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Optimal daratumumab-based regimen for patients with newly diagnosed and previously untreated multiple myeloma: systematic review and component network meta-analysis

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Abstract

Background Daratumumab (Dara)-based regimens have been investigated in randomized controlled trials (RCTs) involving patients with newly diagnosed and previously untreated multiple myeloma (NDMM), but the optimal daratumumab-based regimen remains unclear. This study compares the efficacy of daratumumab-containing regimens for NDMM patients and explores optimal combinations.

Methods Databases were searched from inception until February 29, 2024. Trials comparing regimens with and without daratumumab, as well as their mutual comparisons, were included. Random effects models for serious adverse events (SAEs) and fixed effects models for other outcomes were utilized in both network meta-analysis (NMA) and component NMA (CNMA), with pooled effects estimated. The efficacy of all possible combinations of daratumumab with other drugs was assessed.

Results A total of 17 trials were included, enrolling 7261 patients, of whom 2083 were treated with daratumumab. The optimal regimens for different outcomes were identified as follows: Dara-bortezomib (V)-melphalan (M)-corticosteroids (D) (Dara-VMD) showed the best results for both overall response rate (ORR) [*RR* = 1.97; 95% *CI*: 1.42 to 2.75; I^2 = 0.00%; 16 trials; 7136 participants; *P* = 0.00] and ≥ very good partial response (≥VGPR) [*RR* = 7.46; 95% *CI*: 4.10 to 13.46; I^2 = 23.96%; 16 trials; 7118 participants; *P* = 0.00]; Dara-V-thalidomide (T)-D (Dara-VTD) was optimal for achieving ≥ complete response (≥ CR) [*RR* = 14.15; 95% *CI*: 3.74 to 53.52; I^2 = 0.00%; 17 trials; 7261 participants; *P* = 0.00]. The individual effects of daratumumab were calculated as follows: [ORR: *RR* = 1.14; 95% *CI*: 1.08 to 1.21; I^2 = 0.00%; 16 trials; 7136 participants; *P* = 0.00; ≥VGPR: *RR* = 1.46; 95% *CI*: 1.36 to 1.58; I^2 = 23.96%; 16 trials; 7118 participants; *P* = 0.00; ≥ CR: *RR* = 1.77; 95% *CI*: 1.55 to 1.99; I^2 = 0.00; 17 trials; 7261 participants; *P* = 0.00; progression-free survival (PFS): hazard ratio (HR) = 0.53; 95% *CI*: 0.43 to 0.65; I^2 = 0.00%; 13 trials; 5977 participants; *P* = 0.00; overall survival (OS): *HR* = 0.68; 95% *CI*: 0.58 to 0.79; I^2 = 28.97%; 12 trials; 5977 participants; *P* = 0.00]. Additionally, the optimal regimens for PFS and OS were

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Dara-lenalidomide (R)-D [*HR* = 0.37; 95% *CI*: 0.23 to 0.61; I^2 = 0.00%; 13 trials; 5977 participants; *P* = 0.00] and Dara-VRD [*HR* = 0.40; 95% *CI*: 0.19 to 0.85; I^2 = 28.97%; 12 trials; 5977 participants; *P* = 0.02], respectively. Finally, CNMA indicated that Dara-VRD, Dara-carfilzomib (K)-RD, Dara-RD, and Dara-cyclophosphamide (C)-RD were four regimens, which could improve remission rate, and reduce death or progression during induction and prolong lifetime.

Conclusions Dara-VRD, Dara-KRD, Dara-RD, and Dara-CRD are optimal daratumumab-based regimens for patients with newly diagnosed and previously untreated multiple myeloma.

Keywords Daratumumab, Newly diagnosed, Multiple myeloma, Lenalidomide, Component network meta-analysis

Introduction

Multiple myeloma (MM) is a haematological malignancy caused by clonal proliferation and uncontrolled immunoglobin secretion from plasma cells in the bone marrow. MM is still incurable, but the prognosis has improved after the broad application of proteasome inhibitors (PIs), such as bortezomib, and novel immunomodulatory drugs (IMiDs), such as lenalidomide. However, most MM patients inevitably relapse. Frequent alternation of therapeutic regimens results in many cases of relapsed and refractory MM (RRMM). Recent research has focused on advancing therapeutic targets such as anti-CD38 monoclonal antibody, BCMA-directed bispecific antibody, and signaling lymphocytic activation molecule family 7 (SLAMF7) monoclonal antibody [1].

Daratumumab (Dara) is an IgG1 κ-type anti-CD38 monoclonal antibody that can induce tumour cell death by the Fc fragment-mediated apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), or complement-dependent cytotoxicity (CDC) [2–4]. Daratumumab has shown encouraging efficacy in many clinical trials and has been one of the front-line recommendations for NDMM and RRMM patients in America [5] and Europe [6]. Recent clinical trials have explored the efficacy of adding daratumumab to conventional regimens for NDMM, such as the GRIFFIN trial [7], ALCYONE trial [8], and MAIA trial [9]. These findings demonstrated the superior effect of the addition of daratumumab. However, daratumumab has not been approved for transplantation-eligible NDMM treatment in China [10] or Australia [11]. During the NDMM induction phase, it is unclear whether regimens containing daratumumab are better or more beneficial than any other regimens not containing it. Furthermore, prospective research comparing multidrug regimens containing daratumumab is rare. Therefore, this review aims to answer two questions:

1. Is there evidence that is supportive enough to provide daratumumab-based regimens with stronger front-line recommendations than conventional regimens for NDMM treatment?
2. What drugs, in combination with daratumumab, are optimal for NDMM? A systemic and comparative analysis of daratumumab-based regimens is necessary to detect unreasonable usage or combination with daratumumab.

Most MM treatments involve multidrug combinations; therefore, component network meta-analysis (CNMA) is suitable. With the utilization of CNMAs, this study explored the rationality of the addition of daratumumab to conventional regimens and the best daratumumab-based regimens for NDMM.

Method

Chapter 11 of *Cochrane Handbook for Systematic Reviews of Interventions* was the methodological guidance of our work [12]. The review was reported according to the PRISMA checklist extension for NMA [13]. The protocol was registered in PROSPERO (ID: CRD42022334501).

Inclusion and exclusion criteria

Inclusion criteria

The trial met all the following conditions:

(1) *Study design*: Randomized control trial (RCT).
(2) *Patients*: Patients with newly diagnosed and previously untreated multiple myeloma, with no limitations on risk classification or disease stage.
(3) *Intervention*: The treatment group should be the regimen containing daratumumab injection for induction, whereas the control group should not be included. To continue network knobs, RCTs that involved mutual comparisons between the regimens of the treatment or control groups were also eligible. Corticosteroids, such as prednisone and dexamethasone, were treated as inactive components and reference groups, so RCTs about corticosteroids compared with the above regimens were also included.
(4) *Outcome*: Trials should at least report the best response before haematopoietic stem cell transplantation (HSCT). The primary outcomes included overall remission (ORR, patients who achieved par-

tial remission or better), very good partial remission (VGPR) or better (≥ VGPR), complete remission (CR) or better (≥ CR), death or progression during induction (DP), and serious adverse events (SAEs). The secondary outcomes were the hazard ratios (HRs) of progression-free survival (PFS) and overall survival (OS).

Exclusion criteria

Cohort studies, case reports, reviews, laboratory research, trials for patients with smouldering myeloma or plasma cell leukaemia, trials in which the first randomization was after transplantation, and articles without complete endpoint reporting were excluded.

Data sources and searching methods

The following databases were searched from inception to February 29, 2024: Embase, PubMed, Wiley Online Library, Cochrane Library, and Web of Science, with items related to myeloma, daratumumab, bortezomib, carfilzomib, lenalidomide, pomalidomide, new, and untreated. Using the PubMed database as an example, the search query was (("1000/01/01"[Date—Publication]: "2024/02/29"[Date—Publication]) AND (randomized clinical trial[Publication Type]) AND ((myeloma[Title]) AND (daratumumab[Title] OR bortezomib[Title] OR carfilzomib[Title] OR lenalidomide [Title] OR pomalidomide[Title])) AND (newly[Title/Abstract] OR untreated[Title/Abstract])). If the trial results were reported in different articles, the latest article or the article with complete data was included (see Supplemental material 1).

Article selection and data extraction

Two researchers (Xiaohua Huang and Jia Zhou) searched the database and selected the articles independently. They strictly followed the inclusion and exclusion criteria and subsequently cross-checked. When a discrepancy occurred, a third researcher (Wei Ma) was consulted. The data were extracted by another two researchers (Yuxiao Qian and Lu Yang) using a questionnaire designed by a researcher (Jing He) and EpiData Manager 4.4.2.0 and EpiData Entry Client 4.4.3.0 software. The following data were extracted: RCT registration ID; year of publication; population characteristics of each group; number of patients accepting transplantations; therapy regimen of each group; sCR, CR, VGPR, PR, DP, and SAE counts; HR and its 95% confidence interval (95% CI) for PFS and OS; and sample size. HR was extracted from survival curves by Engauge Digitizer (version 12.1) if it was not reported, which was based on the method of Jayne F. Tierney [14].

Assessment of bias and network meta-analysis

The quality of the eligible literature was assessed using the risk-of-bias assessment tool version 2 recommended by the *Cochrane Handbook for Systematic Review of Interventions* [15]. The relative risk (RR) and its 95% CI were used as the effect size to calculate the pooled relative efficacy of each treatment for ≥ CR (sCR + CR), ≥ VGPR (sCR + CR + VGPR), ORR (sCR + CR + VGPR + PR), DP, and SAEs. We performed both standard NMA and CNMA following frequentist approaches [16–18].

First, grouped by different outcomes, network graphs were drawn to clarify the relationships between interventions.

Second, in NMA, the τ^2 value and I^2 value were reported to quantify the inconsistency and heterogeneity. Inconsistency and heterogeneity were subsequently tested, and the Q-value and P-value were reported. If $I^2 <$ 50%, insignificant heterogeneity was accepted, and a fixed effect model (NMA) was applied. Otherwise, the random effect model NMA was utilized. Then, we synthesized evidence by integrating direct and indirect estimation for each comparison into a pooled effect [RR (95% CI) and HR (95% CI)]. The NMA league tables for each outcome were drawn.

Third, in the CNMA, the additive model without any interactive item was the initial CNMA model, and the difference between the CNMA and NMA was estimated using the Cochrane Q test. If the initial model was significantly different from the NMA model, the addition of interactive items (daratumumab interacting with one or more other drugs) to the initial CNMA model was considered. With the assistance of a scatter plot of Q and P, the interactive model corresponding to the vertex of the scatter plot was eligible. The overall effect of each component was subsequently estimated. The effects of arbitrary complex interventions, which included daratumumab in combination with one or more other drugs, were calculated to explore the optimal Dara regimens theoretically. The CNMA league tables of complex interventions were drawn.

Finally, the relative rank was estimated using P scores [19]. The risk of SAEs was estimated using the CNMA and pairwise meta-analysis, and a sensitivity test of the primary outcome was also applied by evaluating the effect difference between the NMA and the CNMA. All the above NMA and CNMA results were visually demonstrated using forest plots. A contour-enhanced funnel plot was drawn, and publication bias was estimated by examining asymmetry using the Harbord method [20].

All the above statistical analyses were performed using the R (version 4.2.1) and netmeta′ packages (version 2.5–0), and $P < 0.05$ was considered to indicate a statistically

significant difference. The GRADE assessment was also conducted.

Results

Literature screening and trial characteristics

A total of 1048 records were identified from the initial retrieval. After removing 341 duplicate records and 33 trials not for NDMM, 674 potentially eligible records were screened. The full texts of 88 records were not further searched after the titles and abstracts were read because of their ineligible study design. Eventually, 444 records were excluded, and 17 RCTs were included (13 articles [7–9, 21–30] and 4 conference abstracts [31–34]). The process of literature screening was shown in Fig. 1.

A total of 7261 patients were involved, of which 2083 patients were treated with 6 regimens in combination with daratumumab: D-RD, D-VCD, D-VMD, D-VRD, D-VTD, and D-KRD. All studies were phase II or III open-label trials except the S0232 trial [27]. Thirteen RCTs included only transplantation-ineligible (TI) NDMM patients [8, 9, 22, 23, 25–30, 32–34], and 4 included transplantation-eligible (TE) patients [7, 21, 24, 31]. For more details, refer to Tables 1, S1, and S2.

Quality assessment

Most RCTs described the randomization method in detail, but there was not enough information to assess the risk of allocation in four abstracts [31–34] and one article [29] because their description of randomization was too simple. Although most RCTs were open label, the risk of deviations from intended treatment was low, except for four that were unclear due to incomplete messages [31–34]. More missing data (dropout or withdrawal) for the primary outcome were observed in two RCTs [23, 27], which resulted in a high risk of imprecise estimation. There was little information in two trials [33, 34] that raised concerns about the high risk of outcome measurement. Five RCTs [22, 23, 29, 30, 32] described

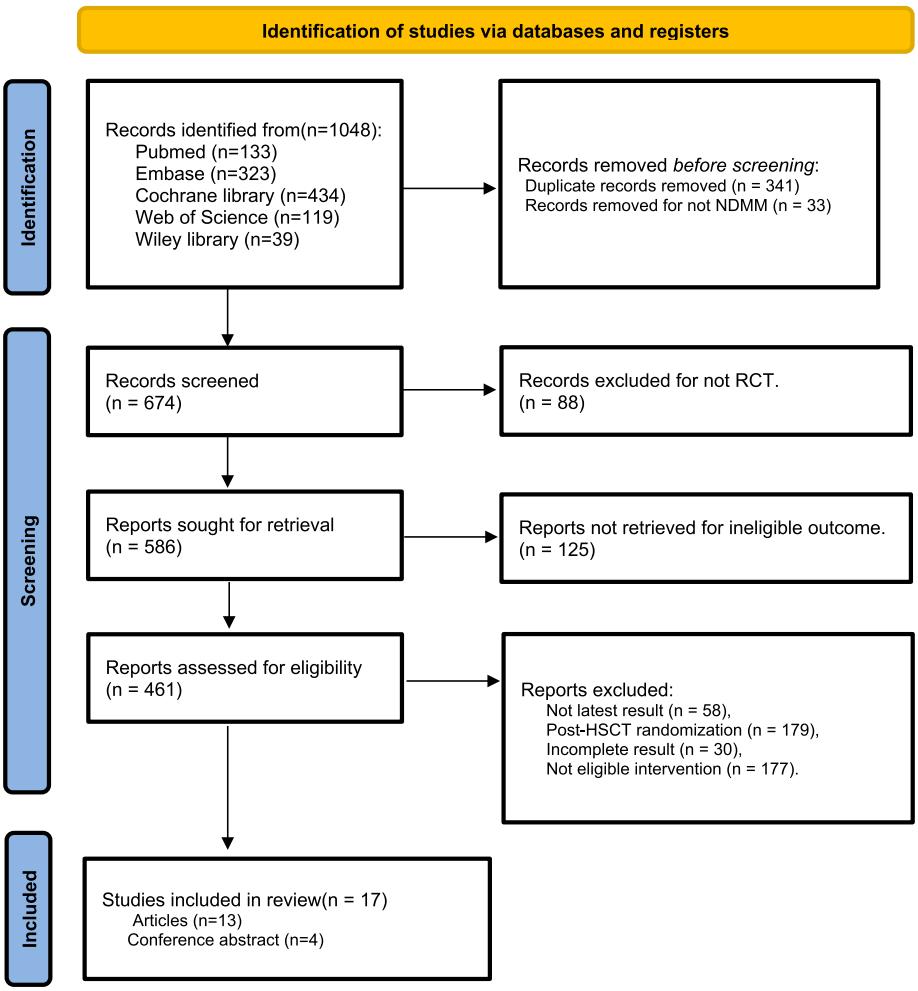


Fig. 1 PRISMA flow diagram

Table 1 Characteristics of eligible trials [7–9, 21–34]

Study name	Regimen	Phase	N	Sex (M/F)	Age	Patients		Risk of bias					
						HR	HSCT	A	B	C	D	E	F
CASSIOPEIA[21]	D-VTD	III	543	317/227	59(22-65)	82	489	+	+	+	+	+	+
	VTD		542	319/223	58(26-65)	86	484						
ALCYONE[8]	D-VMD	III	350	160/190	71(50-91)	53	0	+	+	+	+	+	+
	VMD		356	167/189	71(41-93)	45	0						
MAIA[9]	D-RD	III	368	189/179	73(50-90)	48	0	+	+	+	+	+	+
	RD		369	195/174	74(45-89)	44	0						
GEM2005[22]	VMD	III	130	69/61	73(68-77)	18	0	+	+	+	−	+	−
	VTD		130	61/69	73(69-76)	9	0						
UPFRONT[23]	VTD	III	167	70/97	73(66-77)	NA	0	+	+	×	−	+	×
	VMD		167	90/77	72(68-77)	NA	0						
GRIFFIN[7]	D-VRD	II	104	58/46	59(29-70)	42	100	+	+	+	+	+	+
	VRD		103	60/43	61(40-70)	37	85						
GEM2017FIT[31]	D-KRD	III	153	NA	NA	NA	NA	+	−	+	+	+	−
	KRD		154	NA	NA	NA	NA						
	VMD		153	NA	NA	NA	NA						
PERSEUS[24]	D-VRD	III	355	211/144	61(32-70)	76	309	+	+	+	+	+	+
	VRD		354	205/149	59(31-70)	78	294						
ENDURANCE[25]	KRD	III	545	315/227	65 (59-71)	159	0	+	+	+	+	+	+
	VRD		542	327/219	64 (57-71)	138	0						
SWOGS0777[26]	VRD	III	235	144/91	63(56-71)	NA	0	+	+	+	+	+	+
	RD		225	120/105	63(56-70)	NA	0						
S0232[27]	RD	III	97	53/44	65(37-89)	NA	NA	+	+	×	+	+	×
	PlaceboD		95	55/40	63(38-87)	NA	NA						
OCTANS[28]	D-VMD	III	146	85/61	69(58-81)	28	0	+	+	+	+	+	+
	VMD		74	46/28	69(57-84)	20	0						
AMaRC 03-16[32]	D-VCD	II	64	49/15	75(64-91)	12	0	+	+	+	−	+	−
	VCD		57	34/23	75(62-89)	7	0						
EVOLUTION[29]	VRD	II	42	24/18	60(42-75)	7	19	−	+	+	−	+	−
	VCD		33	19/19	62(40-75)	7	10						
IFM2013-04[30]	VTD	III	170	103/66	59(34-65)	32	0	+	+	+	−	+	−
	VCD		170	108/61	60(26-65)	29	0						
Lalit2019[33]	VRD	III	65	73/52	58(31-70)	8	0	−	−	+	×	+	×
	VCD		60			7	0						
Anjali2017[34]	VRD	III	74	54/20	56(31-70)	NA	0	−	−	+	×	+	×
	RD		69	43/26	52(28-69)	NA	0						

HR high risk, *NA* not available, *HSCT* haematopoeitic stem cell transplantation, risk of bias: A, bias due to randomization; B, bias due to deviations from intended intervention; C, bias due to missing data; D, bias due to outcome measurement; E, bias due to selection of reported result; F, overall bias. Judgement: green cross, low; yellow minus, some concerns; red cross, high

the outcome measurements. Nevertheless, they did not introduce any method (such as sample examination in a central laboratory) to avoid measurement bias, so there were some concerns in domain 4. No selectively reported results were observed. In general, the risk of bias in the included RCTs mainly originated from missing data and outcome measurements (Table 1, Fig. S1, and Supplemental Materials 3).

Results of the network meta-analysis

Network graph

The included RCTs generated five connective and two disconnected networks (Fig. 2, S2). Owing to missing data, the NMA and CNMA were both applied for all primary outcomes, whereas PFS and OS were analysed only by the CNMA. Corticosteroids were set as the reference for all estimations of the network meta-analysis.

Test of heterogeneity and inconsistency

No significant inconsistency or heterogeneity was observed in any of the outcomes, except for SAEs.

We noticed a significant difference between the NMA and CNMA models when the interaction of components was ignored; therefore, an interactive model needed to be established. Six pair interactions (daratumumab with the other five drugs) and five triplet interactions (Dara-KR,

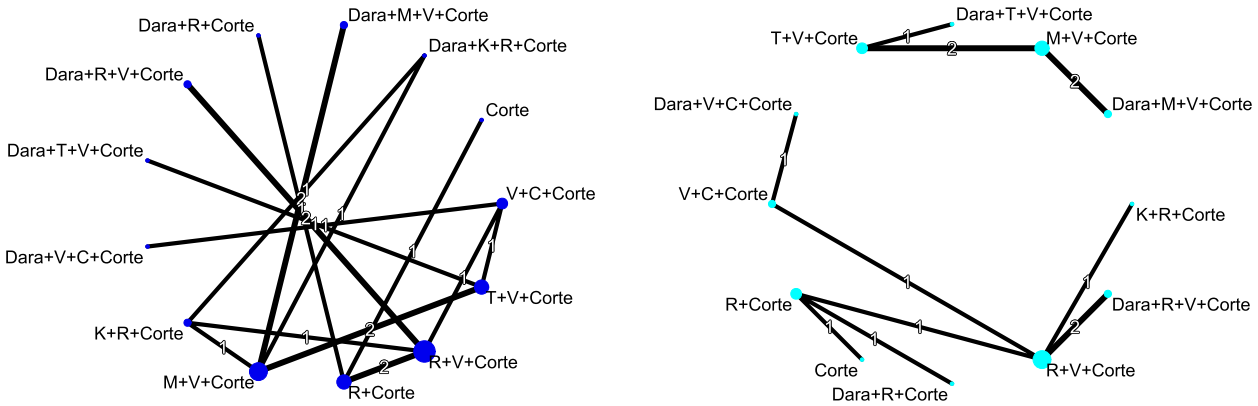


Fig. 2 Network graph for different outcomes: the line thickness represents the number of comparisons, and the size of the node represents the number of studies

DaraV with other drugs) were calculated. The relationships between the *Q*- and *P*-values and the number of interactive items were shown in Fig. S3. The optimal interactions were shown in Table S3.

Results of conventional network meta-analysis

The results of conventional NMA indicated that compared with corticosteroids, the six reported Dara regimens in recent articles (Dara-VMD, Dara-RD, Dara-VTD, Dara-KRD, Dara-VCD, Dara-VRD) could significantly improve the rates of ORR, ≥ VGPR, and ≥ CR. The regimens with the best efficacy were Dara-VMD for both the ORR [$RR = 1.97$; 95% *CI*: 1.42 to 2.75; $I^2 = 0.00\%$; 16 trials; 7136 participants; $P = 0.00$] and ≥ VGPR [$RR = 7.46$; 95% *CI*: 4.10 to 13.46; $I^2 = 23.96\%$; 16 trials; 7118 participants; $P = 0.00$] and Dara-VTD for ≥ CR [$RR = 14.15$; 95% *CI*: 3.74 to 53.52; $I^2 = 0.00\%$; 17 trials; 7261 participants; $P = 0.00$]. Dara-VRD [$RR = 0.04$; 95% *CI*: 0.00 to 0.51; $I^2 = 0.00\%$; 15 trials; 6993 participants; $P = 0.01$] and Dara-KRD [$RR = 0.03$; 95% *CI*: 0.00 to 0.95; $I^2 = 0.00\%$; 15 trials; 6993 participants; $P = 0.05$)] also decreased the risk of DP during induction (Fig. 3). Mutual comparisons were shown in the league table (Fig. S4). These findings suggest that regimens with daratumumab were not always significantly superior to those without daratumumab. For example, the front-line conventional triplet-drug regimen VRD was inferior to Dara-VRD in terms of ORR [vs. VRD, $RR = 1.04$; 95% *CI*: 1.01 to 1.07; $I^2 = 0.00\%$; 16 trials; 7136 participants; $P = 0.00$], ≥ VGPR [vs. VRD, $RR = 1.07$; 95% *CI*: 1.03 to 1.12, $I^2 = 23.96\%$; 16 trials; 7118 participants; $P = 0.00$], and ≥ CR [vs. VRD, $RR = 1.26$; 95% *CI*: 1.16 to 1.36; $I^2 = 0.00\%$; 17 trials; 7261 participants; $P = 0.00$] improvement, while it was

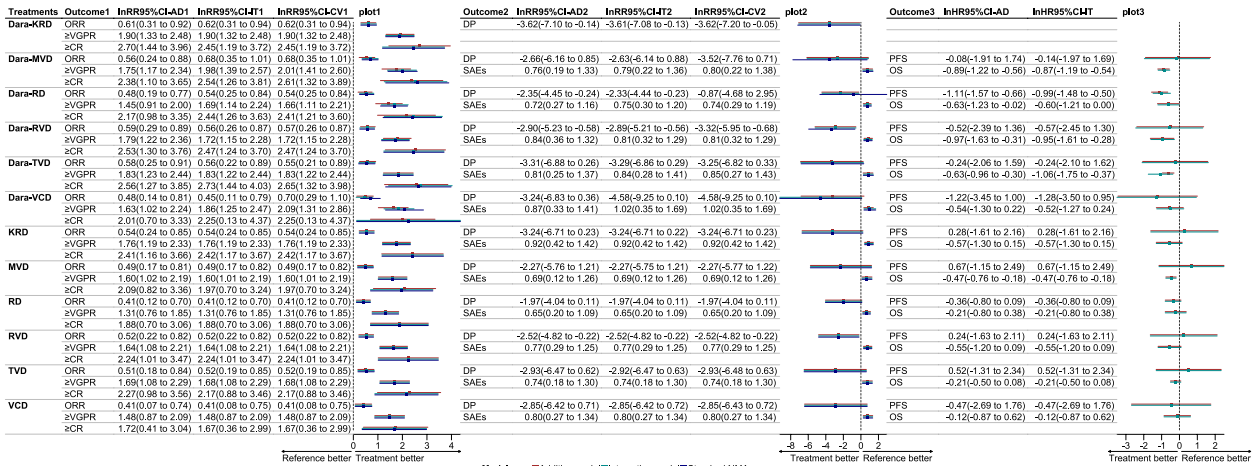


Fig. 3 Effect of reported treatments: compared to corticosteroids. AD, additive model; IT, interactive model; CV, conventional NMA

comparable to Dara-KRD, Dara-RD, Dara-VTD, and Dara-VCD in terms of improvement in ORR and ≥ CR.

A scatter plot (Fig. S5) suggested the consistency of SUCRA and P-score ($r=0.93$, $P<0.001$). The best interventions for different outcomes were Dara-VMD for ORR, Dara-VMD for ≥ VGPR, Dara-VTD for ≥ CR, and Dara-VCD for DP. KRD was observed to be superior to some regimens with daratumumab, such as Dara-VCD and Dara-RD (Fig. S6).

Results of the component network meta-analysis

Effect of components

The pooled effect of each component (drug) was estimated (Fig. 4). Daratumumab significantly improved the ORR [*RR*=1.14; 95% *CI*: 1.08 to 1.21; $I^2=0.00\%$; 16 trials; 7136 participants; $P=0.00$], ≥ VGPR [*RR*=1.46; 95% *CI*: 1.36 to 1.58; $I^2=23.96\%$; 16 trials; 7118 participants; $P=0.00$], ≥ CR [*RR*=1.77; 95% *CI*: 1.55 to 1.99; $I^2=0.00$; 17 trials; 7261 participants; $P=0.00$], PFS [*HR*=0.53; 95% *CI*: 0.43 to 0.65; $I^2=0.00\%$;13 trials; 5977 participants; $P=0.00$], and OS [*HR*=0.68; 95% *CI*: 0.58 to 0.79; $I^2=28.97\%$; 12 trials; 5977 participants; $P=0.00$]. The means of the beneficial interactive items were DaraM for the ORR [*RR*=1.16; 95% *CI*: 1.08 to 1.25; $I^2=0.00\%$; 16 trials; 7136 participants; $P=0.00$]. However, DaraK, DaraT, DaraV, and Dara-VR negatively influenced remission, which might have a rectification effect on the additive model.

Efficacy of all Dara regimens

A comparable estimation of the efficacy of the interactive CNMA model was shown in Fig. 3. These findings suggested that Dara-RD improved PFS [*HR*=0.37; 95% *CI*: 0.23 to 0.61; $I^2=0.00\%$; 13 trials; 5977 participants; $P=0.00$], and that both Dara-VMD [*HR*=0.42; 95% *CI*: 0.31 to 0.58; $P=0.00$], Dara-VRD [*HR*=0.39; 95% *CI*: 0.20 to 0.76; $P=0.02$], and Dara-VTD [*HR*=0.35; 95% *CI*: 0.17 to 0.69; $P=0.01$] prolonged OS [the above HR estimation of OS was from a model with $I^2=28.97\%$; 12 trials; 5977 participants] (Fig. 5). Other Dara regimens, as reported in trials, were not superior to conventional regimens in terms of PFS for NDMM. Dara-RD [*HR*=0.37; 95% *CI*: 0.23 to 0.61; $I^2=0.00\%$; 13 trials; 5977 participants; $P=0.00$] and Dara-VRD [*HR*=0.40; 95% *CI*: 0.19 to 0.85; $I^2=28.97\%$; 12 trials; 5977 participants; $P=0.02$] were optimal and significant regimens for PFS (82%) and OS (90%), respectively (Fig. S6).

The effects of 27 daratumumab-based regimens were estimated (Figs. 5 and 6, and S7). Regarding remission, those columns with smaller blue areas had better efficacy. Although multidrug regimens were more effective numerically, some simple regimens were comparable to complex regimens, such as Dara-RD and Dara-VCD [for ORR, *RR*=1.00; 95% *CI*: 0.83 to 1.22; $I^2=0.00\%$; 16 trials; 7136 participants; $P=0.96$; for ≥ CR, *RR*=0.82; 95% *CI*: 0.5 to 1.82; $I^2=0.00\%$; 17 trials; 7261 participants; $P=0.49$]. The risk of serious adverse events (AEs) increased with the addition of drugs. Survival benefit did not correlate with drug number; for example, the PFS of patients treated with Dara-RD was longer than that of patients treated with most other regimens. Therefore, considering both efficacy and safety, we categorized the combination with daratumumab as follows (Fig. 5). In general, Dara-VRD, Dara-KRD, Dara-RD, and Dara-CRD were four regimens with good efficacy in terms of response and survival, which could improve remission

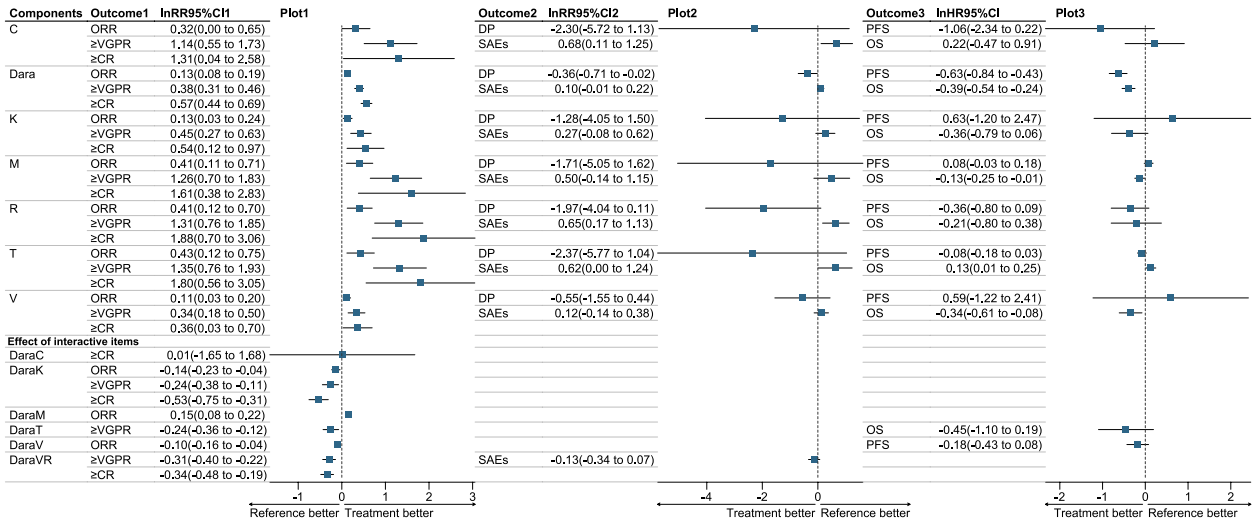


Fig. 4 Effect of components: compared to corticosteroids and based on interactive model

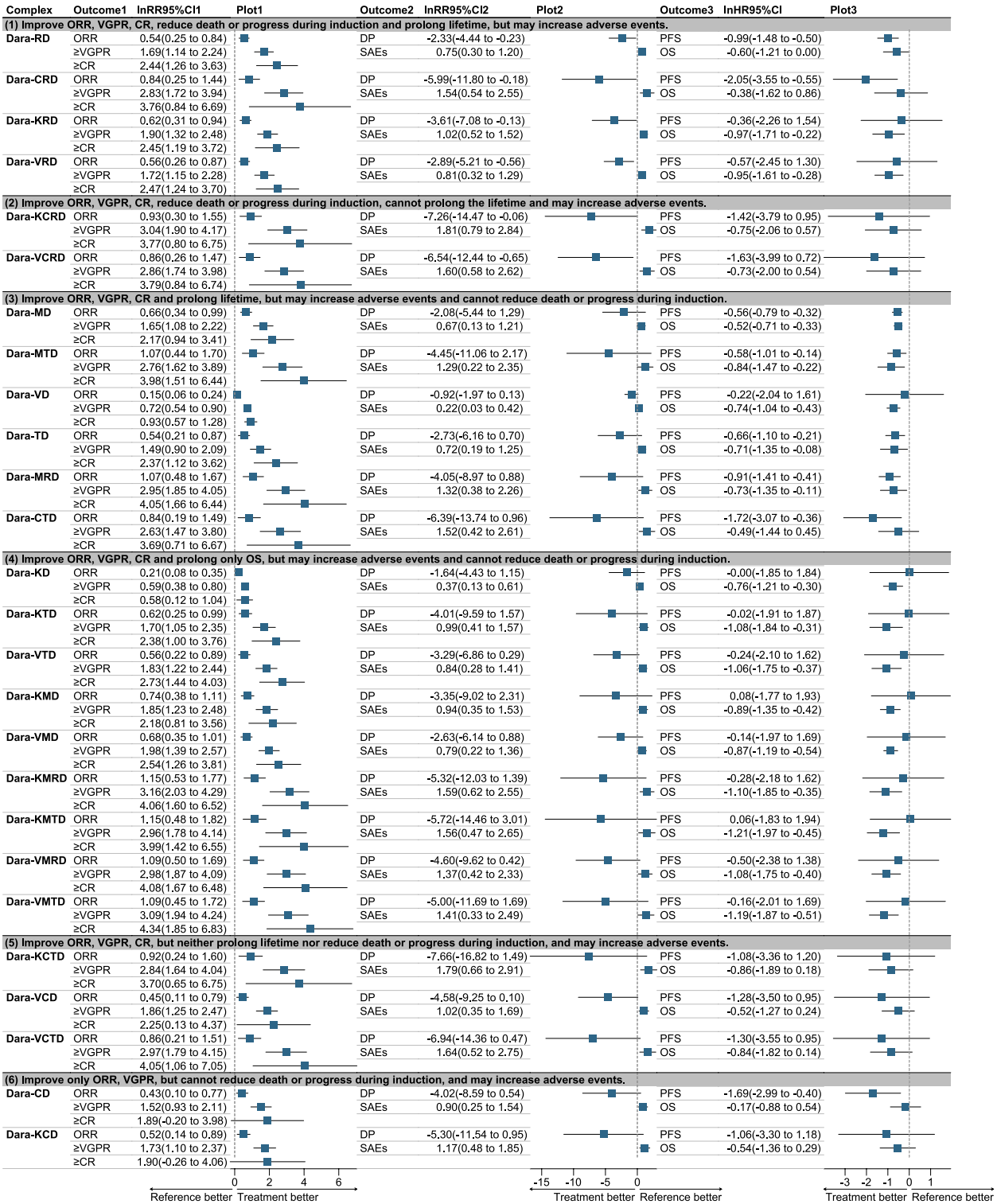
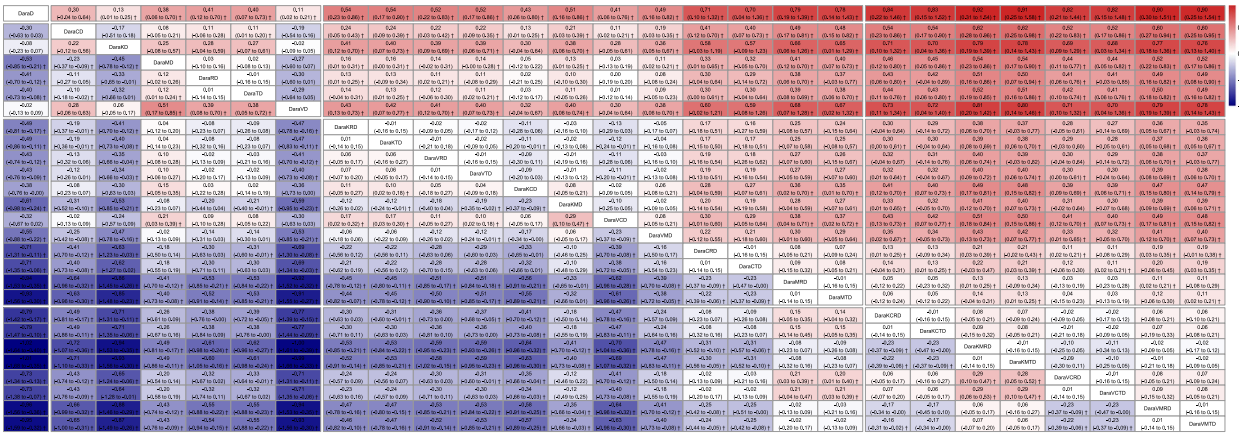


Fig. 5 Forest plot for effect of daratumumab arbitrary combination with other drugs: the estimation was based on interactive CNMA model

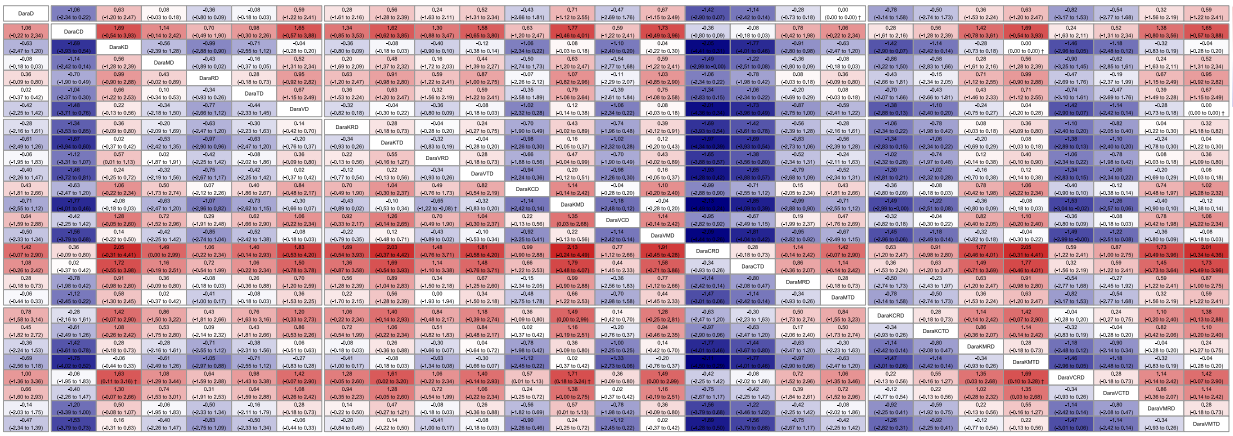
rate and reduce death or progression during induction and prolong lifetime. The regimens with daratumumab and cyclophosphamide did not improve OS.

Common adverse events

Compared with corticosteroids, daratumumab alone did not significantly increase the risk of any type of SAE



(a) CNMA league table for ORR



(b) CNMA league table of PFS

Fig. 6 League table for CNMA. The value above the diagonal represents estimations of the additive model, while those under the diagonal mean estimations of the interactive model in theory. The results are grouped by the drugs quantity. †Statistically meaningful effect ($P < 0.05$)

(*RR* = 1.11, 95% *CI*: 0.99 to 1.25, $I^2 = 57.91\%$, 14 trials, 6533 participants, $P = 0.07$). The regimen reported in the articles with the best safety was Dara-VMD (*RR* = 2.23, 95% *CI*: 1.25 to 3.97, $I^2 = 57.91\%$, 14 trials, 6533 participants, $P = 0.07$). The combinations close to the left side of the league table, which consisted of fewer drugs and more blue areas of the league table, were relatively safer choices (Fig. S7d). A pairwise meta-analysis indicated that the addition of daratumumab increased the risk of the following grade 3 or higher AEs: pneumonia, hyperglycaemia, decreased lymphocyte count, infection, decreased neutrophil count, and decreased platelet count (Fig. S8).

Publication bias, GRADE assessment, and sensitivity analysis

Significant asymmetry was observed for SAEs ($t = -3.01$, $P = 0.01$). Publication bias of SAEs might exist (Fig. S9). The GRADE assessment was described in Supplemental material 4. The result of the interactive CNMA was also treated as a sensitivity analysis. The statistical estimation was robust in the NMA and CNMA models, so the conclusions were believed to be trustworthy and reliable.

Discussion

PIs, novel IMiDs, and corticosteroids constitute the backbone of NDMM treatment. Most patients with NDMM benefit from the above triplet–drug combination regimens. However, MM is a disease with significant heterogeneity. Some NDMM patients fail conventional treatment, and novel targets for RRMM patients are currently a popular research topic. Many recently approved drugs, such as the anti-CD38 monoclonal antibody daratumumab, the SLAMF7 agent elotuzumab [35], and the exportin-1 inhibitor selinexor [36], inhibit myeloma cells through different mechanisms. The efficacy of daratumumab in RRMM has been proven by many multicentre phase II/III RCTs, such as the POLLUX trial [37],

CANDOR trial [38], and APOLLO trial [39]. Our work more precisely estimated the effect and safety of daratumumab-based regimens than before and further overcomes the limitations of previous systematic reviews:

1. Some researchers have performed systematic reviews and pairwise meta-analyses to explore the pooled effect sizes of different daratumumab-based regimens [40–43]. However, those systematic reviews did not consider the heterogeneity and inconsistency of different combinations, and some pooled effect sizes were NDMM integrated with RRMM [41, 42]. The recent meta-analyses of daratumumab were both pairwise meta-analyses, and only two to four trials were included. We performed the first network meta-analysis on daratumumab-based regimens for NDMM, which did not include any trials for RRMM. Therefore, in our study, more trials, patients, and endpoints were considered than before, and our work offered a more accurate estimation of daratumumab in NDMM treatment.
2. The estimation of the recent meta-analysis was limited to reported regimens [40–43]. The efficacy and safety of unreported daratumumab-based regimens, such as Dara-CRD and Dara-KCD, are unknown. We used the CNMA strategy to perform a more extensive and deeper analysis of daratumumab-based regimens' efficacy and safety. The theory of component network meta-analysis was first proposed by Welton N. J [44], and Rucker G. provided a detailed illustration of the practice method of the CNMA based on the frequentist approach [16, 18]. CNMA can either compare many interventions at the same time as NMA can or estimate the effects of both disconnected networks and all possible combinations that have not been published. Hence, CNMA overcomes the limitations of pairwise meta-analysis and conventional NMA, and it is suitable for multidrug regimen analysis. We explored not only the individual effect size of daratumumab but also the efficacy and safety of unreported daratumumab-based regimens.

This review aims to explore the rationality of front-line usage and the optimal combination of daratumumab for previously untreated NDMM patients. The comparable results of NMA and CNMA indicated that daratumumab itself was effective for NDMM, and its addition to specific regimens, such as Dara-VD and Dara-VRD, improved its efficacy. However, daratumumab also increased the risk of some severe AEs, and the effects of some conventional regimens were similar to those of Dara regimens. Furthermore, the efficacy of daratumumab in combination with cyclophosphamide was observed. Therefore, the utilization of daratumumab together with cyclophosphamide for NDMM should be cautious, and those combinations are not superior and are sometimes inferior to traditional regimens.

Daratumumab is believed to act as an antimyeloma agent through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, induction of apoptosis, and modulation of CD38 enzyme activities [3, 45]. Additionally, daratumumab functions in immunomodulation by decreasing the number of CD38+ immune regulatory cells and decreasing the number of immune-suppressive cells, which is associated with increased antimyeloma ability [46]. Hence, the activity of daratumumab against MM is dependent on the normal function of immunity.

Cyclophosphamide activation is associated with dose. High doses of cyclophosphamide (120 mg/kg up to several grams/kg) act as alkylating agents, mediating its cytotoxicity through DNA damage, whereas low dosages (1 to 3 mg/kg) play a role in immunomodulation [47]. When cyclophosphamide was administered at a dosage of 500 mg per week three times, a significant reduction in total lymphocytes was observed [48], and our review also suggested an obviously high risk of lymphocyte depletion associated with daratumumab usage. The doses of cyclophosphamide included in the studies were high, which might be one reason why the combination of daratumumab with cyclophosphamide led to inferior efficacy. However, the value of this combination still deserves attention because laboratory cell research has shown that low doses of cyclophosphamide combined with daratumumab can potentiate daratumumab-mediated macrophage antimyeloma activity [49]. Clinical research on low-dose cyclophosphamide with daratumumab for NDMM may be valuable in the future.

Another interesting finding of our research is the impressive efficacy of daratumumab with lenalidomide, which could even improve the negative effect of daratumumab with cyclophosphamide. Both daratumumab and lenalidomide are agents that act against MM through anticancer immune reactions. Lenalidomide, a second-generation IMiD, has been widely used to treat haematological malignancies. Lenalidomide inhibits myeloma cells by arresting the cell cycle; stimulating T cells, NK cells, and dendritic cells; and inhibiting angiogenesis [50]. Lenalidomide can synergistically augment Dara-dependent cell-mediated cytotoxicity, ADCC, and CDC against myeloma cells [51]. This may be the consequence of immune cell profile modulation, phenotypic transformation of natural killer cells, activation of $CD8^+$ T cells, and enhancement of memory T-cell reproduction [52, 53]. In summary, a deeper synergistic immune effect may be potentiated by daratumumab in combination with lenalidomide.

Our work may serve as a reference for the rational application of daratumumab for NDMM patients, and no similar analysis has been published recently. However, limitations of this review should be noted. First, we only considered the interactive effect of daratumumab with other drugs, while the mutual effect between other drugs has not been explored. Nevertheless, even when interactive items of other drugs were included, the interactive effect was counteracted when the efficacy of daratumumab was estimated. On the other hand, our emphasis and interest were daratumumab. Therefore, the interaction of daratumumab with other drugs was primarily considered. Second, there was no direct comparison between Dara regimens, and all effect sizes of daratumumab originated from indirect comparisons. Therefore, direct evidence for the comparison of Dara regimens is still needed. Third, the risk of bias needs to be considered. There were four trials with a high risk of bias. In UPFRONT [23] and S0232 [27], baseline balance was assessed in ITT pts, but 15–30% of the patients were missing in the assessment of efficacy, which might decrease the reliability of the outcome. The author did not provide a detailed or brief analysis of the above problem. Furthermore, publication bias of SAEs also exists. Most of the log effect sizes of SAEs were allocated to the left side of the funnel plot, which indicates the underestimation of the harmfulness of daratumumab. Therefore, real-world data and long-term surveillance are needed.

Conclusion

Conclusively, front-line usage of daratumumab is effective for previously untreated NDMM patients. Dara-VRD, Dara-KRD, Dara-RD, and Dara-CRD are four optimal regimens with good efficacy in terms of response and survival and lower risk of death or progression during induction.

Abbreviations

Dara	Daratumumab
C	Cyclophosphamide
K	Carfilzomib
M	Melphalan
R	Lenalidomide
T	Thalidomide
V	Bortezomib
Corte, D	Corticosteroids

Supplementary Information

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Supplementary Material 1. Search Strategy.

Supplementary Material 2: Figures and tables. Supplementary figures. Figure S1 Summary of risk of bias. Figure S2 Network graph for different outcomes: The line thickness represents the number of comparisons, and the size of the node represents the number of studies. Figure S3 Scatter plots of *Q*,*P* value and number of interactive terms (a) plot for ORR, (b) plot for ≥VGPR， (c) plot for ≥CR, (d) plot for DP, (e) plot for SAEs, (f) plot for PFS, (g) plot for OS. The spot size and histograms above the scatter plots means the count of same value of Q in specified number of interactions. Figure S4 League table of NMA The value above the diagonal presents reported estimations of articles, while those under the diagonal means mutual comparison in theory. ‡: Statistically meaningful effect ($P<0.05$). Figure S5 Scatter plot and correlation curve of SUCRA and P-SCORE. Figure S6 Possibility of top relative rank in different outcome ORR: Overall response, VGPR: Very good partial remission, CR: Complete remission, DP: Death or progress (during induction), SAEs: Serious adverse events, PFS: Progress free survival, OS: Overall survival. Figure S7 League table for CNMA The value above the diagonal represents estimations of the additive model, while those under the diagonal mean estimation of the interactive model in theory. The results are grouped by the drugs quantity. †: Statistically meaningful effect ($P<0.05$). Figure S8 Forest plot for common serious AEs of daratumumab. Figure S9 Counter enhance funnel plot for publication bias. Supplementary tables. Table S1 Details of eligible trials. Table S2 Outcome information. Table S3 Heterogeneity and inconsistency.

Supplementary Material 3. ROB.

Supplementary Material 4. GRADE assessment.

Authors' contributions

XH, JH, and HL designed the study and questionnaire for data collection. XH and JZ searched the database. YQ and LY selected the literature and input the data. ZW and DW checked the data and assessed the quality of the included trials. HX and YQ performed the statistical analysis and wrote the manuscript. ML checked the writing and language. WM and HL checked the statistical results. All authors approved the final version of the manuscript.

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Declarations

Competing interests

The authors declare that they have no competing interests.

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References

1. Chen Q, Zhang M, Zheng S, Tong Y, Tan Y. Therapeutic progress in relapsed/refractory multiple myeloma. Ann Hematol 2024;103(6):1833–1841. (In eng). https://doi.org/10.1007/s00277-024-05730-y.
2. Sanchez L, Wang Y, Siegel DS, Wang ML. Daratumumab: a first-in-class CD38 monoclonal antibody for the treatment of multiple myeloma. J Hematol Oncol. 2016;9(1):51. https://doi.org/10.1186/s13045-016-0283-0.
3. Nooka AK, Kaufman JL, Hofmeister CC, et al. Daratumumab in multiple myeloma. Cancer. 2019;125(14):2364–82.
4. Gozzetti A, Ciofini S, Simoncelli M, et al. Anti CD38 monoclonal antibodies for multiple myeloma treatment. Hum Vaccin Immunother. 2022;18(5):2052658. https://doi.org/10.1080/21645515.2022.2052658.

5. NCCN Clinical Practice Guidelines in Oncology: multiple myeloma (Version 3.2023). (https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf).
6. Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2021;32(3):309–22. https://doi.org/10.1016/j.annonc.2020.11.014.
7. Chari A, Kaufman JL, Laubach JP, et al. Daratumumab Plus Lenalidomide, Bortezomib, and Dexamethasone (D-RVd) in Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM) Patients (Pts): Final Analysis of Griffin Among Clinically Relevant Subgroups. Blood. 2022;140(Supplement 1):7278–81. https://doi.org/10.1182/blood-2022-162339.
8. Mateos M-V, Cavo M, Blade J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. Lancet. 2020;395(10218):132–41. https://doi.org/10.1016/s0140-6736(19)32956-3.
9. Basu S, Kumar SK, Moreau P, et al. Daratumumab plus Lenalidomide/dexamethasone in transplant-ineligible patients with newly diagnosed multiple myeloma: MAIA update. Br J Haematol. 2023;201:17–8. https://doi.org/10.1111/bjh.18718.
10. Hematologists Society of Chinese Medical Doctor Association HSoCMA. Guidelines for the diagnosis and management of multiple myeloma in China (2022 revision). Zhonghua nei ke za zhi 2022;61(5).
11. Clinical Practice Guideline-MULTIPLE MYELOM. (https://myeloma.org.au/wp-content/uploads/2022/09/MSAG_Myeloma-Clinical-Practice-Guideline-2022_Final-1.pdf).
12. Chaimani. A, Caldwell. DM, Li. T, Higgins. JP, Salanti. G. Undertaking network meta-analyses. In: JPT. H, J. T, J. C, et al., eds. Cochrane Handbook for Systematic Reviews of Interventions version 6.5 (updated August 2024): Cochrane; 2024.
13. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777–84. https://doi.org/10.7326/M14-2385.
14. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16. https://doi.org/10.1186/1745-6215-8-16.
15. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366: l4898. https://doi.org/10.1136/bmj.l4898.
16. Rücker G, Petropoulou M, Schwarzer G. Network meta-analysis of multicomponent interventions. Biometrical journal Biometrische Zeitschrift. 2020;62(3):808–21. https://doi.org/10.1002/bimj.201800167.
17. Shim SR, Kim S-J, Lee J, Rücker G. Network meta-analysis: application and practice using R software. Epidemiology and health. 2019;41: e2019013. https://doi.org/10.4178/epih.e2019013.
18. Rücker G, Schmitz S, Schwarzer G. Component network meta-analysis compared to a matching method in a disconnected network: A case study. Biom J. 2021;63(2):447–61.
19. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol. 2015;15:58. https://doi.org/10.1186/s12874-015-0060-8.
20. Harbord RM, Egger M, Sterne JAC. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Stat Med. 2006;25(20):3443–57. https://doi.org/10.1002/sim.2380.
21. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet. 2019;394(10192):29–38. https://doi.org/10.1016/S0140-6736(19)31240-1.
22. Mateos MV, Oriol A, Martínez-López J, et al. GEM2005 trial update comparing VMP/VTP as induction in elderly multiple myeloma patients: do we still need alkylators? Blood. 2014;124(12):1887–93. https://doi.org/10.1182/blood-2014-05-573733.
23. Niesvizky R, Flinn I, Rifkin RM, et al. Efficacy and safety of three bortezomib-based induction and maintenance regimens in previously untreated, transplant-ineligible multiple myeloma (MM) patients (Pts): final results from the randomized, phase 3b, US community-based UPFRONT study (NCT00507416). Blood. 2013;122(21):1966. https://doi.org/10.1182/blood.v122.21.1966.1966.
24. Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2024;390(4):301–13. https://doi.org/10.1056/NEJMoa2312054.
25. Kumar SK, Jacobus SJ, Cohen AD, et al. Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol. 2020;21(10):1317–30. https://doi.org/10.1016/S1470-2045(20)30452-6.
26. Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017;389(10068):519–27. https://doi.org/10.1016/s0140-6736(16)31594-x.
27. Zonder JA, Crowley J, Hussein MA, et al. Lenalidomide and high-dose dexamethasone compared with dexamethasone as initial therapy for multiple myeloma: a randomized Southwest Oncology Group trial (S0232). Blood. 2010;116(26):5838–41. https://doi.org/10.1182/blood-2010-08-303487.
28. Fu W, Bang S-M, Huang H, et al. Bortezomib, melphalan, and prednisone with or without daratumumab in transplant-ineligible Asian patients with newly diagnosed multiple myeloma: the phase 3 OCTANS study. Clin Lymphoma Myeloma Leuk. 2023;23(6):446–455.e4. https://doi.org/10.1016/j.clml.2023.02.009.
29. Kumar S, Flinn I, Richardson PG, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood. 2012;119(19):4375–82. https://doi.org/10.1182/blood-2011-11-395749.
30. Moreau P, Hulin C, Macro M, et al. VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial. Blood. 2016;127(21):2569–74. https://doi.org/10.1182/blood-2016-01-693580.
31. Mateos M-V, Paiva B, Cedena Romero MT, et al. GEM2017FIT trial: induction therapy with bortezomib-melphalan and prednisone (VMP) followed by lenalidomide and dexamethasone (Rd) versus carfilzomib, lenalidomide and dexamethasone (KRd) plus/minus daratumumab (D), 18 cycles, followed by consolidation and maintenance therapy with lenalidomide and daratumumab: phase III, multicenter, randomized trial for elderly fit newly diagnosed multiple myeloma (NDMM) patients aged between 65 and 80 years. Blood2023:209–209.
32. Mollee P, Reynolds J, Janowski W, et al. A randomized study of bortezomib, cyclophosphamide and dexamethasone induction (VCD) versus VCD and daratumumab induction followed by daratumumab maintenance (VCDD) for the initial treatment of transplant-ineligible patients with multiple myeloma (AMaRC 03–16). Blood2021:2728–2728.
33. Kumar L, Chellapuram SK, Sahoo R, Gupta R. VRd versus VCd as induction therapy for newly diagnosed multiple myeloma: a phase III, randomized study. Clin Lymphoma Myeloma Leuk. 2019;19(10): e361. https://doi.org/10.1016/j.clml.2019.09.597.
34. Mookerjee A, Gupta R, Jasrotia S, et al. Bortezomib, lenalidomide and low-dose dexamethasone (VRD) versus lenalidomide and low-dose dexamethasone (Ld) for newly-diagnosed multiple myeloma- a randomized phase III study. Blood. 2017;130(Supplement 1):906–906. https://doi.org/10.1016/S2352-3026(23)00366-6.
35. Mai EK, Goldschmid H, Miah K, et al. Elotuzumab, lenalidomide, bortezomib, dexamethasone, and autologous haematopoietic stem-cell transplantation for newly diagnosed multiple myeloma (GMMG-HD6): results from a randomised, phase 3 trial. The Lancet Haematology. 2024;11(2):e101–13. https://doi.org/10.1016/S2352-3026(23)00366-6.
36. Grosicki S, Simonova M, Spicka I, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. Lancet (London, England). 2020;396(10262):1563–73. https://doi.org/10.1016/S0140-6736(20)32292-3.
37. Dimopoulos MA, Oriol A, Nahi H, et al. Overall survival with daratumumab, lenalidomide, and dexamethasone in previously treated multiple myeloma (POLLUX): a randomized, open-label, phase III trial. Journal

of clinical oncology : official journal of the American Society of Clinical Oncology. 2023;41(8):1590–9. https://doi.org/10.1200/JCO.22.00940.
38. Dimopoulos M, Quach H, Mateos M-V, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. Lancet (London, England). 2020;396(10245):186–97. https://doi.org/10.1016/S0140-6736(20)30734-0.
39. Dimopoulos MA, Terpos E, Boccadoro M, et al. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. Lancet Oncol. 2021;22(6):801–12. https://doi.org/10.1016/S1470-2045(21)00128-5.
40. Sekine L, Ziegelmann PK, Manica D, et al. Upfront treatment for newly diagnosed transplant-ineligible multiple myeloma patients: a systematic review and network meta-analysis of 14,533 patients over 29 randomized clinical trials. Crit Rev Oncol Hematol. 2019;143:102–16. https://doi.org/10.1016/j.critrevonc.2019.07.001.
41. Wang J, Arroyo-Suarez R, Dasari S, Sekaran K, Tse W. Early versus late response to daratumumab-based triplet therapies in patients with multiple myeloma: a pooled analysis of trials POLLUX. CASTOR and MAIA Leukemia & lymphoma. 2022;63(7):1669–77. https://doi.org/10.1080/10428194.2022.2038376.
42. Chong LL, Soon YY, Soekojo CY, Ooi M, Chng WJ, de Mel S. Daratumumab-based induction therapy for multiple myeloma: a systematic review and meta-analysis. Crit Rev Oncol Hematol. 2021;159: 103211. https://doi.org/10.1016/j.critrevonc.2020.103211.
43. Langer P, John L, Monsef I, Scheid C, Piechotta V, Skoetz N. Daratumumab and antineoplastic therapy versus antineoplastic therapy only for adults with newly diagnosed multiple myeloma ineligible for transplant. Cochrane Database Syst Rev 2024;5(5):Cd013595. (In eng). https://doi.org/10.1002/14651858.CD013595.pub2.
44. Welton NJ, Caldwell DM, Adamopoulos E, Vedhara K. Mixed treatment comparison meta-analysis of complex interventions: psychological interventions in coronary heart disease. Am J Epidemiol. 2009;169(9):1158–65. https://doi.org/10.1093/aje/kwp014.
45. Overdijk MB, Verploegen S, Bögels M, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. mAbs 2015;7(2):311--21. https://doi.org/10.1080/19420862.2015.1007813.
46. Krejcik J, Casneuf T, Nijhof IS, et al. Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. Blood. 2016;128(3):384–94. https://doi.org/10.1182/blood-2015-12-687749.
47. Swan D, Gurney M, Krawczyk J, Ryan AE, O'Dwyer M. Beyond DNA damage: exploring the immunomodulatory effects of cyclophosphamide in multiple myeloma. Hemasphere. 2020;4(2): e350. https://doi.org/10.1097/hs9.0000000000000350.
48. Santos Ads, Santos HHdM, Salvino MA, et al. Immune Profiling Evaluation of newly diagnose multiple myeloma (NDMM) transplant eligible (TE) patients treated with daratumumab, cyclophosphamide, thalidomide and dexamethasone. Preliminary Results. Blood 2020;136:3–4. https://doi.org/10.1182/blood-2020-141438.
49. Naicker SD, Feerick CL, Lynch K, et al. Cyclophosphamide alters the tumor cell secretome to potentiate the anti-myeloma activity of daratumumab through augmentation of macrophage-mediated antibody dependent cellular phagocytosis. Oncoimmunology. 2021;10(1):1859263. https://doi.org/10.1080/2162402X.2020.1859263.
50. Kim Y, Schmidt-Wolf IGH. Lenalidomide in multiple myeloma. Expert Rev Anticancer Ther. 2015;15(5):491–7. https://doi.org/10.1586/14737140.2015.1033407.
51. van der Veer MS, de Weers M, van Kessel B, et al. Towards effective immunotherapy of myeloma: enhanced elimination of myeloma cells by combination of lenalidomide with the human CD38 monoclonal antibody daratumumab. Haematologica. 2011;96(2):284–90. https://doi.org/10.3324/haematol.2010.030759.
52. Casneuf T, Adams rHC, van de Donk NWCJ, et al. Deep immune profiling of patients treated with lenalidomide and dexamethasone with or without daratumumab. Leukemia 2021;35(2):573--584. https://doi.org/10.1038/s41375-020-0855-4.
53. Thangaraj JL, Jung SH, Vo MC, et al. Expanded natural killer cells potentiate the antimyeloma activity of daratumumab, lenalidomide, and dexamethasone in a myeloma xenograft model. Cancer Immunol Immunother. 2023;72(5):1233–46. https://doi.org/10.1007/s00262-022-03322-1.

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