulted in a significantly improved survival compared to triplet regimens, with a pooled HR of 0.60 (95% CI, 0.48–0.75; $P < 0.00001$). The heterogeneity among studies was low, as indicated by Cochran's Q test ($P = 0.63$) and an I^2 statistic of 0%. For PFS, the pooled HR was 0.49 (95% CI, 0.37–0.65; $P < 0.00001$), with a moderate level of heterogeneity (Cochran's Q, $P = 0.10$; $I^2 = 52\%$). These findings are illustrated in the forest plot (Fig. 1).

Sensitivity analyses using the leave-one-out method, which involved omitting one study at a time, yielded HRs ranging from 0.57 to 0.68 for OS and from 0.41 to 0.52 for PFS (Supplementary Figs. 2 and 3). Notably, excluding the NRCS from the analysis had minimal impact, yielding HRs of 0.61 (95% CI, 0.48–0.77; $P < 0.0001$) for OS and 0.52 (95% CI, 0.39–0.69; $P < 0.00001$) for PFS (Supplementary Figs. 2C and 3C). These findings underscore the robustness of the pooled estimates, confirming that no single study significantly influenced the results.

Pooled Kaplan-Meier survival curves (Fig. 2) indicate that, at 84 months, the OS rate for patients receiving quadruplet therapy was 82.5%, compared to 69.9% for those receiving triplet therapy. The median OS for the quadruplet group was not reached, while the median OS for the triplet group was 133 months (HR 0.52; 95% CI, 0.43–0.63; $P < 0.0001$). For PFS, the 84-month rate was 56.6% for quadruplet therapy, versus 40.8% for triplet therapy, with the median PFS not reached for the quadruplet group and 65.8 months for the triplet group (HR 0.58; 95% CI, 0.52–0.67; $P < 0.0001$).

Pooled Kaplan-Meier survival curves, based exclusively on RCT and excluding the NRCS, were generated to assess the NRCS's contribution to the overall estimate. At 84 months, the OS rate was 82.6% for patients receiving quadruplet therapy, compared to 73.2% for those receiving triplet therapy (HR 0.62; 95% CI, 0.49–0.77; $P < 0.0001$). For PFS, the 84-month rates were 55.3% for quadruplet therapy and 35.7% for triplet therapy (HR 0.56; 95% CI, 0.48–0.65; $P < 0.0001$). Median OS and PFS were not reached in either group (Supplementary Fig. 4).

A per-protocol subgroup analysis comparing the D-VRD regimen to VRD further confirmed the benefit of adding daratumumab. This analysis showed a significant improvement in both OS (pooled HR 0.68; 95% CI, 0.48–0.97; $P = 0.03$), with low heterogeneity (Cochran's Q, $P = 0.64$; $I^2 = 0\%$), and PFS (pooled HR 0.41; 95% CI, 0.31–0.54; $P < 0.00001$), also with low heterogeneity (Cochran's Q, $P = 0.84$; $I^2 = 0\%$). These results are depicted in the forest plot (Fig. 3).

Survival data from pooled Kaplan-Meier curves (Fig. 4) reveal that, at 48 months, the OS rate for patients treated with D-VRD was 90.2%, compared to 82.2% for those receiving VRD. The median OS for the D-VRD group was not reached, whereas the median OS for the VRD group was 133 months (HR 0.53; 95% CI, 0.39–0.71; $P < 0.0001$). For the PFS, the 48-month rate was 85.3% for D-VRD versus 62.9% for VRD, with the median PFS not reached for the D-VRD group and 72.3 months for the VRD group (HR 0.33; 95% CI, 0.26–0.43; $P < 0.0001$).

Table 1. Baseline characteristics of each study included in the meta-analysis.

Study Name	Study Design	Treatment	*N*	Age (years, median)	Male (%)	ISS			High risk cytogenetic (%)	Follow-up (months)	HR for OS (95% CI)	HR for PFS (95% CI)
						I (%)	II (%)	III (%)				
CASSIOPEIA (Moreau et al.) [4–6]	Phase 3 RCT	D-VTD	543	59	58.2	38.0	47.0	15.0	15.0	80.1	0.55 (0.42–0.73)	0.61 (0.52–0.72)
		VTD	542	58	58.9	42.0	43.0	15.0	16.0	80.1		
GRIFFIN (Voorhees et al.) [7, 8]	Phase 2 RCT	D-VRD	104	59	56.0	47.0	38.0	13.0	16.0	49.6	0.90 (0.31–2.56)	0.45 (0.21–0.95)
		VRD	103	61	58.0	49.0	36.0	14.0	14.0	49.6		
PERSEUS (Sonneveld et al.) [9]	Phase 3 RCT	D-VRD	355	61	59.4	52.4	32.1	15.5	21.4	47.5	0.73 (0.47–1.14)	0.42 (0.30–0.59)
		VRD	354	59	57.9	50.4	35.4	14.2	22.0	47.5		
Joseph et al. [20, 21]	NRCS-RWD	D-VRD	326	62	55.5	49.6	30.2	20.2	15.4	19.1	0.53 (0.27–1.04)	0.34 (0.17–0.68)
		VRD	1000	61	54.6	45.8	30.8	23.4	17.8	88.4		

The cytogenetic risk was assessed using fluorescence in situ hybridization; high risk was defined as the presence of del(17p), t(4;14), or t(14;16).
CI indicates confidence interval, *D-VRD*, daratumumab, bortezomib, lenalidomide, and dexamethasone, *D-VTD*, daratumumab, bortezomib, thalidomide, and dexamethasone, *HR*, hazard ratio, *ISS*, International Staging System, *N*, number of patients, *NRCS-RWD*, non-randomized controlled study based on real world data, *OS*, overall survival, *PFS*, progression-free survival, *RCT*, randomized controlled trial, *VRD*, bortezomib, lenalidomide, and dexamethasone, and *VTD*, bortezomib, thalidomide, and dexamethasone.

Quality assessment

Three of the included studies showed a low risk of bias, according to the RoB 2 tool (Supplementary Fig. 5), whereas one showed a moderate risk, according to the ROBINS-I (Supplementary Fig. 6). The funnel plot exhibited a symmetrical distribution of studies around the combined effect size, suggesting that there is no substantial publication bias (Supplementary Fig. 7). The certainty of the evidence, assessed via the GRADE approach, was rated as moderate for both OS and PFS (Supplementary Fig. 8).

DISCUSSION

This SR and MA provide a robust and unique evaluation of daratumumab-based quadruplet regimens, compared to traditional triplet regimens in the frontline treatment of TE-NDMM patients. By pooling data from 3327 patients across multiple studies, our analysis highlights significant improvements in OS and PFS when daratumumab is incorporated into standard therapies.

The findings align with the evolving treatment paradigm for TE-NDMM, where the inclusion of novel agents has shifted the standard of care. Historically, the VRD has been widely accepted as the standard induction regimen [23–25]. However, recent trials, including CASSIOPEIA, GRIFFIN and PERSEUS, have demonstrated the superiority of adding daratumumab to triplet regimens, establishing quadruplet regimens as the new standard [4–9].

The pivotal phase III CASSIOPEIA trial established the D-VTD regimen, which significantly improved PFS, compared to VTD alone [6]. This led to the European Medicines Agency approval of D-VTD as the new standard for induction regimen prior to ASCT and it has been incorporated into clinical guidelines [26]. Subsequently, the phase II GRIFFIN trial demonstrated the clear benefits of D-VRD for induction and consolidation, followed by daratumumab and lenalidomide maintenance, showing significantly longer PFS compared to VRD with lenalidomide maintenance [8]. The phase III PERSEUS trial further supported these findings, confirming the superiority of D-VRD over VRD regarding response rates, MRD negative rates, and PFS [9].

Emerging data suggest that incorporating carfilzomib into quadruplet regimens may offer additional benefits. The phase II MASTER trial showed promising results with the D-KRD regimen (daratumumab, carfilzomib, lenalidomide, and dexamethasone), achieving an 81% MRD negativity rate [27, 28]. Similarly, the phase II IFM 2018-04 study reported high MRD negativity (94%) and a 30-month PFS of 80% in high-risk TE-NDMM patients treated with D-KRD and tandem transplantation [29]. However, no direct comparisons exist between carfilzomib- and bortezomib-based quadruplets, leaving unanswered questions regarding their relative efficacy.

Isatuximab, another anti-CD38 monoclonal antibody, has also been incorporated into quadruplet regimens. The phase III GMMG-HD7 trial demonstrated higher MRD negativity rates with I-VRD (isatuximab, VRD) compared to VRD alone (50% vs 36%) [30]. Additionally, the phase II GMMG-CONCEPT and phase III ISKIA trials evaluated isatuximab, carfilzomib, lenalidomide, and dexamethasone (I-KRD) [31, 32]. The ISKIA trial reported MRD negativity rates of 77% with I-KRD versus 67% with KRD (OR 1.67; $P = 0.049$) [32]. However, these studies have yet to provide long-term OS or PFS data due to limited follow-up durations [30–32].

Lenalidomide maintenance remains the standard of care due to its OS benefit compared to observation [33]. Except for the CASSIOPEIA trial, which compared daratumumab maintenance with observation, all other quadruplet trials—GRIFFIN [8], PERSEUS [9], ISKIA [32], GMMC-HD7 [30], GMMC-CONCEPT [31] and MASTER [28]—incorporated either a prolonged consolidation with three drugs or a two-drug maintenance regimen involving an anti-CD38 antibody plus lenalidomide, whereas the control arms received lenalidomide monotherapy. Consequently, the long-term benefits reported in these studies likely reflect the cumulative effects of anti-CD38 antibody therapy across the induction, consolidation and maintenance phases. However, it remains unclear whether the PFS advantage observed in these trials is predominantly attributable to daratumumab use during induction phase, maintenance phase, or a synergistic effect across both phases.

Traditionally, PFS has served as the primary endpoint in MM clinical trials to assess treatment efficacy [34]. However, MRD negativity has emerged as a more sensitive and timely surrogate endpoint for long-term outcomes [35, 36]. Despite its utility, many trials lack sufficient follow-up to demonstrate OS benefits conclusively. In this context, the MA has become a valuable and important tool. By aggregating data from various trials, the MA can provide more robust and comprehensive insights into the survival benefits. Therefore, we present a MA focused on survival outcomes.

Our MA demonstrates a significant survival benefit with daratumumab-based quadruplet regimens. The pooled HR for OS was 0.60 (95% CI: 0.48–0.75), corresponding to a 40% reduction in the risk of death compared to triplet regimens. Except for the CASSIOPEIA trial, no other individual study has shown a similar OS

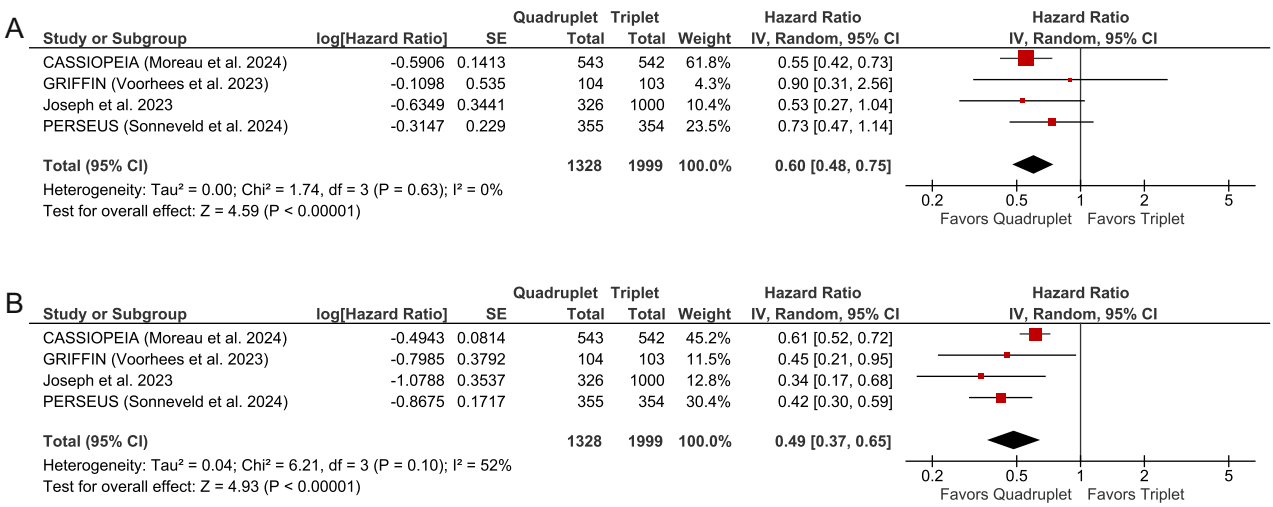

Fig. 1 Meta-analysis comparing survival outcomes between daratumumab-based quadruplet and triplet induction regimens in transplant-eligible newly diagnosed multiple myeloma patients. A Forest plot of HR for OS; **B** Forest plot of HR for PFS.

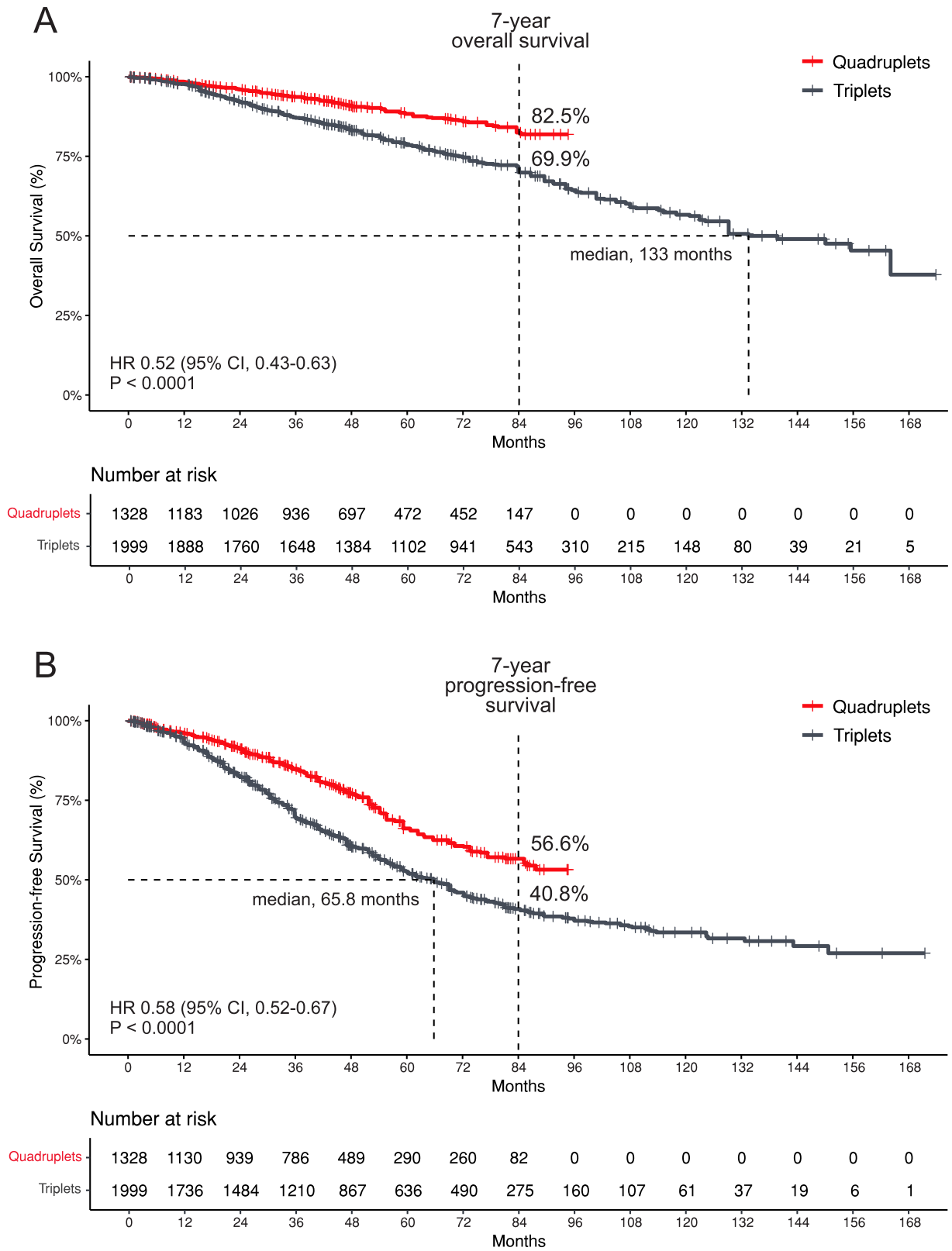

Fig. 2 Pooled Kaplan-Meier survival curves based on reconstructed individual patient data, comparing survival outcomes between daratumumab-based quadruplet and triplet induction regimens in transplant-eligible newly diagnosed multiple myeloma patients. A OS; **B** PFS.

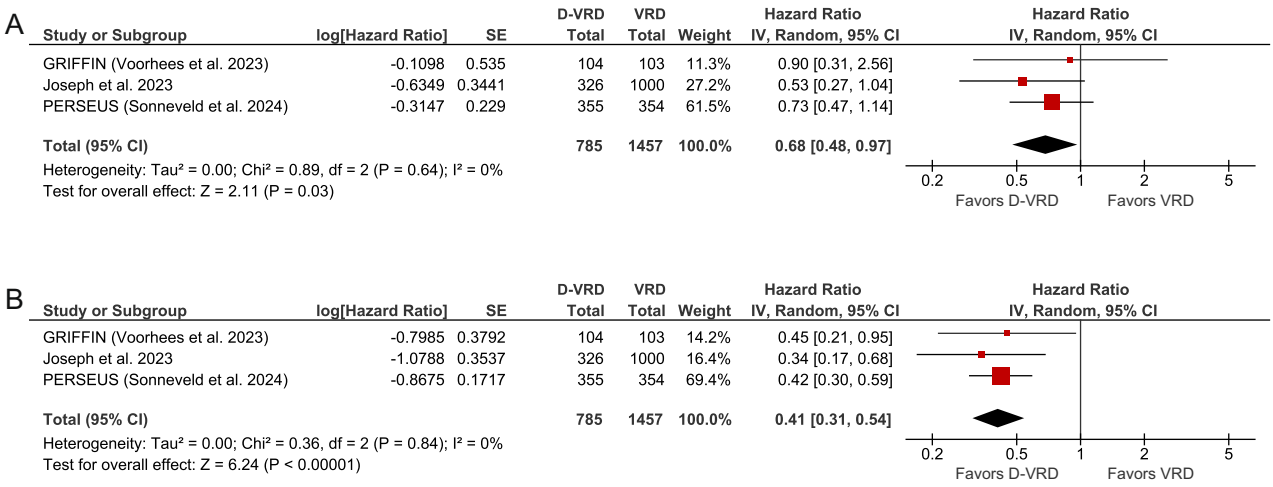

Fig. 3 Meta-analysis comparing survival outcomes between D-VRD and VRD in transplant-eligible newly diagnosed multiple myeloma patients. A Forest plot of HR for OS; **B** Forest plot of HR for PFS.

benefit [4–6]. This pooled analysis underscores the efficacy of daratumumab-based regimens, given that the OS is the most reliable endpoint in hematology-oncology clinical trials [37].

Additionally, the marked improvement in PFS with a pooled HR of 0.49 (95% CI: 0.37–0.65) further supports the enhanced disease control provided by these regimens. Daratumumab addition reduces the risk of disease progression or death by 51%, thereby enhancing both the depth and durability of the response. These findings are consistent with the results from the individual trials CASSIOPEIA, GRIFFIN, and PERSEUS [4–9].

A per-protocol subgroup analysis comparing D-VRD to VRD provides further insights into the benefits of adding daratumumab to the VRD regimen. The inclusion of daratumumab resulted in a remarkable improvement in the OS, with a 32% reduction in the risk of death, and the PFS, showing a 59% reduction in the risk of disease progression or death, for patients receiving D-VRD, compared to those on VRD alone. While individual clinical trials, such as GRIFFIN and PERSEUS did not demonstrate a significant impact of daratumumab on the OS—likely due to their shorter follow-up periods of 49.6 and 47.5 months, respectively—this MA highlights that D-VRD significantly outperforms VRD in terms of the OS [7–9]. These results are particularly important, given that VRD has long been established as the standard of care for TE-NDMM.

When calculating the pooled HR for the OS, we observed low heterogeneity in both comparisons: daratumumab quadruplet regimens versus triplet regimens (Cochran's Q, $P = 0.63$; $I^2 = 0\%$) and D-VRD versus VRD (Cochran's Q, $P = 0.64$; $I^2 = 0\%$). This minimal heterogeneity indicates that the studies included in this analysis are highly consistent in their results, thereby enhancing the reliability and generalizability of the meta-analytic findings.

In this MA, we employed two distinct methodological approaches: a standard MA of aggregate data and a reconstructed patient data analysis to generate survival curves. Both methods demonstrated strong agreement in estimating the effectiveness of the daratumumab-based quadruplet regimen on the OS and PFS (Figs. 1–4). The simultaneous application of these approaches enabled a more robust and comprehensive dataset interpretation [38].

Both RCT and NRCS were included in this MA to address gaps in the evidence. While RCTs provide high-quality evidence on efficacy, NRCS were included to capture real-world effectiveness not adequately addressed by RCTs [10]. A sensitivity analyses using the leave-one-out method were performed to evaluate the impact of their inclusion to the overall estimate. The results remained consistent even after repeating the MA omitting the NRCS from the analysis (Supplementary Figs. 2C, 3C, and 4).

Prior meta-analyses have established that daratumumab-based regimens demonstrate superior efficacy outcomes relative to control groups, as evidenced by enhanced overall response rates, complete responses, stringent complete responses, and increased MRD negativity. Conversely, these regimens are associated with a significantly higher incidence of adverse events, notably grade ≥3 neutropenia, grade ≥3 infections, pneumonia, and grade ≥3 thrombocytopenia [39–46]. Unlike most previous analyses that aggregated patients with both transplant-eligible and transplant-ineligible MM, our study focuses exclusively on TE-NDMM patients, thereby offering a more precise and tailored comparison of treatment regimens within this specific population. Furthermore, we provide a comprehensive analysis of OS in TE-NDMM patients, a critical endpoint that has not been thoroughly addressed in earlier meta-analyses.

Despite the compelling evidence, several limitations must be acknowledged. First, all data were derived or calculated from published studies rather than individual patient data, introducing potential heterogeneity due to variability in study designs, patient characteristics, and maintenance therapies, which may affect the generalizability of our findings. Second, in the PERSEUS and GRIFFIN trials, the observed benefits of quadruplet regimens may reflect the cumulative effects of daratumumab across induction, consolidation, and maintenance phases. Third, in the CASSIOPEIA trial, the randomization of patients to daratumumab maintenance or observation in the second phase may have influenced outcomes. Fourth, the limited reporting of postprotocol therapies raises concerns about the potential impact of suboptimal treatment, particularly the absence of anti-CD38 antibodies upon relapse in the control arms, which may undermine the observed OS benefit. Additionally, the relatively short follow-up duration in some studies limits the assessment of long-term outcomes, which may evolve with extended follow-up. Finally, the inclusion of one non-randomized controlled study, despite its rigorous and favorable quality assessment, introduces a potential source of bias.

In conclusion, this MA consolidates evidence that daratumumab-based quadruplet regimens significantly improve the overall survival in the frontline treatment of TE-NDMM, compared to traditional triplet regimens. These results provide valuable guidance for selecting optimal first-line treatments, especially in the absence of long-term follow-up data from ongoing randomized trials.

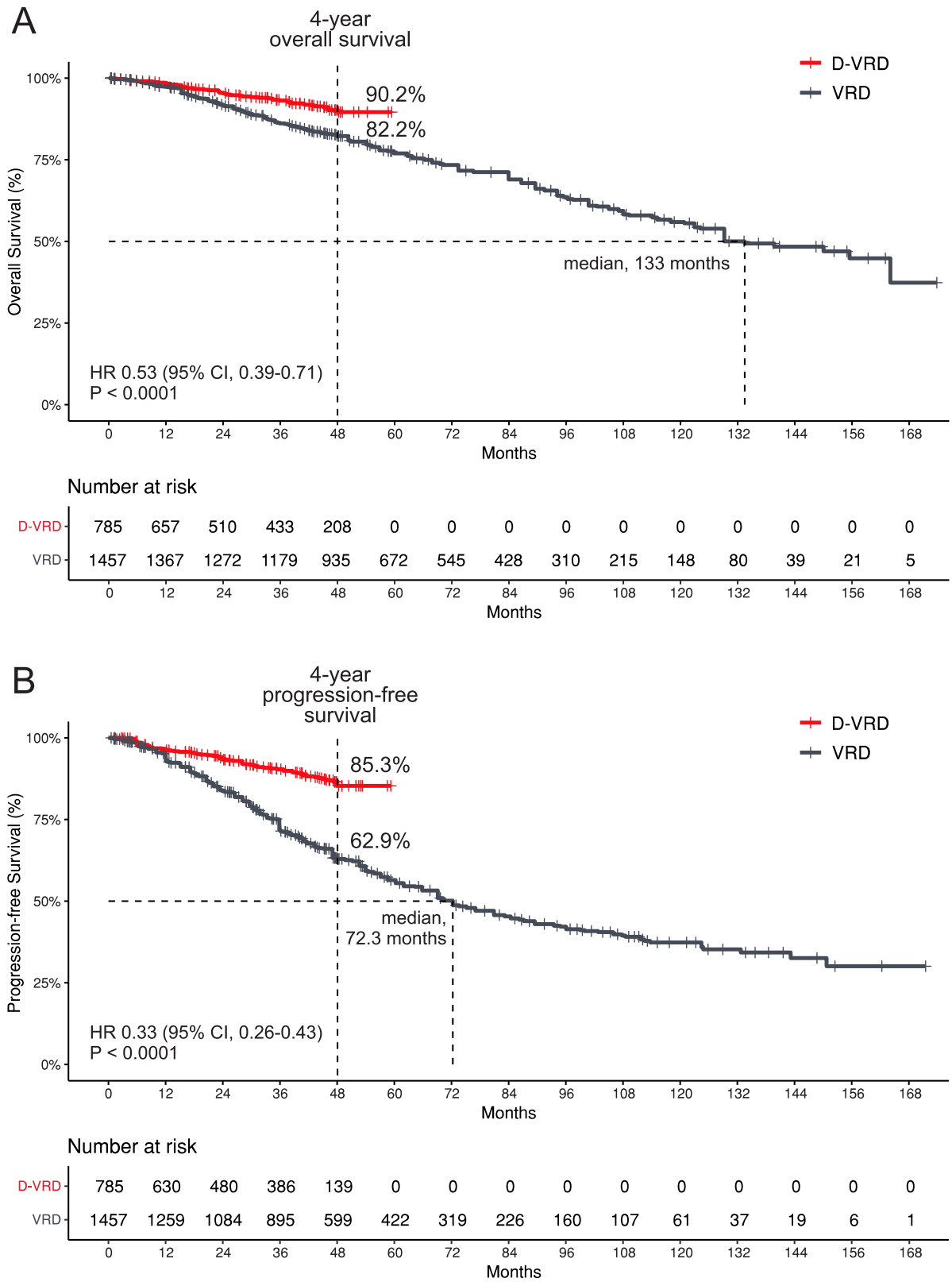

Fig. 4 Pooled Kaplan-Meier survival curves based on reconstructed individual patient data, comparing survival outcomes between D-VRD and VRD in transplant-eligible newly diagnosed multiple myeloma patients. A OS; **B** PFS.

DATA AVAILABILITY

This meta-analysis was conducted using data sourced from previously published studies, all of which are publicly accessible. The authors did not have access to individual patient-level data from the included studies. All pertinent datasets generated and analyzed during this study are provided within the article and its supplementary materials. For further inquiries or requests for additional data, please contact the corresponding author.

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AUTHOR CONTRIBUTIONS

JTDSF designed the research and analyzed the data. JTDSF and LOC were responsible for data acquisition and interpretation. JTDSF drafted the manuscript, while LOC, EQC, VH, and AM contributed to its revision. All authors approved the final manuscript.

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