Comparison of Monoclonal Antibodies targeting CD38, SLAMF7 and PD-1/PD-L1 in combination with Bortezomib/Immunomodulators plus Dexamethasone/Prednisone for the treatment of Multiple Myeloma: An Indirect-Comparison Meta-Analysis of Randomized Controlled Trials

Wu Ye
Sichuan University
Xia Wu
Sichuan University
Xiaoyan Liu
Sichuan University
Xue Zheng
Sichuan University
Jili Deng
Sichuan University
Yuping Gong (gongyuping2010@aliyun.com)
Sichuan University West China Hospital https://orcid.org/0000-0002-2437-9348

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Abstract

Background

In recent years, there were many clinical trials assessed the efficacy and safety of monoclonal antibodies (MAbs) in combination with proteasome inhibitors or immunomodulators plus dexamethasone/prednisoneare for the treatment of multiple myeloma (MM). The treatment outcomes of comparing different MAbs in combination with above-mentioned agents remain unknown. We conducted this meta-analysis to compare indirectly the efficacy and safety of MAbs targeting CD38, SLAMF7 and PD-1/PD-L1 in combination with bortezomib/immunomodulators plus dexamethasone/ prednisone in patients with MM.

Methods

We electronically searched for randomized controlled trials (RCTs) in which at least one of the three MAbs was included among multiple arms. We included eleven eligible RCTs with 5367 patients in the meta-analysis. Statistical analysis used StataMP14 and Indirect Treatment Comparisons software.

Results

We synthesized hazard ratios (HR) for progression-free survival (PFS) and overall survival (OS), relative risk (RR) for overall response rate, complete response (CR) or better, very good partial response (VGPR) or better, VGPR, partial response, stable disease and grade 3 or higher adverse events among the three groups. The HR for PFS of the CD38 group vs SLAMF7 group, CD38 group vs PD-1/PD-L1 group and SLAMF7 group vs PD-1/PD-L1 group were 0.662(95CI0.543-0.806), 0.317(95CI 0.221–0.454) and 0.479(95CI0.328-0.699) respectively. The HR for OS of the CD38 group vs SLAMF7 group was 0.812(0.584–1.127). The RR for CR or better in the CD38 group versus SLAMF7 group was 2.253(95CI1.284-3.955). The RR for neutropenia of the CD38 group versus SLAMF7 group was 1.818(95CI1.41-2.344).

Conclusions

Treatment with the CD38 group resulted in longer PFS and better treatment response than the SLAMF7 and PD-1/PD-L1 group. In addition, the SLAMF7 group prolonged PFS compared with the PD-1/PD-L1 group, and had a lower incidence of grade 3 or higher neutropenia than the CD38 and PD-1/PD-L1 group. In

Introduction

Multiple Myeloma (MM) is a hematological cancer characterized by proliferation of malignant plasma cells in the bone marrow. MM represents the second most frequent hematological malignancy, accounting 1% of all cancer and 13% of hematological tumors, with ~ 9,000 new cases per year[1]. The protein CD38 (cluster of differentiation 38) is a multifunctional enzyme that degrades NAD and modulates cellular NAD homeostasis, CD38 has also been identified as a cell-surface marker in hematologic cancers such as MM[2]. MM cells express high levels of CD38, while CD38 is expressed at relatively low levels on normal lymphoid, myeloid cells and in some non-hematopoietic tissues and a cytotoxic anti-CD38 antibody has been approved by the FDA for use in this disease[3]. SLAMF7 (CS1, CRACC, CD319) is over-expressed in MM and makes it a target for immunotherapy[4–6]. Elotuzumab is a humanized therapeutic monoclonal antibody directed to the surface glycoprotein SLAMF7 and have been observed improving clinical outcomes in the treatment of MM patients in combination with lenalidomide or bortezomib[7, 8].The programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) pathway is a negative regulator of immune activation that is upregulated in MM and is a critical component of the immunosuppressive tumor micro-environment[9]. In MM, PD-1/PD-L1 blockade was analyzed by using nivolumab, pembrolizumab, and durvalumab[10], PD-1 pathway blockade is ineffective as a single agent[11].

In recent years, there were many clinical trials assessed the efficacy and safety of MAbs in combination with proteasome inhibitors or immunomodulators plus dexamethasone/prednisoneare in the treatment of MM. However, there has been no clinical study comparing the effect of MAbs directed to different targets in combination with above-mentioned drugs. This meta-analysis indirectly compared the efficacy and safety of the MAbs targeting CD38, SLAMF7 and PD-1/PD-L1 in combination with bortezomib/immunomodulators plus dexamethasone/prednisone in patients with MM.

Methods

The meta-analysis was conducted in accordance with the quality of reporting of meta-analysis (PRISMA) statements, and the protocol was registered with PROSPERO, number CRD42020171456.

Inclusion and exclusion criteria

Inclusion criteria: 1. The experimental groups were the MAbs targeting CD38, SLAMF7 or PD-1/PD-L1 in combination with bortezomib/immunomodulators plus dexamethasone/prednisone; The control group were blank control, placebo or conventional drugs. 2. The patients were diagnosed as Multiple Myeloma and the background of the treatment of patients was not limited, which can be the initial treatment or recurrent treatment. 3. Study outcomes include progression-free survival (PFS), overall response rate (ORR), complete response (CR), partial response (PR), grade 3 or higher hematological adverse events and common non-hematological adverse events. 4. Studies must be randomized controlled trials (RCTs) and were officially published.

Exclusion criteria: 1. The same study was published repeatedly. 2. The studies had incomplete results, and we obtained no supplementary data after contacting the author. 3. Basic research and animal

experimental research were excluded. 4. Studies had a insufficient follow-up time or more than 20% of the patients included in the study were lost to follow-up.

Search strategy and studies screening

Systematic literature searches were conducted using PubMed, Embase, Medline, Web of Science, Cochrane Library and Chinese Biomedical Database (before 26 Feb 2020). The retrieval terms and methods were as following: 1#: “Monoclonal Antibodies” OR “CD38” OR “PD-1/PD-L1” OR “SLAMF7” OR “CD319” OR “CS1” OR “19A” OR “CRACC” OR “Daratumumab” OR “Isatuximab” OR “MOR202” OR “TAK-079” OR “Pembrolizumab” OR “Nivolumab” OR “Elotuzumab”, 2#: “Bortezomib” OR ”Immunomodulatory” OR “Lenalidomide” OR “Pomalidomide” OR “Thalidomide”, 3#:“Dexamethasone” OR “Prednisone”, 4#: “Multiple Myeloma”, 5#: 1#AND2#AND3#AND4#. Two authors independently reviewed the titles and abstracts to screen potentially eligible studies, then two authors reviewed the full text to screen qualified articles independently. Disagreements between authors were solved by consensus or consultation with a third investigator, if necessary.

Critical appraisal of the included studies

According to “Cochrane collaboration’s tool for assessing risk of bias”, the evaluation contents include the following aspects: 1. Blind methods; 2. Randomized methods; 3. Allocation concealment; 4. Incomplete outcomes; 5. Selective reporting; 6. Other biases. Two authors assessed the quality of the studies independently, disagreements between authors were solved by consensus or consultation with a third investigator.

Data extraction

All data from eligible trials were independently extracted by two investigators. Disagreements were resolved by discussion. Abstracted study characteristics included the first author, year of publication, number of patients, the experimental and control group, follow-up time, outcomes of survival analysis, treatment response and adverse events.

In the meta-analysis, the primary endpoint was progression-free survival (PFS), which was calculated from the date of randomization to the time of disease progression, recurrence, or death. The secondary endpoints includes overall survival (OS), which was measured from the date of randomization until death from any cause or the last follow-up observation of patients[12], overall response rate (ORR), complete response (CR) or better, very good partial response (VGPR) or better, VGPR, partial response (PR), stable disease (SD) and grade 3 or higher common hematological and non-hematological adverse events.

Statistical analysis

First step: To estimate the pooled hazard ratio (HR) for survival outcomes or relative risk (RR) for the treatment response and the incidence of adverse event, we firstly performed a conventional pairwise meta-analysis using the StataMP14 command ‘metan’. Statistical heterogeneity was assessed in each

pairwise comparison using I-squared statistics. A random-effects model was utilized when statistically significant heterogeneity existed, otherwise a fixed-effects model was utilized.[13] Hazard ratio (HR) with corresponding 95%CI for PFS or OS will be used to compare the survival outcomes. Relative risk (RR) with 95% CI will be used to compare the treatment response and the incidence of adverse event .

Second step: We used the Indirect Treatment Comparisons(ITC) software to compare HR or RR from the first step.

Results

The screening results and characteristics of the included studies

The electronic literature search retrieved a total of 184 articles from PubMed, Embase, Medline, Web of Science, Cochrane Library and Chinese Bio-medical Database. The flowchart of the study selection process was presented in **Fig.1**. Preliminary screening after reading title and abstract, excluding review articles, fundamental researches and so on, there were remaining 41 studies. Then reading full text screens again and excluding single arm and phase1 studies, subgroup-analysis studies, study-design, cohorts study, and no-data-available studies, we obtained 15 articles totally, which includes 11 RCTs and 4 update-analysis studies[14-17]. Eventually, 11 RCTs with 5367 patients were included in quantitative synthesis. Six RCTs[18-23] explored the efficacy and safety of the MAbs targeting CD38 (daratumumab, isatuximab) group, three RCTs[24-26] explored the efficacy and safety of the MAbs targeting SLAMF7 (elotuzumab) group and two RCTs[27, 28] explored the efficacy and safety of MAbs targeting PD-1/PD-L1 (pembrolizumab) group. Characteristics of the included studies was presented in **Table 1** and characteristics of the patients at baseline was presented in **Supplementary material**.

According to “Cochrane collaboration’s tool for assessing risk of bias”, we roughly assessed the quality of included trials, which was considered to be high quality. The details of study quality assessment was presented in **Table 2**.

Progression-Free Survival

All of the 11 RCTs provided PFS and hazard ratio[12]. Firstly, we synthesized the pooled HR of the MAbs targeting CD38, SLAMF7 and PD-1/PD-L1 groups versus their corresponding control group respectively by stataMP14 software, as shown in **Fig.2a, 2b**. The pooled HR for PFS of the MAbs targeting CD38, SLAMF7 and PD-1/PD-L1 groups vs their corresponding control groups were 0.45(95CI0.40-0.50), 0.68(95CI0.57-0.79) and 1.42(95CI0.95-1.88) respectively. Secondly, we indirectly calculated HR for PFS of the MAbs targeting CD38 group vs SLAMF7 group, CD38 group vs PD-1/PD-L1 group and SLAMF7 group vs PD-1/PD-L1group respectively by ITC software, the HR for PFS of them were 0.662(95CI0.543-0.806), 0.317(95CI0.221-0.454) and 0.479(95CI0.328-0.699) respectively. The MAbs targeting CD38 group and SLAMF7 group prolonged PFS compared with their corresponding control groups, and the MAbs targeting CD38 group had a longer PFS than the SLAMF7 group by indirect-comparison. In contrast, the MAbs targeting PD-1/PD-L1 group was the worst among the three group. In subgroup-

analysis of the MAbs targeting CD38 group, the HR for PFS of the daratumumab group vs the control group was 0.40(95CI0.32-0.48), as compared with 0.60(95CI0.41-0.78) in the isatuximab group, the daratumumab group may result in longer PFS than the isatuximab group in patients with relapsed or refractory MM.

Overall Survival

Two RCTs about the MAbs targeting CD38 and three RCTs about the MAbs targeting SLAMF7 provided OS and HR, the pooled HR were 0.56(95CI0.41-0.70) and 0.69(95CI0.56-0.82) respectively, as shown in **Fig.3**. The HR for OS of the MAbs targeting CD38 group vs the MAbs targeting SLAMF7 group was 0.812(95CI0.584-1.127) by indirect-comparison. There was no significant difference in overall survival between the two groups.

ORR, CR or better, VGPR or better, VGPR, PR, SD

We used the same method as above-mentioned, the pooled RR for ORR, CR or better, VGPR or better, VGPR, PR and SD in the MAbs targeting CD38 group versus the control group were 1.21(95CI1.10-1.33), 1.78(95CI1.61-1.98), 1.63(95CI1.29-2.05), 1.39(95CI1.02-1.89), 0.70(95CI0.56- 0.87) and 0.42(95CI 0.27-0.66) respectively, as shown in **Fig.4a, 4b**. According to primary or recurrent treatment and classification of antibodies, we conducted subgroup analysis, and found that there were no significant relations between heterogeneity and the two factors. The pooled RR for ORR, CR or better, VGPR or better, VGPR, PR and SD in the MAbs targeting SLAMF7 group versus the control group were 1.24(95CI0.99-1.56), 0.79(95CI0.45-1.36), 1.25(95CI1.02-1.54), 1.40(95CI1.10-1.78), 0.46(95CI0.28-0.77) and 0.66(95CI0.48-0.90) respectively, as shown in **Fig.5a, 5b**. The pooled RR for ORR in the MAbs targeting PD-1/PD-L1 group versus the control group was 0.97(95CI0.82-1.13). The RR for ORR, CR or better, VGPR or better, VGPR, PR and SD in the MAbs targeting CD38 group versus the SLAMF7 group were 0.976(95CI0.763-1.248), 2.253(95CI1.284-3.955), 1.304(95CI0.956- 1.778), 0.993(95CI0.671-1.468), 1.522(95CI0.876-2.642) and 0.636(95CI0.368-1.099) respectively by indirect comparison. The RR for ORR in the MAbs targeting CD38 group vs the PD-1/PD-L1 group and in the SLAMF7 group vs the PD-1/PD-L1 group were 1.247(95CI1.035-1.503) and 1.278 (95CI0.968-1.688) respectively. As for treatment response, the MAbs targeting CD38 group was better than the SLAMF7 group in term of CR or better. The MAbs targeting PD-1/PD-L1 group had a worse treatment response than the MAbs targeting CD38 group and SLAMF7 group.

Grade 3 or higher hematological and non-hematological adverse events

The pooled RR for neutropenia, anemia, thrombocytopenia, lymphopenia, pneumonia, diarrhea and fatigue in the MAbs targeting CD38 group versus the control group were 1.40(95CI1.17-1.67), 0.82(95CI0.66-1.01), 1.15(95CI0.92-1.43), 1.70(95CI1.26-2.29), 1.51(95CI1.21-1.89), 1.33(95CI0.92- 1.91) and 2.00(95CI1.33-3.02) respectively, as shown in **Fig.6a, 6b**. The pooled RR for neutropenia, anemia, thrombocytopenia, lymphopenia, pneumonia, diarrhea and fatigue in the MAbs targeting SLAMF7 group versus the control group were 0.77(95CI0.64-0.92), 0.88(95CI0.67-1.17), 0.97(95CI 0.73-1.28), 1.63(95CI1.43-1.85), 1.32(95CI0.88-1.98), 1.33(95CI0.73-2.41) and 1.19 (95CI 0.75-1.91) respectively, as

shown in **Fig.7**. The pooled RR for neutropenia, anemia, pneumonia, diarrhea and fatigue in the MAbs targeting PD-1/PD-L1 group versus control group were 1.16(95CI0.97-1.38), 1.45(95CI0.89-2.36), 1.14(95CI0.65-1.99), 2.98(95CI0.71-12.44) and 0.40(95CI0.15-1.08) respectively, as shown in **Fig.8**. The RR for neutropenia, anemia, thrombocytopenia, lymphopenia, pneumonia, diarrhea and fatigue in the MAbs targeting CD38 group versus the SLAMF7 group were 1.818(95CI1.41-2.344), 0.932(95CI0.656-1.323), 1.186(95CI0.83-1.694), 1.043(95CI0.753-1.444), 1.144(95CI0.72-1.817), 1.00(95CI0.497-2.014) and 1.681(95CI 0.903-3.13) respectively by indirect comparison. The RR for neutropenia, anemia, pneumonia, diarrhea and fatigue in the MAbs targeting CD38 group versus the PD-1/PD-L1 group by indirect comparison were 1.207(95CI0.94-1.55), 0.566(95CI 0.332-0.963), 1.325(95CI0.725-2.419), 0.446(95CI0.102-1.956) and 5.00 (95CI1.717 -14.56) respectively. The RR for neutropenia, anemia, pneumonia, diarrhea and fatigue in the MAbs targeting SLAMF7 group versus the PD-1/PD-L1 group were 0.664(95CI0.515-0.855), 0.607(95CI0.346-1.064), 1.158(95CI0.58-2.311), 0.446(95 CI0.095-2.105) and 2.975(95CI0.998-8.867) respectively by indirect comparison. As for the incidence of the adverse events, the MAbs targeting CD38 group had a lower risk of anemia while a higher risk of fatigue than the PD-1/PD-L1 group. The MAbs targeting SLAMF7 group had a lower risk of neutropenia than the PD-1/ PD-L1and CD38 group.

The indirect-comparison results of efficacy and safety among the three groups were summarized in **Table 3**.

Discussion

Multiple myeloma (MM) is a currently incurable hematologic tumor with heterogeneous clinical behavior and prognosis.[29] With the application of proteasome inhibitors and immunomodulatory drugs in the treatment of MM, the survival outcomes have significantly improved. However, most patients will inevitably have a relapse even after complete response and then the disease becomes refractory to treatment.[12, 30] The application of monoclonal antibodies brings new hope for the treatment of MM. CD38 is uniformly expressed at high levels on MM cells and, to a lesser extent, on the surface of normal hematopoietic and non-hematopoietic cells, making this molecule an interesting target for immunotherapeutic approaches.[29] The CD38 antibodies, including daratumumab, isatuximab, and MOR202, are generally well tolerated and induce partial response or better in approximately 30% of heavily pretreated MM patients as monotherapy and are attractive partners in combination regimens.[4, 31] The signaling lymphocytic activation molecule family (SLAMF7; also known as CS1 or CD319) is highly expressed on plasma cells from MM as well as natural killer (NK) cells and is a well-known therapeutic target of elotuzumab.[8] Anti-SLAMF7 mAb can activate natural cytotoxicity of NK cells as well as enhance ADCC (antibody-dependent cell-mediated cytotoxicity) and thus makes an effective target for immunotherapy of MM.[4]Improved clinical outcomes have been observed following treatment of MM patients with elotuzumab in combination with lenalidomide or bortezomib.[7] In the biology of multiple myeloma (MM), immune dysregulation has emerged as a critical component for novel therapeutic strategies.[10] PD-1 (programmed death-1) is an immune checkpoint receptor that modulates T-cell activity in peripheral tissues via interaction with its ligands, PD-L1 (programmed death-ligand 1)

and PD-L2 (programmed death-ligand 2).[32] Specifically, the binding with PD-1 ligand (PD-L1) on the surface of tumor plasma cells down-regulates T cell-proliferation, thus contributing to the immune escape of tumor cells.[10] In MM it seems that an approach based on combination treatment might be appropriate as unsatisfactory results have been yielded by monotherapy with PD-1/PD-L1 antibodies.[33, 34] At present, monoclonal antibodies targeting PD-1/PD-L1 include nivolumab, pembrolizumab and durvalumab. This meta-analysis compared the efficacy and safety of the MAbs targeting CD38, SLAMF7 or PD-1/PD-L1 in combination with bortezomib/immunomodulators plus dexamethasone/prednisone in the treatment of multiple myeloma. As for survival outcomes, the MAbs targeting CD38 group resulted in longer PFS than the MAbs targeting SLAMF7 and PD-1/PD-L1 group, in addition, the MAbs targeting SLAMF7 group had a longer PFS than the MAbs targeting PD-1/PD-L1 group. So as for PFS, we can conclude that the MAbs targeting CD38 group was the best, followed by the MAbs targeting SLAMF7 group and the MAbs targeting PD-1/PD-L1 group was worst by indirect comparison. As for treatment response, the MAbs targeting CD38 group had a better response than the MAbs targeting SLAMF7 group in term of “CR or better”, there was no significant difference among ORR, VGPR or better, VGPR, PR and SD between the two groups. As for the incidence of grade 3 or higher hematological and non-hematological adverse events, the MAbs targeting CD38 group had a higher incidence of neutropenia and a similar incidence of anemia, thrombocytopenia, lymphopenia, pneumonia and diarrhea compared with the MAbs targeting SLAMF7 group. The MAbs targeting PD-1/PD-L1 group had a higher or similar incidence of adverse events compared with the MAbs targeting CD38 group or SLAMF7 group excluding fatigue.

Conclusions

In general, the MAbs targeting CD38 in combination with bortezomib/ immunomodulators plus dexamethasone/prednisone had an important therapeutic value in patients with MM. Although the treatment of the MAbs targeting SLAMF7 group was not as effective as the MAbs targeting CD38 group, it had a lower incidence of adverse events and may be more suitable for patients with poor drug tolerance. As for the MAbs targeting PD-1/PD-L1 group, the therapeutic effect was poor and the incidence of adverse events was not reduced or even higher, whether compared with the control group or the other two groups, so the therapeutic regimen was no longer suitable for clinical patients with MM. There are several limitations in the meta-analysis, the number of the included studies about the MAbs targeting SLAMF7 or PD-1/PD-L1 group was relatively not enough, and heterogeneity existed among studies when we synthesized the pooled RR for treatment response in the MAbs group vs the control group. The MAbs directed to different targets combining with other agents had different effects, therefore the study is meaningful to provide reference for clinicians when they think about choosing an antibody to combine with other drugs for the treatment of MM.

Abbreviations

PFS: progression-free survival, OS: overall survival, ORR: overall response rate, CR: complete response, VGPR: very good partial response, PR: partial response, SD: stable disease, HR: hazard ratio, RR: relative risk, MM: multiple myeloma

Declarations

Ethics approval and consent to participate: This article does not contain any studies with human participants or animals performed by any of the authors.

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Figures

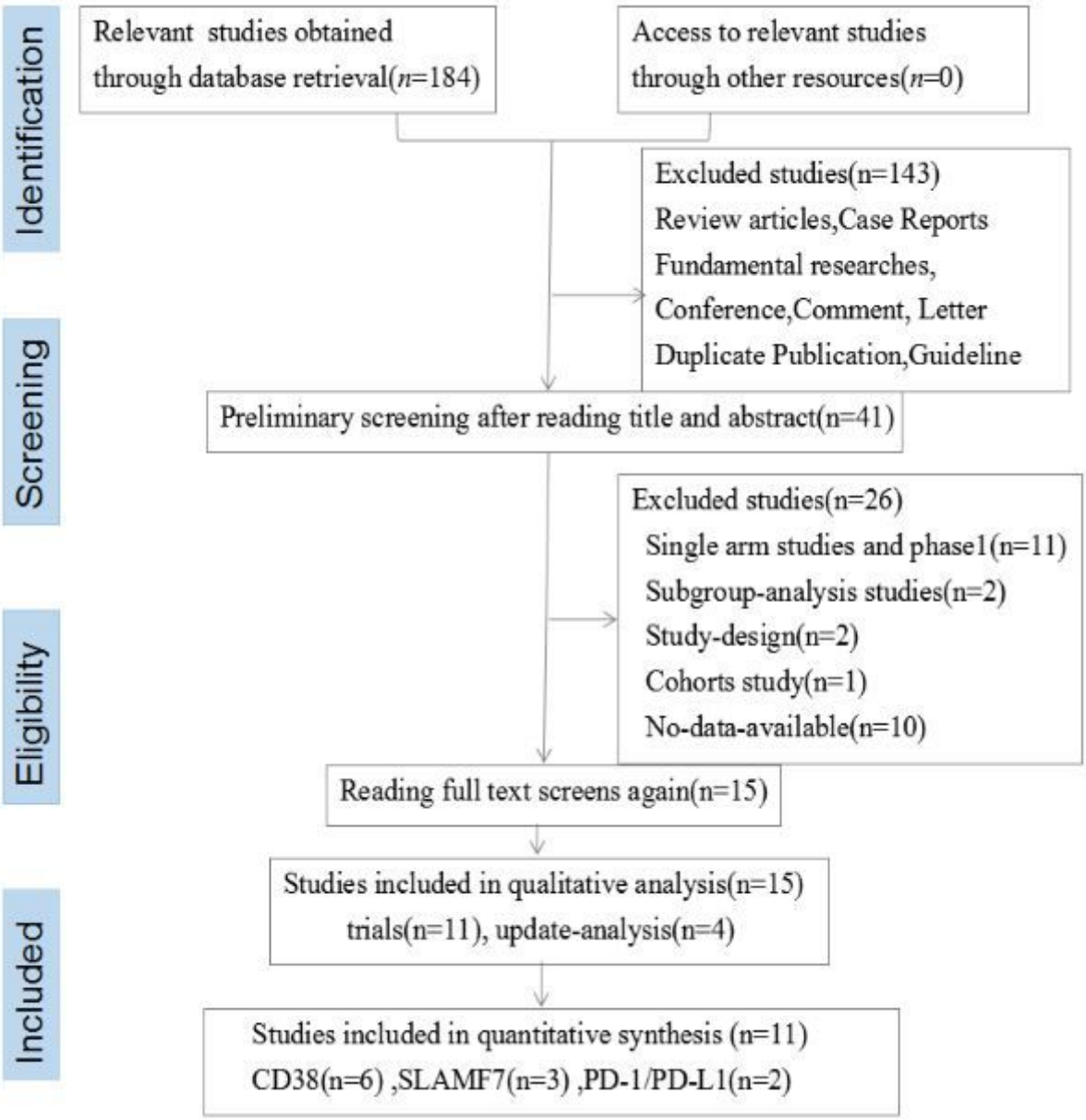

Figure 1

Screening process of randomized controlled trials included in the meta-analysis

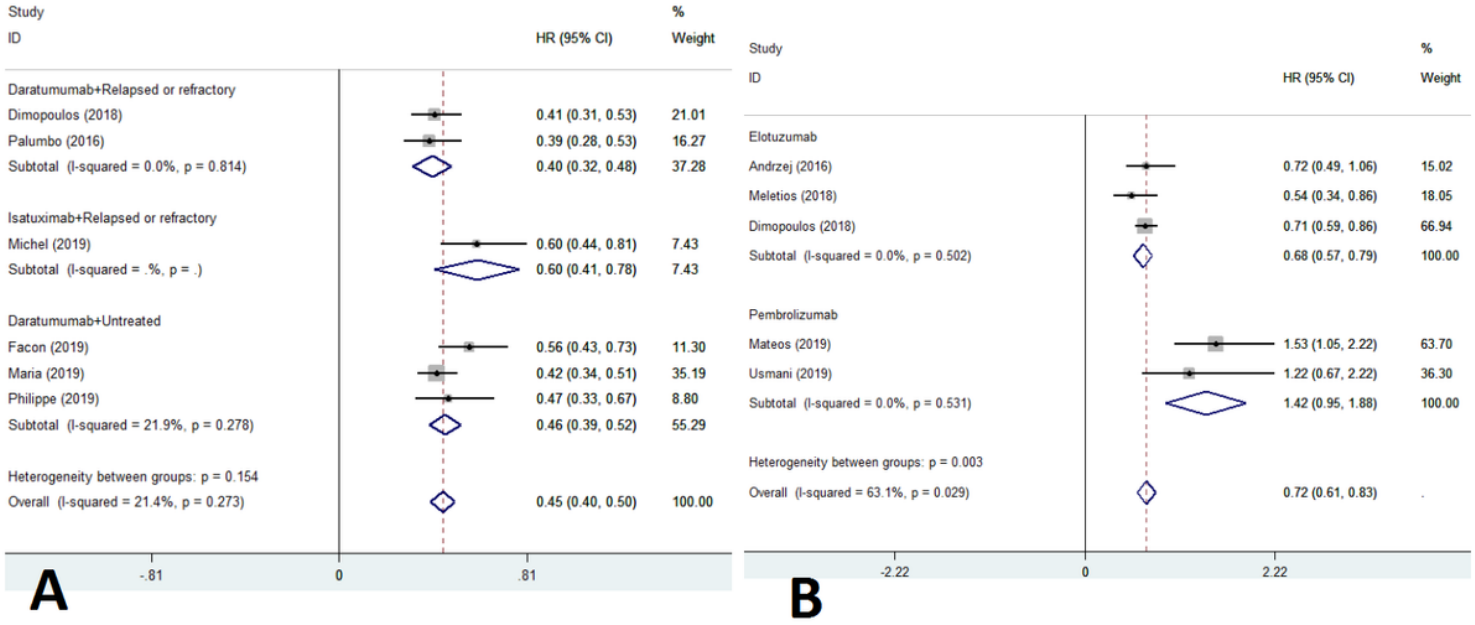

Figure 2

a Forest plots of the pooled HR for progression-free survival of the MAbs targeting CD38 (daratumumab, isatuximab) group versus the control group in patients with relapsed or refractory MM and untreated MM. The HR<1 favours the MAbs group b Forest plots of the pooled HR for progression-free survival of the MAbs targeting SLAMF7 (elotuzumab) group and PD-1/PD-L1 (pembrolizumab) group versus their corresponding control group in patients MM. The HR<1 favours the MAbs group

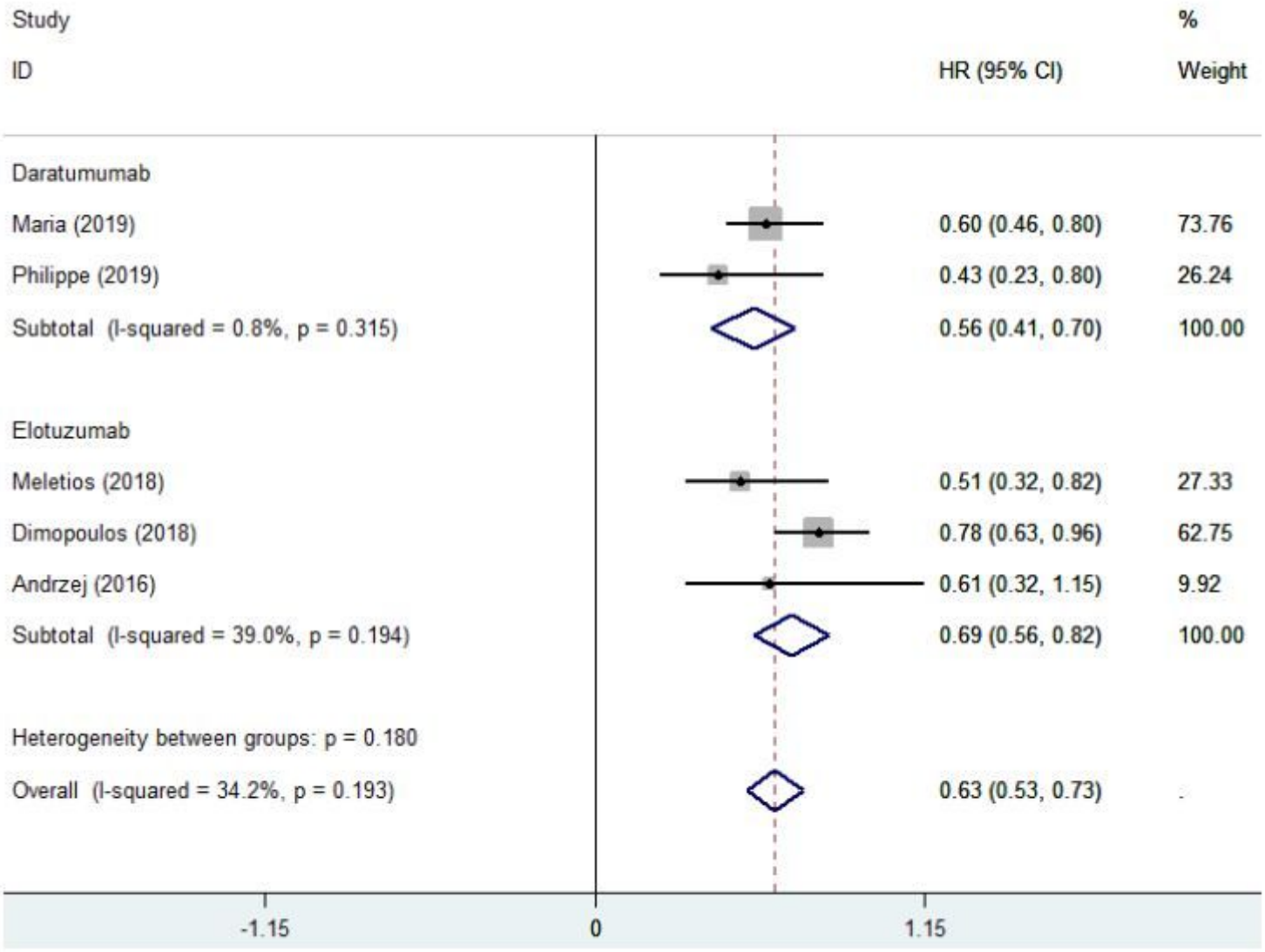

Figure 3

Forest plots of the pooled HR for overall survival of the MAbs targeting CD38 (daratumumab) group and SLAMF7(elotuzumab) group versus their corresponding control group in patients with MM. The HR<1 favours the MAbs group

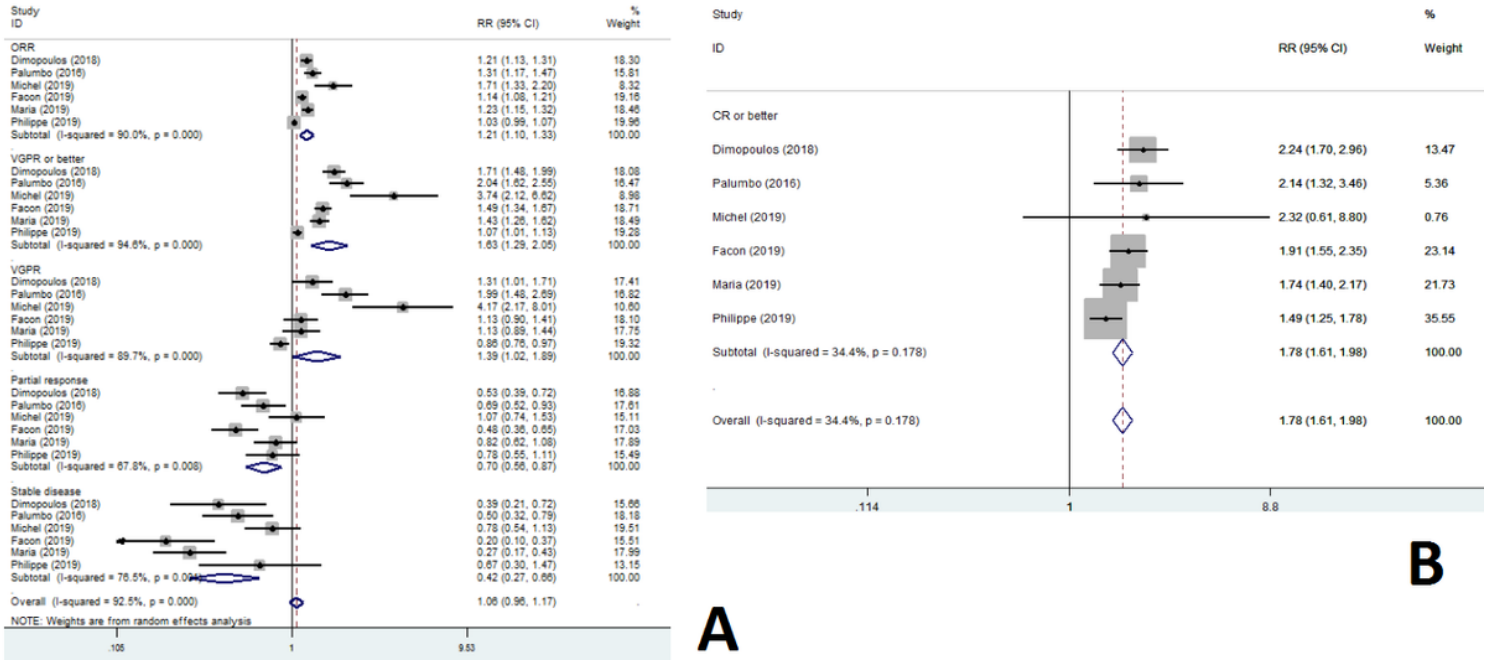

Figure 4

a Forest plots of the pooled RR for ORR, VGPR or better, VGPR, partial response and stable disease in the MAbs targeting CD38 group versus the control group in patients with MM. Abbreviation：overall response rate (ORR), very good partial response (VGPR). The RR>1 favours the MAbs group b Forest plots of the pooled RR for complete response or better in the MAbs targeting CD38 group versus the control group in patients with MM. The RR>1 favours the MAbs group

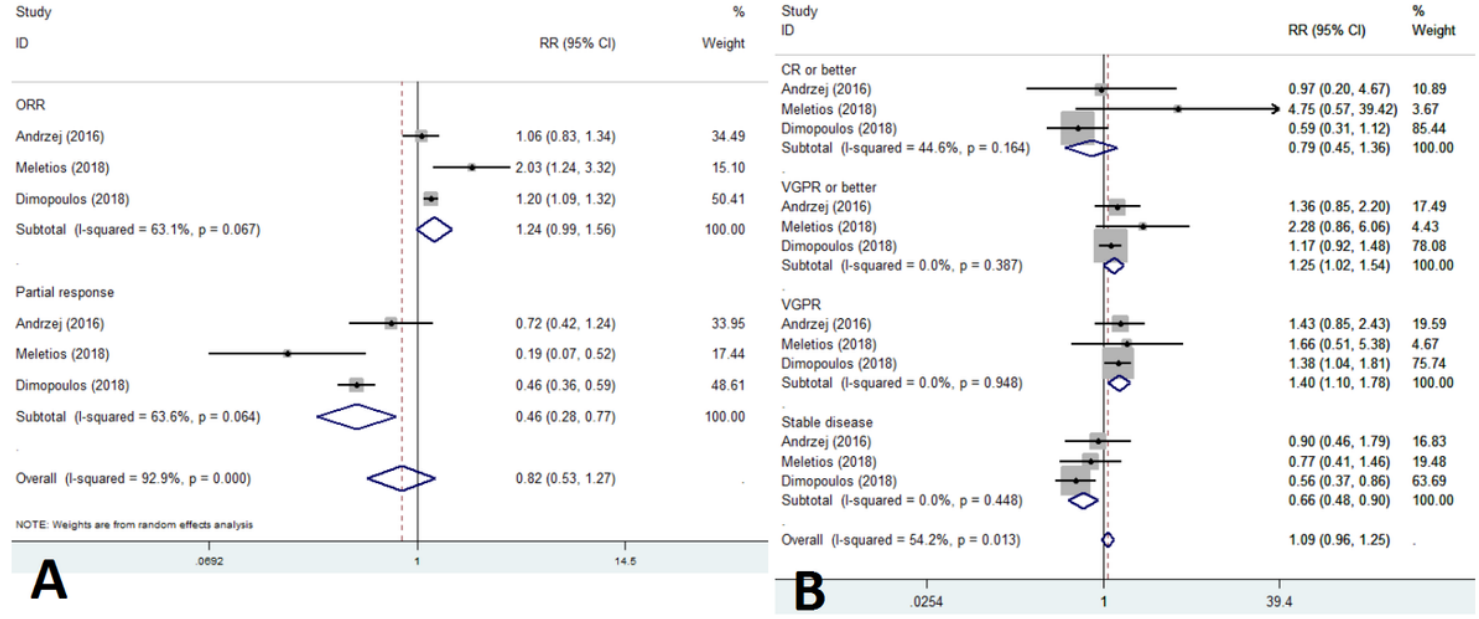

Figure 5

a Forest plots of the pooled RR for ORR and partial response in the MAbs targeting SLAMF7 group versus the control group in patients with MM. Abbreviation：overall response rate (ORR). The RR>1 favours the MAbs group b Forest plots of the pooled RR for CR or better ,VGPR or better, VGPR and stable disease in

the MAbs targeting SLAMF7 group versus the control group in patients with MM. Abbreviation：complete response(CR), very good partial response(VGPR). The RR>1 favours the MAbs group

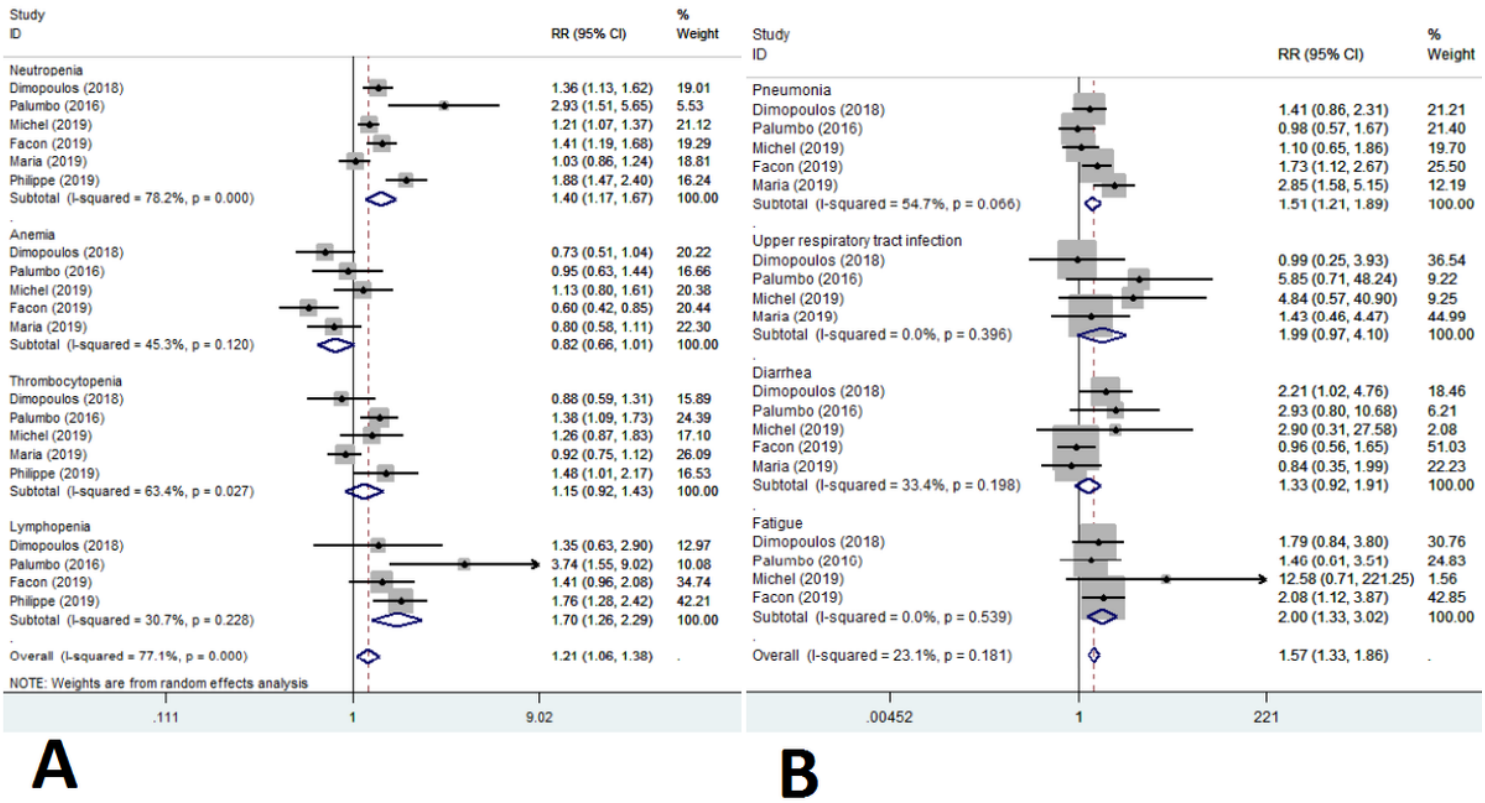

Figure 6

a Forest plots of the pooled RR for grade 3 or higher hematological adverse events (neutropenia, anemia, thrombocytopenia and lymphopenia) in the MAbs targeting CD38 group versus the control group in patients with MM.The RR<1 favours the MAbs group b Forest plots of the pooled RR for grade 3 or higher non-hematological adverse events (pneumonia, upper respiratory tract infection, diarrhea and fatigue) in the MAbs targeting CD38 group versus the control group in patients with MM. The RR<1 favours the MAbs group

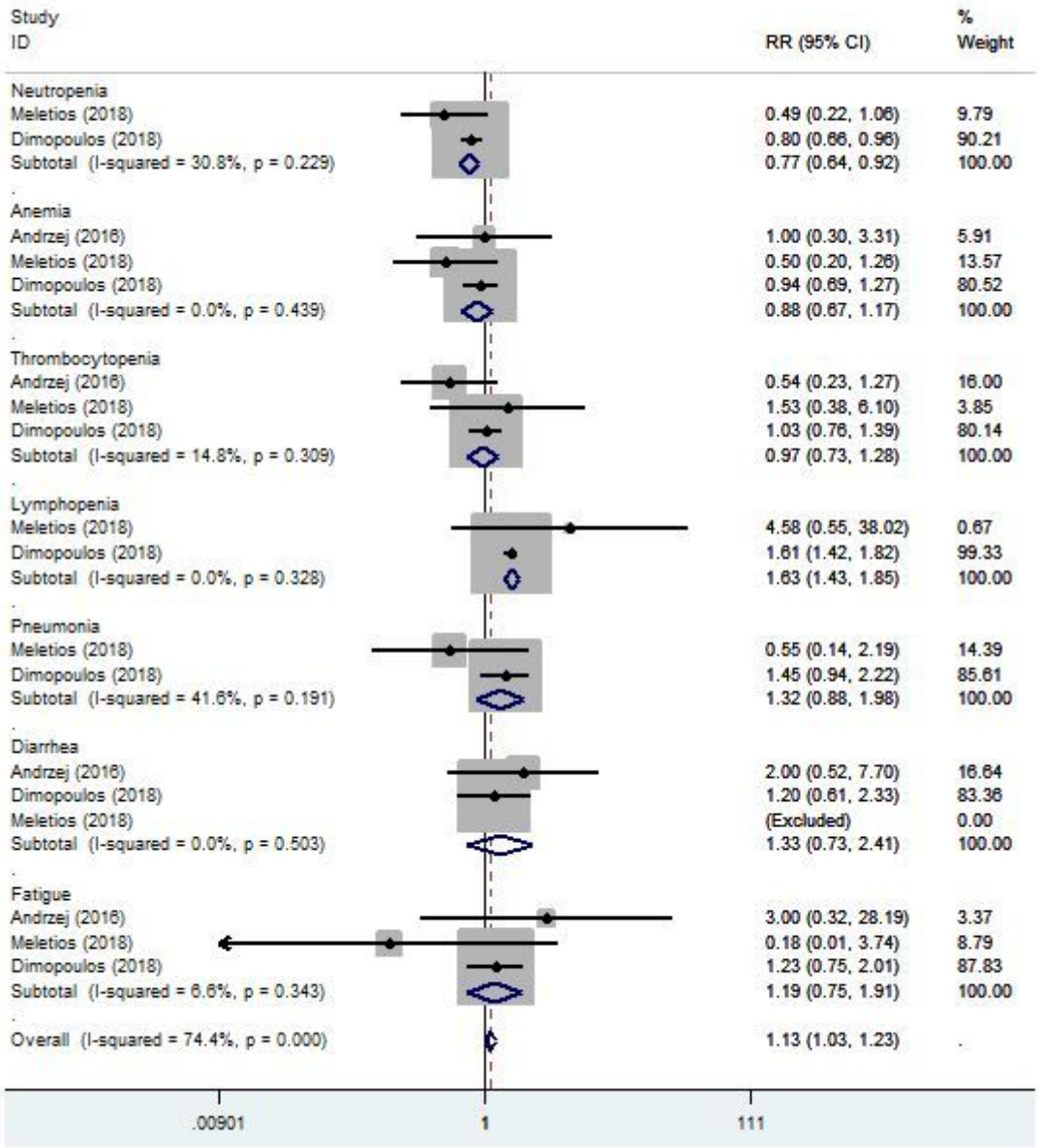

Figure 7

Forest plots of the pooled RR for grade 3 or higher hematological and non-hematological adverse events (neutropenia, anemia, thrombocytopenia, lymphopenia, pneumonia, diarrhea and fatigue) in the MAbs targeting SLAMF7 group versus the control group in patients with MM. The RR<1 favours the MAbs group

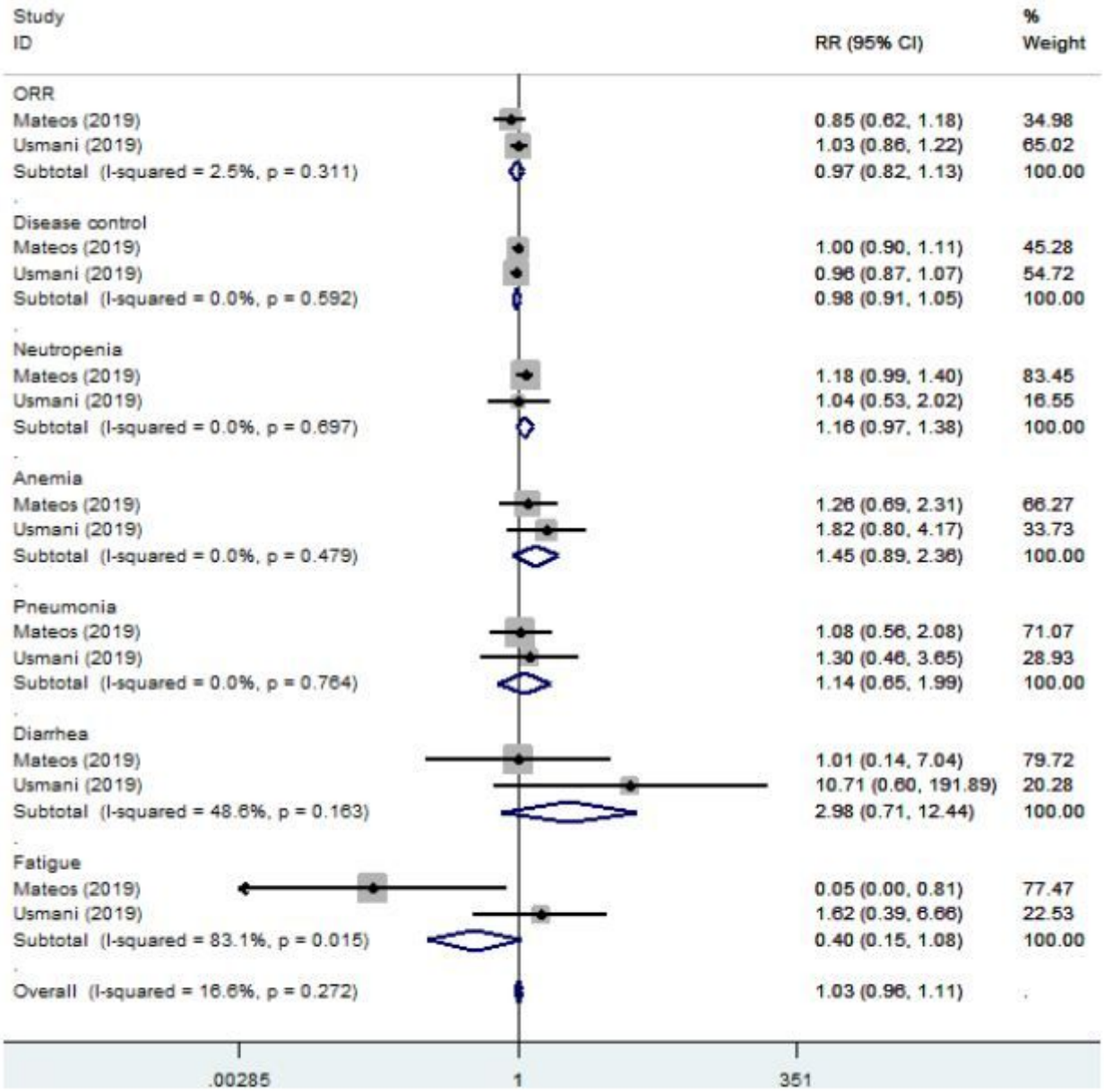

Figure 8

Forest plots of the pooled RR for ORR (overall response rate), disease control and grade 3 or higher hematological and non-hematological adverse events (neutropenia, anemia, pneumonia, diarrhea and fatigue) in the MAbs targeting PD-1/PD-L1 group versus the control group in patients with MM. The RR for ORR and disease control >1 favours the MAbs group. The RR for adverse events <1 favours the MAbs group

Supplementary Files

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