

# Immunomodulatory drug and dexamethasone-containing triple versus doublet combination treatments for relapsed or refractory multiple myeloma: a meta-analysis of phase III randomized controlled trials

**Minjie Gao**

Ningbo First Hospital

**Xiao Yan**

Ningbo First Hospital

**Fei Li**

First Affiliated Hospital of Nanchang University

**Kaihong Xu**

Ningbo First Hospital

**Qitian Mu**

Ningbo First Hospital

**Lixia Sheng**

Ningbo First Hospital

**Yi Wang**

Ningbo First Hospital

**Van S. Tompkins**

Iowa State University

**Guifang Ouyang** (✉ [nbhematology@163.com](mailto:nbhematology@163.com))

Ningbo First Hospital <https://orcid.org/0000-0002-3411-3666>

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## Primary research

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# Abstract

## Background

Triplet therapy has become the standard of care for relapsed or refractory multiple myeloma (RRMM) over the past few years. Prior to that, doublet therapy including dexamethasone and an immunomodulatory were standard. Several systematic studies have been conducted and many combinations with variable triplet therapies but have not always used the former standard therapy as a benchmark. The objective of this meta-analysis was to evaluate the efficacy and safety of triplet combinations that included dexamethasone and an immunomodulatory drug versus a doublet combination of just dexamethasone and an immunomodulatory for the treatment of RRMM.

## Methods

A comprehensive literature search (PubMed, EMBASE, Cochrane Library) for phase III randomized controlled trials for efficacy and safety of triplet versus doublet combinations that specifically included dexamethasone and an immunomodulatory drug for treatment of RRMM. Efficacy (ORR, PFS, OS) and adverse events ( $\geq$  grade 3) were assessed using traditional statistical measures for aggregate data.

## Results

Of 235 potential reports, 6 met the inclusion criteria (N = 115–792 participants). The methodological quality was  $\geq 4$  Jadad score for each. Triplet treatment had higher ORR (HR = 0.74, 95%CI: 0.65–0.84,  $P \leq 0.001$ ), PFS (HR = 0.63, 95%CI: 0.52–0.75,  $P \leq 0.001$ ), and OS (HR = 0.74, 95%CI: 0.65–0.84,  $P \leq 0.001$ ). The incidence of  $\geq$  grade 3 diarrhea and fatigue were significantly higher in the triplet combination group. There was a trend toward increased incidence of  $\geq$  grade 3 neutropenia, thrombocytopenia, thromboembolism, and peripheral neuropathy in the triplet therapy group. Notably, triplet therapy had a significantly lower rate of anemia compared to doublet therapy.

## Conclusions

This study reinforces current guidelines and recommendations for triplet combinations containing dexamethasone and an immunomodulatory drug.

## Introduction

Multiple myeloma (MM), a malignant disease of monoclonal plasma cells, accounts for approximately 10% of hematologic cancers(1) and is the second most common hematologic malignancy(2, 3). The introduction of agents such as immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies have improved treatment outcomes (4–7). Patients with MM often respond to initial therapy

but ultimately relapse and become refractory to further treatment, underscoring the need for new therapeutic approaches for these patients (8–10). The addition of immunomodulatory drugs (eg, thalidomide, lenalidomide, and pomalidomide) to dexamethasone showed clinical benefits in this patient population (11–13). Unfortunately, the prognosis of patients with relapsed or refractory disease remained poor.

As other agents were developed (eg bortezomib, carfilzomib, ixazomib, elotuzumab, or daratumumab), the question arose as to whether triplet regimens – combinations of these or dexamethasone or immunomodulatory agents – exhibited better progression-free survival (PFS) and overall survival (OS) with acceptable side-effect profiles compared with the prior standard doublet regimen. Several randomized controlled trials (RCTs) have been conducted to investigate this in relapsed or refractory MM (RRMM), but the results have been controversial (14–19). Attempting to collate this information, Sun et al. (2017), Botta et al. (2017), van Beurden-Tan et al. (2017), and Dimopoulos et al. (2018) have each performed meta-analyses of triplet versus doublet therapy regimen RCTs for RRMM patients, but none of these studies focused specifically on dexamethasone with an immunomodulatory drug (20–23). Therefore, we conducted this meta-analysis to compare the efficacy and safety of triplet combinations that included dexamethasone and an immunomodulatory agent versus the former standard of care doublet combination of dexamethasone and an immunomodulatory drug in patients with RRMM.

## Methods

### Search strategy and study selection

Clinical trials were included in this study if they met the following criteria: (1) study design: phase III RCTs to include both efficacy and safety comparisons to the standard; (2) study population: patients with RRMM; (3) acceptable comparisons: immunomodulatory drug and dexamethasone-containing triple combination versus doublet combination of immunomodulatory drug and dexamethasone; and (4) the study was required to evaluate both therapy efficacy and safety. The search strategy was as follows: databases, including PubMed, EMBASE, and the Cochrane Library, were searched by two reviewers (MjG and XY) to identify pertinent studies using the following search terms: “multiple myeloma”, “relapsed or refractory”, and “prospective study or clinical trials”. Other potentially relevant studies were also manually searched based on the reference lists from the trials identified. Language was restricted to English. If multiple publications of the same trial were retrieved, only the most complete data was included. Studies were excluded if they did not meet the inclusion criteria (24, 25). All data retrieved were updated to August 2019.

### Data extraction and methodological quality assessment

Two independent data analysts (MjG and KhX) extracted trial details including author, study design, sample size, median age, and treatment regimens. Outcomes of interest were overall response rate (ORR), progression-free survival (PFS), overall survival (OS) and  $\geq$  grade 3 toxicities. Any disagreements were resolved by consultation with a third analyst (LxS). Methodological quality of each trial was evaluated by

two independent reviewers (MjG and KhX) using the Jadad scale including randomization, double-blinding, and withdrawal/dropout. The maximal score for an included study was 5 and studies were classified as high (score 3–5) or low (0–2) (26). Given the small numbers of trials included in this meta-analysis, publication bias was not formally assessed (27, 28).

## Statistical analysis

Statistical analyses of the overall hazard ratio (HR) for survival data (OS, PFS) and the risk ratio (RR) for dichotomous outcomes (ORR, toxicities) were performed. Results are reported with 95% confidence intervals (CIs) on the test for overall effect. The main modality of presenting numerical data in visual form was the forest plot. Heterogeneity was estimated using a chi-square test. When the  $P_{heterogeneity} < 0.1$  or the  $I^2 > 50\%$ , the heterogeneity was considered statistically significant (29). A fixed effect model was employed for outcomes without heterogeneity; a randomized effect model with inverse variance using a restricted maximum likelihood variance estimator was employed if heterogeneity was detected. Statistical significance was determined by  $P < 0.05$ . All P-values were two-sided. All CIs had a two-sided probability coverage of 95%. All analyses were performed in Stata 11.0.

## Results

### Search results

The initial literature search yielded 235 potentially relevant studies, of which 218 were excluded after screening titles and abstracts. The full text of the remaining 17 studies were reviewed. Most of these were subsequently excluded ( $n = 11$ ) for failing inclusion criteria, leaving a total of 6 studies (14–19) used in the meta-analysis. Figure 1 shows a diagram of the study selection process.

### Characteristics of the trials

The trial results were published between 2012 and 2019 and had sample sizes ranging from 115 to 792 patients. The basic characteristics of the included studies are listed in Table 1. Four trials (14, 15, 17, 19) investigated the role of the triple combination by adding a proteasome inhibitor to an immunomodulatory drug and dexamethasone, while another two trials (16, 18) added a monoclonal antibody. Among all six trials, five used lenalidomide (14–18), one used thalidomide (19), and none used pomalidomide. The patients in the two treatment groups had relatively similar ages across all six trials (14–19). The demographic and clinical characteristics of patients of each study are listed in Table 2.

Table 1  
 Characteristics of Phase III RCT studies included in the meta-analysis

Author/year	Treatment regimens	No. of patients	Median age (range)
Dimopoulos et al., 2016	Expt: Daratumumab 16 mg/kg + L 25 mg + D 40 mg	286	65 (34–89)
	Ctrl: L 25 mg + D 40 mg	283	65 (42–87)
Moreau et al., 2016	Expt: Ixazomib 4 mg + L 25mg + D 40 mg	360	66 (38–91)
	Ctrl: P 4 mg + L 25 mg + D 40 mg	362	66 (30–89)
Hou et al., 2017	Expt: Ixazomib 4 mg + L 25 mg + D 40 mg	57	61 (30–76)
	Ctrl: P 4 mg + L 25 mg + D 40 mg	58	62 (36–80)
Stewart et al., 2015	Expt: Carfilzomib (intl 20 mg/m <sup>2</sup> , maint 27 mg/m <sup>2</sup> ) + L 25 mg + D 40 mg	396	64 (38–87)
	Ctrl: L 25 mg + D 40 mg	396	65 (31–91)
Dimopoulos et al., 2017	Expt: Elotuzumab 10 mg/kg + L 25 mg + D 40 mg	321	67 (37–88)
	Ctrl: L 25 mg + D 40 mg	325	66 (38–91)
Garderet et al., 2012	Expt: Bortezomib 1.3 mg/m <sup>2</sup> + T 200 mg + D 40 mg	134	60 (29–76)
	Ctrl: T 200 mg + D 40 mg	135	63 (39–75)
Expt: triplet combination; Ctrl: doublet combination; L: lenalidomide; D: dexamethasone; P: placebo; intl: initial; maint: maintenance; T: thalidomide			

Table 2  
Patients' characteristics in included studies

Study	Dimopoulos et al/2016	Moreau et al/2016	Hou et al/2017	Stewart et al/2015	Dimopoulos et al/2017	Garderet et al/2012
Age	65	66	61	64	66	61
Median (yr)	48	48	72	50	NA	NA
≤65 year (%)	52	52	28	50	NA	NA
≥ 65 year (%)						
ECOG performance status (%)	51	94	97	90.5	NA	NA
0 1 or 2	49	6	3	9.5	NA	NA
Cytogenetic profile (%)	16	19	NA	12.6	NA	NA
High risk	84	57	NA	40	NA	NA
Standard risk	0	24	NA	47.3	NA	NA
unknown						
Previous regimens (%)	NA	61	44	43	48	NA
1	NA	39	56	57	52	NA
≥ 2						
Previous therapies (%)	55	57	86	20	54	8
Immunomodulatory drugs	NA	12	9	20	6	0
Lenalidomide	NA	45	84	0	48	8
Thalidomide						
ISS disease stage (%)	49	64	60	NA	43	58
I	31	24	32	NA	32	26
II	20	12	8	NA	21	16
III	0	0	0	NA	4	0
Not reported						
NA: not available						

Study	Dimopoulos et al/2016	Moreau et al/2016	Hou et al/2017	Stewart et al/2015	Dimopoulos et al/2017	Garderet et al/2012
Previous stem-cell transplantation (%)	63	57	17	NA	54	100
NA: not available						

The methodological quality of the included studies is summarized in Table 3. All six trials described acceptable methods of randomization. Two trials (15, 17) reported blinding of both the participants and outcome assessors. All six trials had clear descriptions of participant dropouts with acceptable dropout rates ( $\leq 20\%$ ). According to the Jadad scale (out of 5), all trials were deemed to be of high quality, with two trials (15, 17) scoring 5 and the remaining four (14, 16, 18, 19) scoring 4 each.

Table 3  
Methodological quality of included trials, assessed according to the Jadad scale

Author [Year]	Randomization	Blinding	Withdrawal/lost to follow-up	Total
Dimopoulos et al., 2016	2	1	1	4
Moreau et al., 2016	2	2	1	5
Hou et al., 2017	2	2	1	5
Stewart et al., 2015	2	1	1	4
Dimopoulos et al., 2017	2	1	1	4
Garderet et al., 2012	2	1	1	4

## Overall survival

Data of five trials (14, 16–19) was eligible for the analysis of OS. Using a fixed-effects model ( $I^2 = 17.8\%$ ,  $P_{heterogeneity} = 0.301$ ), the pooled results indicated that triplet therapy significantly improved OS over doublet therapy with a HR of 0.74 (95%CI: 0.65–0.84,  $P \leq 0.001$ ; Fig. 2).

## Progression-free survival

Data on PFS was extracted from all the six trials (14–19). Using a random-effects model ( $I^2 = 65.6\%$ ,  $P_{heterogeneity} = 0.013$ ), we observed that triplet therapy significantly improved PFS, with a HR of 0.63 (95%CI: 0.52–0.75,  $P \leq 0.001$ ; Fig. 3) compared to doublet therapy.

## Overall response rate

Data on ORR was available in all the six trials (14–19). Using a random-effects model ( $I^2 = 58.0\%$ ,  $P_{heterogeneity} = 0.036$ ), the pooled results showed that there was a significant improvement for triplet

therapy, with a RR of 1.21 (95%CI: 1.14–1.30,  $P \leq 0.001$ ; Fig. 4).

## Safety

All six trials (14–19) reported the incidence of  $\geq$  grade 3 adverse events. As shown in Table 4, there was a statistically significant increase in those having experienced  $\geq$  grade 3 diarrhea (RR = 1.44; 95%CI: 1.01–2.05,  $P = 0.045$ ) and fatigue (RR = 1.38; 95%CI: 1.03–1.85,  $P = 0.031$ ) in the triplet therapy group. Though no statistically significant differences in  $\geq$  grade 3 neutropenia (RR = 1.02; 95%CI: 0.81–1.29,  $P = 0.846$ ), thrombocytopenia (RR = 1.34; 95%CI: 0.98–1.82,  $P = 0.065$ ), thromboembolism (RR = 1.23; 95%CI: 0.85–1.79,  $P = 0.263$ ) or peripheral neuropathy (RR = 1.46; 95%CI: 0.98–2.18,  $P = 0.063$ ) were observed between the two treatment groups, the latter three show increases with triplet therapy. Notably, patients who had triplet therapy had a significantly lower rate of anemia than those who received doublet therapy (RR = 0.83; 95%CI: 0.71–0.98,  $P = 0.03$ ).

Table 4  
Summary of  $\geq$  grade 3 adverse events meta-analysis comparing triplet versus doublet therapy in RRMM

$\geq$ grade 3 adverse events	No. of trials	$I^2$	$P_{heterogeneity}$	RR (95%CI)	$P$
Anemia	6	41.3%	0.130	0.83 (0.71–0.98)	0.03
Neutropenia	6	74.1%	0.002	1.02 (0.81–1.29)	0.846
Thrombocytopenia	6	64.7%	0.015	1.34 (0.98–1.82)	0.065
Thromboembolism	5	44.9%	0.123	1.23 (0.85–1.79)	0.263
Peripheral neuropathy	5	22.5%	0.276	1.46 (0.98–2.18)	0.063
Fatigue	6	0%	0.527	1.38 (1.03–1.85)	0.031
Diarrhea	5	11.6%	0.34	1.44 (1.01–2.05)	0.045

## Discussion

Currently, management of MM remains challenging and relapse of MM and disease progression is common even after achievement of complete remission. With many novel agents available to treat RRMM patients, there is a need to identify the optimal combinations to achieve an appropriate balance between efficacy and safety. Immunomodulatory drugs in combination with dexamethasone have shown great clinical benefit in patients with RRMM (12, 30). The main goal of this meta-analysis was to systematically analyze the efficacy and toxicity of triple combinations specifically containing dexamethasone and an immunomodulatory in treatment for RRMM. Our results suggested that triple combinations containing dexamethasone and an immunomodulatory significantly increased ORR and, importantly, improved PFS and OS, indicating a survival advantage with an added treatment agent. These findings are fully congruent with Dimopoulos et al. (2018) (23) who used a Bayesian approach to a meta-

analysis and found that triplet therapies were superior to doublet therapies. The focus of that study was distinct in that they used immunomodulatory treatment in at least two arms within the same study as a criterion, whereas we focused on the combination of dexamethasone and an immunomodulatory. Using classical statistics, our study confirms their finding that adding a third agent (specifically daratumumab in their study) to an immunomodulatory and dexamethasone was most efficacious – an identical finding to that of both Botta et al. (2017) (21) and van Beurden-Tan et al. (2017) (22). Thus, our results are in line with current guidelines and treatment recommendations for RRMM.

Similar to Botta et al. (2017) (21), this study also assessed adverse effects, though their work compared bortezomib-containing versus immunomodulatory-containing regimens. With the focus on dexamethasone and an immunomodulatory, we found the incidence of  $\geq$  grade 3 diarrhea and fatigue were significantly higher in the triplet combination group. There was a trend toward increased incidence of  $\geq$  grade 3 neutropenia, thrombocytopenia, thromboembolism, and peripheral neuropathy in the triplet therapy group, but these did not reach statistical significance compared to doublet therapy. Cautious interpretation is advised here as these studies may have been under powered; thus, while more trials and patients are needed to determine whether the trends underly reality, it appears as though these adverse effects are more likely to be observed in patients on triplet therapies including dexamethasone and an immunomodulatory. Interestingly, we found that triplet therapy had a lower rate of anemia compared to doublet therapy. Anemia is a typical symptom of MM, so the lower rate of anemia may reflect better efficacy of the triplet therapy.

This meta-analysis had some limitations. The work was based on published studies, not an analysis of individual patient data, which limited time-to-event analyses. Our analysis was also limited to the available published data, which omits unpublished or ongoing trials and is subject to a reasonable risk of reporting bias. This study is underpowered for assessment of publication bias by current statistical approaches (31). Despite these limitations, our meta-analysis includes a comprehensive search for eligible studies, the careful consideration of study quality, and a rigorous analytical approach.

The focus on studies that included only dexamethasone and immunomodulatory drug treatments for comparisons allows for informed treatment decisions based on these two standard therapies. This last point is a key difference between this study and that of Sun et al. (2017). Sun et al. (2017) also included a report that compared treatments with bortezomib and dexamethasone along with studies that included treatments with immunomodulatory agents and dexamethasone(20). While survival outcomes were similar between the two studies, a clear difference was observed for one major adverse outcome: anemia. Our analysis suggests triplet therapy including an immunomodulatory and dexamethasone may reduce the occurrence of anemia over doublet therapy. This is the first meta-analysis of RCTs in patients with RRMM suggesting that triplet combinations that include dexamethasone and an immunomodulatory drug have a favorable risk-benefit profile compared with treatments that only include dexamethasone and an immunomodulatory drug. This is completely consistent with a recent report from Alahmadi et al. (2019), who found that adding cyclophosphamide to lenalidomide and dexamethasone had clinical benefit with manageable toxicities(32), and Attal et al.(2019), who found that adding isatuximab to

pomalidomide and dexamethasone enhanced PFS(33). Given the high degree of variability of real patient populations and treatment outcomes in RRMM(34), our study provides additional evidence for clinicians as they consider whether immunomodulatory and dexamethasone-based combinations are the best treatment options for their patients.

## Abbreviations

RRMM: relapsed or refractory multiple myeloma; PFS: progression-free survival; OS: overall survival; RCTs: randomized controlled trials; MM, multiple myeloma; HR, hazard ratio; RR, risk ratio.

## Declarations

### Ethics approval and consent to participate

Not applicable

### Consent for publication

Not applicable

### Availability of data and materials

All data used in this report were derived from the public domain and available as part of the original studies used for analyses.

### Competing interests

The authors declare that they have no competing interests.

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### Author contributions

Minjie Gao, Yi Wang and Guifang Ouyang conceived and designed the study. Minjie Gao, Xiao Yan, Fei Li, Kaihong Xu and Lixiang Sheng collected and analyzed data. Minjie Gao and Qitian Mu drafted the manuscript. Van S. Tompkins and Guifang Ouyang revised the manuscript. All authors read and approved the final manuscript.

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## Figures

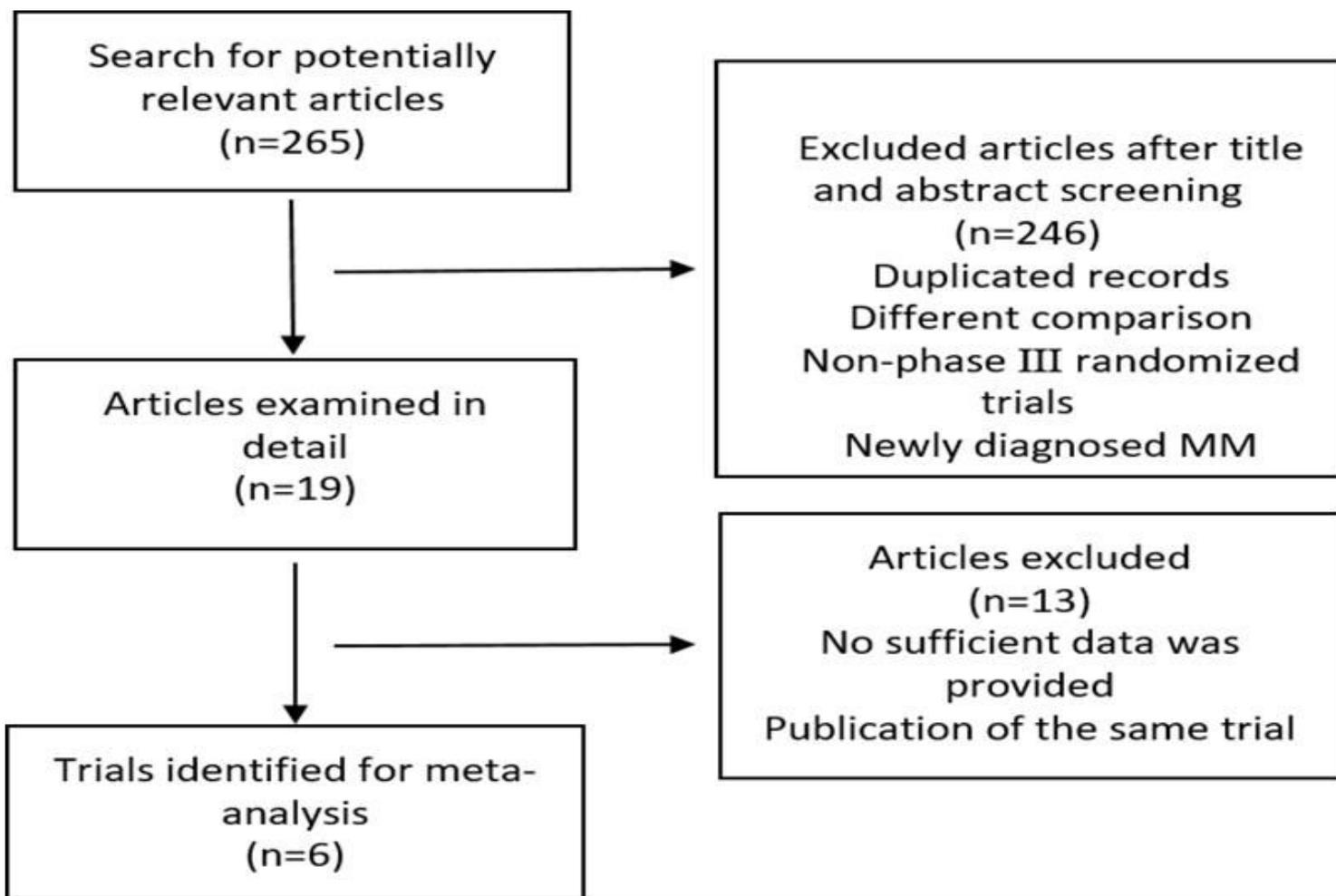
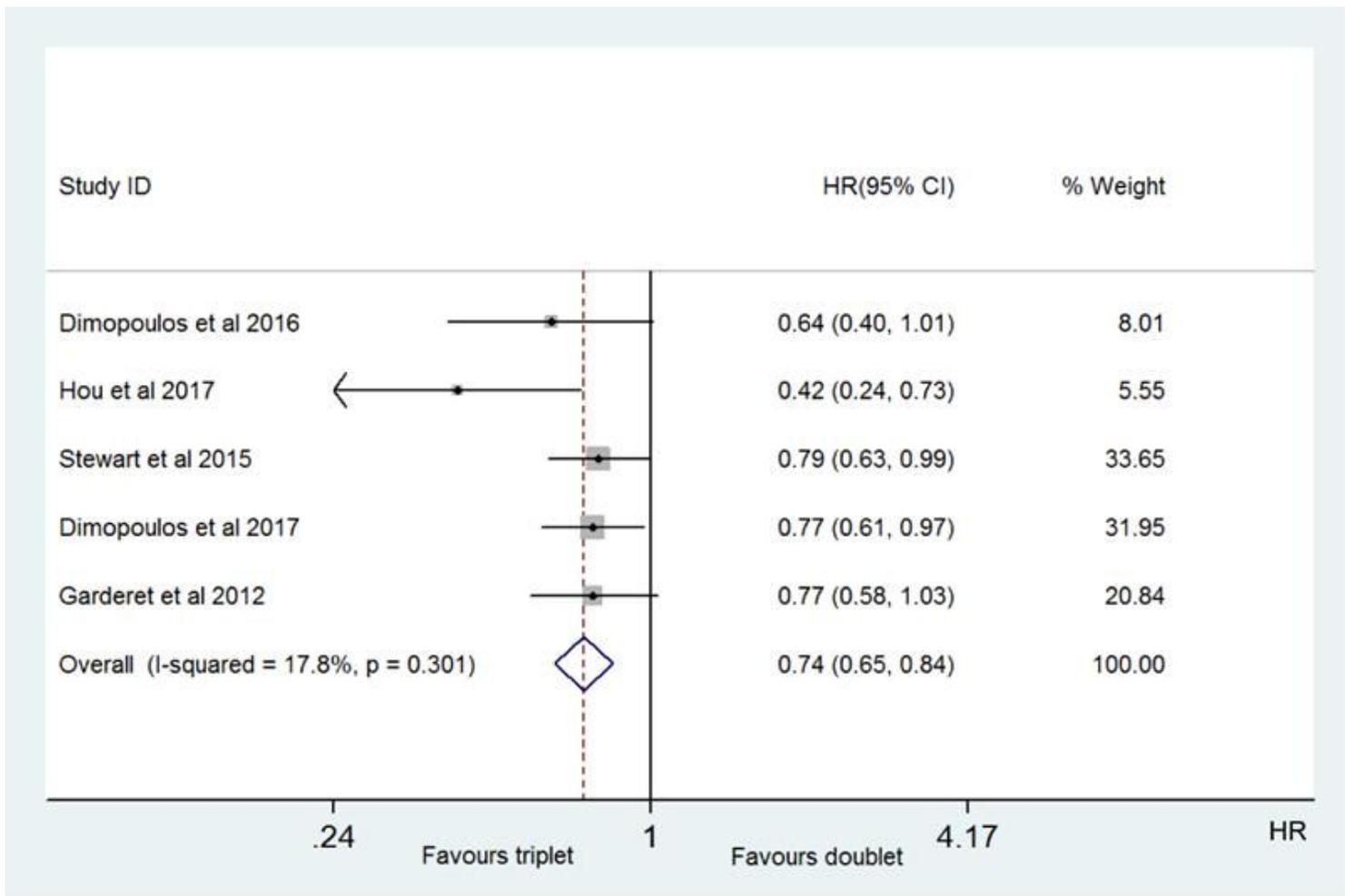


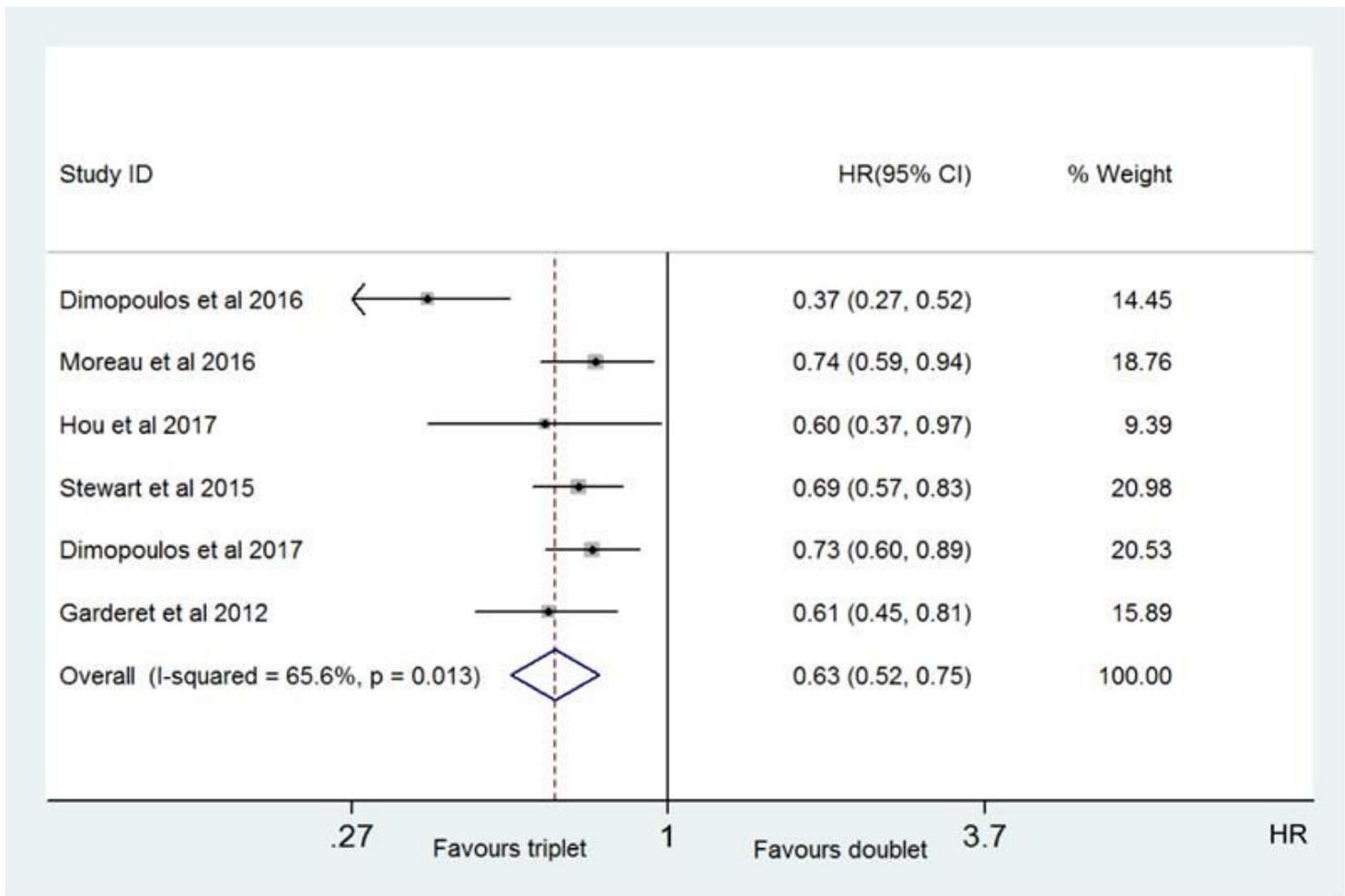
Figure 1

Flowchart diagramming the selection of studies.



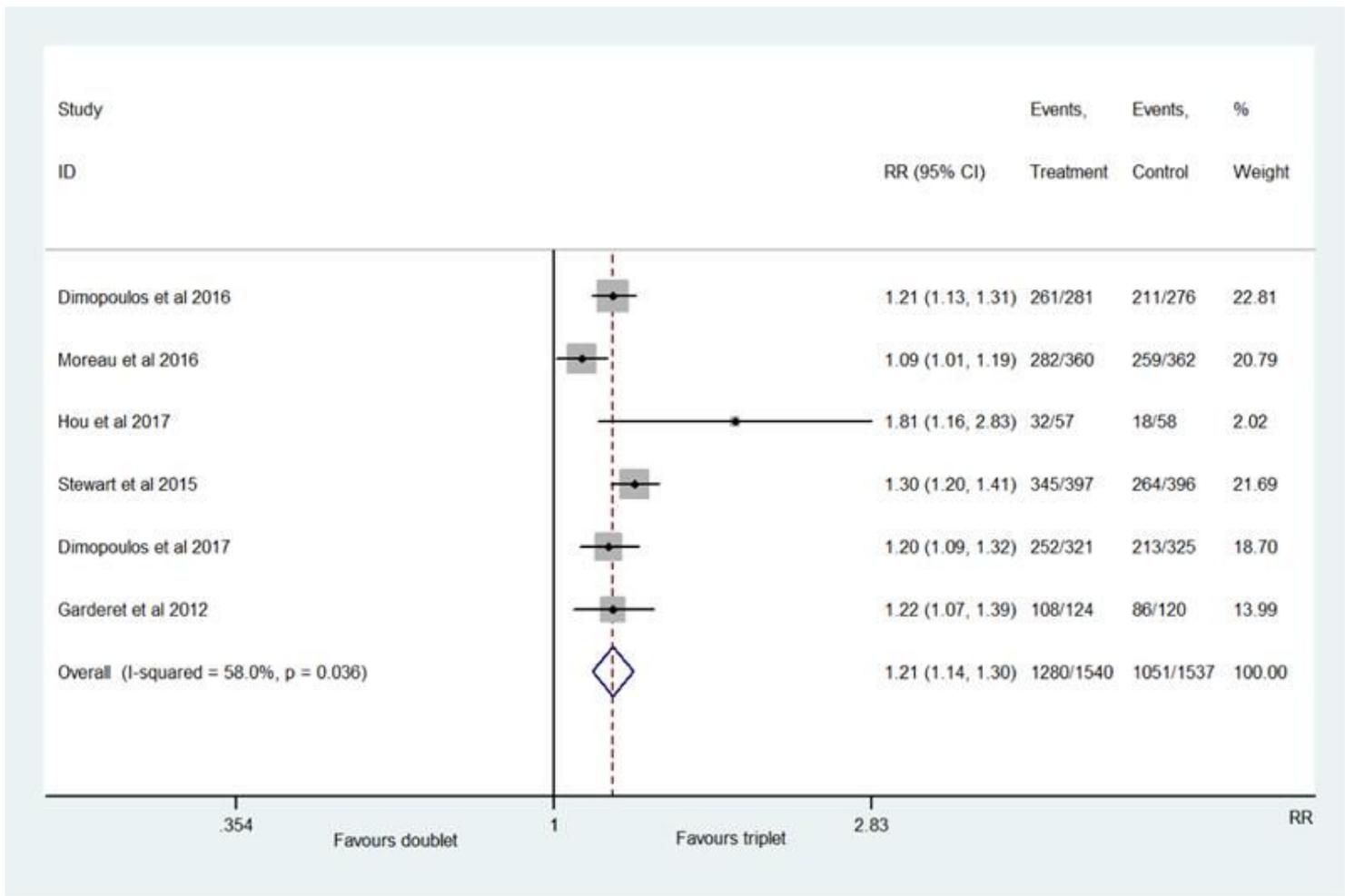
**Figure 2**

Individual trials and overall hazard ratios for OS associated with immunomodulatory drug and dexamethasone-containing triple combinations versus the doublet combination of an immunomodulatory drug and dexamethasone in RRMM. The horizontal axis represent hazard ratio (HR) and the results are presented on a log scale. Fixed-effects model.



**Figure 3**

Individual trials and overall hazard ratios for PFS associated with immunomodulatory drug and dexamethasone-containing triplet therapy versus regimens of only an immunomodulatory drug and dexamethasone in RRMM. The horizontal axis represent hazard ratio (HR) and the results are presented on a log scale. Random-effects model.



**Figure 4**

Individual trials and overall risk ratios for ORR associated with immunomodulatory drug and dexamethasone-containing triple combinations versus a regimen with only an immunomodulatory drug and dexamethasone in RRMM. The horizontal axis represent risk ratio (RR) and the results are presented on a log scale. Random-effects model.