Received: 15 December 2020 | Accepted: 12 January 2021

DOI: 10.1002/prp2.797

REVIEW

Daratumumab provides a survival benefit in relapsed and refractory Multiple Myeloma, independent of baseline clinical characteristics: A meta-analysis

Congcong Cao[1] | Xin Zhou[2] | Qun Ma[3]

[1]Hematology Department, The People's Hospital of Pingyi County, Linyi, 273300, Shandong, China

[2]General Surgery Department, Feixian People's Hospital, Linyi, China

[3]Radiology Department, The People's Hospital of Pingyi County, Linyi, China

Correspondence
Congcong Cao, Hematology Department, The People's Hospital of Pingyi County, Linyi, 273300, Shandong, China.
Email: pycccmac@163.com

Abstract

Daratumumab was approved in patients with relapsed or refractory multiple myeloma (MM) who previously received proteasome inhibitors or immunomodulatory drugs. However, the efficacy and safety of the addition of daratumumab in subpopulations of patients with relapsed or refractory MM is still unknown. We systematically searched MEDLINE, EMBASE, and Cochrane for randomized controlled trials (inception to September 2020). All phase 3 randomized controlled trials (RCTs) which were conducted in patients with relapsed or refractory MM and compared the efficacy or safety with the addition of daratumumab versus control were adopted. Three studies including 1497 patients met our criteria. The addition of daratumumab increased the rates of overall response (RR 1.21, 95% CI 1.15–1.28, $p < .001$), complete response or better (RR 2.43, 95% CI 2.00–2.96, $p < .001$), very good partial response or better (RR 1.63, 95% CI 1.48–1.80, $p < .001$) compared with those with control. No clear evidence of heterogeneity was found in comparisons of progression-free survival obtained from subsets of studies grouped by the age of participant, ISS disease stage, type of measurable MM, the level of baseline renal function, cytogenetic profile. The results showed progression-free survival benefit was consistent between the treatment groups regarding previous clinical therapy information. Patients receiving daratumumab had higher risks of lymphopenia and infusion-related reactions of any grade and grade 3 or 4. In conclusions, this study provides a clear proof of beneficial effects of daratumumab-based therapy in patients with relapsed or refractory MM with an acceptable safety profile. The progression-free survival benefit was consistent regardless of patient's baseline characteristics or previous therapy agents.

KEYWORDS
daratumumab, meta-analysis, phase 3 randomized controlled trials, relapsed or refractory MM

Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration; MeSH, Medical Subject Headings; MM, multiple myeloma; RCTs, randomized controlled trials.

1 | INTRODUCTION

Multiple myeloma (MM) is a hematological malignancy in which an abnormal B-cell clone produces high levels of non-functional monoclonal immunoglobulins, organ dysfunction, and death.[1] Despite the advancements of proteasome inhibitors, immunomodulatory agents and autologous transplantation in the treatment of MM, some patients with MM fail to respond to these first-line therapies which result the disease becomes refractory.[2–4] Relapse can even occur in patients with complete response to standard therapies. Therefore, several novel pharmacological treatments for relapsed or refractory MM have been developed.

Daratumumab, a human IgGκ monoclonal antibody targeting CD38, plays an important role in direct antimyeloma effects and immune-mediated actions.[5,6] Daratumumab has been combined with proteasome inhibitors or immunomodulatory drug for the treatment of relapsed or refractory MM.[6–8] Several randomized controlled trials (RCTs) have observed the clinical benefits of combining daratumumab with standards of care in patients with relapsed or refractory MM.[9–11] Daratumumab was approved in 2015 by the Food and Drug Administration (FDA) in USA and in 2016 by the European Medicines Agency (EMA) in patients with relapsed or refractory MM who had previously received proteasome inhibitors or immunomodulatory drugs.[12,13] However, we could not determine whether the addition of daratumumab confers an overall survival benefit in patients with older age, higher ISS disease stage, or those received previous first-line agents' therapy. Individual trials were not significantly powered to evaluate the efficacy of daratumumab across various subgroups.

Therefore, for the first time, we conducted this meta-analysis to assess the efficacy and safety of the addition of daratumumab in subpopulations of patients with relapsed or refractory MM after one to two prior treatment regimes.

2 | MATERIALS AND METHODS

2.1 | Search strategy

Three databases of MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) were extensively searched by using related keywords. The text words and Medical Subject Headings (MeSH) of all spellings of known "daratumumab," "CD38," "randomized controlled trials (RCTs)," "randomized study," "Phase 3," "relapsed MM," "refractory MM" were used as search terms covering the entire time span of three databases. The language was restricted to English. This study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[14]

2.2 | Study selection and inclusion criteria

The studies conducted in patients with relapsed or refractory MM that evaluated the efficacy or safety of the addition of daratumumab were adopted. The inclusion criteria of studies were defined as follows: (1) the intervention was the addition of daratumumab; (2) studies aiming at relapsed or refractory MM; (3) studies that reported outcomes, including overall response, complete response or better, very good partial response or better or adverse effects of daratumumab. Criteria for overall response were defined as the patients who achieved partial response or better, according to International Myeloma Working Group criteria, during or after trial treatment. Complete response was defined by negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and less than 5% plasma cells in bone marrow. A very good partial response or better was defined as below: serum and urine M-component detectable by immunofixation but not on electrophoresis, or ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 h or complete response, during or after the trial treatment; (4) study design was RCT. Of these studies, we excluded studies due to lack of available data.

2.3 | Data extraction and quality of evidence

Two investigators reviewed abstracts and full-text articles of relevant studies. Subsequently, they extracted the information of demographic and disease characteristics, clinical therapy information, survival outcomes, and adverse events independently with standard data extraction forms. The demographic and disease characteristics details were as follows: patients age, gender, International Staging System (ISS), cytogenetic risk group, Eastern Cooperative Oncology Group (ECOG), baseline creatinine clearance (Ccr), time since initial diagnosis to randomization, type of measurable disease and follow-up period. A third reviewer checked and confirmed the accuracy of the data. Disagreements were settled through consultation with a third reviewer. The risk of bias of studies was assessed based on the Cochrane Collaboration's tool for assessing risk of bias and applied ratings of high, unclear, or low.[15]

2.4 | Statistical analysis

We calculated relative risk (RR) and 95% confidence interval (CI) for categorical variables. The random-effects model was applied to these analyses. We analyzed heterogeneity by I^2 statistic to describe the percentage of variability. Subgroup analysis was performed to determine the effect point of intervention measures. Begg Funnel plot was performed to assess potential publication bias. The results were considered significant with two-sided $p < .05$. STATA 12.0 software was used to conduct the meta-analysis.

3 | RESULTS

Overall, we identified 303 articles, eventually, three studies relevant to the addition of daratumumab in 1497 patients with

relapsed or refractory MM were included (Figure 1). Baseline characteristics of included studies were given in Table 1. The papers were published from 2016 to 2020. The mean age was 64 years old and the male percentage was 54.6%–59.5%. The percentage of ISS stage III ranged from 18% to 23.5%. The patients with high-risk cytogenetic profile ranged from 14% to 22.7%. The majority of patients belonged to ECOG 0–1 and with Ccr >60 ml/min/1.73 m^2. The time since initial diagnosis to randomization was 34.6–48 months, and the period of follow-up was 7.4–44.3 months. The patients' number in each study ranged from 466 to 557. Patients in the intervention group were treated with daratumumab and dexamethasone in combination with carfilzomib, bortezomib, or lenalidomide. Patients in the active control group were treated with dexamethasone in combination with carfilzomib, bortezomib, or lenalidomide. Intravenous daratumumab at a dose of 16 mg/kg of body weight was administered in three studies.

Table 2 presented previous clinical therapy information of included studies. The median number of previous lines of therapy was 2 in two studies and 1 in one study. The proportion of patients with a previous stem cell transplant ranged from 49% to 63.6% and that with previous proteasome inhibitor exposure was 67.3%–93%. Immunomodulatory drug was administrated in 55%–80.2% patients and 90%–95% patients received alkylating agents.

3.1 | Quality assessment

We evaluated the quality of each study by Cochrane risk of bias tool, including sequence generation, allocation concealment, performance bias, detection bias, incomplete outcome data, selective reporting, and other possible sources of bias. The summary of the risk of bias is presented in Figure 2.

3.2 | Overall response

The results of overall response were offered in three studies. Overall response was seen in 723 (86.8%) of 833 patients in the daratumumab group and in 474 (71.4%) of the 664 patients in the active control group. The addition of daratumumab increased overall response rate (RR 1.21, 95% CI 1.15–1.28, $p < .001$) compared with active control group with no evidence of heterogeneity ($I^2 = 45.3\%$, $p = .16$, Figure 3).

3.3 | Complete response or better

Complete response or better was achieved by 294 (35.3%) of 833 patients in the daratumumab group and 101 (15.2%) of 664 patients in the active control group. The rate of complete response or better

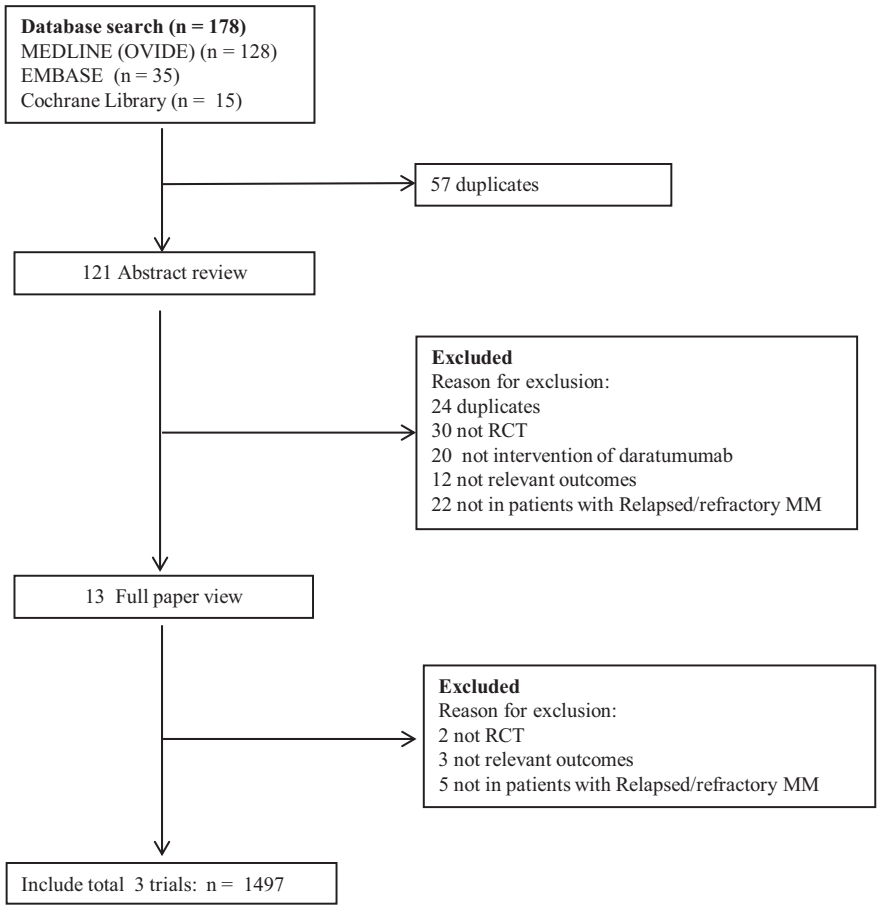

FIGURE 1 Process for identifying studies eligible for the meta-analysis

TABLE 1 Baseline characteristics of included studies

Study	Country	Characteristics of Patients treated with daratumumab/control												
		Treatment	Dosage	Placebo	Age (year)	Male (%)	White (%)	ISS stage (I, II, III %)	Cytogenetic risk group (Standard and high risk, %)	ECOG (0 and 1, 2%)	Baseline creatinine clearance >60 ml/min/1.73 m^2 (%)	Time since initial diagnosis to randomization (months)	Type of measurable disease (IgG%)	Follow up (months)	No. of patients
CANDOR	USA	Daratumumab + Carfilzomib + dexamethasone	16 mg/kg weekly	Carfilzomib + dexamethasone	64/64.5	57/57	73/75	47, 33, 20/51, 31, 18	33, 15/34, 17	95, 5/95, 5	87.8/82.5[a] (>=50)	37.5/34.6	NA	17	312/154
CASTOR	Italy	Daratumumab + bortezomib + dexamethasone	16 mg/kg weekly	Bortezomib + dexamethasone	64/64	54.6/59.5	72.4/65.7	39, 37.5, 23.5/38.9, 40.5, 20.6	77.3, 22.7/78.7, 21.3	NA	76.5/70.0	46.4/44.6	49.8/55.9	7.4	240/234
POLLUX	Canada	Daratumumab + lenalidomide + dexamethasone	16 mg/kg weekly	Lenalidomide + dexamethasone	65/65	NA	72.4/65.7	47.9, 32.5, 19.6/49.5, 30.4, 20.1	84.6, 15.4/83.4, 16.6	96.2, 3.8/ 94.7, 5.3	71.3/75.8	42/48	52.7/55.8	44.3	281/276

[a]Baseline creatinine clearance ≥50 ml/min.

was higher in the daratumumab group than in the active control group (RR 2.43, 95% CI 2.00–2.96, $p < .001$) with no evidence of heterogeneity ($I^2 = 0\%$, $p = .77$, Figure 4).

3.4 | Very good partial response or better

A total of 584 (70.1%) of 833 patients in the daratumumab group and 279 (42.0%) of 664 patients in the active control group had very good partial response or better. Daratumumab treated patients showed a higher rate of very good partial response or better than those patients with control treated (RR 1.63, 95% CI 1.48–1.80, $p < .001$; Figure 5) with an evidence of heterogeneity ($I^2 = 66.6\%$, $p = .05$).

3.5 | Subgroup analysis of progression-free survival

We explored the questions whether the addition of daratumumab confers a progression-free survival benefit in patients with different baseline demographic and disease characteristics, or those received previous first-line agents' therapy. Subgroup analysis was performed by patient's baseline demographic and disease characteristics (Figure 6). No clear evidence of heterogeneity was found in comparisons of progression-free survival obtained from subsets of studies grouped by the age of participant (> or ≤65), ISS disease stage (I, II, III), type of measurable MM (IgG or not), baseline renal function (Ccr >or ≤60 ml/min/1.73 m^2), cytogenetic profile (high risk or standard risk).

Subgroup analysis by previous clinical therapy information, including number of previous lines of therapy (yes or no), prior lenalidomide treatment (yes or no), prior proteasome inhibitor (yes or no), previous immunomodulatory drug exposure (yes or no), refractory to PI (yes or no), refractory to immunomodulatory drug (yes or no), refractory to last line of prior therapy (yes or no) also was conducted. The results showed progression-free survival benefit was consistent between the treatment groups regarding any of the subgroups (Figure 7).

3.6 | Adverse events

Common hematological and non-hematological treatment-emergent all-grade adverse events were presented in Table 3. Patients receiving daratumumab had higher incidences of lymphopenia (RR 1.65, 95% CI 1.11–2.47), peripheral sensory neuropathy (1.33, 1.02–1.73), upper respiratory tract infection (1.40, 1.12–1.74), diarrhea (1.52, 1.23–1.80), pneumonia (1.34, 1.02–1.77), dyspnea (1.46, 1.11–1.92), hypertension (1.59, 1.14–2.22), and cough (1.75, 1.30–2.36). The common grade 3 or 4 adverse events were listed in Table 4. Only the incidences of lymphopenia (1.67, 1.05–2.62), diarrhea (2.63, 1.46–4.73), fatigue (1.94, 1.16–3.22), dyspnea (2.75, 1.72–4.38) were higher in the daratumumab group than in the control group.

TABLE 2 Previous clinical therapy characteristics of included studies

Study	Previous therapy in daratumumab/control group								
	Previous lines of therapy (no.)	Transplant (%)	CD38 antibody therapy (%)	Proteasome inhibitor (%)	Immunomodulatory drug (%)	Bortezomib (%)	Lenalidomide (%)	Alkylating agent (%)	Disease refractory to last line of therapy (%)
CANDOR 2020	2/2	63/49	<1/0	93/90	66/71	92/87	39/48	NA	NA
CASTOR 2016	2/2	62.2/60.3	NA	67.3/69.6	71.3/80.2	NA	NA	95.6/90.7	30.3/34.4
POLLUX 2020	1/1	62.9/63.6	NA	85.7/85.5	55.5/55.1	NA	NA	93.7/95.4	28/26.9

A growing trend was not observed for grade 3 or 4 with respect to peripheral sensory neuropathy, upper respiratory tract infection, and diarrhea.

3.7 | Risk of bias

Statistical testing showed no evidence of publication bias for overall response (Begg's test $z = 0.52$, $p = .60$), which was displayed in Figure 8.

4 | DISCUSSION

To our knowledge, this is the first meta-analysis in patients with relapsed or refractory MM to evaluate the efficacy and safety of daratumumab-based therapy. Three studies with 1497 patients with MM after one to two prior treatment lines were included. The results confirmed that the addition of daratumumab had shown superior efficacy over control group, which significantly increased response rate. In this study, we conducted abundant subgroup analyses based on 12 pre-specified factors and validated that the efficacy was consistent with any of the subgroups of different population that were defined according to baseline characteristics or previous therapy agents. The addition of daratumumab was associated with a higher incidence of adverse events of any grade and Grade 3 or 4, primarily lymphopenia and infusion-related reactions. Daratumumab-treated patients were less likely to experience fatal adverse events. These results indicated daratumumab is an effective and relative safe treatment in patients with relapsed or refractory MM.

A growing body of evidence indicated that daratumumab-based regimen can overcome resistance or refractoriness to early-line treatment. In the current study, the rate of complete response or better was almost 2.5 times as high for patients with daratumumab compared with those with the standard regimen. The rates of patients achieving overall response and very good partial response or better in daratumumab group were higher than in control group. It showed an additive benefit of daratumumab in combination with proteasome inhibitors or immunomodulatory drugs and dexamethasone in the context of relapsed or refractory MM.

Recently, various daratumumab-based triplet regimens have received regulatory approval.[11,16–19] However, the survival benefit of this regimen in various subgroups is undefined. A total of 12 subgroup analyses stratified by baseline characteristics and prior lines of therapy were done in these studies. Consistent with effective outcomes in the overall population of MM, the progression-free survival benefit was not modified by the pre-specified subgroups. The treatment benefit that was associated with daratumumab was similar in patients <65 years of age or older, those with ISS stage I, II, or III, those with type IgG MM or non-IgG, those with CCr >60 ml/min or <60 ml/min, and those with higher cytogenetic risk or standard risk. Considering the consistent progression-free survival outcomes in patients with above subgroups, we believe that the outcomes

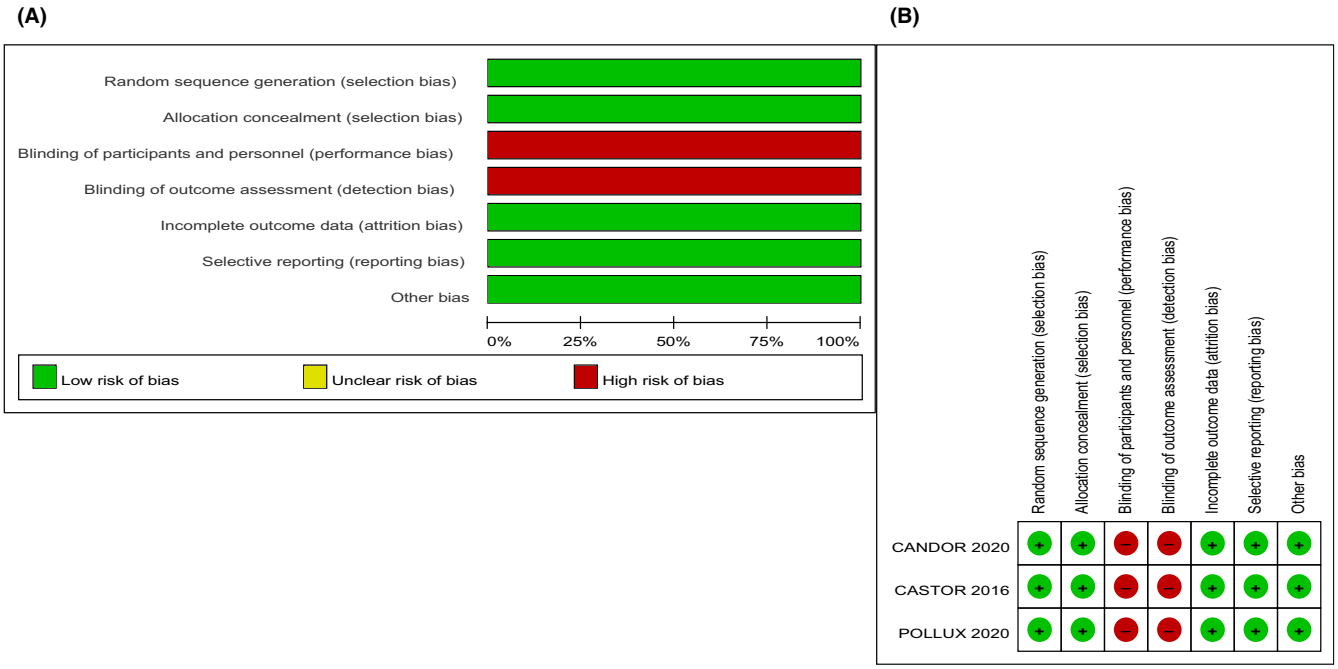

FIGURE 2 Risk of bias graph (A) and risk of bias summary (B)

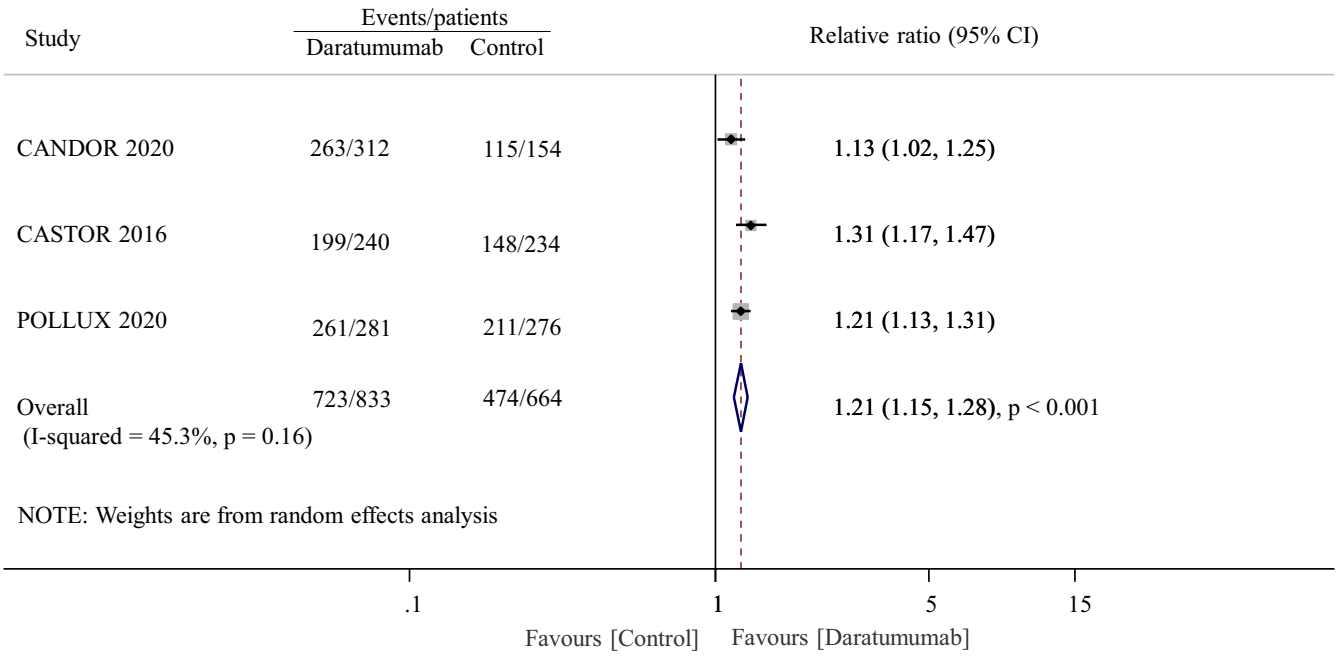

FIGURE 3 Effect of daratumumab on overall response in patients with relapsed/refractory MM

were not influenced by the difference of patients' demographic and disease characteristics.

Furthermore, the treatment effect of daratumumab was consistent regardless of number of prior lines of therapy (one or two), previous lenalidomide exposure, previous proteasome inhibitor exposure, previous immunomodulatory drug exposure, refractoriness to proteasome inhibitor, refractoriness to immunomodulatory drug, or refractoriness to last line of prior therapy, indicating daratumumab-based regimen could provide therapeutic benefit even in those with one or two previous lines of therapy and those with previous proteasome inhibitors and immunomodulatory agents.[20,21] Daratumumab plus proteasome inhibitors or immunomodulatory drugs and dexamethasone enhance direct cytotoxicity on myeloma cells, inhibited the role of regulatory T cells, as well as enhanced the activity in CD4, CD8, and NK-cell subsets.[22–24] With increased use of frontline daratumumab therapy, more studies are

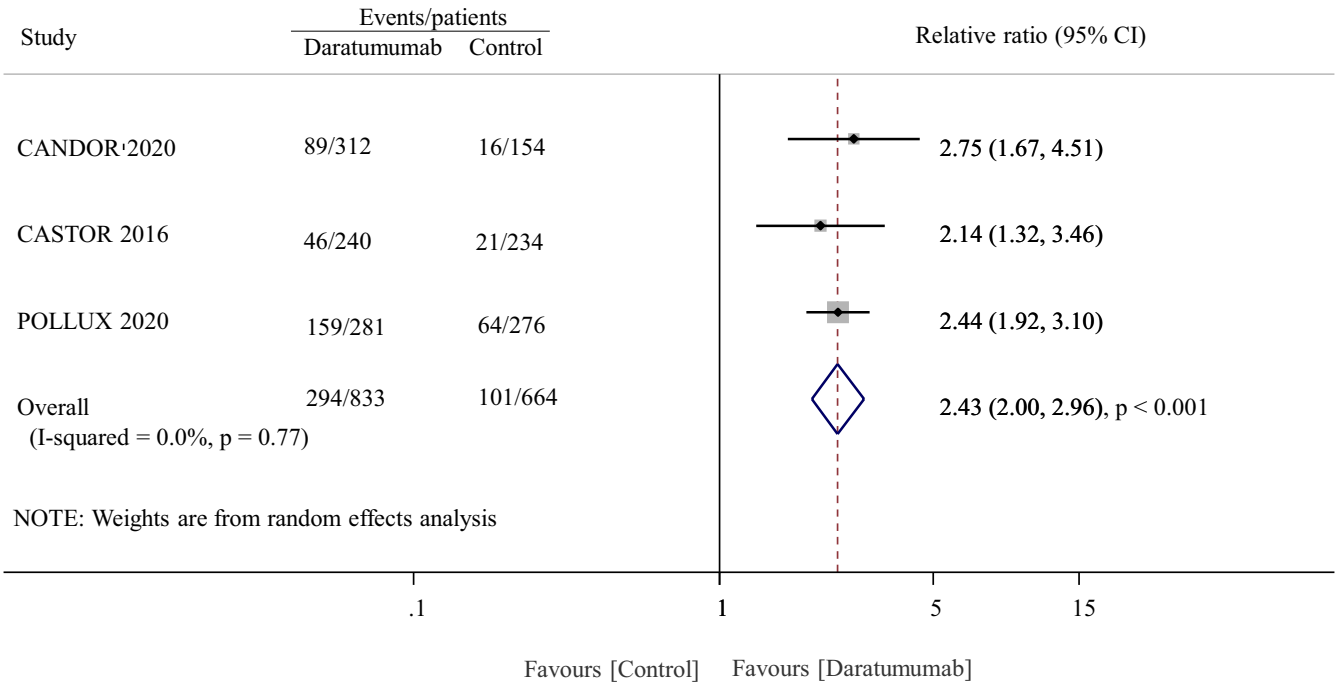

FIGURE 4 Effect of daratumumab on complete response or better in patients with relapsed/refractory MM

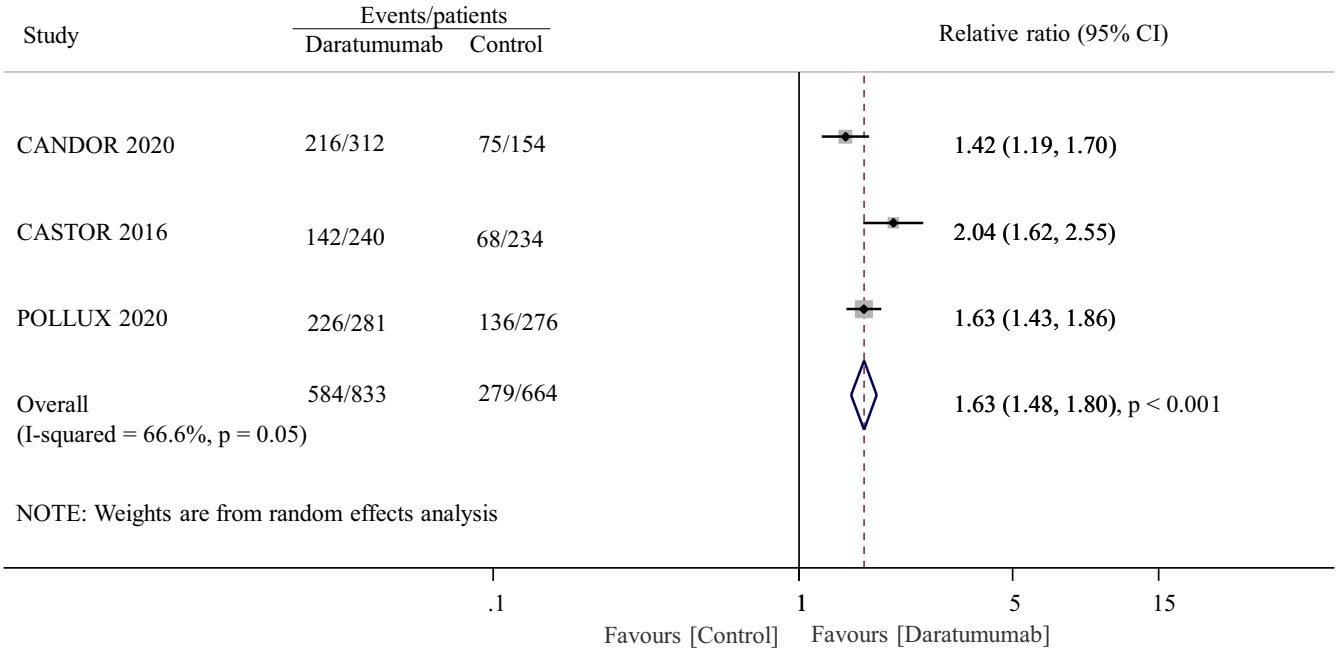

FIGURE 5 Effect of daratumumab on very good partial response or better in patients with relapsed/refractory MM

needed to clarify which triplet regimens would be better for patients who have been exposed to prior lines of therapy.

Safety is an important concern with daratumumab-based therapy in patients with relapsed or refractory MM.[25,26] The combination of daratumumab to proteasome inhibitors or immunomodulatory agents and dexamethasone was associated with a higher incidence of adverse events, primarily lymphopenia and infusion-related reactions.[27] The infection was the most disconcerting adverse event. Despite higher rates of lymphopenia in the daratumumab group, there was no difference of infection including upper respiratory tract infection and pneumonia of any grade and grade 3 or 4. The infusion-related reactions occurred primarily during the first infusion, most of the adverse events were clinically manageable. The number of adverse events of grade 3 or 4 was slightly higher in the daratumumab group than in the

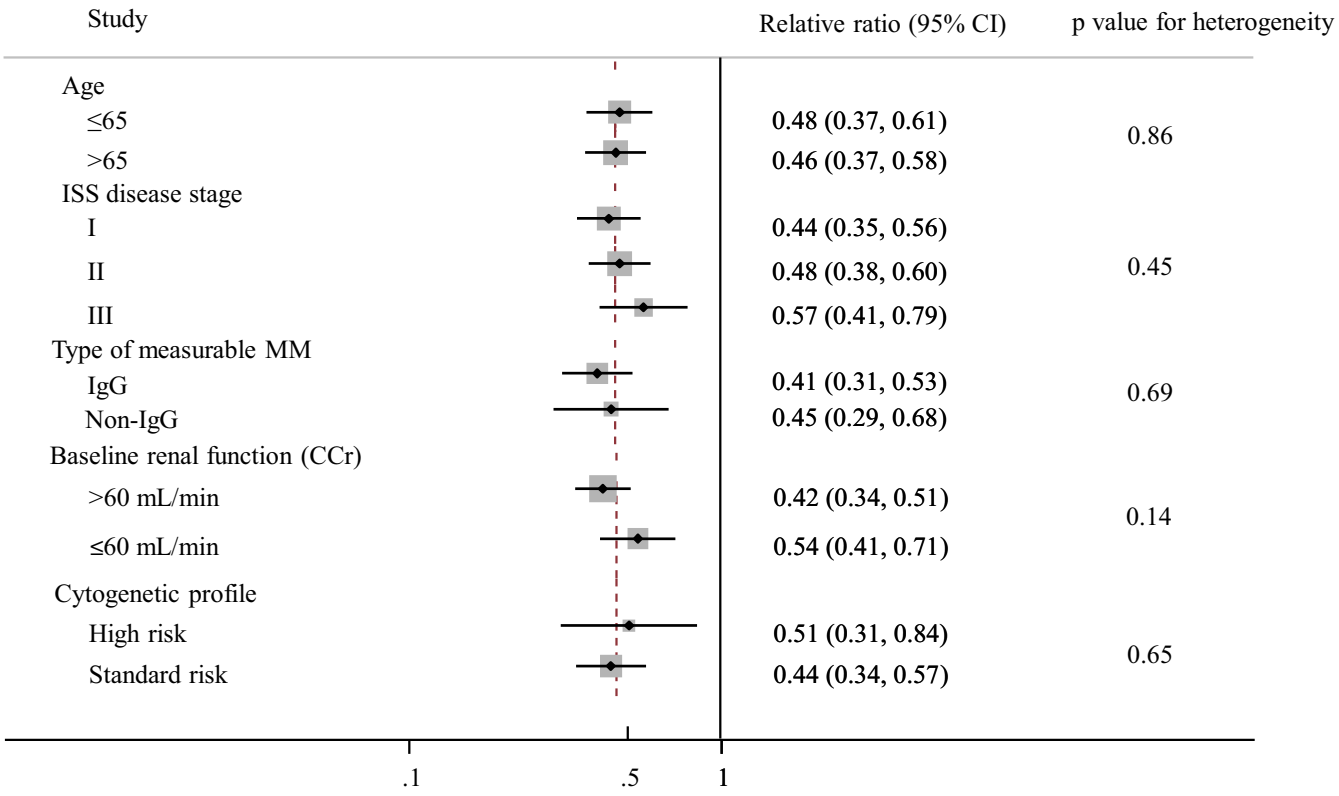

FIGURE 6 Analysis of basic characteristics for the effect of daratumumab for progression-free survival in subgroups

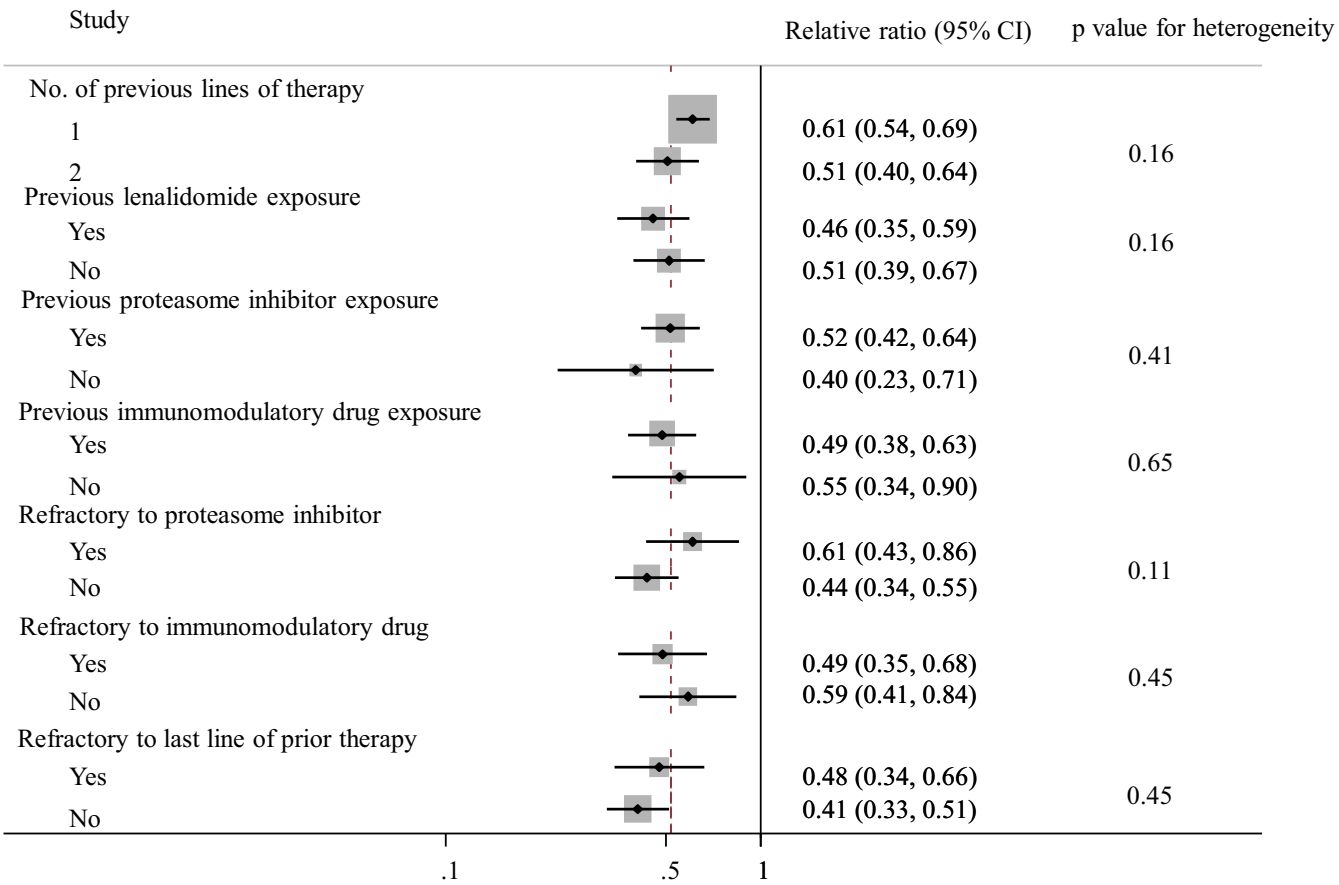

FIGURE 7 Analysis of previous therapy information for the effect of daratumumab for progression-free survival in subgroups

TABLE 3 Adverse events of any grade reported in the included studies

Adverse events	Daratumumab (n/834)	Control (n/671)	RR	95% CI	*p* value
Hematologic adverse events					
Neutropenia	265	172	1.24	0.99–1.54	.05
Thrombocytopenia	345	237	1.17	0.96–1.42	.11
Anemia	276	236	0.94	0.77–1.15	.56
Lymphopenia	78	38	1.65	1.11–2.47	.01
Nonhematologic adverse event					
Peripheral sensory neuropathy	168	102	1.33	1.02–1.73	.04
Upper respiratory tract infection	271	156	1.40	1.12–1.74	.00
Diarrhea	339	180	1.52	1.23–1.8	<.001
Fatigue	227	164	1.11	0.88–1.39	.35
Pneumonia	155	93	1.34	1.02–1.77	.04
Dyspnea	167	92	1.46	1.11–1.92	.01
Hypertension	115	58	1.59	1.14–2.22	.01
Asthenia	150	111	1.09	0.83–1.42	.54
Cough	157	72	1.75	1.30–2.36	<.001
Constipation	141	113	1.00	0.77–1.31	.99
Peripheral edema	107	66	1.30	0.94–1.80	.11
Pyrexia	111	67	1.33	0.97–1.83	.08
Nausea	82	51	1.29	0.89–1.86	.17

Abbreviation: RR, relative risk.

TABLE 4 Adverse events of grade 3 or 4 reported in the included studies

Adverse events	Daratumumab (n/834)	Control (n/671)	RR	95% CI	*p* value
Hematologic adverse events					
Neutropenia	214	136	1.27	0.99–1.61	.05
Thrombocytopenia	227	147	1.24	0.99–1.57	.07
Anemia	136	120	0.91	0.69–1.19	.49
Lymphopenia	60	29	1.67	1.05–2.62	.03
Nonhematologic adverse event					
Peripheral sensory neuropathy	14	16	0.70	0.34–1.45	.34
Upper respiratory tract infection	17	9	1.52	0.67–3.43	.31
Diarrhea	49	15	2.63	1.46–4.73	.001
Fatigue	53	22	1.94	1.16–3.22	.009
Pneumonia	104	64	1.31	0.94–1.81	.11
Dyspnea	82	24	2.75	1.72–4.38	<.001
Hypertension	26	12	1.74	0.87–3.48	.11
Asthenia	10	9	0.89	0.36–2.21	.81
Cough	1	2	0.40	0.04–4.45	.85
Constipation	4	2	1.61	0.29–8.81	.89
Peripheral edema	2	4	0.40	0.07–2.20	.28
Pyrexia	12	10	0.97	0.41–2.25	.99
Nausea	6	2	2.41	0.48–11.99	.45

Abbreviation: RR, relative risk.

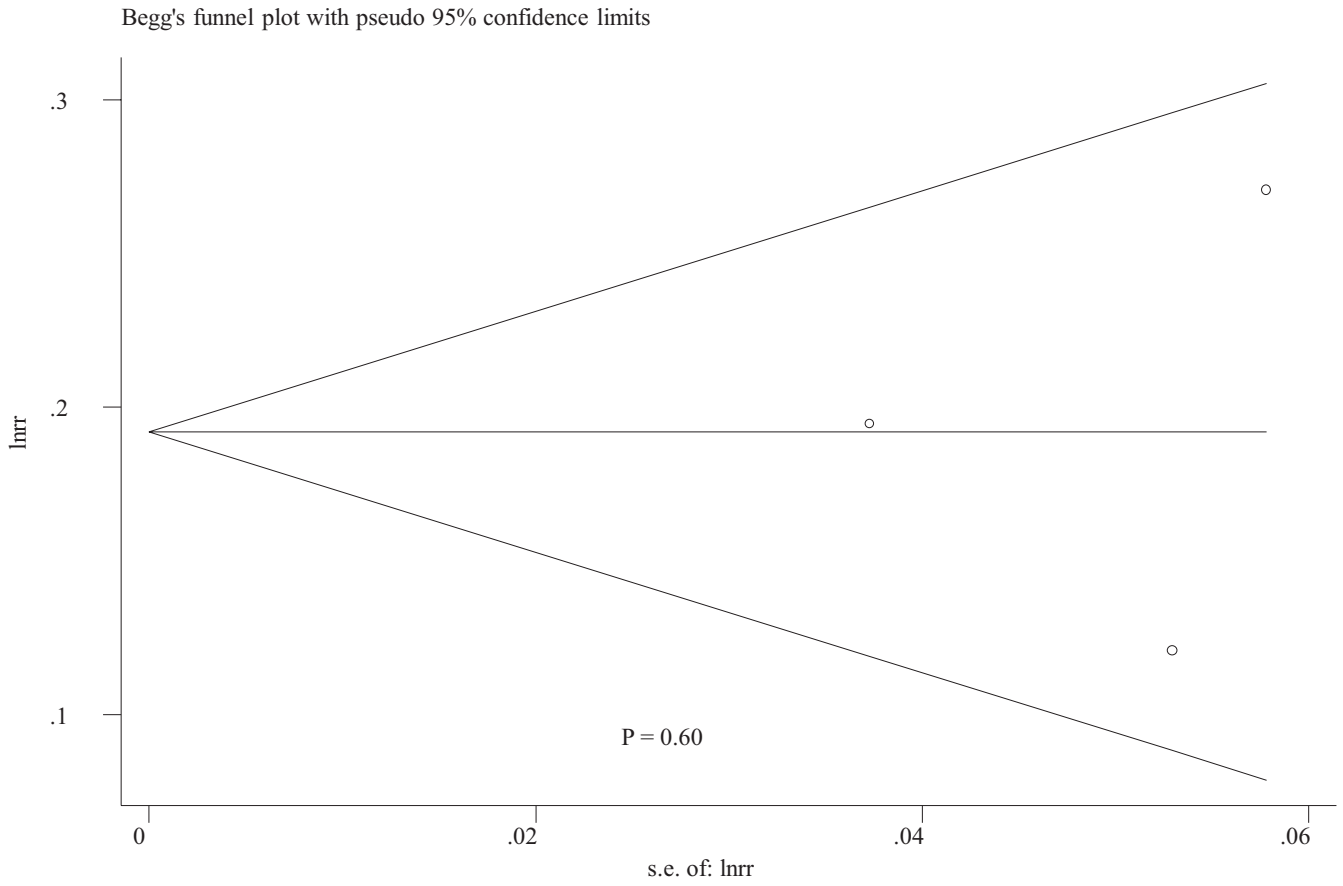

FIGURE 8 Forest plot for evaluation of publication bias for overall response

control group. Frequent monitoring which patients are likely to be most affected by various dararu mumab-based triplet regimens and timely management of side effects would be appropriate for patients to achieve maximum benefit with minimum risk.

The strength of this meta-analysis was the rigorous methodology we used. However, limitations must be highlighted. Firstly, we only included three phase 3 RCTs which compared daratumumab therapy for relapsed or refractory MM. Phase 1 and 2 RCTs, cohort studies, and observational studies that reported relevant outcomes with low quality of evidence were not included. Secondly, these three studies were all open-label design, which could have resulted in a higher proportion of patients dropping out early from treatment in the control group. Thirdly, the relatively short follow-up time of enrolled patients may prevent a definite conclusion on progression-free survival benefit obtained. The limitations of the current study mean that high-quality RCTs with a large sample size and a longer follow-up period are needed to elucidate the efficacy of daratumumab-based therapy in patients with relapsed or refractory MM.

5 | CONCLUSIONS

This study provides a clear proof of beneficial effects of daratumumab-based therapy in patients with relapsed or refractory MM with an acceptable safety profile. The progression-free survival benefit was consistent regardless of patient's baseline characteristics or previous therapy agents. These results suggest that daratumumab-based therapy should immediately initiate after failure of prior first- or second-line treatment.

ACKNOWLEDGMENTS

We thank all authors whose publications could be included in our meta-analysis.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Congcong Cao designed the study. Xin Zhou and Qun Ma searched and collected the data. Congcong Cao, Xin Zhou and Qun Ma analyzed the results. Congcong Cao drafted the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

DATA AVAILABILITY STATEMENT

All data generated and analyzed in the study are available from the corresponding author upon reasonable request.

ORCID

Congcong Cao https://orcid.org/0000-0002-2360-5868

REFERENCES

1. Palumbo A, Anderson K. Multiple myeloma. *N Engl J Med*. 2011;364:1046-1060.
2. Minnie SA, Hill GR. Immunotherapy of multiple myeloma. *J Clin Invest*. 2020;130:1565-1575.
3. Joshua DE, Bryant C, Dix C, Gibson J, Ho J. Biology and therapy of multiple myeloma. *Med J Aust*. 2019;210:375-380.
4. Moreau P, Attal M, Facon T. Frontline therapy of multiple myeloma. *Blood*. 2015;125:3076-3084.
5. Kuroda J, Nagoshi H, Shimura Y, Taniwaki M. Elotuzumab and daratumumab: emerging new monoclonal antibodies for multiple myeloma. *Expert Rev Anticancer Ther*. 2013;13:1081-1088.
6. 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;128:384-394.
7. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;375:1319-1331.
8. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. *N Engl J Med*. 2015;373:1207-1219.
9. 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*. 2020;396:186-197.
10. Bahlis NJ, Dimopoulos MA, White DJ, et al. Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of POLLUX, a randomized, open-label, phase 3 study. *Leukemia*. 2020;34:1875-1884.
11. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;375:754-766.
12. Bhatnagar V, Gormley NJ, Luo L, et al. FDA approval summary: daratumumab for treatment of multiple myeloma after one prior therapy. *Oncologist*. 2017;22:1347-1353.
13. Tzogani K, Penninga E, Schougaard Christiansen ML, et al. EMA review of daratumumab for the treatment of adult patients with multiple myeloma. *Oncologist*. 2018;23:594-602.
14. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
15. Chari A, Suvannasankha A, Fay JW, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. *Blood*. 2017;130:974-981.
16. Mateos M-V, Nahi H, Legiec W, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. *Lancet Haematol*. 2020;7:e370-e380.
17. Chari A, Martinez-Lopez J, Mateos M-V, et al. Daratumumab plus carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma. *Blood*. 2019;134:421-431.
18. Spencer A, Lentzsch S, Weisel K, et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. *Haematologica*. 2018;103:2079-2087.
19. Oostvogels R, Jak M, Raymakers R, Mous R, Minnema MC. Efficacy of retreatment with immunomodulatory drugs and proteasome inhibitors following daratumumab monotherapy in relapsed and refractory multiple myeloma patients. *Br J Haematol*. 2018;183:60-67.
20. Clemens PL, Yan X, Lokhorst HM, et al. Pharmacokinetics of daratumumab following intravenous infusion in relapsed or refractory multiple myeloma after prior proteasome inhibitor and immunomodulatory drug treatment. *Clin Pharmacokinet*. 2017;56:915-924.
21. Kitadate A, Kobayashi H, Abe Y, et al. Pre-treatment CD38-positive regulatory T cells affect the durable response to daratumumab in relapsed/refractory multiple myeloma patients. *Haematologica*. 2020;105:e37-e40.
22. Viola D, Dona A, Caserta E, et al. Daratumumab induces mechanisms of immune activation through $CD38^+$ NK cell targeting. *Leukemia*. 2020;105:e37-e40.
23. Mahaweni NM, Bos G, Mitsiades CS, Tilanus M, Wieten L. Daratumumab augments alloreactive natural killer cell cytotoxicity towards $CD38^+$ multiple myeloma cell lines in a biochemical context mimicking tumour microenvironment conditions. *Cancer Immunol Immunother*. 2018;67:861-872.
24. Lombardi J, Boulin M, Devaux M, et al. Safety of ninety-minute daratumumab infusion. *J Oncol Pharm Pract*. 2020;1078155220951231.
25. Cejalvo MJ, Ribas P, de la Rubia J. The safety of daratumumab for the treatment of multiple myeloma. *Expert Opin Drug Saf*. 2017;16:753-760.
26. Jia YJ, Liu H, Wang LR, et al. The efficacy and safety of daratumumab in relapsed and refractory multiple myeloma. *Zhonghua Nei Ke Za Zhi*. 2020;59:347-352.
27. Kobayashi H, Tsushima T, Terao T, et al. Evaluation of the safety and efficacy of daratumumab outside of clinical trials. *Int J Hematol*. 2019;109:665–672.

How to cite this article: Cao C, Zhou X, Ma Q. Daratumumab provides a survival benefit in relapsed and refractory Multiple Myeloma, independent of baseline clinical characteristics: A meta-analysis. *Pharmacol Res Perspect*. 2021;9:e00797. https://doi.org/10.1002/prp2.797