Multiple drug combinations of bortezomib, lenalidomide, and thalidomide for first-line treatment in adults with transplant-ineligible multiple myeloma: a network meta-analysis

Review information

Review type: Intervention

Review number: 18/04

Authors

Vanessa Piechotta[1], Tina Jakob[1], Peter Langer[1], Ina Monsef[1], Christof Scheid[2], Lise J Estcourt[3], Sunday Ocheni[4], Sebastian Theurich[5], Kathrin Kuhr[6], Benjamin Scheckel[1,7], Anne Adams[6], Nicole Skoetz[8]

[1]Cochrane Haematology, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany
[2]Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Stem Cell Transplantation Program, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany
[3]Haematology/Transfusion Medicine, NHS Blood and Transplant, Oxford, UK
[4]Department of Haematology & Immunology, University of Nigeria, Enugu, Nigeria
[5]Department of Medicine III, University Hospital LMU, Ludwig-Maximilians-Universität München, Munich, Germany
[6]Institute of Medical Statistics and Computational Biology, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany
[7]Institute of Health Economics and Clinical Epidemiology, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany
[8]Cochrane Cancer, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

Citation example: Piechotta V, Jakob T, Langer P, Monsef I, Scheid C, Estcourt LJ, Ocheni S, Theurich S, Kuhr K, Scheckel B, Adams A, Skoetz N. Multiple drug combinations of bortezomib, lenalidomide, and thalidomide for first-line treatment in adults with transplant-ineligible multiple myeloma: a network meta-analysis. Cochrane Database of Systematic Reviews 2019 , Issue 11 . Art. No.: CD013487. DOI: 10.1002/14651858.CD013487 .

Contact person

Vanessa Piechotta

Research Associate and PhD Student
Cochrane Haematology, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf
Faculty of Medicine and University Hospital Cologne, University of Cologne
Kerpener Str. 62
Cologne
NRW
50937
Germany

E-mail: vanessa.piechotta@uk-koeln.de

Dates

Assessed as Up-to-date:	14 February 2019
Date of Search:	14 February 2019
Next Stage Expected:	3 June 2021
Protocol First Published:	Not specified
Review First Published:	Issue 11 , 2019
Last Citation Issue:	Issue 11 , 2019

What's new

Date	Event	Description
25 November 2019	Amended	Minor formatting edit to improve readability of the Summary of Findings table in the published PDF.

History

Date	Event	Description

Abstract

Background

Multiple myeloma is a bone marrow-based hematological malignancy accounting for approximately two per cent of cancers. First-line treatment for transplant-ineligible individuals consists of multiple drug

combinations of bortezomib (**V**), lenalidomide (**R**), or thalidomide (**T**). However, access to these medicines is restricted in many countries worldwide.

Objectives

To assess and compare the effectiveness and safety of multiple drug combinations of V, R, and T for adults with newly diagnosed transplant-ineligible multiple myeloma and to inform an application for the inclusion of these medicines into the World Health Organization's (WHO) list of essential medicines.

Search methods

We searched CENTRAL and MEDLINE, conference proceedings and study registries on 14 February 2019 for randomised controlled trials (RCTs) comparing multiple drug combinations of V, R and T for adults with newly diagnosed transplant-ineligible multiple myeloma.

Selection criteria

We included RCTs comparing combination therapies of V, R, and T, plus melphalan and prednisone (MP) or dexamethasone (D) for first-line treatment of adults with transplant-ineligible multiple myeloma. We excluded trials including adults with relapsed or refractory disease, trials comparing drug therapies to other types of therapy and trials including second-generation novel agents.

Data collection and analysis

Two review authors independently extracted data and assessed risk of bias of included trials. As effect measures we used hazard ratios (HRs) for overall survival (OS) and progression-free survival (PFS) and risk ratios (RRs) for adverse events. An HR or RR < 1 indicates an advantage for the intervention compared to the main comparator MP. Where available, we extracted quality of life (QoL) data (scores of standardised questionnaires). Results quoted are from network meta-analysis (NMA) unless stated.

Main results

We included 25 studies (148 references) comprising 11,403 participants and 21 treatment regimens. Treatments were differentiated between restricted treatment duration (treatment with a pre-specified amount of cycles) and continuous therapy (treatment administered until disease progression, the person becomes intolerant to the drug, or treatment given for a prolonged period). Continuous therapies are indicated with a "**c**". Risk of bias was generally high across studies due to the open-label study design.

Overall survival (OS)

Evidence suggests that treatment with **RD** (HR 0.63 (95% confidence interval (CI) 0.40 to 0.99), median OS 55.2 months (35.2 to 87.0)); **TMP** (HR 0.75 (95% CI 0.58 to 0.97), median OS: 46.4 months (35.9 to 60.0)); and **VRDc** (HR 0.49 (95% CI 0.26 to 0.92), median OS 71.0 months (37.8 to 133.8)) probably increases survival compared to median reported OS of 34.8 months with MP (moderate certainty). Treatment with **VMP** may result in a large increase in OS, compared to MP (HR 0.70 (95% CI 0.45 to 1.07), median OS 49.7 months (32.5 to 77.3)), low certainty).

Progression-free survival (PFS)

Treatment with **RD** (HR 0.65 (95% CI0.44 to 0.96), median PFS: 24.9 months (16.9 to 36.8)); **TMP** (HR 0.63 (95% CI 0.50 to 0.78), median PFS:25.7 months (20.8 to 32.4)); **VMP** (HR 0.56 (95% CI 0.35 to 0.90), median PFS: 28.9 months (18.0 to 46.3)); and **VRDc** (HR 0.34 (95% CI 0.20 to 0.58), median PFS: 47.6 months (27.9 to 81.0)) may result in a large increase in PFS (low certainty) compared to MP (median reported PFS: 16.2 months).

Adverse events

The risk of **polyneuropathies** may be lower with **RD** compared to treatment with MP (RR 0.57 (95% CI 0.16 to 1.99), risk for RD: 0.5% (0.1 to 1.8), mean reported risk for MP: 0.9% (10 of 1074 patients affected), low certainty). However, the CIs are also compatible with no difference or an increase in neuropathies. Treatment with **TMP** (RR 4.44 (95% CI1.77 to 11.11), risk: 4.0% (1.6 to 10.0)) and **VMP** (RR 88.22 (95% CI 5.36 to 1451.11), risk: 79.4% (4.8 to 1306.0)) probably results in a large increase in polyneuropathies compared to MP (moderate certainty). No study reported the amount of participants with grade ≥ 3 polyneuropathies for treatment with **VRDc**.

VMP probably increases the proportion of participants with **serious adverse events** (SAEs) compared to MP (RR 1.28 (95% CI 1.06 to 1.54), risk for VMP: 46.2% (38.3 to 55.6), mean risk for MP: 36.1% (177 of 490 patients affected), moderate certainty). RD, TMP, and VRDc were not connected to MP in the network and the risk of SAEs could not be compared.

Treatment with **RD** (RR 4.18 (95% CI 2.13 to 8.20), NMA-risk: 38.5% (19.6 to 75.4)); and **TMP** (RR 4.10 (95% CI 2.40 to 7.01), risk: 37.7% (22.1 to 64.5)) results in a large increase of **withdrawals from the trial due to adverse events** (high certainty) compared to MP (mean reported risk: 9.2% (77 of 837 patients withdrew)). The risk is probably slightly increased with **VMP** (RR 1.06 (95% CI 0.63 to 1.81), risk: 9.75% (5.8 to 16.7), moderate certainty), while it is much increased with **VRDc** (RR 8.92 (95% CI 3.82 to 20.84), risk: 82.1% (35.1 to 191.7), high certainty) compared to MP.

Quality of life

QoL was reported in four studies for seven different treatment regimens (MP, MPc, RD, RMP, RMPc, TMP, TMPc) and was measured with four different tools. Assessment and reporting differed between studies and could not be meta-analysed. However, all studies reported an improvement of QoL after initiation of anti-myeloma treatment for all assessed treatment regimens.

Authors' conclusions

Based on our four pre-selected comparisons of interest, continuous treatment with VRD had the largest survival benefit compared with MP, while RD and TMP also probably considerably increase survival. However, treatment combinations of V, R, and T also substantially increase the incidence of AEs, and lead to a higher risk of treatment discontinuation. Their effectiveness and safety profiles may best be analysed in further randomised head-to-head trials. Further trials should focus on consistent reporting of safety outcomes and should use a standardised instrument to evaluate QoL to ensure comparability of treatment-combinations.

Plain language summary

Multiple drug combinations of bortezomib, lenalidomide and thalidomide for initial treatment of adults with transplant-ineligible multiple myeloma

Background

Multiple myeloma is a type of blood cancer. It accounts for approximately 2% of all cancers and is still considered incurable. For people with newly diagnosed multiple myeloma (NDMM), who are unsuitable for a procedure where damaged blood cells are replaced with healthy ones (stem-cell transplant), treatment is usually a multiple drug combination of bortezomib, lenalidomide, or thalidomide, plus melphalan and prednisolone (MP) or dexamethasone (D). Multiple drug combinations are approved for initial anti-myeloma therapy, however, access to these medicines is restricted in many countries worldwide.

Aim of the review

To compare the benefits and harms of selected anti-myeloma drugs (bortezomib (**V**), lenalidomide (**R**), thalidomide (**T**)) for transplant-unsuitable NDMM.

Study characteristics

We searched selected medical databases and trial registries until 14th February 2019. We included studies comparing multiple drug combinations of V, R, and T for the treatment of people with NDMM who were unsuitable for a stem-cell transplant. We differentiated between fixed treatment duration and continuous therapy. Fixed therapy is a pre-specified number of cycles, while a continuous therapy is given until the disease gets worse, the person finds the drug hard to tolerate, or when the treatment is given for a prolonged period. Continuous therapies are indicated with a "**c**".

Key results

We identified 25 studies involving 11,403 transplant-unsuitable adults with NDMM, and comparing 21 different treatment regimens.

Survival

People who had the standard treatment, MP, lived for an average of 35 months. People treated with **RD**, **TMP**, and **VRDc** probably live for much longer (moderate certainty). Treatment with **VMP** may also lead to much longer survival, compared to MP (low certainty). People treated with RD lived for an additional 20.4 months; with TMP an additional 11.6 months; with VRDc an additional 36.2 months, and with VMP an additional 14.9 months.

Harms

On average, 0.9% (9 out of 1000) of people treated with MP experienced peripheral nerve damage (polyneuropathies).The evidence was inconclusive whether treatment with **RD** decreases the risk of developing a polyneuropathy, compared to MP. The estimated risk of polyneuropathies with **RD** was 0.5%. Treatment with **TMP** and **VMP** probably increases the risk of experiencing polyneuropathies compared to MP (moderate certainty). The estimated risk with **TMP** was 4.0%, and with **VMP** 79.4%. No **VRDc** treatment study reported the number of participants with severe polyneuropathies.

On average, 36.1% (361 out of 1000) of people on MP-treatment experienced at least one serious adverse event (SAE). **VMP** probably increases the proportion of participants with SAEs compared to MP to 46.2% (moderate certainty).

On average, 9.2% (92 out of 1000) of people treated with MP stop the treatment because of adverse events (AEs). Treatment with **RD**, **TMP**, and **VRDc** leads to a much higher proportion of people stopping treatment because of AEs than MP (high certainty). The risk of stopping treatment with **RD** is 38.5%; with **TMP** 37.7%, with **VRDc** 82.1%. Treatment with **VMP** probably increases the risk of stopping treatment because of AEs compared to MP (9.75%, moderate certainty).

Quality of life

Quality of life (QoL) was reported in four studies for seven different treatments and was measured with four different tools. Assessment and reporting differed between studies and could not be meta-analysed. However, all

studies reported an improvement in QoL after anti-myeloma treatment was started for all assessed treatments.

Conclusions

VRDc showed the highest overall survival benefits, compared to MP. **RD** and **TMP** also improved OS compared to MP. However, these combinations of drugs also led to more adverse events compared to MP, and led to more people stopping treatment. More trials are needed that look carefully at both harms and QoL.

Background

Description of the condition

Multiple myeloma, also known as plasma cell myeloma, is a bone marrow-based hematological malignancy. Myeloma arises from asymptomatic premalignant monoclonal plasma cells via a multistep process of genetic and microenvironmental changes (Palumbo 2011). In contrast to other hematological malignancies, multiple myeloma is usually preceded by an age-progressive benign condition called monoclonal gammopathy of undetermined significance (MGUS), which further progresses to smouldering (asymptomatic) myeloma and finally to symptomatic myeloma (Anderson 2011; Kuehl 2012).

Early diagnosis of the condition is complicated by widely varying symptoms. Some patients might be symptom-free, while others present with common symptoms like fatigue, bone pain (mostly in the back, or hips), bone fractures, symptoms of light chain amyloidosis, or high calcium levels in the blood. Amongst others, the latter might lead to kidney problems, abdominal pain, or extreme thirst (The American Cancer Society 2018). The criteria for myeloma diagnosis have been revised in 2014 by the International Myeloma Working Group. These criteria are: presence of at least 10% clonal plasma cells in the bone marrow or biopsy-proven or extramedullary plasmacytoma and one (or more) myeloma-defining events (Table 1) (Rajkumar 2014).

To date, multiple myeloma is still considered incurable and accounts for approximately ten per cent of all hematological malignancies and two per cent of all cancers (Cancer Research UK 2018). Globally, there were 138,509 incident cases in 2016 (Cowan 2018). The incident rate increased worldwide by 126% between 1990 and 2016 and is strongly related to age (Cancer Research UK 2018; Cowan 2018). Based on the latest statistics in the USA, the median age of myeloma diagnosis across all races and both genders is 69 years of age (National Cancer Institute 2018). The prognosis of five-year survival differs widely between high-income countries and low- and middle-income countries. In the UK, 47% of people diagnosed with multiple myeloma are predicted to survive for at least five years (32.5% for at least 10 years). The reported five-year survival for men is 49.8%, and for women 43.8% (Cancer Research UK 2018). Later diagnosis and limited access to specialised health care reduces the survival period. In comparison, a recent study in Nigeria reported a five-year survival rate of only 7.6% (Nwabuko 2017).

Description of the intervention

First-line treatment for people with newly diagnosed multiple myeloma

The recommended first-line standard treatment for people with newly diagnosed multiple myeloma (NDMM) in good clinical condition consists of induction chemotherapy followed by high-dose chemotherapy with autologous stem cell transplantation (Moreau 2017). Some individuals with myeloma might be unsuitable for transplantation because of co-morbidities, frailty, or limited financial resources (Anderson 2015; Cowan 2018). The combination of melphalan and prednisone (MP) was the former standard treatment for individuals unsuitable for transplantation. This was modified after the introduction of so-called "novel agents" in the late 1990s to early 2000s. Since then, the preferred first-line therapy regimens for transplant-ineligible individuals, consists of two-, three- or multiple-drug combinations of novel agents. These agents belong to different drug classes including: proteasome inhibitors, e.g. bortezomib; immunomodulatory drugs, e.g. lenalidomide and thalidomide; and corticosteroids, e.g. dexamethasone and prednisone (Anderson 2015; Kumar 2018; Moreau 2017).

The introduction of immunomodulatory drugs and proteasome inhibitors in the treatment of transplant-ineligible individuals with NDMM has shown a major improvement in overall and progression-free survival (OS and PFS, respectively). Adding thalidomide (T) and lenalidomide (R) to the melphalan and prednisone (MP) standard regimen led to an increase of OS (40 months versus 31 months, respectively) (Wijermans 2010), and PFS in 65 to 75 year old adults (median PFS with RMP: (lenalidomide,melphalan and prednisone) 15 months versus median PFS with MP: 12 months) (Palumbo 2012), respectively. Extending the standard regimen with bortezomib (V) likewise increased OS (median OS with MP alone: 43.1 months versus 56.4 months with added bortezomib), resulting in a 31% death-risk reduction following VMP versus MP (San Miguel 2013). Furthermore, various two- and three-drug combinations of bortezomib, thalidomide, lenalidomide, dexamethasone, and cyclophosphamide are recommended options for the treatment of transplant-ineligible individuals with NDMM after showing highly satisfying results in OS and PFS (Anderson 2015; Moreau 2017). Selecting the best first-line myeloma treatment when faced with multiple effective drug regimens is challenging. Evidence-based, as well as consensus-based clinical practice guidelines recommend multiple treatment combinations, without stating a clear ranking of the options (Kumar 2018; Moreau 2017).

Fixed and continuous treatments

Nowadays anti-myeloma therapies are either administered as fixed or continuous therapies. Fixed therapy usually refers to a treatment with a fixed or pre-specified number of cycles. Continuous therapies in transplant-ineligible myeloma refers to: a therapy which is administered until progressive disease or emerging intolerances, a therapy where the treatment is given for a prolonged period but is still limited (e.g. until a plateau in response), or a therapy where an initial therapy is followed by maintenance treatment (Ludwig 2017b). The aim of continuous therapies is to prolong PFS and OS through improving the depth of the response and suppression of minimal residual disease (Richardson 2018). In the early days, anti-myeloma therapies were administered for a fixed duration of cycles, because long-term therapy with conventional chemotherapy agents led to an accumulating, indefensible toxicity. Introducing immunomodulatory drugs and proteasome inhibitors allowed the exploration of continuous therapies, as toxicities of these agents are less severe (Ludwig 2017b). However, although these agents are less toxic, accumulating toxicities of these drug classes are expected to be important. We therefore wanted to focus on drug-specific adverse events (polyneuropathy, neutropenia, anaemia, thrombocytopenia, thromboembolism, and infections) in this review.

Immunomodulatory drugs and proteasome inhibitors can reduce bone marrow activity (myelosuppression), which may lead to a decrease in red blood cells (anaemia), white blood cells (neutropenia), and platelets (thrombocytopenia) (Miceli 2008). Myelosuppression, especially severe neutropenia can substantially increase the risk of infections. Thalidomide decreases the neutrophil count during the treatment period (days one to 11), whereas lenalidomide decreases the platelet count. During the rest period (days 12 to 21), blood counts return to baseline. During bortezomib treatment thrombocytopenia is the most common haematological toxicity, occurring in around one third of patients, whereas significant neutropenia and anaemia are uncommon.

Bortezomib-induced peripheral neuropathy usually occurs within the first five courses of bortezomib administration and shows a significant dose-limiting toxicity of approximately 30 mg/m². Thereafter, typically it does not appear to increase (Argyriou 2008; Windebank 2008).

Generally, the risk for venous thromboembolism is increased in adults with myeloma. Single agent thalidomide or lenalidomide treatment does not increase this risk further. Hovewer, combining immunomodulatory drugs with steroids substantially increases the risk of venous thromboembolism (Palumbo 2008). Most events occur during the first six months of treatment (Kimpton 2016).

In this context, we decided to divide treatment regimens between fixed and continuous therapies to not only compare the effectiveness of treatment regimens, but also of different treatment durations, and to assess whether toxicity of continuous therapies is tolerable.

How the intervention might work

Proteasome-inhibitors and immunomodulatory drugs belong to a new generation of anti-cancer agents that work by targeting the microenvironment of the tumour, including specific cell receptors, proteins and signalling pathways (Bianchi 2015).

Approved proteasome inhibitors for myeloma treatment include the first-in-class agent bortezomib, and the second-generation agents carfilzomib, and ixazomib. The mode of action in the treatment of multiple myeloma is generally similar for all proteasome inhibitors. It is based on the supreme sensitivity of myeloma cells to the inhibition of the 26S proteasome. This is a critical complex of the ubiquitin-proteasome system and responsible for regulation and degradation of the majority of intracellular proteins. These proteins are involved in cell cycle progression, cell growth, and survival. In multiple myeloma, the ubiquitin-proteasome system is dysregulated, resulting in increased activity of proteasome 26S. This leads to a reduction in the levels of important proteins, like the tumour suppressor p53 and the inhibitor of the anti-apoptotic protein nuclear factor-κB, IκB. The continuous activity of the nuclear factor-κB transcription pathway enables myeloma cells to proliferate rapidly and drive tumour progression. Inhibition of the 26S proteasome leads to multiple downstream effects, resulting in growth arrest and cell death. As cancer cells have an increased level of proteasome activity in general, the pro-apoptotic effects of proteasome inhibitors can therefore be directly targeted (Gandolfi 2017; Moreau 2012).

Immunomodulatory drugs are glutamic acid derivatives presenting a wide range of biological activities. Their anti-myeloma properties consist of their immunomodulatory, anti-angiogenic, anti-inflammatory, and anti-proliferative properties, though their exact mechanism of action remains unclear. The molecular target of immunomodulatory drugs is Cereblon (reviewed in Asatsuma-Okumura 2019) and their binding to Cereblon leads to reduction of Ikaros zinc finger family proteins (IKZF) 1 and 3 by ubiquintination and degradation. IKFZ1 and 3 are critical for myeloma cell survival and downregulation of IKFZ1 and 3 suppressed myeloma cell lines in vitro (Fink 2015; Lu 2014). Three immunomodulatory drugs are clinically used for the treatment of multiple myeloma: thalidomide and its analogues, lenalidomide and pomalidomide (the latter only used in relapsed or refractory myeloma) (Quach 2010). Despite their similar structure, thalidomide, lenalidomide, and pomalidomide differ in their pharmacological properties (Holstein 2017). The immunomodulatory activities are based on the upregulation of T-cell (CD4+ and CD8+) and natural killer T-cell production and downregulation of regulatory T-cells, leading to an increased proliferation of natural killer cells and raised cytotoxicity (Bianchi 2015; Quach 2010). The T-cell proliferative effects of

lenalidomide are 50 to 2000 times higher than that of thalidomide and the effectiveness of T-cell IL-2 and IFNγ production augmentation is 300 to more than 1200 times higher (Quach 2010). Likewise, lenalidomide is more effective in decreasing the production of TNF-α, IL-1β, IL-6, and IL-12 than thalidomide (Holstein 2017). Increasing natural killer cell proliferation results in enhanced death of myeloma cell lines. In addition to the potentiation of natural killer cell proliferation, lenalidomide (not thalidomide) enhances antibody-dependent cellular cytotoxicity and natural cytotoxicity of natural killer cells, resulting in induced myeloma cell death (Quach 2010). The cytotoxic capacities of lenalidomide originate from multiple mechanisms, comprising inter alia the inhibition of nuclear factor-κB, downregulation of C/EBPβ (resulting in a decrease of interferon regulatory factor 4 production), activation of caspases, augmented expression of pro-apoptotic factors and likewise, deduction of anti-apoptotic factors, and the interruption of the PI3K/Akt pathway (Holstein 2017).

Combination therapies of proteasome inhibitors, immunomodulatory drugs and corticosteroids result in synergistic or enhanced activity of the anti-cancer agents on anti-myeloma properties (Gandolfi 2017). Corticosteroids probably enhance anti-cancer activity through the downregulation of IL-6-induced signalling pathways. Synergistic effects of proteasome inhibitors and immunomodulatory drugs are probably due to the combined effects of overlapping activation of caspase pathways, the activation of the proapoptotic BH-3 protein BIM, the downregulation of interferon regulatory factor 4, the proto-oncogene MYC, and the apoptosis regulator MCL1 in myeloma cells, and the inhibition of myeloma cell migration and angiogenesis (Gandolfi 2017).

Why it is important to do this review

Double- and triple-drug combinations of novel agents, such as bortezomib, lenalidomide, and thalidomide, are commonly used in high-income countries for first-line treatment of adults with multiple myeloma who are unsuitable for transplantation. However, high prices of these anti-myeloma medicines are limiting their availability in low- and middle-income countries (LMICs). According to the World Health Organization (WHO), about 150 countries worldwide use the WHO's list of essential medicines (EML) as a guidance for the development of national EMLs and reimbursement lists (IMS Institute for Healthcare Informatics 2015; World Health Organization 2019). However, currently anti-myeloma medicines are not in the EML. We therefore decided to prepare an application for the '22nd WHO Expert Committee on the Selection and Use of Essential Medicines' for the inclusion of anti-myeloma medicines into the EML. In several discussions with the respective WHO working group, we decided to focus on bortezomib, lenalidomide, and thalidomide, which belong to the first generation of proteasome-inhibitors and immunomodulatory drugs and are all approved for first-line treatment. In HICs, a second-generation of novel agents (e.g. the monoclonal antibody daratumumab) have already been introduced into treatments, however, they are much more expensive. We have therefore concentrated on bortezomib, lenalidomide and thalidomide only, as they more likely to be affordable and available in LMICs.

As there are few randomised controlled trials (RCTs) that perform direct head-to-head comparisons of different drug combinations, a systematic review and network meta-analysis was needed to evaluate the cumulative clinical evidence for the effectiveness and safety of these combinations and to create a clinically meaningful ranking of the treatments. The aim of our systematic review and network meta-analysis was to provide a comprehensive overview on the effectiveness and harms of novel agents for non-transplant first-line multiple myeloma treatment. The network meta-analysis allowed a hierarchy of the therapeutic options, in particular, if the benefits of one option compared to another translated into a clinically important difference. This comprehensive overview was necessary for clinical decision making, and has the potential to affect international guidelines, clinical pathways, and decision support systems for treatment strategies.

The results of this network meta-analysis will be published in the Cochrane Library and presented at national and international expert meetings and conferences (e.g. European Hematology Association). The results of the network meta-analysis have the potential to influence the design of new RCTs on novel agents for myeloma treatment. As patient-related outcomes were evaluated, a direct impact on patient care and treatment is expected.

Objectives

To compare the effectiveness of different combinations of one or more novel agents (bortezomib, lenalidomide, thalidomide) as treatment of adults with transplant-ineligible newly diagnosed multiple myeloma (NDMM) to generate a clinically meaningful treatment ranking according to their efficacy and safety and to inform an application for the inclusion of these medicines into the WHO's list of essential medicines.

Methods

Criteria for considering studies for this review

Types of studies

The protocol for this review was registered with PROSPERO (Piechotta 2018). We included studies if they were individually randomised controlled trials (RCTs). We included both full-text and abstract publications if sufficient information on study design, characteristics of participants and interventions provided. There was no limitation with respect to the length of follow-up.

We excluded studies that were cluster-randomised, non-randomised, case reports and clinical observations.

Types of participants

We included trials involving adults according to the definition in the studies (usually ≧ 18 years of age), with a newly confirmed diagnosis of multiple myeloma, irrespective of type and stage of cancer and gender. We assumed that participants who fulfil the inclusion criteria were equally eligible to be randomised to any of the interventions we planned to compare.

We excluded trials including adults with relapsed or refractory multiple myeloma.

Types of interventions

We included trials that included participants receiving a combination therapy of selected immunomodulatory drugs and/or proteasome inhibitors (bortezomib (**V**)*, lenalidomide (**R**)**, thalidomide (**T**)) in combination with a glucocorticoid (dexamethasone (**D**), or prednisone (**P**)) or a glucocorticoid and alkylating agent (cyclophosphamide (**C**)), or melphalan (**M**)) in at least one treatment arm for first-line treatment of transplant-ineligible myeloma patients.

* V stands for 'Velcade®', the proprietary name of bortezomib.

** R stands for 'Revlimid®', the proprietary name of lenalidomide.

Nowadays, the recommended treatment for adults with transplant-ineligible newly diagnosed multiple myeloma (NDMM) is either a double- or a triple-drug combination therapy (Kumar 2018; Moreau 2017), consisting of:

- **immunomodulatory drug** (R or T) in combination with a **glucocorticoid** (D, P) or **glucocorticoid and alkylating agent** (CD, CP or MP)
- **proteasome inhibitor** (V) in combination with a **glucocorticoid** (D, P) or **glucocorticoid and alkylating agent** (CD, CP or MP)
- **immunomodulatory drug** (R or T) in combination with **proteasome inhibitor** (V), and a **glucocorticoid** (D, P) or **glucocorticoid and alkylating agent** (CD, CP or MP)

Regimens, which include either an immunomodulatory drug or a proteasome inhibitor will be referred to as double-drug combinations. We will refer to triple-drug combinations, when a immunomodulatory drug and a proteasome inhibitor is included in the regimen.

Combinations of these interventions at any dose and by any route were compared to each other in a full network. We included trials with any treatment duration and divided treatment regimens between fixed and continuous therapies (Description of the intervention).To increase the amount of potential comparisons and to strengthen the network, we also included studies comparing the described double- or triple-drug combinations to the former standard treatment MP. As the aim of this review was to inform an application for the WHO list of essential medicines, the focus of this review was to compare the effectiveness and safety of V, R, and T. Therefore, if we identified additional new drugs for first-line treatment of multiple myeloma, these were excluded from the network and this review.

We assumed that any participant that meets the inclusion criteria was, in principle, equally likely to be randomised to any of the eligible interventions. We planned to group interventions by evaluating different drug doses together as one drug of interest, according to the product characteristics.

We excluded trials including participants receiving neither V, R, or T (triple or double combination) in at least one treatment arm, and trials including participants receiving no corticosteroid. We excluded trials evaluating the effectiveness and safety of the interventions of interest for supportive treatment during stem cell transplantation, or maintenance therapy, or both. Medications used to treat myeloma in subsequent lines of therapy might be the same as for first-line treatment, but to ensure that the assumption that participants within the included trials were similar, we focused on first-line treatment.

Comparison of direct interest

There are few randomised controlled trials comparing directly the effectiveness and safety of double- and triple-combination therapies of the agents of interest (V, R, T) for first-line treatment of adults with multiple myeloma. Therefore, there is a high degree of uncertainty about whether their effectiveness is comparable, and if not, which one is more effective or safer or both.

Additional interventions to supplement the analysis

Included trials should be comparable in terms of clinical and methodological criteria to ensure the transitivity assumption has been met (Chaimani 2017). Therefore, we did not include any additional interventions.

Types of outcome measures

We included all trials fitting the inclusion criteria mentioned above, irrespective of reported outcomes. We estimated the relative ranking of the competing interventions according to each of the following outcomes.

- Overall survival (OS): we used the longest follow-up available

- Progression-free survival (PFS): we used the longest follow-up available
- Grade 3 or 4 adverse events (AEs)* (with a special focus on polyneuropathy, neutropenia, anaemia, thrombocytopenia, thromboembolism, and infections): number of participants with at least one event
- Serious adverse events (SAEs): number of participants with at least one event
- Withdrawals due to AEs: number of participants
- Quality of life (QoL) measured at certain time points with a validated instrument (e.g. EORTC QLQ-C30)
  - short (one to three months)
  - medium (six to nine months)
  - long (12 months and longer

*The Grades are referring to the severity of AEs according to the Common Terminology Criteria for Adverse Events (CTCAE): Grade 1 refers to mild AEs; Grade 5 to death related to AEs

Search methods for identification of studies

Electronic searches

We searched the following databases without language restrictions. We searched for all possible comparisons formed by the interventions of interest. Thalidomide was the first of our agents of interest, which was used for anti-myeloma therapy. Therefore, we started the search in 1998, as thalidomide had been mentioned for the first time for myeloma treatment in 1999 (Singhal 1999).

- Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 2) in the Cochrane Library
- MEDLINE Ovid (1946 to 14 February 2019)

Medical subject headings (MeSH) or equivalent and text word terms were used. There were no language restrictions. Searches were tailored to individual databases. The search strategy for CENTRAL is in Appendix 1, the search strategies for MEDLINE in Appendix 2. No member of the author team had access to Embase at the time of the search, so we did not include Embase in our search strategy. We will search Embase in any future updates of this review.

Searching other resources

In addition, we searched the following databases/sources.

- Study registries (up to 14 February 2019, search criteria in Appendix 3)
  - EU clinical trials register: https://www.clinicaltrialsregister.eu/ctr-search/search
  - World Health Organization: http://apps.who.int/trialsearch/
  - Clinicaltrials.gov: https://clinicaltrials.gov/
  - ISRCTN: http://www.isrctn.com/
- Conference proceedings of annual meetings of the following societies for abstracts, were hand searched for abstracts published since 1 January 2010 up to 14 February 2019. Search criteria in Appendix 4).
  - American Society of Hematology
  - American Society of Clinical Oncology
  - European Hematology Association
- MEDLINE Ovid (1946 to 14 February 2019) for systematic reviews (Appendix 2): Additionally to searching MEDLINE for randomised controlled trials, we searched for systematic reviews and meta analyses on multiple myeloma. We screened all records to identify systematic reviews and meta analyses investigating immunotherapies for transplant-ineligible newly diagnosed multiple myeloma. We screened the included studies reference lists and compared them with the records of our Electronic searches.
- We checked reference lists of reviews and retrieved articles for additional studies and we performed citation searches on key articles.
- We contacted experts in the field for unpublished and ongoing trials.
- We contacted authors where necessary for additional information.

Data collection and analysis

Selection of studies

Two review authors (VP, NS) independently screened the results of the search strategies for eligibility for this review by reading the abstracts using Covidence software (Covidence systematic review software). We coded the abstracts as either 'include' or 'exclude'. In the case of disagreement, or if it was unclear whether we should retrieve the abstract or not, we obtained the full-text publication for further discussion. Independent review authors eliminated studies that clearly did not satisfy the inclusion criteria, and obtained full-text copies of the remaining studies. Two review authors read these studies independently to select relevant studies, and in the event of disagreement, a third author adjudicated. We did not anonymise the studies before assessment. We included a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (Figure 1) in the full review that shows the status of identified studies (Moher 2009) as recommended in Part 2, Section 11.2.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). We included studies in the review irrespective of whether measured outcome data were reported in a ‘usable’ way.

Data extraction and management

Two review authors (VP, BS) extracted data using a standardised data extraction form developed in Covidence (Covidence systematic review software). If the review authors were unable to reach a consensus, we consulted a third review author (NS) for final decision. If required, we contacted the authors of specific studies for supplementary information (Higgins 2011a). We contacted Prof. Jesús San Miguel (contact author of the VISTA trial (San Miguel 2008)) and asked how the primary endpoint time-to-progression was defined. The author responded that he is currently travelling, and suggested to search for the definition in the supplemental material of the paper. After agreement has been reached, we entered data into Review Manager (RevMan 2014). We extracted the following information.

- General information:
  - author, title, source, publication date, country, language, duplicate publications.
- Quality assessment:
  - sequence generation, allocation concealment, blinding (participants, personnel, outcome assessors), incomplete outcome data, selective outcome reporting, other sources of bias.
- Study characteristics:
  - trial design, aims, setting and dates, source of participants, inclusion/exclusion criteria, comparability of groups, subgroup analysis, treatment cross-overs, compliance with assigned treatment, length of follow-up.
- Participant characteristics:
  - newly diagnosed individuals, cytogenetic subtype, additional diagnoses, age, gender, ethnicity, number of participants recruited/allocated/evaluated, participants lost to follow-up, type of treatment (multi-agent standard treatment (intensity of regimen, number of cycles)).
- Interventions:
  - type, dose and cycles of treatment; duration of follow-up.
- Outcomes:
  - overall survival (OS), progression-free survival (PFS), grade 3 and 4 adverse events, serious adverse events(SAEs), polyneuropathies, neutropenia, anaemia, thrombocytopenia, thromboembolisms, infections, quality of life, withdrawals due to adverse events.
- Notes:
  - sponsorship/funding for trial and notable conflict of interest of review authors.

We collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. We collected characteristics of the included studies in sufficient detail to populate a Characteristics of included studies table in the full review.

Data on potential effect modifiers

We extracted from each included study data on the following.

- Intervention and population characteristics that may act as effect modifiers (age, stage of disease, performance score, treatment duration, duration of follow-up, region)
- Year of publication

Assessment of risk of bias in included studies

Two review authors (VP, BS) independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b), with any disagreements resolved by discussion. In order to rate the certainty of the evidence, risk of bias was assessed per endpoint rather than per study only. We completed a 'Risk of bias' table for each included study using the 'Risk of bias' tool in RevMan (RevMan 2014).

We assessed the following for each study.

- Random sequence generation (checking for possible selection bias): we assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). Studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number) were excluded.
- Allocation concealment (checking for possible selection bias): the method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated). Studies that do not conceal allocation (e.g. open list) were excluded.
- Blinding of participants and personnel (checking for possible performance bias). we assessed the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We assessed methods as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding, such as identical tablets matched in appearance or smell, or a double-dummy technique); unclear risk of bias (study states that it was blinded but did not provide an adequate description of how it was achieved). Studies that were not double-blinded are considered to have high risk of bias.
- Blinding of outcome assessment (checking for possible detection bias). we assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We

assessed the methods as: low risk of bias (study has a clear statement that outcome assessors were unaware of treatment allocation, and ideally describes how this was achieved); unclear risk of bias (study states that outcome assessors were blind to treatment allocation, but lacks a clear statement on how it was achieved). Studies where outcome assessment were not blinded were considered as having a high risk of bias. We assessed blinding of outcome assessment in three separate outcome-categories:
  - not dependent on outcome assessor: OS;
  - partly dependent on outcome assessor: PFS;
  - dependent on outcome assessor: safety outcomes.
- Selective reporting (checking for reporting bias): we assessed whether primary and secondary outcome measures were pre-specified and whether these were consistent with those reported: low risk of bias (study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that were of interest in the review have been reported in the pre-specified way, or the study protocol was not available but it was clear that the published reports include all expected outcomes, including those that were pre-specified); unclear risk of bias (insufficient information to permit judgement of 'low risk' or 'high risk'); high risk of bias (not all of the study's pre-specified primary outcomes have been reported or one or more primary outcomes were reported using measurements, analysis methods or subsets of the data that were not pre-specified or one or more reported primary outcomes were not pre-specified or one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis, or the study report fails to include results for a key outcome that would be expected to have been reported for such a study).
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data): we assessed the methods used to deal with incomplete data in two separate outcome categories:
  - time to event data: low risk (censored Kaplan-Meier curves were provided and study discontinuations were described and balanced between arms); unclear risk (neither Kaplan-Meier curves, nor flow-charts were accessible); high risk ('last observation carried forward' analysis);
  - safety data: low risk (safety data was only reported for patients, who received at least one study drug); high risk (intention-to-treat population was used to report safety data, however it was stated that participants changed to the other study arm or stopped the study before they received the first dose); unclear risk (it was not described, which population was used to report safety outcomes.

Measures of treatment effect

Relative treatment effect

We used intention-to-treat data. For binary outcomes, we extracted number of patients and number of events per arm and calculated risk ratios (RRs) with 95% confidence intervals (CIs) for each trial. For time-to-event outcomes, we extracted hazard ratios (HRs) from published data according to Parmar 1998 and Tierney 2007. We checked whether the study authors had checked the proportional hazards assumption. For quality of life (QoL) data, we had planned to calculate continuous outcomes as mean differences (MDs) when assessed with the same instruments; otherwise we had planned to calculate standardised mean differences (SMDs) with 95% CIs. As reporting of QoL data was scarce, network meta-analysis was not possible and MDs and SMDs were not calculated. We will do as described in an update of this review.

Relative treatment ranking

We obtained a treatment hierarchy using P scores (Rücker 2015). P scores allow ranking treatments on a continuous zero to one scale (higher P score is indicating the better treatment) in a frequentist network meta-analysis.

Unit of analysis issues

Studies with multiple treatment groups

As recommended in Chapter 16.5.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c), for studies with multiple treatment groups we combined arms as long as they could be regarded as subtypes of the same intervention.

When arms could not be pooled this way, we included multi-arm trials using an network meta-analysis approach that accounted for the within-study correlation between the effect sizes by re-weighting all comparisons of each multi-arm study (Rücker 2012; Rücker 2014). For pairwise meta-analysis, we treated multi-arm studies as multiple independent comparisons and did not combine these data in any analysis.

Dealing with missing data

As suggested in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c), we took the following steps to deal with missing data.

Whenever possible, we contacted the original investigators to request relevant missing data. We contacted Prof. Jesús San Miguel (contact author of the VISTA trial (San Miguel 2008)) and asked how the primary endpoint time-to-progression was defined. The author responded that he is currently travelling, and suggested to search for the definition in the supplemental material of the paper. There we could also find data on PFS. If the number of participants evaluated for a given outcome was not reported, we used the number of participants randomised per treatment arm as the denominator. If only percentages but no absolute number of events were reported for

binary outcomes, we calculated numerators using percentages. If estimates for mean and standard deviations were missing, we calculated these statistics from reported data whenever possible, using approaches described in Chapter 7.7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). If data were not reported numerically but graphically, we estimated missing data from figures. We addressed in the Discussion section the potential impact of missing data on findings of the review.

Assessment of heterogeneity

Assessment of clinical and methodological heterogeneity within treatment comparisons

To evaluate the presence of clinical heterogeneity, we generated summary statistics for the important clinical and methodological characteristics across all included studies. Within each pairwise comparison, we assessed the presence of clinical heterogeneity by visually inspecting the similarity of these characteristics.

Assessment of transitivity across treatment comparisons

To ensure that the assumption of transitivity was justified, we assessed whether the characteristics of included studies were similar; for example inclusion criteria, study period, dosing, route of administration, co-medication. Furthermore, we assessed whether the patient characteristics were similar across treatment comparisons; for example age, gender, stage of disease, Eastern Cooperative Oncology Group (ECOG) performance score.

Assessment of statistical heterogeneity and inconsistency

To evaluate the presence of heterogeneity and inconsistency in the entire network, we gave the generalised heterogeneity statistic Q_{total} and the generalised I^2 statistic, as described in Schwarzer 2015. We used the decomp.design command in the R package netmeta (R 2018; Rücker 2018) for decomposition of the heterogeneity statistic into a Q statistic for assessing the heterogeneity between studies with the same design and a Q statistic for assessing the designs inconsistency to identify the amount of heterogeneity/inconsistency within as well as between designs.

To evaluate the presence of inconsistency locally, we compared direct and indirect treatment estimates of each treatment comparison. This can serve as a check for consistency of a network meta-analysis (Dias 2010). For this purpose, we used the netsplit command in the R package netmeta, which enables the splitting of the network evidence into direct and indirect contributions (R 2018; Rücker 2018). For each treatment comparison, we presented direct and indirect treatment estimates plus the network estimate using forest plots. In addition, for each comparison we gave the z-value and P value of test for disagreement (direct versus indirect). It should be noted that in a network of evidence there may be many loops and with multiple testing there is an increased likelihood to find an inconsistent loop by chance. Therefore, we were cautious deriving conclusions from this approach.

If we found substantive heterogeneity and/or inconsistency, we explored possible sources by performing pre-specified sensitivity and subgroup analyses (see below). In addition, we reviewed the evidence base, reconsidered inclusion criteria as well as discussed the potential role of unmeasured effect modifiers to identify further sources.

Assessment of reporting biases

In pairwise comparisons with at least 10 trials, we examined the presence of small-study effects graphically by generating funnel plots. As we had no such comparison, we were unable to assess small-study effects. In future updates, we will use linear regression tests (Egger 1997) to test for funnel plot asymmetry. A P value less than 0.1 will be considered significant for this test (Sterne 2011). We will examine the presence of small-study effects for the OS only.

Moreover, we searched study registries, to identify completed, but not published trials.

Data synthesis

Methods for direct treatment comparisons

Pairwise comparisons were part of the network meta-analysis, thus we did not plan to perform pairwise meta-analysis in addition. In order to outline available direct evidence, we provided forest plots for pairwise comparisons, without giving an overall estimate. Only when data could not combined in a network meta-analysis, e.g. due to inconsistency, did we performed pairwise meta-analyses according to recommendations provided in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We used random-effects models. We used the R package meta (R 2018; Schwarzer 2018) for statistical analyses. When trials were clinically too heterogenous to be combined, we performed only subgroup analyses without calculating an overall estimate.

Methods for indirect and mixed comparisons

Where we considered the data to be sufficiently similar to be combined, we performed a network meta-analysis using the frequentist weighted least squared approach described by Rücker 2012. We used a random-effects model, taking into account the correlated treatment effects in multi-arm studies. We assumed a common estimate for the heterogeneity variance across the different comparisons. To evaluate the extent to which treatments were connected, we gave a network plot for all outcomes. For each comparison, we gave the

estimated treatment effect along with its 95% CI. We graphically presented the results using forest plots, with melphalan/prednisone as reference. We used the R package netmeta (R 2018; Rücker 2018) for statistical analyses.

GRADE

Quality of the evidence

Two review authors independently rated the certainty of the evidence for pre-selected outcomes (OS, PFS, SAEs, withdrawals due to AEs, polyneuropathies, QoL) and comparisons (RD, TMP, VMP, and VRDc, respectively compared to MP), respectively. We used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system to rank the certainty of the evidence using the GRADEprofiler Guideline Development Tool software (McMaster 2015), and the guidelines provided in Chapter 12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions (*Schünemann 2011a) and specifically for network meta-analyses (Puhan 2014).

The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the body of evidence for each outcome. The GRADE system uses the following criteria for assigning grade of evidence.

- High = we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate = we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- Low = our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low = we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

The GRADE system uses the following criteria for assigning a certainty level to a body of evidence (Chapter 12, Schünemann 2011a).

- High: randomised trials; or double-upgraded observational studies.
- Moderate: downgraded randomised trials; or upgraded observational studies.
- Low: double-downgraded randomised trials; or observational studies.
- Very low: triple-downgraded randomised trials; or downgraded observational studies; or case series/case reports.

We decreased grade if:

- serious (-1) or very serious (- 2) limitation to study quality;
- important inconsistency (- 1);
- some (-1) or major (- 2) uncertainty about directness;
- imprecise or sparse data (- 1);
- high probability of reporting bias (- 1).

'Summary of findings' table

We included a 'summary of findings' table to present the main findings in a transparent and simple tabular format. In particular, we included key information concerning the certainty of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the outcomes OS, PFS, SAEs, withdrawals due to AEs, polyneuropathies and QoL for the treatment combinations of RD, TMP, VMP, and VRDc, respectively compared to MP.

To obtain the median survival times (OS and PFS, respectively) for each of our selected comparisons, we applied the network meta-analysis hazard ratio (NMA-HR) to the assumed median survival times of our comparator melphalan and prednisone as recommended in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019) and by Tierney 2007, e.g.:

median OS for patients treated with intervention x = median survival for patients treated with comparator/ corresponding NMA-HR (intervention x versus comparator).

Subgroup analysis and investigation of heterogeneity

We considered performing subgroup analyses using the following characteristics.

- Follow-up (short-term (< 5 years) versus long-term >= 5 years)
- Multiple myeloma international staging system (I, II, III)
- Age (<75 versus >75)
- Region (low- and middle-income versus high-income)

Subgroup analysis could not be performed due to the characteristics of included studies. The detailed reasons for incomplete subgroup analysis have been outlined in the Differences between protocol and review section of this review.

Sensitivity analysis

To test the robustness of the results, we conducted fixed-effect pairwise and network meta-analyses. We

reported the estimates of the fixed-effect only if they showed a difference to the random-effects model. We had planned to explore the influence of quality components with regard to low and high risk of bias.

Risk of bias sensitivity analysis could not be performed for each outcome due to overall high risk of included studies. The detailed reasons for incomplete sensitivity analysis have been outlined in the 'Differences between protocol and review' section of this review.

Results

Results

Description of studies

Results of the search

The primary electronic searches performed in June 2018 and February 2019 yielded a total of 9416 potentially relevant references related to the treatment of multiple myeloma. Of these, we identified 1706 as duplicates and excluded 7509 at the initial stage of screening because they did not fulfil our predefined inclusion criteria. The remaining 209 publications were retrieved as full-text publications or abstract publications for detailed evaluation, out of which 61 (33 studies) were excluded. Reasons for exclusion included: regimen included novel agents which were excluded for our review; comparator not of interest; induction regimen not of interest and/or followed by transplantation; transplant-setting; prior therapy or relapsed/refractory myeloma; not randomised controlled trial (RCT); and sequential versus alternating regimens (no evaluation of individual drug combination possible). Five additional records were identified through the screening of reference lists of relevant studies. So finally, 25 studies (148 references) with 11,403 patients were formally included in this review. One study did not report any of our pre-specified outcomes and could therefore not be included in the main analyses of this review. Overall, we could include 24 studies with 11,337 patients in the main analysis.

The overall number of trials screened, identified, selected, excluded and included are documented in a PRISMA flow diagram (Figure 1).

Included studies

A total of 25 trials met our pre-specified eligibility criteria. The trials included a total of 11,403 randomised participants from Europe, Asia, North- and South America, and the Pacific region, with a median age ranging from 52 to 78.5 years. The first patient enrolment started in August 2001 (Ludwig 2009), and two trials are still ongoing (Magarotto 2016; Pawlyn 2017). Twenty trials were published as full texts, four trials were only published as an abstract (Katsuoka 2013; Kim 2007; Mookerjee 2017; Pawlyn 2017), and one trial has only been published as a letter to the editor (Jacobus 2016). Individual patient data of six trials comparing thalidomide plus melphalan plus prednisone (TMP) versus melphalan plus prednisone (MP) has also been meta-analysed (Fayers 2011; Palumbo 2013). Presuming higher comparability between the single studies, we extracted all available data from this meta-analysis as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). The characteristics of the included studies are summarised in the table Characteristics of included studies.

Design

All included trials were RCTs. The majority of trials were open-label, however two studies (Palumbo 2012; Waage 2010) were double-blind and placebo-controlled. Of the 25 included trials, 20 were two-armed RCTs; and five were three-armed RCTs (Bahlis 2017; Hungria 2016; Magarotto 2016; Niesvizky 2015; Palumbo 2012). The duration of treatment varied in each study based on differences in the duration and number of treatment cycles and the possibility of continuous treatment or maintenance treatment.

- In seven trials, participants received a previously defined amount of treatment cycles (Beksac 2011; Facon 2007; Hulin 2009; Hungria 2016; Jacobus 2016; Sacchi 2011; San Miguel 2008).
- In seven trials, all participants received maintenance treatment (Durie 2017;Ludwig 2009; Magarotto 2016; Mateos 2014; Niesvizky 2015; Stewart 2015; Zweegman 2016).
- In five trials, only participants in one arm of the study received maintenance treatment:
  - in the trial of Palumbo 2012, one arm received lenalidomide maintenance treatment, two arms received placebo maintenance;
  - in two trials one arm received maintenance treatment and one arm did not; whereas both arms received initial treatment until a plateau in response was reached (Waage 2010; Wijermans 2010);
  - In two trials the experimental arm received maintenance treatment and the control arm did not (Palumbo 2006; Palumbo 2014).
- In the trial of Bahlis 2017, one arm received continuous treatment, and two arms received a fixed amount of treatment cycles.
- In two trials, participants were randomised between maintenance and observation regardless of previous therapy (Morgan 2011; Pawlyn 2017).
- Three trials did not provide any information regarding maintenance treatment (Katsuoka 2013; Kim 2007; Mookerjee 2017).

Sample sizes

The smallest trial had a sample size of 18 participants (Katsuoka 2013), while the largest trial had a sample size of 1852 participants (Pawlyn 2017).

Location

The majority of trials were multi-centre trials and included participants from Europe, Asia, North- and South America, Australia, and the Pacific region. Seventeem trials included participants from European Countries (Bahlis 2017; Beksac 2011; Facon 2007; Hulin 2009; Ludwig 2009; Magarotto 2016; Mateos 2014; Morgan 2011; Palumbo 2006; Palumbo 2012; Palumbo 2014; Pawlyn 2017; Sacchi 2011; San Miguel 2008; Waage 2010; Wijermans 2010; Zweegman 2016), six trials from northern America (Bahlis 2017; Durie 2017; Jacobus 2016; Niesvizky 2015; San Miguel 2008; Stewart 2015), and Asia (Bahlis 2017; Katsuoka 2013; Kim 2007; Palumbo 2012; San Miguel 2008; Stewart 2015), respectively; two trials from southern America (Hungria 2016; San Miguel 2008), and one trial from Australia (Palumbo 2012) and the Pacific region (Bahlis 2017), respectively.

Participants

All trials included adults (at least 18 years old) with newly diagnosed multiple myeloma (NDMM) with measurable disease according to either the Durie-Salmon staging system or International Staging System (ISS). Participants were either ineligible for transplant because they were too old (more than 65 years old) or because of significant co-morbidities or because stem cell transplantation was not planned. Women of childbearing age had to agree to use adequate contraception.

Interventions

In addition to the differentiation between drug combinations, treatment regimens were differentiated into fixed therapy (first-line therapy was stopped after a pre-specified amount of therapy cycles) and continuous therapy (first-line treatment followed by maintenance therapy, continuous first-line therapy, or continuous first-line therapy until a plateau phase (response) was reached). Accordingly, the included participants were randomised to a total of 21 different treatment regimens.

- Melphalan and prednisone (MP)
- Continuous melphalan and prednisone (MPc)
- Lenalidomide plus cyclophosphamide plus dexamethasone (RCD)
- Continuous lenalidomide plus cyclophosphamide plus prednisone (RCPc)
- Lenalidomide and dexamethasone (RD)
- Continuous lenalidomide and dexamethasone (RDc)
- Lenalidomide plus melphalan plus prednisone (RMP)
- Continuous lenalidomide plus melphalan plus prednisone (RMPc)
- Thalidomide plus cyclophosphamide plus dexamethasone (TCD)
- Continuous thalidomide and dexamethasone (TDc)
- Thalidomide plus melphalan plus prednisone (TMP)
- Continuous thalidomide plus melphalan plus prednisone (TMPc)
- Bortezomib and dexamethasone (VD)
- Continuous bortezomib and dexamethasone (VDc)
- Bortezomib plus melphalan plus prednisone (VMP)
- Continuous bortezomib plus melphalan plus prednisone (VMPc)
- Bortezomib plus lenalidomide plus dexamethasone (VRD)
- Continuous bortezomib plus lenalidomide plus dexamethasone (VRDc)
- Continuous bortezomib plus thalidomide plus dexamethasone (VTDc)
- Continuous bortezomib plus thalidomide plus melphalan plus prednisone (VTMPc)
- Continuous bortezomib plus thalidomide plus prednisone (VTPc)

Outcome measures

Survival outcomes

Out of the 25 trials, included in this review, 24 reported overall survival (OS) (Bahlis 2017; Beksac 2011; Durie 2017; Facon 2007; Hulin 2009; Hungria 2016; Jacobus 2016; Kim 2007; Ludwig 2009; Magarotto 2016; Mateos 2014; Mookerjee 2017; Morgan 2011; Niesvizky 2015; Palumbo 2006; Palumbo 2012; Palumbo 2014; Pawlyn 2017; Sacchi 2011; San Miguel 2008; Stewart 2015; Waage 2010; Wijermans 2010; Zweegman 2016) and progression-free survival (PFS) (Bahlis 2017; Beksac 2011; Durie 2017; Facon 2007; Hulin 2009; Hungria 2016; Jacobus 2016; Kim 2007; Ludwig 2009; Magarotto 2016; Mateos 2014; Mookerjee 2017; Morgan 2011; Niesvizky 2015; Palumbo 2006; Palumbo 2012; Palumbo 2014; Pawlyn 2017; Sacchi 2011; San Miguel 2008; Stewart 2015; Waage 2010; Wijermans 2010; Zweegman 2016).

The Cox proportional hazards model was used by all study authors to calculate hazard ratios (HRs) of survival outcomes. However, it is not clear whether all of the trials checked the assumption of proportional hazards.

Safety outcomes

Grade 3 or 4 adverse events were reported in nine studies (Durie 2017; Katsuoka 2013; Ludwig 2009; Magarotto 2016; Niesvizky 2015; Palumbo 2006; Stewart 2015; Wijermans 2010; Zweegman 2016). Reporting of

individual grade 3 and 4 adverse events (AEs) was more frequent: polyneuropathy was reported in 18 trials (Bahlis 2017; Beksac 2011; Facon 2007; Hulin 2009; Hungria 2016; Katsuoka 2013; Magarotto 2016; Mateos 2014; Niesvizky 2015; Palumbo 2006; Palumbo 2012; Palumbo 2014; Pawlyn 2017; Sacchi 2011; San Miguel 2008; Stewart 2015; Waage 2010; Zweegman 2016); infections in 15 trials (Bahlis 2017; Beksac 2011; Durie 2017; Facon 2007; Magarotto 2016; Mateos 2014; Morgan 2011; Niesvizky 2015; Palumbo 2006; Palumbo 2012; Palumbo 2014; Sacchi 2011; Waage 2010; Wijermans 2010; Zweegman 2016); thromboembolism in 14 trials (Facon 2007; Hulin 2009; Hungria 2016; Mateos 2014; Mookerjee 2017; Morgan 2011; Palumbo 2006; Palumbo 2014; Sacchi 2011; San Miguel 2008; Stewart 2015; Waage 2010; Wijermans 2010; Zweegman 2016); neutropenia in 14 trials (Bahlis 2017; Facon 2007; Hulin 2009; Hungria 2016; Magarotto 2016; Mateos 2014; Niesvizky 2015; Palumbo 2006; Palumbo 2014; Pawlyn 2017; Sacchi 2011; San Miguel 2008; Stewart 2015; Zweegman 2016); anaemia in 14 trials (Bahlis 2017; Facon 2007; Hungria 2016; Ludwig 2009; Magarotto 2016; Mateos 2014; Mookerjee 2017; Niesvizky 2015; Palumbo 2006; Palumbo 2012; Palumbo 2014; San Miguel 2008; Stewart 2015; Zweegman 2016); and thrombocytopenia in 12 trials (Bahlis 2017; Facon 2007; Hungria 2016; Ludwig 2009; Magarotto 2016; Mateos 2014; Niesvizky 2015; Palumbo 2006; Palumbo 2012; Palumbo 2014; San Miguel 2008; Zweegman 2016). Serious adverse event (SAE) data were available in eight studies (Bahlis 2017; Durie 2017; Jacobus 2016; Mateos 2014; Niesvizky 2015; Palumbo 2012; San Miguel 2008; Stewart 2015). The outcome “withdrawals due to adverse events” was defined in retrospect and reported in 16 studies (Bahlis 2017; Durie 2017; Hulin 2009; Hungria 2016; Ludwig 2009; Magarotto 2016; Mateos 2014; Niesvizky 2015; Palumbo 2006; Palumbo 2012; Palumbo 2014; Sacchi 2011; San Miguel 2008; Waage 2010; Wijermans 2010; Zweegman 2016).

Quality of Life

Quality of life (QoL) was assessed and reported in four trials (Bahlis 2017; Palumbo 2012; Waage 2010; Wijermans 2010).

See Characteristics of included studies for further details.

Excluded studies

After the screening of abstracts we excluded 7509 references that obviously did not match the inclusion criteria.

In the full text stage, 33 studies, comprising 26 references, were excluded after detailed evaluation due to the following main reasons.

- Twelve trials included a novel agent in the treatment regimen, which was excluded for our review (Facon 2017; Facon 2018; Ludwig 2017a; Mateos 2018; NCT01850524; NCT01863550; NCT02586038; NCT03710603; Palumbo 2016; San Miguel 2014; Takezako 2017; Usmani 2014)
- Eight trials included interventions not of interest (Anonymous 2003; Facon 2006; Hernández 2004; Niesvizky 2003; Rajkumar 2006b; Rajkumar 2008; Merz 2015; Zonder 2010)
- Three trials, the induction regimens were not of interest or followed by transplantation or both (Hejlova 2000; NCT00522392; Morgan 2002)
- Four studies were conducted in a transplant setting (Brioli 2014; Kumar 2012; NCT00734877; Harousseau 2003)
- Three trials, participants received a prior therapy or were relapsed/refractory (Barlogie 2004; Foa 2007; Offidani 2004)
- Two trials were non-randomised (Montefusco 2013; White 2007)
- One trial reported sequential versus alternating regimens; no evaluation of individual drug combinations was possible (Mateos 2016)

These publications we described under Characteristics of excluded studies.

Risk of bias in included studies

The summary of the methodological quality of the included studies for all assessed domains across included studies and per included study are presented in Figure 2.

Allocation (selection bias)

In total, 14 of the 25 included studies (56%) reported a central randomisation process and were therefore judged at low risk of bias (Bahlis 2017; Beksac 2011; Durie 2017; Hulin 2009; Ludwig 2009; Magarotto 2016; Mateos 2014; Morgan 2011; Niesvizky 2015; Palumbo 2006; Palumbo 2012; Sacchi 2011; Stewart 2015; Waage 2010). The remaining 11 studies (44%) did not provide enough information to assess sequence generation and allocation concealment and risk of selection bias was therefore judged to be unclear (Facon 2007; Hungria 2016; Jacobus 2016; Katsuoka 2013; Kim 2007; Mookerjee 2017; Palumbo 2014; Pawlyn 2017; San Miguel 2008; Wijermans 2010; Zweegman 2016).

Blinding (performance bias and detection bias)

As, in general, RCTs in oncology are performed as open-label trials, we assumed participants and personnel were not blinded unless blinding was explicitly stated. Two of the 25 included trials were (12%) double-blind trials and were therefore judged to be at low risk of bias (Palumbo 2012; Waage 2010). The remaining 23 studies (88%), were either stated as, or assumed to be open-label trials and were therefore judged

to be at high risk of bias.

Blinding of outcome assessment was assessed in three outcome categories: overall survival (OS), progression-free survival (PFS), and safety outcomes. The outcome OS is not dependent on the outcome assessor as participants are either alive or dead at the time of OS assessment. Therefore the risk of bias in this category was judged to be low for all studies.

Progression-free survival (PFS) and safety outcomes can be dependent on the outcome assessor. Studies were presumed not to be blinded for outcome assessment, if not otherwise specified. As mentioned above, blinding was described in two of 25 studies (12%) and risk of bias was therefore judged as low (Palumbo 2012; Waage 2010). Twenty-three of the remaining studies were judged to be at high risk of bias .

Incomplete outcome data (attrition bias)

Missing outcome data were assessed in two categories: time to event data, and safety outcomes. Study discontinuation was reported in 22 of 25 studies (88%) and balanced between arms. Furthermore, Kaplan-Meier curves were provided. Risk of bias for incomplete survival data was judged to be at low risk for these studies. Three studies (12%) did not provide Kaplan-Meier curves or study-flow-charts (Katsuoka 2013; Kim 2007; Mookerjee 2017). As information was insufficient, risk of bias for incomplete survival data was judged to be unclear for these studies.

Safety outcomes were judged to be at low risk of bias, if all reported participants received at least one assigned study drug. This was described in twenty-two of the included studies. For three of the included studies (Katsuoka 2013; Kim 2007; Mookerjee 2017), only an abstract was available. As it was not described in the abstract if all reported patients received at least one assigned study drug, the risk of bias was judged to be unclear.

Selective reporting (reporting bias)

In total, 16 of 25 included (64%) studies reported all primary and secondary outcomes as pre-specified in their protocol (Bahlis 2017; Durie 2017; Facon 2007; Hulin 2009; Ludwig 2009; Magarotto 2016; Morgan 2011; Niesvizky 2015; Palumbo 2006; Palumbo 2012; Palumbo 2014; Sacchi 2011; Stewart 2015; Waage 2010; Wijermans 2010; Zweegman 2016). In these studies, risk of bias for selective reporting was judged as low.

However, primary and secondary outcomes were not reported as pre-specified in three studies and risk of bias for selective reporting was judged to be high. Pre-specified primary and secondary outcomes have been altered in one study (Beksac 2011). Response rate was supposed to be evaluated after 12 months, but was reported after four six-week cycles. Furthermore, time to progression was supposed to be evaluated, but disease-free survival was reported instead. One study conducted an unplanned interim analysis (Hungria 2016). As interim results suggested poorer outcomes in one arm compared to the other two arms, only descriptive results were further reported. Furthermore, more than 10% of data were missing, without explanations in one arm. One study did not report PFS, overall response rate, and quality of life, although pre-specified (San Miguel 2008). Risk of bias for selective reporting was unclear in five studies, four of which were only reported as abstracts and the other as a letter to the editor.

For five of the included studies, no protocol was available and full-text publications are still pending (Jacobus 2016; Katsuoka 2013; Kim 2007; Mookerjee 2017; Pawlyn 2017). Therefore, potential reporting bias could not be assessed and was judged to be unclear. The remaining study did not report duration of response, although previously specified (Mateos 2014). As response rate and complete response have been reported as pre-specified, risk of bias was judged to be unclear.

Other potential sources of bias

Other bias was detected in two of 25 studies (8%) and judged to be high. One study closed enrolment prematurely due to slow accrual (Jacobus 2016), one study conducted an unplanned interim analysis (Hungria 2016) and further altered analysis of results. In the 23 remaining studies no other bias was assumed and therefore risk judged to be low.

Effects of interventions

Overall survival (OS)

Overall survival was reported in 24 studies (19 two-arm studies, five three-arm studies), and analysis was conducted with 22 studies. Two studies (Kim 2007; Mookerjee 2017) and two direct comparisons of a three-arm study (Hungria 2016) were excluded because the hazard ratio (HR) was not reported and could not be estimated. Briefly, Kim 2007 did not find a significant difference in OS betweenTD (thalidomide and dexamethasone) and TCD (thalidomide plus cyclophosphamide plus dexamethasone). Mookerjee 2017 reported a median OS of 30.2 months (95% CI 28.2 to 32.2) for patients treated with VRD (bortezomib plus lenalidomide plus dexamethasone) and a median OS of 28.6 months (95% confidence interval (CI) 26 to 31.3) for patients treated with RD (lenalidomide plus dexamethasone). Hungria 2016 only reported Kaplan-Meier curves and a corresponding HR for the comparison of TMP (thalidomide plus melphalan plus prednisone) versus TCD. The HR for the comparisons TMP versus TD and TCD versus TD could not be estimated. Median OS for patients treated with TMP was 42 months; for patients treated with TCD 32.4 months and for patients treated with TD 54.6 months, respectively.

All 21 treatment regimens and a total of 11,071 participants could be included in the network meta-analysis (NMA). However, the network was not fully connected and consists of three subnetworks comprising 30 pairwise comparisons (Figure 3). We performed NMA for OS-subnetworks 1 and 2 (OS-subnetwork 3 consisted of only two treatment regimens). Results for all network comparisons, including the ranking of treatments are shown in Table 2, and Figure 4, per OS-subnetwork. Moderate heterogeneity (I^2 = 53.9%) was observed between studies in OS-subnetwork 1. Continuous VRDc (hazard ratio (HR) 0.49, 95% CI 0.26 to 0.92); VTMPc (HR 0.49, 95% CI 0.26 to 0.93); fixed treatment withRD (HR 0.63, 95% CI 0.40 to 0.99); and TMP (HR 0.75, 95% CI 0.58 to 0.97) showed a clinically meaningful improvement of OS compared to MP, respectively. According to OS, VRDc and VTMPc were the best treatment options in OS-subnetwork 1 (P score 0.90 and 0.89, respectively), whilst TDc was worst (P score 0.07).

Results of OS-subnetwork 2 suggest a survival advantage for VMPc compared to VTPc (HR 0.67, 95% CI 0.49 to 0.9). No other treatment combinations within OS-subnetwork 2 were favoured over another (Table 2; Figure 4).

Only one study was included in OS-subnetwork 3. Jacobus 2016 reported a median OS of 69.22 months (95% CI 59.70 to not estimable (NE)) for participants treated with VRD and 60.22 months (95% CI 37.06 to NE) for participants treated with VD (HR 0.77 (95% CI 0.35 to 1.70).

We rated the certainty of the evidence for OS according to the GRADE system for RD, TMP, bortezomib plus melphalan plus prednisone (VMP), and VRDc. Moderate-certainty evidence indicates that the use of RD, TMP, and VRDc for first-line treatment of multiple myeloma patients probably results in a large increase in OS. Low-certainty evidence indicates that the use of VMP as initial myeloma therapy may result in a large increase in OS (Summary of findings table 1).

The test for disagreement showed statistically significant disagreement between direct and indirect estimates in closed loops for RCPc-RDc-RMPc (P = 0.0148) and MP-TMP (P = 0.0453) (Figure 5). The only closed loop in OS-subnetwork 2 consists of a multi-arm study, so there is no indirect evidence.

Progression-free survival (PFS)

Twenty-four studies (19 two-arm studies, five three-arm studies) reported the outcome PFS, of which 22 studies were included in the analysis. We had to exclude two studies (Kim 2007; Mookerjee 2017) and two direct comparisons of a three-arm study (Hungria 2016) from the analysis, as no HRs were reported and there were insufficient data to estimate the missing value. Briefly, Kim 2007 did report a PFS of 8.6 (± 1.2) months for patients treated with TD and 19.4 (± 4.8) months for patients treated with TCD (P < 0.05). Mookerjee 2017 reported a median PFS of 27.8 months (95% CI 25.4 to 30.2) for patients treated with VRD and a median PFS of 28 months (95% CI 24.6 to 31.4) for patients treated with RD. Hungria 2016 only reported Kaplan-Meier curves and a corresponding HR for the comparison of TMP versus TCD. The HR for the comparisons TMP versus TD and TCD versus TD could not be estimated. Median OS for patients treated with TMP was 24.1 months; for patients treated with TCD 25.9 months and for patients treated with TD 21.5 months, respectively.

All 21 treatment regimens and a total of 11,071 participants could be included in NMA. The network was not fully connected and consists of three subnetworks comprising 31 pairwise comparisons (figure 6 in Appendix 5). NMA was conducted for PFS-subnetworks 1 and 2 (subnetwork 3 consisted of only two treatment regimens). Results, per PFS-subnetwork, are shown in Table 3 for all network comparisons. Between-study heterogeneity was moderate (I^2 = 55.3%) in PFS-subnetwork 1. In general, continuous treatment regimens were superior to fixed therapy with MP, and nine out of 13 compared bortezomib, lenalidomide, or thalidomide combinations showed a substantial improvement of PFS compared to MP, respectively (figure 7 in Appendix 5). VRDc and VTMPc achieve best effects on PFS outcomes in PFS-subnetwork 1 (P score: 0.92 and 0.92, respectively). The treatments with the smallest effects on PFS in this subnetwork are RCD (P score: 0.08), TCD (P score: 0.09) and MP (P score 0.13).

Evidence of PFS-subnetwork 2 suggests no advantages for any treatment combinations within this subnetwork (Table 3; figure 7 in Appendix 5).

Only one study was included in PFS-subnetwork 3. Jacobus 2016 reported a median PFS of 20 months (95% CI 11 to 43) for participants treated with VRD and 18 months (95% CI 9 to 37) for participants treated with VD (HR 0.96, 95% CI 0.53 to 1.75).

We rated the certainty of the evidence for PFS according to the GRADE system for RD, TMP, VMP, and VRDc. We rated the evidence for all of these comparisons as low certainty, meaning that the use of RD, TMP, VMP, and VRDc for first-line treatment of MM patients may result in a large increase in PFS (Summary of findings table 1).

The test for disagreement showed almost statistically significant disagreement between direct and indirect estimates in closed loops for MP-TMP (P = 0.0594) (figure 8 in Appendix 5). The only closed loop in PFS-subnetwork 2 consists of a multi-arm study, so there is no indirect evidence.

Adverse events

Adverse events (AEs) were not consistently reported across studies. To be able to meta-analyse results, we could only consider AEs when the number of participants with at least one event of at least grade 3 was reported. We

could not consider cumulated events, subgrouping by degrees of severity, or other subgroups.

Adverse events grade 3 and 4

Adverse events grade 3 and 4 were reported in nine studies (Durie 2017; Katsuoka 2013; Ludwig 2009; Magarotto 2016; Niesvizky 2015; Palumbo 2006; Stewart 2015; Wijermans 2010; Zweegman 2016) (seven two-arm studies, two three-arm studies), for 13 treatment regimens and a total of 3318 participants. However, the included studies did not fulfil the similarity assumption and are therefore not comparable in NMA. Decisive effect modifiers to withdraw the assumption for similarity were different supportive therapies and various reporting styles of grade 3 and 4 AEs (e.g. different length of treatment, AEs occurring in > 5% or > 10% of the patients, differentiation between non-haematological and haematological AEs). Pairwise comparisons are illustrated in (figure 9 in Appendix 5), per trial.

Polyneuropathy

Polyneuropathies were reported in 18 studies (Bahlis 2017; Beksac 2011; Facon 2007; Hulin 2009; Hungria 2016; Katsuoka 2013; Magarotto 2016; Mateos 2014; Niesvizky 2015; Palumbo 2006; Palumbo 2012; Palumbo 2014; Pawlyn 2017; Sacchi 2011; San Miguel 2008; Stewart 2015; Waage 2010; Zweegman 2016) (13 two-arm studies, five three-arm studies), for 19 treatment regimens and a total of 8978 patients. However, the network was not fully connected and consists of two subnetworks comprising 28 pairwise comparisons (figure 10 in Appendix 5).

We performed NMA for both polyneuropathy-subnetworks. Results for all network comparisons, including the ranking of treatments are shown in Table 4, per polyneuropathy-subnetwork. Low heterogeneity (I^2 = 3.4 %) was observed between studies for polyneuropathy-subnetwork 1.

The risk ratio (RR) for polyneuropathies is highest for patients receiving bortezomib-based therapies (RR 88.22, 95% CI 5.36 to 1451.110 to (RR 441.08, 95% CI 7.74 to 25,145.52) compared to MP) (figure 11 in Appendix 5). Furthermore, the RR for polyneuropathy appears to be smaller for patients receiving lenalidomide-based therapies, compared to patients receiving thalidomide-based therapies (Table 4). Polyneuropathies are less prevalent in fixed and continuous treatment with lenalidomide plus melphalan plus prednisone (RMP) compared to fixed and continuous treatment with thalidomide plus melphalan plus prednisone (TMP) (RR 0.11, 95% CI 0.03 to 0.40) to (RR 0.32, 95% CI 0.11 to 0.91) ,and less prevalent in fixed and continuous treatment with RD compared to TD (RR 0.14, 95% CI 0.03 to 0.69) to (RR 0.18, 95% CI 0.04 to 0.85). According to polyneuropathies, RCD (P score 0.91), RD (P score 0.83), and RDc (P score 0.78) are the treatments within subnetwork 1 with the smallest incidence whereas, VD (P score 0.04), VTMPc (P score 0.06), and VMP (P score 0.14) are the treatments with the highest incidence.

Evidence of polyneuropathy-subnetwork 2 suggests no advantages for any treatment combinations within this subnetwork (Table 4; (figure 11 in Appendix 5).

We rated the certainty of the evidence for polyneuropathies according to the GRADE system for RD, TMP, and VMP. VRDc was not included in NMA as no study reported the amount of participants with grade ≥ 3 polyneuropathies. Therefore we did not have an estimate for which we could rate the certainty. Low-certainty evidence suggests that participants treated with RD may have a smaller risk for polyneuropathies, compared to participants treated with MP. However, the CIs are also compatible with no difference or an increase in neuropathies. Moderate-certainty evidence suggests treatment with TMP and VMP probably results in a large increase in polyneuropathies, respectively compared to MP.

The test for disagreement showed no statistically significant difference between direct and indirect estimates (figure 12 in Appendix 5). The only closed loop in subnetwork 2 consists of a multi-arm study, so there is no indirect evidence.

Neutropenia

A total of 14 studies (Bahlis 2017; Facon 2007; Hulin 2009; Hungria 2016; Magarotto 2016; Mateos 2014; Niesvizky 2015; Palumbo 2006; Palumbo 2014; Pawlyn 2017; Sacchi 2011; San Miguel 2008; Stewart 2015; Zweegman 2016) (10 two-arm studies, four three-arm studies) reported neutropenia. These studies comprised 16 treatment regimens (22 pairwise comparisons), a total of 8046 participants and were connected to two subnetworks (figure 13 in Appendix 5).

For both neutropenia-subnetworks NMA could be performed. Table 5 shows the results for all network comparisons, including the ranking of treatments, per neutropenia-subnetwork. Moderate heterogeneity (I^2 = 40 %) was observed between studies for neutropenia-subnetwork 1.

For neutropenia, the RR appears to be similar for medications and treatment durations (figure 14 in Appendix 5). Seven out of 11 compared treatment options have substantially less neutropenia than RMPc (RR 0.11, 95% CI 0.01 to 0.85) to (RR 0.43, 95% CI 0.26 to 0.70), out of which four also have substantially less neutropenia than TMP (RR 0.52, 95% CI 0.36 to 0.75) to (RR 0.60, (95% CI 0.40 to 0.91) (Table 5). Within neutropenia-subnetwork 1, TD (P-score: 0.91) is the treatment with the least neutropenia-incidence; incidence is highest for RMPc (P-score: 0.03).

Within neutropenia-subnetwork 2, evidence suggests the highest risk of neutropenia for patients treated with VMPc (P score: 0.00) and the smallest risk of neutropenia for patients treated with VDc (P score: 0.89) (Table 5; figure 14 in Appendix 5).

There is no statistically significant difference between direct and indirect estimate (figure 15 in Appendix 5). The only closed loop in neutropenia-subnetwork 2 consists of a multi-arm study, so there is no indirect evidence.

Anaemia

Anaemia was reported in 14 studies (Bahlis 2017; Facon 2007; Hungria 2016; Ludwig 2009; Magarotto 2016; Mateos 2014; Mookerjee 2017; Niesvizky 2015; Palumbo 2006; Palumbo 2012; Palumbo 2014; San Miguel 2008; Stewart 2015; Zweegman 2016), (nine two-arm studies, five three-arm studies), for 19 treatment regimens and a total of 6713 participants. The network was not fully connected, resulting in three subnetworks, comprising 24 pairwise comparisons (figure 16 in Appendix 5).

We performed NMA for anaemia-subnetworks 1 and 2 (anaemia-subnetwork 3 consisted of only two treatment regimens). Results, per anaemia-subnetwork and for all network comparisons, including the ranking of treatments are shown in Table 6. Between-study heterogeneity (I^2= 59 %) was moderate for anaemia-subnetwork 1.

The RR for anaemia appears to be similar for medications and treatment durations (figure 17 in Appendix 5). Five out of 12 compared treatment options have a clinically meaningful smaller incidence of anaemia than RMPc (RR 0.32, 95% CI 0.12 to 0.88) to (RR 0.53, 95% CI 0.30 to 0.94), out of which, three also have substantially less neutropenia than RMP (RR 0.31, 95% CI 0.10 to 0.99) to(RR 0.34, 95% CI 0.12 to 0.97) (Table 6). According to the treatment ranking of anaemia-subnetwork 1, VRD (P-score: 0.82), RD (P score: 0.73), and VMP (P score: 0.69) are the therapy regimens, with the smallest incidence of anaemia, compared to all other therapy regimens, included in this subnetwork. The therapy regimens with the highest incidence of anaemia in anaemia-subnetwork 1 are RMPc (P score 0.17), and RMP (P score 0.17), and TD (P score 0.22).

Results of anaemia-subnetwork 2 suggest a smaller risk of anaemia for VDc compared to VMPc (RR 0.25, 95% CI 0.07 to 0.86). No other treatment combinations within anaemia-subnetwork 2 were favoured over another (Table 6; figure 17 in Appendix 5).

Only one study was included in anaemia-subnetwork 3 (Ludwig 2009). Anaemia was experienced by six of 134 participants treated with TDc and 15 of 134 participants treated with MPc (P = 0.067).

There is no statistically significant difference between direct and indirect estimate (figure 18 in Appendix 5). The only closed loop in anaemia-subnetwork 2 consists of a multi-arm study, so there is no indirect evidence.

Thrombocytopenia

Thrombocytopenia was reported in 12 studies (Bahlis 2017; Facon 2007; Hungria 2016; Ludwig 2009; Magarotto 2016; Mateos 2014; Niesvizky 2015; Palumbo 2006; Palumbo 2012; Palumbo 2014; San Miguel 2008; Zweegman 2016), (seven two-arm studies, five three-arm studies), and could be analysed with data from 11 studies. One three-arm study was excluded from the analysis due to zero events in all arms (Hungria 2016). Thrombocytopenia was reported for 16 treatment regimens and a total of 6190 patients. However, the network was not fully connected and consists out of three subnetworks comprising 19 pairwise comparisons (figure 19 in Appendix 5).

We performed NMA for thrombocytopenia-subnetwork 1 and 2 (thrombocytopenia-subnetwork 3 consisted of only two treatment regimens). Results for all network comparisons, including the ranking of treatments are shown in Table 7, per thrombocytopenia-subnetwork. No heterogeneity (I^2 = 0 %) was observed between studies for thrombocytopenia-subnetwork 1.

Patients receiving any other treatment option of thrombocytopenia-subnetwork 1 than fixed or continuous treatment with RMP have a clinically meaningful smaller risk for thrombocytopenia (RR 0.26, 95% CI 0.18 to 0.39) to (RR 0.49, 95% CI 0.29 to 0.82) (Table 7). According to the ranking of treatments TMPc (P score: 0.93) is the treatment within thrombocytopenia-subnetwork 1 with the least thrombocytopenia-incidence and RMP (P score 0.03), and RMPc (P score 0.09), are the treatments with the highest incidence (figure 20 in Appendix 5).

Within thrombocytopenia-subnetwork 2, evidence suggests the highest risk of thrombocytopenia for participants treated with VMPc (P score 0.00) and the smallest risk of thrombocytopenia for participants treated with VDc (P score 0.91) (Table 7; figure 20 in Appendix 5).

Only one study was included in thrombocytopenia-subnetwork 3 (Ludwig 2009). Thrombocytopenia was experienced by two of 134 participants treated with TDc and 16 of 134 participants treated with MPc (P < 0.001).

There is no statistically significant difference between direct and indirect estimates (figure 21 in Appendix 5). The only closed loop in thrombocytopenia-subnetwork 2 consists of a multi-arm study, so there is no indirect evidence.

Thromboembolism

A total of 14 studies (Facon 2007; Hulin 2009; Hungria 2016; Mateos 2014; Mookerjee 2017; Morgan 2011; Palumbo 2006; Palumbo 2014; Sacchi 2011; San Miguel 2008; Stewart 2015; Waage 2010; Wijermans 2010; Zweegman 2016), (13 two-arm studies, one three-arm study) reported thromboembolism. We had to exclude one study from the analysis due to zero events (Morgan 2011), and therefore the outcome could be analysed with data from 13 studies. Thromboembolisms were reported for 13 treatment regimens and a total of 4277 participants. The network was not fully connected and consists of three subnetworks comprising 15

pairwise comparisons (figure 22 in Appendix 5).

We performed NMA for thromboembolism-subnetwork 1 (thromboembolism-subnetworks 2 and 3 consisted of only two treatment regimens). Results for all network comparisons, including the ranking of treatments are shown in Table 8. Low heterogeneity (I^2 = 26.9 %) was observed between studies for thromboembolism-subnetwork 1.

The RR for thromboembolism appears to be similar for medications and treatment durations (Table 8). Incidence of thromboembolism is substantially smaller in MP-treated patients than patients treated with RMPc (RR 0.15, 95% CI 0.03 to 0.87)); TMPc (RR 0.14, 95% CI 0.03 to 0.67); and TDc (RR 0.08, 95% CI 0.01 to 0.98)) (figure 23 in Appendix 5). In terms of the risk of thromboembolism, MP (P score: 0.93), followed by VMP (P score 0.80), are the best treatment options within subnetwork 1 and TDc (P score: 0.21), TCDc (P score: 0.25), and TMPc (P score: 0.32) the worst.

Only one study was included in thromboembolism-subnetwork 2 (Mateos 2014). Thromboembolism were experienced by 1 of 130 participants treated with VMPc and 3 of 130 participants treated with VTPc (P= 0.5). Also, only one study was included in thromboembolism-subnetwork 3 (Mookerjee 2017). Thromboembolism were experienced by 1 of 74 participants treated with VRD and 0 of 69 participants treated with RD.

As the only closed loop in thromboembolism-subnetwork 1 consists of multi-arm studies, there is no indirect evidence.

Infections

Infections were reported in 15 studies (Bahlis 2017; Beksac 2011; Durie 2017; Facon 2007; Magarotto 2016; Mateos 2014; Morgan 2011; Niesvizky 2015; Palumbo 2006; Palumbo 2012; Palumbo 2014; Sacchi 2011; Waage 2010; Wijermans 2010; Zweegman 2016) (11 two-arm studies, four three-arm studies), for 17 treatment regimens and a total of 7470 participants. However, the network was not fully connected and consists of three subnetworks comprising 23 pairwise comparisons (figure 24 in Appendix 5).

We performed NMA for infections-subnetworks 1 and 2 (infections-subnetwork 3 consisted out of two treatment regimens, only). Results for all network comparisons, including the ranking of treatments are shown in Table 9, per infections-subnetwork. Moderate heterogeneity (I^2 = 34.8 %) was observed between studies for infections-subnetwork 1.

The RR for infections appears to be similar for medications and treatment durations (Table 9). MP-treated patients have substantially fewer infections than patients treated with RMPc (RR 0.40, 95% CI 0.21 to 0.77); RDc (RR 0.37, 95% CI 0.19 to 0.73); VRDc (RR 0.35, (95% CI 0.13 to 0.92); RMP (RR 0.34, 95% CI 0.16 to; 0.75);, and TMPc (RR 0.33, 95% CI 0.15 to 0.73); (figure 25 in Appendix 5). Within infections-subnetwork 1, and according to the ranking of treatments, incidence of infections is the smallest for MP (P score 0.96), and most frequent for TMPc (P score 0.21), followed by RMP (P score 0.27), VRDc and RDc (P score 0.29, respectively).

Results of infections-subnetwork 2 suggest a smaller risk of infections for VTPc compared to VMPc (RR 0.11, 95% CI 0.01 to 0.86); and VDc (RR 0.09, 95% CI 0.01 to 0.76), respectively. No other treatment combinations within infections-subnetwork 2 were favoured over another (Table 9; figure 25 in Appendix 5).

Only one study was included in infections-subnetwork 3 (Palumbo 2014). Infections were experienced by 32 of 250 participants treated with VTMPc and 23 of 253 participants treated with VMP (P = 0.18).

The test for disagreement showed almost statistically significant disagreement between direct and indirect estimates in closed loops for RMP-MP-RMPc (P = 0.0660) (figure 26 in Appendix 5). The only closed loop in infections-subnetwork 2 consists of a multi-arm study, so there is no indirect evidence.

Serious adverse events (SAEs)

Serious adverse events were not consistently reported across studies. To be able to meta-analyse results we could only consider harms when the number of participants with at least one SAE was reported. We could not consider cumulated events or perform subgroup analyses.

Serious adverse events were reported in eight studies (Bahlis 2017; Durie 2017; Jacobus 2016; Mateos 2014; Niesvizky 2015; Palumbo 2012; San Miguel 2008; Stewart 2015) (five two-arm studies, three three-arm studies) and were measured for 14 treatment regimens and a total of 7306 participants. However, the network was not fully connected and consists of three subnetworks comprising 14 pairwise comparisons (figure 27 in Appendix 5).

NMA was performed for all SAE-subnetworks. Results for all network comparisons, including the ranking of treatments are shown in Table 10. Global approach to check for inconsistency and heterogeneity between studies was not applicable.

Relative risk for patients to experience at least one SAE appears to be similar across therapy regimens (figure 28 in Appendix 5). In SAE-subnetwork 1, according to the ranking of treatments SAEs are most likely for VRDc (P score: 0.06) and least likely for TMP (P score 0.94). In SAE-subnetwork 2, SAEs are most likely for VTPc (P score 0.01) and least likely for VMPc (P score 0.86). In SAE-subnetwork 3, SAEs are most likely for TMPc (P score 0.05) and least likely for MP (P score 0.92).

The only closed loops in the SAE-subnetworks consists of multi-arm studies, so there is no indirect evidence.

We could only rate the certainty of the evidence for SAEs for VMP, as RD, TMP, and VRDs are not connected to MP in the network. Moderate-certainty evidence suggests that VMP as initial therapy for MM probably slightly increases occurrence of SAEs (Summary of findings table 1).

Withdrawals due to adverse events (AEs)

The number of participants who stopped assigned therapy and terminated their participation in the study due to AEs, were reported in 16 studies (Bahlis 2017; Durie 2017; Hulin 2009; Hungria 2016; Ludwig 2009; Magarotto 2016; Mateos 2014; Niesvizky 2015; Palumbo 2006; Palumbo 2012; Palumbo 2014; Sacchi 2011; San Miguel 2008; Waage 2010; Wijermans 2010; Zweegman 2016) (11 two-arm studies, five three-arm studies), for 19 treatment regimens and a total of 7052 participants. However, the network was not fully connected and consists of two subnetworks comprising 26 pairwise comparisons (figure 29 in Appendix 5).

We performed NMA for both withdrawals due to AEs-subnetworks. Results for all network comparisons, including the ranking of treatments, are shown in Table 11. Low heterogeneity (I^2 = 25.5 %) was observed between studies for withdrawals due to AEs- subnetwork 1.

Patients who received fixed or continuous MP-therapy had a substantially lower risk of withdrawing from the study due to AEs than nine out of 13 treatments withdrawals due to AEs- subnetwork 1 (RR 0.09, 95% CI 0.03 to 0.25) to (RR 0.47 (95% CI 0.22 to 0.99); (figure 30 in Appendix 5). Participants treated with VRDc had a substantially higher risk of withdrawing from the study due to AEs than11 of the compared treatments of withdrawals due to AEs- subnetwork 1 (RR 0.09. 95% CI 0.03 to 0.25) to (RR 0.46 (95% CI 0.22 to 0.98) (Table 11). Treatment discontinuation due to AEs is most frequent for VRDc (P score 0.01), followed by RD (P score 0.22), and TMP (P score 0.22), and least frequent for MPc (P score 0.91), followed by MP (P score 0.86), and VMP (P score 0.84), in withdrawals due to AEs-subnetwork 1.

Evidence of withdrawals due to AEs-subnetwork 2 suggests no advantages for any treatment combinations within this subnetwork (Table 11; (figure 30 in Appendix 5).

We rated the certainty of the evidence for withdrawals due to AEs according to the GRADE system for RD, TMP, VMP, and VRDc. High-certainty evidence suggests that treatment with RD, TMP, and VRDc for first-line treatment of MM result in a large increase in withdrawals due to AEs. Moderate-certainty evidence suggest that the use of VMP as initial therapy for MM probably results in little to no difference in withdrawals due to AEs, compared to MP (Summary of findings table 1).

The test for disagreement showed no statistically significant difference between direct and indirect estimates (figure 31 in Appendix 5). The only closed loop in withdrawals due to AEs- subnetwork 2 consists of a multi-arm study, so there is no indirect evidence.

Quality of life (QoL)

Quality of life was reported in four of the 25 included trials (Bahlis 2017; Palumbo 2012; Waage 2010; Wijermans 2010), and measured for seven treatment regimens and a total of 2260 participants. All trials used the validated European Organization of Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 to evaluate QoL. Participants self-assessed QoL at multiple time points, which could be assigned to three different periods: short (one to three months after start of treatment), medium (six to nine months after start of treatment), long (12 months and longer, after start of treatment). Bahlis 2017 and Palumbo 2012 further applied the EORTC QLQ-MY20, and Wijermans 2010 the EORTC QLQ-MY24; questionnaires, which were specifically designed for adults with multiple myeloma. Bahlis 2017 additionally evaluated QoL using the EuroQoL EQ-5D questionnaire. As the treatment regimens used in the trials did not correspond with each other, no network could be built, and we could therefore not perform NMA on this outcome.

In summary, data from Bahlis 2017* showed that the global health status of patients treated with RD and TMP improved from baseline over the duration of the study and disease symptoms decreased (mean change from baseline after three months: RD: + 4.5, TMP: + 4; mean change from baseline after six months: RD: + 5, TMP: + 5.5; mean change from baseline after 12 months: RD: + 3.5, TMP: + 5; mean change from baseline after 18 months: RD: + 5, TMP: + 4). Evaluated on the basis of EORTC QLQ-MY20, disease symptoms were substantially lower in patients receiving RD compared to TMP three months after start of treatment (mean change from baseline after three months: RD: -10, TMP: -7; $P < 0.05$), and side effects of treatment were lower in patients receiving RDc compared to TMP, continuously from cycle one until 12 months post-baseline (mean change from baseline after three months: RD: + 1.0, TMP: + 4; mean change from baseline after six months: RD: + 0.5, TMP: + 3.5; mean change from baseline after 12 months: RD: + 1.5, TMP: + 5; $P < 0.05$, respectively), indicating a better health-related QoL.

An improvement of QoL, evaluated on the basis of EORTC QLQ-C30, of patients receiving TMPc and MPc improved after the initiation of anti-myeloma treatment (Waage 2010; Wijermans 2010). Wijermans 2010 reported a mean QLQ-C30 global health score of 49 (95% CI 45 to 52) for MPc and a mean score of 54 (95% CI50 to 58) for TMPc at baseline, respectively and increased after treatment induction (P time < 0.001; P arm = 0.05):

- eight months: MPc: 65 (95% CI 57 to 73); TMPc: 66 (95% CI 59 to 73)
- 12 months: MPc: 62 (95% CI 58 to 66); TMPc: 63 (95% CI 58 to 67)

- 18 months: MPc: 64 (95% CI 57 to 70); TMPc: 70 (95% CI 65 to 75)
- after re-treatment/relapse/progression: MPc: 54 (95% CI 51 to 58); TMPc 63 (95% CI 59 to 68)

Waage 2010* reported a mean QLQ-C30 global health score of 48 (95% CI 43 to 52) for MPc and a mean score of 47 (95% CI 43 to 53) for TMPc at baseline, respectively and increased after treatment induction.

- 12 months: MPc: 65 (95% CI 60 to 70); TMPc: 63 (95% CI 58 to 68)
- 24 months: MPc: 60 (95% CI 52 to 68); TMPc: 62 (95% CI 56 to 70)
- 36 months: MPc: 72 (95% CI 66 to 81); TMPc: 62 (95% CI 51 to 76)

From baseline until completion of cycle, 10 health-related QoL scores increased steadily for RMPc (+ 12.2 (standard deviation (SD): 25.4), $P < 0.001$), RMP (+ 8.8 (SD; 24.7), $P < 0.001$), and MP (+ 6.2 (SD: 24.6), $P < 0.05$) and the difference was statistically significant for all groups (Palumbo 2012). The largest increase in global health scores was reported for RMPc (baseline score: 49.6 (SD: 23.5)). However, the baseline-score was lower in this group compared to RMP (baseline score: 53.2 (SD: 23.5)) and MP (baseline score: 52.8 (SD: 22.8)), respectively.

**These data were read from graphs.*

Discussion

Summary of main results

The aim of this systematic review and network meta-analysis was to synthesise all available evidence on first-line treatment options for adults with multiple myeloma in non-transplant settings. We identified 25 eligible randomised controlled trials (RCTs) that included 11,403 participants. A total of 21 different treatment regimens were investigated in these studies. All studies could be included in network meta-analyses. Overall risk of bias was generally high across studies because they were open-label studies. The certainty of the evidence for pre-selected treatment comparisons was low to moderate for survival outcomes, and moderate to high for safety outcomes. The main outcomes and comparisons are summarised in the Summary of findings table 1.

Survival

Evidence suggests that treatment with RD, TMP, and VRDc probably results in a large increase in overall survival (**OS**), compared to MP. The use of VMP as initial myeloma therapy may result in a large increase in OS, compared to MP. Furthermore, treatment with RD, TMP, VMP, and VRDc may result in a large increase in progression-free survival (**PFS**) compared to MP.

Harms

The evidence suggests that the risk for **polyneuropathies** may be smaller for treatment with RD compared to treatment with MP. However, the confidence intervals (CIs) are also compatible with no difference or an increase in neuropathies. Treatment with TMP and VMP probably results in a large increase in polyneuropathies compared to MP. No study reported the outcome polyneuropathies for participants treated with VRDc. By comparing all included drug combinations with each other, the evidence suggests a lower risk for polyneuropathies for patients receiving lenalidomide- and thalidomide-based therapies compared to bortezomib-based therapies. **Serious adverse events** (SAEs) are probably higher in participants treated with VMP compared to MP. RD, TMP, and VRDc were not connected to MP in the network, therefore the risk ofSAEs could not be compared for these comparisons. By comparing the drug combinations with each other, the evidence suggests no discernible difference for any treatment combination. Treatment with RD, TMP, and VRDc results in a large increase in **withdrawals due to AEs** compared to MP. For participants treated with VMP, the risk of withdrawal due to adverse events is probably slightly increased, compared to MP.

Quality of life (QoL)

Quality of life was reported in four of the included studies for seven different treatment regimens (MP, MPc, RD, RMP, RMPc, TMP, TMPc) and was measured with four different tools. Assessment and reporting of QoL differed between studies and could not be meta-analysed. The comparison to MP is therefore not possible. However, all studies reported an improvement of health-related QoL after the start of anti-myeloma treatment for all assessed treatment regimens.

When interpreting the results of this network meta-analysis, it is important to consider that network meta-analyses are no substitute for direct head-to-head comparisons. Therefore results may best be confirmed by additional RCTs of multiple drug combinations. Furthermore, it should be considered that results lacking statistical significance do not necessarily discredit disparities, which may be clinically relevant for some individuals.

Application for the inclusion of bortezomib, lenalidomide, or thalidomide into the WHO's list of essential medicines

Based on the effects of the interventions an application for the '22nd WHO Expert Commitee on the Selection and Use of Essential Medicines' for the inclusion of bortezomib, lenalidomide, or thalidomide into the EML was prepared. The full application can be accessed here:
https://www.who.int/selection_medicines/committees/expert/22/applications/myeloma/en/

The Expert committee recommended to include all three of the proposed medicines (World Health Organization 2019a). The 21st list can be accessed here: https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1

Overall completeness and applicability of evidence

In this systematic review and network meta-analysis, we could include 25 published RCTs, comparing first-line treatment options including combinations of bortezomib, lenalidomide, and thalidomide for adults with transplant-ineligible multiple myeloma. Twenty of these studies were published as full texts and provided detailed information on the study design, participants, methods and outcomes (Bahlis 2017; Beksac 2011; Durie 2017; Facon 2007; Hulin 2009; Hungria 2016; Ludwig 2009; Magarotto 2016; Mateos 2014; Morgan 2011; Niesvizky 2015; Palumbo 2006; Palumbo 2012; Palumbo 2014; Sacchi 2011; San Miguel 2008; Stewart 2015; Waage 2010; Wijermans 2010; Zweegman 2016). Five trials were either published as an abstract (Katsuoka 2013; Kim 2007; Mookerjee 2017; Pawlyn 2017) or letter (Jacobus 2016), and therefore did not provide all relevant information. Most studies provided hazard ratios (HRs) for survival outcomes, or enough information to calculate HRs, so that we could include all 21 treatment options in network meta-analyses. However, it was not clear whether all of the trials checked the assumption of proportional hazards. If this assumption is not met and cox proportional hazards model was used, it is not clear what impact this would have on the meta-analysis. Also, networks were not fully connected, so that only treatments which were included in the same subnetwork could be compared to each other. Reporting of AEs differed between studies and led to a limited comparability. At the protocol stage, we decided to use the most frequently reported way for network meta-analysis (amount of participants with at least one event grade $\geq$ 3 (or at least one SAE)). Therefore, to be able to include reported data into network meta-analyses, we could only consider AEs, when the amount of participants with at least one event grade $\geq$ 3 (or at least one SAE) were reported. We could not consider cumulated events or breakdowns in degrees of severity or further subgroups. As a result, network meta-analysis was not possible for the outcome grade 3 and 4 AEs due to severe inconsistency. Furthermore, not all trials reported the amount of participants with at least one event. As a result, data were not available for every treatment combination, reducing the informative value of our results. We determined moderate inconsistency within the networks for the outcomes OS, PFS, neutropenia anaemia, and infections. The inconsistency could not be explained statistically and originates probably from the fact that our included trials slightly differ on some effect modifiers (definition of transplant-ineligibility, subsequent therapies, duration of follow-up, age, stage of disease, performance score, study start date, prophylaxis, and regions). Nevertheless, from a clinical point of view, our included studies remain largely comparable as these differences are generally small. As previously described, only four trials reported data on health-related quality of life and network meta-analysis was not possible for this outcome. Considering the points outlined, we conclude that the completeness and applicability of evidence in this systematic review and network meta-analysis ranged from high for the outcome withdrawal for adverse events to low for PFS (Summary of findings table 1).

We did not aim to evaluate adequate prophylactic treatments for the prevention of common adverse events which are associated to the investigated treatments in this review. Therefore we did not analyse whether or which prophylaxis was administered to the participants in our included trials. Adequate prophylaxis may not be universally available. However, co-administration of appropriate evidence-based prophylaxis is highly important and may reduce the most frequent adverse events (e.g. infections, thromboembolism) (Key 2019; Taplitz 2018).

Disparities in myeloma incidences by racial ethnicity have been largely explored in recent years and higher incidence rates for black people compared to white people have been discovered (Waxman 2010). Based on these findings, Kirtane 2017 retrospectively explored survival disparities among racial ethnicities. Data suggested that black, Hispanic, and Asians achieve lower survival improvements with immunotherapies compared to white. However, the authors concluded that these differences may rather occur from restricted access to effective treatment modalities. The interaction of participants racial ethnicities and response to anti-myeloma therapy was further explored with patient-level data from nine clinical trials with newly diagnosed multiple myeloma (NDMM) (Ailawadhi 2018). Efficacy analysis did not identify statistically significant differences in OS, PFS, or response rates between race-ethnicity groups. Considering these findings, we conclude that the evidence in this systematic review and network meta-analysis is equally applicable for low- and middle-income countries(LMICs) and high-income countries (HICS).

In addition to the studies, included in this review, we are aware of a further two completed and 10 ongoing studies, comparing multiple drug combinations of novel agents for first-line treatment of transplant-ineligible multiple myeloma patients. All of these trials included novel second-generation agents: daratumumab (Jacobus 2016; Facon 2018; Mateos 2018; NCT03710603), siltuximab (San Miguel 2014), elotuzumab (Takezako 2017; Usmani 2014), pembrolizumab (Palumbo 2016), carfilzomib (Facon 2017; Ludwig 2017a; NCT01863550), and ixazomib (NCT01850524; NCT02586038). As outlined in the Why it is important to do this review section of this review, treatment combinations including these agents have already been introduced into anti-myeloma therapy in HICs. However, as our review was prepared for a specific guidance, we included treatment combinations with novel agents of the first generation, only. Please refer to the following sections for more details: Why it is important to do this review and Methods. Besides these trials, we

identified no further ongoing trials matching our inclusion criteria for this review.

Quality of the evidence

The risk of bias was assessed in 25 studies and ten sub-categories. We decided to expand the 'Risk of bias' criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). In order to be able to rate the certainty in the evidence for our pre-selected outcomes, we assessed each category whether a judgement would apply for the study in general or whether the judgement could vary between endpoints. We decided that detection bias and attrition bias are endpoint-dependent 'Risk of bias' categories. Therefore, we assessed the blinding of outcome assessment in three subcategories (not dependent on outcome assessor: OS; partly dependent on outcome assessor:PFS; dependent on outcome assessor: safety outcomes) and incomplete outcome data in two subcategories (time-to-event data: survival outcomes; safety data: safety outcomes). A full-text publication was available for 20 studies, for four studies an abstract only, and for one study a letter only. For the five studies without full-text publications, we were unable to assess the full risk of bias. All trials described their participants as being randomly assigned to the respective treatment options. However, the process of random sequence generation and allocation concealment was only described in 14 trials. For the remaining 11 trials, the risk of selection bias was unclear. Most of the included studies had an open-label study design, resulting in an overall high performance and detection bias. Blinding in cancer settings is usually difficult as treatment durations differ, depending on assigned drug combinations. Moreover, the included drugs are differently administered by default: lenalidomide and thalidomide as an daily oral dose; bortezomib once to twice weekly subcutaneous. Detection bias for OS was generally judged as low, as the occurrence and the assessment of this outcome is independent from blinding of participants and personnel. Attrition bias was generally low between studies and judged as unclear for the studies with a published abstract only. We compared whether reported outcomes corresponded with the outcomes, which have been defined at protocol stage, to detect potential reporting bias. This was not the case for three studies (Beksac 2011; Hungria 2016; San Miguel 2008). Beksac 2011 and San Miguel 2008 altered some of their pre-specified outcomes. Hungria 2016 did not carry-on one arm of the trial due to unsatisfying interim results. Risk of reporting bias was judged to be high for these three trials. As described in the results, we could identify other bias in three of the included trials. Overall, we judged the risk of bias within and across studies to be high.

We rated the certainty in the evidence for four pre-selected treatment-regimens (RD, TMP, VMP, VRDc), respectively compared to MP, and the six most patient-relevant outcomes (OS, PFS, SAEs, Withdrawals due to AEs, polyneuropathies, QoL) (see Summary of findings table 1). The certainty of OS estimates for RD, TMP, and VRDc was rated to be moderate. We downgraded by one level for inconsistency due to moderate heterogeneity in OS subnetwork 1 (Figure 3). The certainty of OS estimates for VMP was rated to be low, as we downgraded by one level for imprecision due to wide confidence intervals in addition to the downgrade due to inconsistency. The certainty of all pre-selected treatment regimens was rated as low for PFS. We downgraded by one level due to high risk of bias and another level for inconsistency due to moderate heterogeneity in PFS subnetwork 1. For the outcome SAE, we could only rate the certainty in the evidence for VMP, as RD, TMP, and VRDc were not connected to MP in the network. We rated the certainty of the SAE estimates for VMP as moderate, as we downgraded by one level for high risk of bias. For the outcome withdrawals due to AEs, we rated the certainty of the estimates to be high for RD, TMP, and VRDc and wish to emphasise the large (negative) effect for all estimates. The certainty of the estimates for VMP was rated to be moderate. We downgraded by one level for imprecision because of wide confidence intervals which included no effect. For the outcome polyneuropathies, we rated the certainty of the estimates to be low for RD and moderate for TMP and VMP and wish to emphasise the large (negative) effect for TMP and VMP. No study reported the outcome polyneuropathies for the treatment with VRDc and we therefore had no estimates for which we could assess the certainty in the evidence. Meta-analysis was not possible for the outcome QoL and we could not assess the certainty in the evidence.

Potential biases in the review process

To avoid potential bias in the review, we only included RCTs and conducted all review steps in duplicate by two independent review authors (study selection, data extraction, 'Risk of bias' assessment, and GRADE of the evidence). Any conflicts were discussed until consensus could be reached. An experienced Information Specialist developed a sensitive search strategy. We searched all relevant databases, trial registries, conference proceedings, and reference lists to minimise potential publication bias. We did not identify any publication bias and are confident that we identified all relevant studies. Overall, we followed Cochrane guidelines and recommendations in every stage of our review and are not aware of any deficiencies in our review process. However, in our opinion, both the 'Risk of bias' assessment and GRADE, are subjective tools in general and therefore are done in duplicate to avoid or minimise subjective influences. Nonetheless, the assessment of one author team can be more rigorous than from another author team and therefore may lead to a different overall judgement of the quality of the included studies and the certainty in the evidence.

Agreements and disagreements with other studies or reviews

To our knowledge this is the first comprehensive review with network meta-analysis comparing safety and effectiveness of multiple drug combinations as initial treatment for adults with newly diagnosed, transplant-ineligible multiple myeloma. Furthermore, this is the first network meta-analysis distinguishing not only between different drug combinations, but also between treatment durations.

We identified four systematic reviews and network meta-analyses that have been conducted to evaluate the effectiveness of different first-line treatment options for adults with transplant-ineligible multiple myeloma. Kuhr 2016 performed a network meta-analysis indirectly comparing VMP and TMP over the common comparator MP. Seven trials were included in this network meta-analysis, all of which are also included in our review. Results showed that VMP and TMP were superior to MP in terms of OS (VMP: hazard ratio (HR) 0.70 (95% confidence interval (CI) 0.57 to 0.86); TMP: HR 0.83 (95% CI 0.66 to 1.03); and PFS (VMP: HR 0.56 (95% CI 0.39 to 0.79); TMP: HR 0.67 (95% CI 0.56 to 0.81); and that VMP may not be superior to TMP (OS: HR 0.85 (95% CI 0.63 to 1.14); PFS: HR 0.83 (95% CI 0.56 to 1.23). These findings are in agreement with our larger network meta-analysis. Furthermore, Kuhr 2016 and colleagues found a statistically significantly lower risk for the incidence of grade 3 and 4 AEs for MP compared to VMP risk ratio (RR 1.13 (95% CI 1.06 to 1.20), and TMP (RR 2.06 (95% CI 1.43 to 2.98), respectively. Network estimates indicated a lower risk for grade 3 and 4 AEs for VMP compared to TMP (RR 0.55 (95% CI 0.38 to 0.80)). Due to strong variations between reporting and defining grade 3 and 4 AEs in our included studies, we could not accept the similarity assumption and therefore not perform network meta-analysis for this outcome.

Additionally to the three compared treatment regimens, which have been compared by Kuhr 2016, and Weisel 2017 also included lenalidomide-based regimens (MPR (in our review referred to as RMP), MPR-R (in our review referred to as RMPc), and RD) in their network meta-analysis. All studies, included by Weisel 2017, were included in our review. Analysis of survival data showed statistically significant superiority of RD compared to all treatment combinations for OS (MP HR 0.46 (95% CI 0.34 to 0.60); MPT: HR 0.75 (95% CI 0.62 to 0.90); MPR: HR 0.38 (95% CI 0.23 to 0.60); MPR-R: HR 0.47 (95% CI 0.31 to 0.71); MPT-T: HR 0.46 (95% CI 0.33 to 0.64); VMP: HR 0.66 (95% CI 0.46 to 0.93)), and PFS (MP: HR 0.39 (95% CI 0.3 to 0.50); MPT: HR 0.69 (95% CI 0.59 to 0.80); MPR: HR 0.39 (95% CI 0.26 to 0.58); MPR-R: HR 0.64 (95% CI 0.46 to 0.89); MPT-T: HR 0.60 (95% CI 0.45 to 0.79), VMP: HR 0.70 (95% CI 0.49 to 0.99)). These results do not completely align with our results. However, according to the P score ranking of our network meta-analysis, results show that fixed and continuous treatment with RD do have the highest benefit on OS out of the treatment combinations, which have been compared by Weisel 2017. Our ranking of treatments according to the P score suggests a higher benefit for continuous RMP for the outcome PFS than RD.

Liu 2017 and colleagues compared first-line treatment options for elderly people with transplant-ineligible myeloma. Despite these inclusion criteria, two trials, analysing reduced-intensity stem cell transplantation (STC) in one arm, were included in their review (Facon 2007; Palumbo 2004). One of these trials was a three-arm study, also comparing MP versus TMP (Facon 2007). We included this study in our review, but excluded the STC-arm from our analysis. Furthermore, one study, evaluating the efficacy of the monoclonal antibody siltuximab plus VMP, was included in the review of Liu 2017, which was not included in ours. PFS results showed superiority of continuous lenalidomide plus dexamethasone (abbreviated to Ld in the article) (HR 0.41 (95% CI 0.21 to 0.79)); MPR-R (HR 0.58 (95% CI 0.41 to 0.84)), MPT (HR 0.57 (95% CI 0.38 to 0.84)) and MPT-T (HR 0.72 (95% CI 0.55 to 0.95)) compared to MP, respectively. and correspond with our results. OS results showed superiority of fixed treatment with RD (given for 18 treatment cycles) (HR 0.55 (95% CI 0.41 to 0.74)); RDc (HR 0.49 (95% CI 0.37 to 0.66)), MPT (HR 0.63 (95% CI 0.51 to 0.78)), and VMP (HR 0.7 (95% CI 0.54 to 0.9)), and inferiority of TD (HR 1.55 (95% CI 1.06 to 12.27)), compared to MP, respectively. In comparison, only the statistically significant OS superiority of RD compared to MP could be confirmed by our results (Table 2).

Blommestein 2019 included 24 trials in their systematic review and network meta-analysis, out of which four were not included in our review (Facon 2006; Mateos 2018; Rajkumar 2008; Zonder 2010). These trials included treatment combinations, which were excluded for our review (dexamethasone alone, dexamethasone + melphalan, dexamethasone + interferon alpha, daratumumab + VMP). Furthermore, Blommestein 2019 also included the STC-arm of Facon 2007 in their analysis. They did not include five trials, which we additionally included, because no full-text publication was available (Jacobus 2016; Katsuoka 2013; Kim 2007; Mookerjee 2017; Pawlyn 2017). Despite these differences, results for the (single reported) outcome PFS align with our network meta-analysis. According to the P score ranking, Blommestein 2019 identified Dara-VMP as the best treatment option, followed by VMPT-VT, VRd, MPR-R. However, we did not include Dara-VMP in our analysis, VTMPc, VRDc, and RMPc took the first three places in our PFS treatment ranking.

In summary, consensus in all network meta-analyses can be reached that drug combinations including one or more novel agents are superior to MP in terms of survival outcomes.

Authors' conclusions

Implications for practice

Considering all 21 comparisons in this network meta-analysis, continuous treatment with VRD (bortezomib plus lenalidomide plus dexamethasone) or VTMP (bortezomib plus thalidomide melphalan and prednisone) showed the highest survival benefits, compared to MP (melphalan and prednisone). RD (lenalidomide and dexamethasone) and TMP (thalidomide melphalan and prednisone) also considerably improved overall survival (OS), respectively compared to MP. However, treatment combinations of bortezomib, lenalidomide and thalidomide also substantially increase incidence of adverse events (AEs), and lead to a higher risk of treatment discontinuation. We included the outcome “withdrawals due to adverse events” so that clinicians in the field can

be informed by data on expected AEs and consequential treatment discontinuations for their choice of therapy. Clinicians in the field should individually evaluate, with their patients, whether the increase in OS achieved with the novel drug combinations is outweighed by the increase in harms including the increase in risk of polyneuropathies.

Implications for research

Substantial clinical evidence from randomised controlled trials (RCTs) support the effectiveness of multiple drug combinations of bortezomib, lenalidomide and thalidomide as first-line treatment for multiple myeloma. Their effectiveness and safety profiles may best be analysed in further randomised head-to-head trials. Further trials should focus on consistent reporting of safety outcomes and should use a standardised instrument to evaluate QoL to ensure comparability of treatment combinations.

Acknowledgements

This review was published in collaboration with the Cochrane Fast-Track Service. We particularly thank Helen Wakeford (Fast-Track Managing Editor), Newton Opiyo (Cancer Network Associate Editor and Sign-off Editor), Toby Lasserson (Sign-off Editor), Kerry Dwan (Statistical Editor), and Heather Maxwell (Copy Editor) for their support. The Fast-Track Service team made comments on the review and managed the editorial process.

We thank Lorenzo Moja and Nicola Magrini, Secretary of the World Health Organization Expert Committee on the Selection and Use of Essential Medicines, for their support and guidance during the planning and conduct of this review.

We thank Robin Featherstone for commenting on the search strategy and Gerald Gartlehner for commenting on the methodology of this review.

We thank the consumer editors Caroline Healy and Céline Fournier who supported the improvement of the comprehensibility of this review.

We thank all external peer-reviewers who read and commented on this review. We thank Fergus Macbeth, Lynda Ware, Anne Eisinga, Angela Dispenzieri, and Giada Bianchi who greatly helped to improve this review.

Contributions of authors

Drafted the protocol	VP, NS, TJ, PL, LE
Clinical expertise and advice	CS, SO, ST
Developed and ran the search strategy	IM
Obtained copies of studies	VP
Selected which studies to include (2 people)	NS, VP
Extracted data from studies (2 people)	VP, BS
Entered data into RevMan	VP
Carried out the analyses	AA, KK
Interpreted the analyses	VP, TJ, CS
Drafted the final review	VP, NS, LE
Will update the review	NS, VP

Declarations of interest

NS: none known.

VP: none known.

PL: none known.

TJ: none known.

IM: none known.

CS: The author has received honoraria and travel support from Janssen, Celgene, Novartis, Bristol Myers Squibb and Takeda

SO: none known.

LE: none known.

ST: none known.

KK: none known.

BS: none known.

AA: none known.

Differences between protocol and review

The protocol for this review was registered with PROSPERO (Piechotta 2018). After further discussions with the WHO EML Cancer Medicines Workung Group and the perusal of the characteristics of included studies, we had to revise some elements of the methodology. These elements are outlined below.

Outcomes

Adequate prophylaxis of treatment-related adverse events is very important, but not easily available in low- and middle-income countries (LMICs). As the aim of this review was to inform an application for the WHO's list of essential medicines, we decided that beside focusing on the efficacy and safety of the studied drug combinations, we should also compare the adherence to the assigned therapies. We added the outcome "withdrawals due to adverse events" after discussions with the WHO EML Cancer Medicines Working Group.

Subgroup analyses

Follow-up (short term (< 5 years) versus long term >= 5 years)

Considering the treatment durations of the included studies, we decided to adapt the planned follow-up subgroup analysis. Instead of comparing a follow-up time of < 1 year to >= 1 year, we decided to compare a follow-up time of < 5 years versus >= 5 years to better focus on the long-term efficacy of the compared treatment combinations.

Subgroup analyses for a follow-up period >= 5 years could not be performed for overall survival (OS) and progression-free survival (PFS) as only two studies (Jacobus 2016; Mateos 2014) reported a median follow-up over five years. Treatment regimens of these two studies were not connected in a network.

Multiple myeloma international staging system (I, II, III)

Subgroup analyses for myeloma disease staging could not be performed as all studies included disease stages I, II, and III.

Age (< 75 versus > 75)

Subgroup analyses for age groups (<75 versus. >=75 years) could not be performed, as only one study (Hulin 2009) included only patients >75 years.

Region (low- and middle-income countries versus high-income countries)

Subgroup analyses for regions (low- and middle-income versus high-income countries) could not be performed, as all trials which included patients from low- and middle-income regions were multicentre studies and also included patients from high-income settings.

Sensitivity analysis

Risk of bias (low versus high)

For OS, robustness of results for VRDc and VTMPc could not be tested in sensitivity analysis for low risk of bias, as all studies which included these treatments (Durie 2017; Palumbo 2014) had an unclear or high risk of bias.

Furthermore, risk of bias sensitivity analysis could not be performed for all other outcomes as Palumbo 2012 and Waage 2010 were the only studies with a low risk of bias. For PFS, polyneuropathies and infections, sensitivity analysis without high risk of bias could not be performed as all studies reporting these outcomes, except Palumbo 2012 and Waage 2010 had a high risk of bias and treatment regimens of these two studies were not connected in a network. For anaemia, thrombocytopenia, severe adverse events (SAEs), withdrawals due to AEs, sensitivity analysis without high risk of bias could not be performed as all studies reporting these outcomes, except Palumbo 2012, which ad a high risk of bias. For thromboembolism, sensitivity analysis without high risk of bias could not be performed as all studies reporting this outcome, except Waage 2010, which had a high risk of bias. For neutropenia, sensitivity analysis without high risk of bias could not be performed as all studies reporting this outcome had a high risk of bias.

Published notes

Characteristics of studies

Characteristics of included studies

Bahlis 2017

Methods	• Design: randomised, open-label, phase III trial; conducted at 246 treatment centres in 18 countries in collaboration with the Intergroupe Francophone du Myélome • Sample size: n = 1623 patients. Arm 1: continuous lenalidomide and dexamethasone (RDc) n = 535, Arm 2: lenalidomide and dexamethasone for 18 cycles (RD) n = 541, Arm 3: thalidomide, melphalan and prednisone (TMP) n = 547 • Duration of treatment: continuous (RDc), 18 cycles (RD), 12 cycles (TMP) • Median follow-up: 45.5 months • Ongoing: no • Trial registration Nr: NCT00689936
Participants	• Patient population: patients with NDMM who were ineligible for stem cell transplant • Inclusion criteria: patients with previously untreated, symptomatic, and measurable MM, patients were either 65 years of age or older or were younger than 65 years of age and ineligible for stem-cell transplantation, Patients had to be able and willing to undergo antithrombotic prophylaxis. • Exclusion criteria: prior anti myeloma treatment (except for radiotherapy and treatment with bisphosphonates or a single course of glucocorticoids), an ECOG performance-status score of more than 2 (on a scale from 0 to 5, with higher numbers indicating greater disability), renal failure requiring dialysis, an absolute neutrophil count below 1000 cells per mm^3, a platelet count (without transfusion) below 50,000 cells per mm^3, a serum aspartate aminotransferase or alanine aminotransferase level that was more than three times the upper limit of the normal range, and peripheral neuropathy of grade 2 or higher. • Baseline Characteristics: ◦ Median age: 73 years ◦ Male/female: 50% to 55% male ◦ ISS: I, II, and III ◦ ECOG performance status: 0-4 ◦ Country/ region: Europe, North America, Asia, Pacific
Interventions	• Arm 1: RD in 28-day cycles until disease progression; lenalidomide at a dose of 25 mg per day was given on days 1 to 21 of each 28-day cycle, and dexamethasone at a dose of 40 mg was given on days 1, 8, 15, and 22. • Arm 2: RD in 28-day cycles for 72 weeks (18 cycles); lenalidomide at a dose of 25 mg per day was given on days 1 to 21 of each 28-day cycle, and dexamethasone at a dose of 40 mg was given on days 1, 8, 15, and 22. • Arm 3: TMP in 42-day cycles for 72 weeks (12 cycles); thalidomide (at a dose of 200 mg per day) were administered in 42-day cycles, melphalan (at a dose of 0.25 mg per kilogram of body weight per day on days 1 to 4), and prednisone (at a dose of 2 mg per kilogram per day on days 1 to 4). • Additional treatments: all patients received low-dose aspirin (70 mg to 100 mg per day) or other antithrombotic prophylaxis. Patients with deep-vein thrombosis or pulmonary embolism within 5 years of randomisation received a low-molecular-weight heparin, heparin, or warfarin for at least the first 4 months of study treatment; thereafter, patients continued the same anticoagulation therapy or switched to low-dose aspirin at the investigator's discretion. Bisphosphonate therapy, supportive therapies, and haemopoietic growth factors could be used at the discretion of the treating physician. The use of myeloid growth factors was encouraged when the absolute neutrophil count was <1000 cells per mm^3. Careful consideration was to be given to avoiding the concomitant use of erythropoiesis-stimulating agents known to potentially increase the risk of thrombosis.
Outcomes	• Primary: PFS with RDc compared to TMP • Secondary: OS, ORR, TTR DR TTTF, TTNT, HRQoL, AE for RDc vs. TMP • Secondary comparisons: RD vs. TMP and RDc vs. RD for all endpoints

Notes	• Sponsor/ Funding: supported by Intergroupe Francophone du Myélome and Celgene. Financial support for this study was provided by Celgene Corporation. • Type of publication (full text or abstract only): full text • Abbreviations: ◦ PFS: progression-free survival ◦ OS: overall survival ◦ ORR: overall response rate ◦ TTR: time to response ◦ DR: duration of response ◦ TTTF. time to treatment failure ◦ TTNT: time to next treatment/ time to second-line anti-myeloma therapy ◦ HRQoL: health-related quality of life ◦ AE: adverse events/safety

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "validated interactive voice-response system"
Allocation concealment (selection bias)	Low risk	Comment: central randomisation
Blinding of participants and personnel (performance bias)	High risk	Quote: "open-label"
Blinding of overall survival assessment (detection bias)	Low risk	Comment: patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Quote: "open-label"
Blinding of safety assessment (detection bias)	High risk	Quote: "open-label"
Incomplete survival data (attrition bias)	Low risk	Comment: censored Kaplan Meier curves
Incomplete safety data (attrition bias)	Low risk	Comment: all reported patients received at least one study drug
Selective reporting (reporting bias)	Low risk	Comment: protocol and results for all pre-specified primary and secondary outcomes available
Other bias	Low risk	Comment: no information to suggest other sources of bias

Beksac 2011

Methods	• Design: randomised controlled phase III trial; conducted in Turkey • Sample size: n = 122; experimental arm (TMP) n = 60, control arm (MP) n = 62 • Duration of treatment: 12 months • Median follow-up: 23 months • Ongoing: no • Trial registration Nr: NCT00934154
Participants	• Patient population: patients with NDMM who were ineligible for stem cell transplant • Inclusion criteria: previously untreated patients with symptomatic MM, patients above the age of 55 yrears not eligible for transplantation, with a performance status of ≧ 2 • Exclusion criteria: asymptomatic myeloma or solitary plasmacytoma of bone or extramedullary plasmacytoma (without evidence of myeloma). Previous or concurrent active malignancies, except surgically removed basal cell carcinoma of the skin or other in situ carcinomas. Previous treatment for myeloma, except minimal local radiotherapy to relieve bone pain. Other illnesses which would preclude chemotherapy administration or patient compliance. Any other serious medical or psychiatric illness which would prevent informed consent. Peripheral neuropathy > NCI criteria grade 2. Pregnant or lactating women and patients of childbearing age who refuse to use contraception. History of hypersensitivity to thalidomide or any component of the medications. • Baseline characteristics: ◦ Median age: 70.6 years ◦ Male/female: 47.4% to 60.3% male ◦ ISS: I, II, III ◦ ECOG performance status: 0-3 ◦ Country: Turkey:
Interventions	• Experimental arm: oral thalidomide at a dose of 100 mg per day, continuously administered, oral melphalan at a dose of 9 mg/m²/day and oral prednisone 60 mg/m²/day were given for 4 days every 6 weeks. • Control arm: oral melphalan at a dose of 9 mg/m²/day and oral prednisone 60 mg/m²/day were given for 4 days every 6 weeks • Additional treatments: low molecular weight heparin, warfarin, or aspirin was given according to thrombosis risk assessment
Outcomes	• Primary: treatment response and toxicities after 4 and 8 cycles of treatment • Secondary: DFS and OS
Notes	• Sponsor/ Funding: Cigdem Sahinbas YILMAZ • Type of publication (full text or abstract only): full text • Abbreviations: ◦ d: day ◦ DFS: disease-free survival ◦ OS: overall survival

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised centrally"
Allocation concealment (selection bias)	Low risk	Quote: "randomised centrally"
Blinding of participants and personnel (performance bias)	High risk	Comment: not described, probably unblinded
Blinding of overall survival assessment (detection bias)	Low risk	Comment: patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Comment: not described, probably unblinded
Blinding of safety assessment (detection bias)	High risk	Comment: not described, probably unblinded
Incomplete survival data (attrition bias)	Low risk	Comment: censored Kaplan Meier curves
Incomplete safety data (attrition bias)	Low risk	Comment: all reported patients received at least one study drug
Selective reporting (reporting bias)	High risk	Comment: protocol available; pre-specified primary and secondary outcomes have been altered. RR was supposed to be evaluated after 12 months, was reported after four 6-week cycles; TTP was supposed to be evaluated, DFS was reported
Other bias	Low risk	Quote: "Data were monitored by an independent contract research organization (CRO; OMEGA, Ankara, Turkey), who also performed statistical analyses (Dr Z. Arat). spss 15.0 (SPSS Inc., Chicago, IL, USA) software was used for data analysis"; Comment: the study appear to be free of other sources of bias

Durie 2017

Methods	• Design: randomised, open-label, phase III trial; conducted at 139 SWOG and NCTN institutions • Sample size: n = 525; experimental arm (VRD) n = 264; control arm (RD) n = 261 • Duration of treatment: 24 weeks • Median follow-up: 55 months • Ongoing: no • Trial registration NR: NCT00644228
Participants	• Patient population: patients with NDMM • Inclusion criteria: patients aged 18 years or older with newly diagnosed myeloma, presence of CRAB criteria with measurable disease (measured by assessment of free light chains), ECOG performance status 0–3, allowable blood count values were: haemoglobin ≥9 g/dL; absolute neutrophil count ≥1 × 10^3 cells per mm^3; platelet count ≥80 000/mm^3 • Exclusion criteria: creatinine clearance ≤30 mL/minute; cardiac status New York Heart Association class III/IV or recent myocardial infarction; active hepatitis B or C or HIV or uncontrolled other infection; previous cancer prior to study registration or enrolment; or poorly controlled diabetes • Baseline characteristics: ◦ Median age: n.r. ◦ Male/female: 58.4% male ◦ ISS: I, II,III ◦ ECOG performance status: n.r. ◦ Country: Northern America
Interventions	• Experimental arm: bortezomib was given at 1.3 mg/m^2 intravenously on days 1, 4, 8, and 11 combined with 25 mg oral lenalidomide once a day on days 1–14 plus 20 mg oral dexamethasone on days 1, 2, 4, 5, 8, 9, 11, and 12; eight 21-day cycles • Control arm: 25 mg oral lenalidomide once a day for days 1–21 plus 40 mg oral dexamethasone on days 1, 8, 15, and 22; six 28-day cycles • Additional treatments: patients in the VRD group received herpes simplex virus prophylaxis. All patients received 325 mg oral aspirin once a day to reduce the risk of thromboembolic complications. Upon completion of induction, all patients received ongoing maintenance with 25 mg oral lenalidomide once a day for 21 days plus 40 mg oral dexamethasone once a day for days 1, 8, 15, and 22 of each 28-day cycle. Stem-cell collection was allowed for those patients considering future transplant.
Outcomes	• Primary: PFS • Secondary: OS, OR, AE, and to bank specimens for future translational medicine research
Notes	• Sponsor/ Funding: this study was funded by grants from NIH/NCI/NCTN grants CA180888, CA180819, CA180821, CA180820; NIH/NCI/NCORP grants CA189858, CA189971, CA189808, CA189821, CA189829, CA189804, CA189953, CA189830, CA189957, CA189853, CA189872, CA189856, CA189860, CA139519, CA189854, CA189952, CA189825; NIH/NCI legacy grants CA04919, CA22433, CA58723, CA68183, CA35996, CA73590, CA12644, CA46282, CA13612, CA37981, CA16385, CA45450, CA46113 and partly by Millennium Pharmaceuticals, The Takeda Oncology Company, and Celgene Corporation for provision of study drug under their respective Cooperative Research and Development Agreements with the NCI. • Type of publication (fullt ext or abstract only): full text • Abbreviations: ◦ n.r.: not reported ◦ PFS: progression-free survival ◦ OS: overall survival ◦ OR: overall response ◦ AE: adverseeEvents/Ssafety

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "dynamic allocation algorithm"
Allocation concealment (selection bias)	Low risk	Comment: central randomisation
Blinding of participants and personnel (performance bias)	High risk	Quote:"no masking to treatment interventions"
Blinding of overall survival assessment (detection bias)	Low risk	Comment: patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Quote:"no masking to treatment interventions"
Blinding of safety assessment (detection bias)	High risk	Quote:"no masking to treatment interventions"
Incomplete survival data (attrition bias)	Low risk	Comment: censored Kaplan Meier curves
Incomplete safety data (attrition bias)	Low risk	Comment: all reported patients received at least one study drug
Selective reporting (reporting bias)	Low risk	Comment: protocol and results for all pre-specified primary and secondary outcomes available
Other bias	Low risk	Quote: "An independent data and safety monitoring committee reviewed unblinded safety data twice a year."

Facon 2007

Methods	• Design: randomised controlled phase III trial; conducted at 73 IFM centres in France, Belgium and Switzerland • Sample size: n = 447 patients; experimental arm (TMP): n = 125; control arm (MP) n = 196; patients receiving transplantation (arm excluded in this review) n = 126 • Duration of treatment: 12, 6-week cycles • Median follow-up: 51.5 months • Ongoing: no • Trial registration Nr: NCT00367185
Participants	• Patient population: patients with NDMM who were ineligible for high dose treatment • Inclusion criteria: patients with stage II or III MM according to Durie-Salmon criteria, aged between 65 and 75 years. Patients younger than 65 years were included if they were ineligible for high-dose treatment. Patients with Durie-Salmon stage I MM could be enrolled if they met the criteria of high-risk stage I disease. Patients were previously untreated except for minimum-dose radiotherapy to localised lesions, which was needed to relieve symptoms • Exclusion criteria: patients with a previous history of another neoplasm (except basocellular cutaneous or cervical epithelioma); primary or associated amyloidosis; a WHO performance index of 3 or greater, if unrelated to MM; substantial renal insufficiency with creatinine serum concentration of 50 mg/L or more; cardiac or hepatic dysfunction; peripheral neuropathy; or were infected with HIV, or hepatitis B or C • Baseline characteristics: ◦ median age: 69.4 years ◦ Male/female: 53% male ◦ ISS: I, II, III ◦ ECOG performance status: n.r. ◦ Country: France, Belgium, Switzerland
Interventions	• Experimental arm: thalidomide was given daily at a dose not exceeding 400 mg per day; Melphalan (0·25 mg/kg) and prednisone (2 mg/kg) were given orally for 4 days per cycle • Control arm: melphalan (0·25 mg/kg) and prednisone (2 mg/kg) were given orally for 4 days per cycle • Additional treatments: n.r.
Outcomes	• Primary: OS • Secondary: Response, PFS, survival after progression, AEs
Notes	• Sponsor/ Funding: Laphal, and later, Pharmion, supplied free thalidomide for the study. The study was sponsored by the Centre Hospitalier et Universitaire de Lille (Lille University Hospital). It was also supported by a research grant from the French Ministry of Health (Projet Hospitalier de Recherche Clinique, CHRU Lille 1998, number 1951), and by the Swiss Group for Clinical Cancer Research (SIAK). • Type of publication (full text or abstract only): full text • Abbreviations: ◦ n.r.: not reported ◦ OS: overall survival ◦ PFS: progression-free survival ◦ AEs:adverse events/toxicities

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not described
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias)	High risk	Comment: not described, probably unblinded
Blinding of overall survival assessment (detection bias)	Low risk	Comment: patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Comment: not described, probably unblinded
Blinding of safety assessment (detection bias)	High risk	Comment: not described, probably unblinded
Incomplete survival data (attrition bias)	Low risk	Comment: censored Kaplan Meier curves
Incomplete safety data (attrition bias)	Low risk	Comment: all reported patients received at least one study drug
Selective reporting (reporting bias)	Low risk	Comment: protocol and results for all pre-specified primary and secondary outcomes available
Other bias	Low risk	Comment: no information to suggest other sources of bias

Hulin 2009

Methods	• Design: randomised placebo-controlled, phase III trial; conducted in France and Belgium • Sample size: n = 232 patients; experimental arm (TMP) n = 113; control arm (MP) n = 116 • Duration of treatment: 72 weeks • Median follow-up: 47.5 months • Ongoing: no • Trial registration Nr: N/A
Participants	• Patient population: patients with NDMM • Inclusion criteria: patients with stage II or III NDMM according to Durie-Salmon criteria and were at least 75 years of age, In addition, patients with Durie-Salmon stage I MM could be enrolled if they met the criteria of high-risk stage I disease, • Exclusion criteria: previous neoplasms (except basocellular cutaneous or cervical epithelioma); primary or associated amyloidosis; a WHO performance index of3 or higher, if unrelated to MM; substantial renal insufficiency with creatinine serum concentration of 50 mg/L or more; cardiac or hepatic clinically significant dysfunction; clinically significant peripheral neuropathy; history of venous thrombosis during the previous 6 months; or HIV infection, or hepatitis B or C infections. • Baseline characteristics: ◦ median age: 78.5 years ◦ Male/female: 45% male ◦ ISS: I, II, III ◦ ECOG performance status: 0-3 ◦ Country: France, Belgium
Interventions	• Experimental arm:100 mg daily dose of thalidomide continuously for 72 weeks, administered at bedtime. In addition, all patients received 12, 6-week cycles of MP: melphalan at 0.2 mg/kg on days 1 to 4; prednisone 2 mg/kg on days 1 to 4. • Control arm: placebo continuously for 72 weeks, administered at bedtime. In addition, all patients received 12, 6-week cycles ofMP: melphalan at 0.2 mg/kg on days 1 to 4; prednisone 2 mg/kg on days 1 to 4. • Additional treatments: clodronate was given orally at a dose of 1040 mg per day continuously to all patients. No anticoagulation prophylaxis was prospectively planned. Transfusions of RBCs and platelets and the administration of neutrophil growth factors or erythropoiesis-stimulating agents were permitted as required. Plasmapheresis at initial treatment and radiotherapy to localised lesions to relieve symptoms during the treatment phase were also permitted.
Outcomes	• Primary: OS • Secondary: AEs, RR, PFS
Notes	• Sponsor/ Funding: Sponsored by the Centre Hospitalier Universitaire de Nancy; by a research grant from the French Ministry of Health (Projet Hospitalier de Recherche Clinique, CHRU Nancy 2001, No. 04.9702); by Laphal; by Pharmion; and by Celgene, which supplied free experimental treatment (thalidomide or placebo) for the study. • Type of publication (full text or abstract only): full text • Abbreviations: ◦ n.r.: not reported ◦ OS: overall survival ◦ PFS: progression-free survival ◦ AEs: adverse events/safety ◦ RR: response rates

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned patients centrally"
Allocation concealment (selection bias)	Low risk	Quote: "randomly assigned patients centrally"
Blinding of participants and personnel (performance bias)	High risk	Comment: not described, probably unblinded
Blinding of overall survival assessment (detection bias)	Low risk	Comment: patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Comment: not described, probably unblinded
Blinding of safety assessment (detection bias)	High risk	Comment: not described, probably unblinded
Incomplete survival data (attrition bias)	Low risk	Comment: Kaplan Meier curve
Incomplete safety data (attrition bias)	Low risk	Comment: all patients received at least one study drug
Selective reporting (reporting bias)	Low risk	Comment: protocol not available, but report includes all expected outcomes
Other bias	Low risk	Comment: no information to suggest other sources of bias

Hungria 2016

Methods	• Design: randomised, open-label, phase III trial; conducted in 4 centres in Argentina and Brazil • Sample size: n = 82 patients; Arm 1 (TMP) n = 32, Arm 2 (CTD) n = 32; Arm 3 (TD) n = 18 • Duration of treatment: nine 4-week cycles • Median follow-up: 37.5 months • Ongoing: no • Trial registration Nr: NCT01532856
Participants	• Patient population: patients with NDMM who were ineligible for stem cell transplant • Inclusion criteria: newly diagnosed, untreated MM in stages II or III of the Durie-Salmon System (DSS), measurable disease confirmed by the presence of monoclonal protein in blood or Bence-Jones proteinuria, adequate haematological (absolute neutrophil count ≥1000/mm^3, haemoglobin ≥8 g/dL,and platelet count ≥50,000/mm^3, with lower values permitted if due to bone marrow infiltration) and biochemical parameters (serum creatinine ≤2 mg/dL, corrected serum calcium ≤14 mg/dL, aspartate and alanine transaminases ≤2.5 times the upper normal limit, and total bilirubin ≤1.5 times the upper normal limit), and ineligibility to undergo high-dose chemotherapy and autologous transplantation • Exclusion criteria: non-secretory MM, positivity for HIV infection or hepatitis B virus, active hepatitis C virus infection, peripheral neuropathy higher than grade 2, life expectancy ≤12 weeks, history of other neoplasm other than non-melanoma skin cancer, myocardial infarction within 6 months prior to inclusion, any active cardiac disorder, or the presence of any condition that, in the opinion of the investigators, could pose undue risk to or compromise the ability to assess treatment results. • Baseline characteristics: ◦ Mean Aae: 72.2 years ◦ Male/female: 34.4% to 55.6% male ◦ ISS: I, II, III ◦ ECOG performance status: 0-4 ◦ Country: Argentina and Brazil
Interventions	• Arm 1: oral melphalan, 4 mg/m^2/day for seven consecutive days every 4 weeks, prednisone, 40 mg/m^2 for seven consecutive days every 4 weeks, and thalidomide, 200 mg/day continuously • Arm 2: oral cyclophosphamide, 50 mg/day continuously, thalidomide, 200 mg/day continuously, and dexamethasone, 40 mg/day on days 1 through 4 and 15 through 18 of the first two cycles, and for four consecutive days every 4 weeks thereafter • Arm 3: thalidomide, 200 mg/day continuously, and dexamethasone, 40 mg/day on days 1 through 4, 9 through 12, and 17 through 20 in odd-numbered cycles and on days 1 through 4 in even-numbered cycles • Additional treatments: n.r.
Outcomes	• Primary: ORR • Secondary: PFS, OS, AEs
Notes	• Sponsor/ Funding: Grupo de Estudos Multicentricos em Onco-Hematologia • Type of publication (full text or abstract only): full text • Abbreviations: ◦ n.r.: not reported ◦ ORR: overall response rate ◦ OS: overall survival ◦ PFS: progression-free survival ◦ AEs: adverse events

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not described
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias)	High risk	Quote: " open-label"
Blinding of overall survival assessment (detection bias)	Low risk	Comment: patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Quote: " open-label"
Blinding of safety assessment (detection bias)	High risk	Quote: " open-label"
Incomplete survival data (attrition bias)	Low risk	Comment: censored Kaplan Meier curves
Incomplete safety data (attrition bias)	Low risk	Comment: all reported patients received at least one study drug
Selective reporting (reporting bias)	High risk	Quote:"an unplanned interim analysis was conducted and suggested that the TD arm displayed inferior efficacy in terms of PFS, when compared with MPT and CTD (...). Therefore, only descriptive results for the TD arm will be presented"; Comment: >10% missing data, without explanations in one arm
Other bias	High risk	Quote:"an unplanned interim analysis was conducted and suggested that the TD arm displayed inferior efficacy in terms of PFS, when compared with MPT and CTD (...). Therefore, only descriptive results for the TD arm will be presented"; Comment: >10% missing data, without explanations in one arm

Jacobus 2016

Methods	• Design: randomised, open-label, phase III trial, conducted at 15 institutions in Northern America • Sample size: n = 48 patients; experimental arm (VRD) n = 23, control arm (VD) n = 25 • Duration of treatment: eight 21-day cycles • Median follow-up: 72 months • Ongoing: no • Trial registration Nr: NCT00522392
Participants	• Patient population: patients with symptomatic MM who had completed a minimum of one cycle and maximum of six cycles of dexamethasone-based induction therapy • Inclusion criteria: age > 18 years, symptomatic MM meeting the following criteria at diagnosis:- Bone marrow plasmacytosis with > 10% plasma cells or sheets of plasma cells or biopsy-proven plasmacytoma during disease course, - Symptomatic disease prompting initiation of therapy- Evidence of end-organ damage (anaemia, hypercalcaemia, bone disease, or renal dysfunction), Dexamethasone-based induction regimen for > 2 cycles, without progressive disease, last cycle of induction treatment < 8 weeks before randomisation Refusal of, or ineligibility for, first-line stem cell transplantation, any previous palliative and/or localised radiation therapy completed > 14 days before randomisation ECOG performance status of 0, 1, or 2Ability to understand trial design and provide informed consent Willingness and ability to take thrombosis prophylaxis, negative pregnancy test and agreement to use adequate contraception (because of the potential teratogenic properties of lenalidomide) • Exclusion criteria: smoldering myeloma and monoclonal gammopathy of undetermined significance, previous exposure to bortezomib, active, uncontrolled seizure disorder (seizures < 6 months before randomisation), uncontrolled concurrent illness that would limit compliance Grade > 2 peripheral neuropathy (CTCAE version 3.0) • Baseline characteristics: ◦ Median age: n.r. ◦ Male/female: n.r. ◦ ISS: n.r. ◦ ECOG performance status: n.r. ◦ Country: USA
Interventions	• Experimental arm: bortezomib (V) 1.3 mg/m2 IV d1, 4, 8 and 11, lenalidomide (R) 15 mg/day orally days 1-14 plus dexamethasone (d) 40 mg/day orally d1, 8 and 15 every 21 days for 8 cycles • Control arm: bortezomib 1.3 mg/m2 IV d1, 4, 8 and 11 plus dexamethasone 40 mg/day orally d1, 8, 15 every 21 days for 8 cycles • Additional treatments: n.r.
Outcomes	• Primary: PFS • Secondary: CR, VGPR, OS, AEs, QoL
Notes	• Sponsor/Funding: Millennium Pharmaceuticals, Inc. in partnership with Johnson & Johnson Pharmaceutical Research & Development LLC • Type of publication (full text or abstract only): letter • Abbreviations: ◦ n.r.: not reported ◦ OS: overall survival ◦ PFS: progression-free survival ◦ VGPR: very good partial response ◦ CR: complete response, ◦ AEs: adverse events /toxicity ◦ QoL: quality of life

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient information, only letter available
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information, only letter available
Blinding of participants and personnel (performance bias)	High risk	Comment: insufficient information, only letter available, probably unblinded
Blinding of overall survival assessment (detection bias)	Low risk	Comment: patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Comment: insufficient information, only letter available, probably unblinded
Blinding of safety assessment (detection bias)	High risk	Comment: insufficient information, only letter available, probably unblinded
Incomplete survival data (attrition bias)	Low risk	Comment: censored Kaplan Meier curves
Incomplete safety data (attrition bias)	Low risk	Comment: all reported patients received at least one study drug
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient information, only letter available
Other bias	High risk	Quote: "closed enrollment prematurely due to slow accural"

Katsuoka 2013

Methods	• Design: randomised phase II trial; conducted in Tohoku area • Sample size: n = 18 patients; experimental arm (VD) n = 9; control arm (VMP) n = 9 • Duration of treatment: seven 6-week cycles • Median follow-up: n.r. • Ongoing: no • Trial registration Nr: UMIN 3472
Participants	• Patient population: untreated transplant-ineligible MM • Inclusion criteria: n.r. • Exclusion criteria: n.r. • Baseline characteristics: ◦ Median age: n.r. ◦ Male/female: n.r. ◦ ISS: n.r. ◦ ECOG performance status: n.r. ◦ Country: Japan
Interventions	• Experimental arm: (VD) two cycles of 1.3 mg/m2 bortezomib twice per week followed by five cycles of 1.3 mg/m2 bortezomib once per week for 6 weeks, dexamethasone dose not reported • Control arm: (VMP) two cycles of 1.3 mg/m2 bortezomib twice per week followed by five cycles of 1.3 mg/m2 bortezomib once per week for 6 weeks, melphalan and prednisone dose not reported • Additional treatments: n.r.
Outcomes	• Primary: ORR • Secondary: SAEs
Notes	• Sponsor/ Funding: n.r. • Type of publication (full text or abstract only): abstract only • Abbreviations: ◦ n.r.: not reported ◦ ORR: overall response rate ◦ SAEs: serious adverse events

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient information, only abstracts available
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information, only abstracts available
Blinding of participants and personnel (performance bias)	High risk	Comment: insufficient information, only abstracts available, probably unblinded
Blinding of overall survival assessment (detection bias)	Low risk	Comment: patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Comment: insufficient information, only abstracts available, probably unblinded
Blinding of safety assessment (detection bias)	High risk	Comment: insufficient information, only abstracts available, probably unblinded
Incomplete survival data (attrition bias)	Unclear risk	Comment: insufficient information, only abstracts available
Incomplete safety data (attrition bias)	Unclear risk	Comment: insufficient information, only abstracts available
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient information, only abstracts available
Other bias	Low risk	Comment: no information to suggest other sources of bias

Kim 2007

Methods	• Design: randomised controlled trial, conducted in South Korea • Sample size: n = 66 patients; experimental arm (TCD) n = 35; control arm (TD) n = 31 • Duration of treatment: 4 or more 28-day cycles • Median follow-up: n.r. • Ongoing: no • Trial registration Nr: NCT00349115
Participants	• Patient population: NDMM patients • Inclusion criteria: n.r. • Exclusion criteria: n.r. • Baseline characteristics: ◦ Median age: 66 years ◦ Male/female: 50% male ◦ ISS: n.r. ◦ ECOG performance status: n.r. ◦ Country: South Korea
Interventions	• Experimental arm: cyclophosphamide 150 mg/m² orally on days 1-4, thalidomide 50 mg/day, daily, and i.v. dexamethasone 20 mg/m² on days 1-5, 15-19 • Control arm: thalidomide 50 mg/day, daily, and i.v. dexamethasone 20 mg/m² on days 1-4, 9-12, 17-20 • Additional treatments: all patients except severe thrombocytopenia received aspirin daily for the prophylaxis of deep vein thrombosis
Outcomes	• Primary: n.r.; aim: to assess efficacy and safety • Secondary: n.r.
Notes	• Sponsor/ Funding: n.r. • Type of publication (full text or abstract only): abstract only • Abbreviations: ◦ n.r.: not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient information, only abstracts available
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information, only abstracts available
Blinding of participants and personnel (performance bias)	High risk	Comment: insufficient information, only abstracts available, probably unblinded
Blinding of overall survival assessment (detection bias)	Low risk	Comment: patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Comment: insufficient information, only abstracts available, probably unblinded
Blinding of safety assessment (detection bias)	High risk	Comment: insufficient information, only abstracts available, probably unblinded
Incomplete survival data (attrition bias)	Unclear risk	Comment: insufficient information, only abstracts available
Incomplete safety data (attrition bias)	Unclear risk	Comment: insufficient information, only abstracts available
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient information, only abstracts available
Other bias	Low risk	Comment: no information to suggest other sources of bias

Ludwig 2009

Methods	• Design: randomised, open-label, phase III trial; conducted in 26 centres in Austria, Czech Republic, Slovakia, Hungary, and Croatia • Sample size: n = 289 patients, experimental arm (TD) n = 145, control arm (MP) n = 144 • Duration of treatment: 9, 28- to 42-day cycles • Median follow-up: 28.1 months • Ongoing: no • Trial registration Nr: NCT00205751
Participants	• Patient population: patients with NDMM who were ineligible for stem cell transplant • Inclusion criteria: patients with previously untreated active MM not eligible for autologous transplantation with Durie Salmon stage II and III and, if they met the criteria of high risk, with stage I, must have presented with adequate bone marrow (white blood cell count > 3000/µL, platelets > 100 000/µL) and hepatic function (SGOT, SGPT, and alkaline phosphatase < 3 times upper limit of normal), with ECOG performance status of 3 or better and with a clear requirement for treatment, meaning that patients needed to be symptomatic from bone pain or present with anaemia (haemoglobin < 10 g/dL) or both, impaired renal function (creatinine > 2.0 mg/dL), or hypercalcaemia (calcium > 10.5 mg/L) • Exclusion criteria: patients with extramedullary or solitary plasmacytoma without evidence of dissemination of disease or with smouldering myeloma, with more than 3 irradiation fields, congestive heart failure (New York Heart Association III and IV), acute infection, uncontrolled medical condition (e.g. diabetes or glaucoma) • Baseline characteristics: ◦ Median age: 72 years ◦ Male/female: 49% to 51% male ◦ ISS: 1,2,3 ◦ ECOG performance status: 3 or better ◦ Country: Austria, Czech Republic, Slovakia, Hungary, and Croatia
Interventions	• Experimental arm: thalidomide 50 mg to 400 mg daily and dexamethasone 40 mg on days 1 to 4 and 15 to 18 on even cycles and on days 1 to 4 on odd cycles during a 28-day cycle • Control arm: melphalan 0.25 mg/kg and prednisolone 2 mg/kg orally on days 1 to 4 during a 28- to 42-day cycle • Additional treatments: n.r.
Outcomes	• Primary: PFS, tolerance • Secondary: RR, TTR, OS
Notes	• Sponsor/ Funding: Austrian Forum against Cancer, by the Austrian Health authorities, the Association of Austrian Social Insurance Carriers, and partly by an investigational grant from Schering-Plough. Sample collections in the Czech Republic were supported by MSM0021622434 and LC06027 • Type of publication (full text or abstract only): full text • Abbreviations: ◦ n.r.: not reported ◦ PFS: progression-free survival ◦ RR: response rates ◦ TTR: time to response ◦ OS: overall survival

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote:"centralized and computerized randomisation system"
Allocation concealment (selection bias)	Low risk	Quote:"centralized and computerized randomisation system"
Blinding of participants and personnel (performance bias)	High risk	Comment: not described, probably unblinded
Blinding of overall survival assessment (detection bias)	Low risk	Comment: patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Comment: not described, probably unblinded
Blinding of safety assessment (detection bias)	High risk	Comment: not described, probably unblinded
Incomplete survival data (attrition bias)	Low risk	Comment: Kaplan Meier curve
Incomplete safety data (attrition bias)	Low risk	Comment: all reported patients received at least one study drug
Selective reporting (reporting bias)	Low risk	Comment: pre-specified secondary outcome QoL not reported
Other bias	Low risk	Comment: no information to suggest other sources of bias

Magarotto 2016

Methods	• Design: randomised, open-label, phase III trial; conducted at 58 centres in Italy and 9 centres in Czech Republic • Sample size: n = 654 patients; Arm 1(RMP): n = 217; Arm 2 (RCP) n = 220, Arm 3 (RD) n = 217 • Duration of treatment:nine 28-day cycles • Median follow-up: 39 months • Ongoing: yes • Trial registration Nr: NCT01093196
Participants	• Patient population: NDMM ineligible for high-dose therapy plus stem-cell transplantation • Inclusion criteria: measurable disease and Karnofsky performance status ≥ 60% • Exclusion criteria: renal impairment (creatinine level ≥ 30 ml/minute), uncontrolled or severe cardiovascular disease and other malignancies within the past 3 years • Baseline characteristics: ◦ Median age: 73-74 ◦ Male/female: 48% to 50% male ◦ ISS: I, II, III ◦ ECOG performance status: n.r. ◦ Country: Italy, Czech Republic
Interventions	• Arm 1: lenalidomide 10 mg/day for 21 days; oral melphalan 0.18 mg/Kg for 4 days in patients 65-75 years old and 0.13 mg/Kg in those >75 years; prednisone 1.5 mg/Kg for 4 days • Arm 2: lenalidomide 10 mg/day for 21 days; oral cyclophosphamide 50 mg every other day for 28 days in patients 65-75 years old and 50 mg every other day for 21 days in those >75 years; prednisone 25 mg every other day • Arm 3: lenalidomide 25 mg/day for 21 days; dexamethasone 40 mg on days 1,8,15,22 in patients 65-75 years old and 20 mg in those >75 years • Additional treatments: aspirin or low-molecular weight heparin or warfarin as antithrombotic prophylaxis
Outcomes	• Primary: PFS • Secondary: RR, TTR, OS, Grade 3 or higher AEs
Notes	• Sponsor/ Funding: Fondazione Neoplasie Sangue Onlus; Research Funding: Francesco Di Raimondo: Celgene, Janssen-Cilag; Antonio Palumbo: Genmab, Janssen-Cilag, Takeda • Type of publication (full text or abstract only): full text • Abbreviations: ◦ n.r.: not reported ◦ PFS: progression-free survival ◦ RR: response rate ◦ TTR: time to first evidence of response ◦ OS: overall survival ◦ AEs: adverse events

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised based on a computer-generated randomisation schedule"
Allocation concealment (selection bias)	Low risk	Quote: "randomised based on a computer-generated randomisation schedule"
Blinding of participants and personnel (performance bias)	High risk	Comment: not described, probably unblinded
Blinding of overall survival assessment (detection bias)	Low risk	Comment: Patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Comment: not described, probably unblinded
Blinding of safety assessment (detection bias)	High risk	Comment: not described, probably unblinded
Incomplete survival data (attrition bias)	Low risk	Comment: Kaplan Meier curves
Incomplete safety data (attrition bias)	Low risk	Comment: all reported patients received at least one study drug
Selective reporting (reporting bias)	Low risk	Comment: protocol available; pre-specified primary and most secondary outcomes reported; pre-specified secondary outcomes TTP and TTNT not reported
Other bias	Low risk	Comment: no information to suggest other sources of bias

Mateos 2014

Methods	• Design: randomised, open-label, phase III trial; conducted at 63 centres in Spain • Sample size: n = 260 patients; experimental arm (VTP) n = 130, control arm (VMP) n = 130 • Duration of treatment: six, 6-week cycles • Median follow-up: 72 months • Ongoing: no • Trial registration Nr: NCT00443235
Participants	• Patient population: 65 years or older newly diagnosed, untreated, symptomatic, measurable MM patients • Inclusion criteria: serum monoclonal protein of more than 10 g/L or urine monoclonal protein of 0.2 g or more per day. Patients had to have haemoglobin of more than 80 g/L, platelet count of 50 × 10^9/L or higher, and absolute neutrophil count of more than 1·0×10^9 cells per L • Exclusion criteria: grade 2 or higher peripheral neuropathy, serum creatinine of more than 176·8 µmol/L, or ECOG performance score of 3 or 4 • Baseline characteristics: ◦ Median age: 73 years ◦ Male/female: 47% to 53% male ◦ ISS: I, II, III ◦ ECOG performance status: n.r. ◦ Country: Spain
Interventions	• Experimental arm: continuous thalidomide at a dose of 100 mg per day (50 mg per day on days 1–15, cycle 1), one cycle of intravenous bortezomib given twice per week for 6 weeks (1·3 mg/m^2 on days 1, 4, 8, 11, 22, 25, 29, and 32), oral prednisone 60 mg/m^2 on days 1–4 • Control arm: one cycle of intravenous bortezomib given twice per week for 6 weeks (1·3 mg/m^2 on days 1, 4, 8, 11, 22, 25, 29, and 32), plus oral melphalan 9 mg/m^2 and oral prednisone 60 mg/m^2 on days 1–4, followed by five cycles of intravenous bortezomib once per week for 5 weeks (1·3 mg/m^2 on days 1, 8, 15, and 22) plus the same doses of melphalan and prednisone • Additional treatments: patients with bone disease received bisphosphonates, and prophylactic aciclovir was recommended. In patients receiving thalidomide, thromboprophylaxis was mandatory with either aspirin or low-molecular-weight heparin
Outcomes	• Primary: RR • Secondary: TTP, PFS, OS
Notes	• Sponsor/ Funding: funded and sponsored by Pethema (Spanish Program for the Treatment of Hematologic Diseases) • Type of publication (full text or abstract only): full text • Abbreviations: ◦ n.r.: not reported ◦ RR: response rate ◦ TTP: time to progression ◦ PFS: progression-free survival ◦ OS: overall survival

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computerised random number generator"
Allocation concealment (selection bias)	Low risk	Quote: "computerised random number generator"
Blinding of participants and personnel (performance bias)	High risk	Quote: "Participants, those giving the interventions, those assessing outcomes, and those analysing the data were not masked to group assignment."
Blinding of overall survival assessment (detection bias)	Low risk	Comment: Patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Quote: "Participants, those giving the interventions, those assessing outcomes, and those analysing the data were not masked to group assignment."
Blinding of safety assessment (detection bias)	High risk	Quote: "Participants, those giving the interventions, those assessing outcomes, and those analysing the data were not masked to group assignment."
Incomplete survival data (attrition bias)	Low risk	Comment: Kaplan Meier curves
Incomplete safety data (attrition bias)	Low risk	Comment: all reported patients received at least one study drug
Selective reporting (reporting bias)	Unclear risk	Comment: protocol available; pre-specified outcome "duration of response" not reported
Other bias	Low risk	Comment: no information to suggest other sources of bias

Mookerjee 2017

Methods	• Design: randomised controlled trial • Sample size: n = 144 patients; experimental arm (VRD) n = 74, control arm (RD) n = 69 • Duration of treatment: four 28-day cycles • Median follow-up: 17.1 months • Ongoing: no • Trial registration Nr: N/A
Participants	• Patient population: NDMM patients • Inclusion criteria: n.r. • Exclusion criteria: n.r. • Baseline characteristics: ◦ Median age: 52-56 ◦ Male/female:62% to 73% male ◦ ISS: n.r. ◦ ECOG performance status: n.r. ◦ Country: n.r.
Interventions	• Experimental arm: bortezomib 1.3 mg/m² SC on days 1, 8, 15 and 22 with lenalidomide 15 mg/day from day 1 to 14, oral dexamethasone 40 mg on days 1,8,15 and 22. • Control arm: lenalidomide 25 mg/day from day 1 to 21, oral dexamethasone 40 mg on days 1,8,15 and 22. • Additional treatments: all patients received 75 mg aspirin daily, acyclovir prophylaxis and monthly zoledronic acid
Outcomes	• Primary: PFS • Secondary: n.r.
Notes	• Sponsor/ Funding: n.r. • Type of publication (full text or abstract only): abstract only • Abbreviations: ◦ n.r.: not reported ◦ PFS: progression-free survival

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient information, only abstracts available
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information, only abstracts available
Blinding of participants and personnel (performance bias)	High risk	Comment: insufficient information, only abstracts available, probably unblinded
Blinding of overall survival assessment (detection bias)	Low risk	Comment: patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Comment: insufficient information, only abstracts available, probably unblinded
Blinding of safety assessment (detection bias)	High risk	Comment: insufficient information, only abstracts available, probably unblinded
Incomplete survival data (attrition bias)	Unclear risk	Comment: insufficient information, only abstracts available
Incomplete safety data (attrition bias)	Unclear risk	Comment: insufficient information, only abstracts available
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient information, only abstracts available
Other bias	Low risk	Comment: no information to suggest other sources of bias

Morgan 2011

Methods	• Design: randomised, open-label, phase III, factorial-design trial; conducted in 120 centres in the UK • Sample size: n = 837 ; experimental arm (CTD) n = 419, control arm (MP) n = 418 • Duration of treatment: 6 to 9, 28-day cycles • Median follow-up: 44 months • Ongoing: no • Trial registration Nr: ISRCTN 68454111
Participants	• Patient population: NDMM, older, less-fit patients • Inclusion criteria: patients 18 years of age or older with NDMM • Exclusion criteria: pregnancy, acute renal failure, asymptomatic myeloma, solitary bone plasmacytoma, extramedullary plasmacytoma, and previous or concurrent active malignancies • Baseline characteristics: ◦ Median age: 73 years ◦ Male/female: 55% to 57% male ◦ ISS: I, II, III ◦ ECOG performance status: n.r. ◦ Country: UK
Interventions	• Experimental arm: cyclophosphamide 500 mg/week; thalidomide 50 mg for 4 weeks and increased every 4 weeks in 50-mg increments to a maximum of 200 mg/day (thalidomide was reduced from a standard dose of 100 mg); and dexamethasone 20 mg/day on days 1 to 4 and 15 to 18 of each 28-day cycle • Control arm: melphalan 7 mg/m² per day and prednisolone 40 mg/day, both given on days 1-4 of each 28-day cycle • Additional treatments: thromboprophylaxis (e.g. warfarin, low molecular weight heparin) was recommended for all patients receiving CTD for the first 12 weeks of treatment. All patients (intensive and non-intensive pathways) were also randomised at study entry to a bisphosphonate, either sodium clodronate (1600 mg/day) or zoledronic acid (4 mg every 21-28 days), with continuation until progression
Outcomes	• Primary: Response, PFS, OS • Secondary: QoL, AEs
Notes	• Sponsor/ Funding: MRC Myeloma IX trial (obtained from the United Kingdom MRC) and Novartis, Schering Health Care, Chugai, Pharmion, Celgene, and Ortho Biotech (unrestricted educational grants), mainly to support trial co-ordination and the laboratory studies • Type of publication (full text or abstract only): full text • Abbreviations: ◦ n.r.: not reported ◦ QoL: Quality of Life ◦ AEs: Adverse events/toxicity

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "automated 24-hour telephone system"
Allocation concealment (selection bias)	Low risk	Quote: "automated 24-hour telephone system"
Blinding of participants and personnel (performance bias)	High risk	Comment: not described, probably unblinded
Blinding of overall survival assessment (detection bias)	Low risk	Comment: patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Comment: not described, probably unblinded
Blinding of safety assessment (detection bias)	High risk	Comment: not described, probably unblinded
Incomplete survival data (attrition bias)	Low risk	Comment: censored Kaplan Meier curves
Incomplete safety data (attrition bias)	Low risk	Comment: all reported patients received at least one study drug
Selective reporting (reporting bias)	Low risk	Comment: 2 pathways in 1 trial; relevant pre-specified primary and secondary results reported, other pre-specified results regarding the other pathway reported in other publications
Other bias	Low risk	Comment: no information to suggest other sources of bias

Niesvizky 2015

Methods	• Design: randomised, open- label, phase III trial; conducted at 159 centres in the USA • Sample size: n = 502 patients; Arm 1(VD) n = 168, Arm 2 (VTD) n = 167, Arm 3 (VMP) n = 167 • Duration of treatment: 24 weeks • Median follow-up: 42.7 months • Ongoing: no • Trial registration Nr: NCT00507416

Participants	• Patient population: patients with NDMM who were ineligible for stem cell transplant • Inclusion criteria: male or female aged ≥18 years; previously untreated symptomatic MM or asymptomatic myeloma with related organ or tissue damage; ineligible for stem cell transplantation due to age, presence of co-morbidities, or patient preference; Karnofsky performance status ≥ 50%; and measurable disease, defined by at least one of the following and requiring systemic therapy; serum M-protein immunoglobulin (Ig) G or IgM >1 g/dL, IgA or IgD > 0.5 g/dL; or a urine light-chain excretion ≥200 mg over 24 hours. • Exclusion criteria: diagnosis of smouldering myeloma or monoclonal gammopathy of undetermined significance; diagnosis of Waldenström's disease or other conditions in which IgM M-protein is present in the absence of a clonal plasma cell infiltration or lytic bone lesions; prior or current treatment with any systemic therapy for myeloma, excluding prior treatment of hypercalcaemia or spinal cord compression with corticosteroids or radiation therapy, respectively; radiation therapy within 2 weeks prior to randomisation; major surgery within 30 days prior to randomisation; history of allergy to any study drug; grade ≥2 peripheral neuropathy within 21 days prior to enrolment; myocardial infarction within 6 months prior to enrolment or New York Heart Association class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischaemia or significant conduction system abnormalities in the opinion of the investigator; and any of the following clinical laboratory measurements within 21 days prior to enrolment; absolute neutrophil count 2 × upper limit of normal; or serum creatinine >2 mg/dL. • Baseline characteristics: ◦ Median age: 73 years ◦ Male/female: 42% to 60% male ◦ ISS: I, II, III ◦ ECOG performance status: n.r. ◦ Country: USA
Interventions	• Arm 1: intravenous bortezomib 1.3 mg/m2, days 1, 4, 8, and 11 plus oral dexamethasone 20 mg, days 1, 2, 4, 5, 8, 9, 11, and12 (cycles 1 to 4), or days 1, 2, 4, and5 (cycles 5 to 8) • Arm 2: bortezomib and dexamethasone as before plus oral thalidomide 100 mg, days 1 to 21 • Arm 3: bortezomib as before plus oral melphalan 9 mg/m2 and oral prednisone 60 mg/m2, both days 1 to 4, every other cycle), followed by 25 weeks (five 35-day cycles) of maintenance with single-agent intravenous bortezomib 1.6 mg/m2, days 1, 8, 15, and 22. • Additional treatments: concomitant treatment with growth factors, bisphosphonates, and recombinant erythropoietin, as well as supportive care with prophylactic antibiotics and antivirals, was permitted. Prophylactic therapy with aspirin, full-dose warfarin, or low-molecular weight heparin was provided for patients in the VTD arm unless medically contraindicated to prevent thromboembolic complications, which may occur with thalidomide-based regimens in combination with dexamethasone. In all treatment arms, prophylaxis for herpes zoster virus was recommended.
Outcomes	• Primary: PFS • Secondary: ORR, CR, VGPR, DR, TTNT, OS, severe AEs, SAEs, QoL

Notes	• Sponsor/ Funding: Millennium Pharmaceuticals, Inc. • Type of publication (full text or abstract only): full text • Abbreviations: ◦ n.r.: not reported ◦ PFS: progression-free survival ◦ ORR: overall response rate ◦ CR: complete response ◦ VGPR: very good partial response ◦ DR: duration of response ◦ TTNT: time to next anti-myeloma treatment ◦ OS: overall survival ◦ AEs: adverse events ◦ SAEs: serious adverse events ◦ QoL: quality of life

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "interactive voice response system on the basis of a computer-generated randomisation schedule"
Allocation concealment (selection bias)	Low risk	Quote: "interactive voice response system on the basis of a computer-generated randomisation schedule"
Blinding of participants and personnel (performance bias)	High risk	Quote: " open-label"
Blinding of overall survival assessment (detection bias)	Low risk	Comment: patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Quote: " open-label"
Blinding of safety assessment (detection bias)	High risk	Quote: " open-label"
Incomplete survival data (attrition bias)	Low risk	Comment: censored Kaplan Meier curves
Incomplete safety data (attrition bias)	Low risk	Comment: all reported patients received at least one study drug
Selective reporting (reporting bias)	Low risk	Comment: protocol and results for all pre-specified primary and secondary outcomes available
Other bias	Low risk	Comment: no information to suggest other sources of bias

Palumbo 2006

Methods	• Design: randomised, open-label, phase III trial; conducted at 54 centres in Italy • Sample size: n = 255 patients; experimental arm (TMP) n = 129, control arm (MP) n = 126 • Duration of treatment: six 4-week cycles • Median follow-up: 38.4 months • Ongoing: no • Trial registration Nr: NCT00232934
Participants	• Patient population: patients with NDMM who were ineligible for stem cell transplant • Inclusion criteria: previously untreated myeloma patients who were older than 65 years (or younger but unable to undergo transplantation), Durie and Salmon stage II or III myeloma, and measurable disease • Exclusion criteria: another cancer, psychiatric disease, and any grade 2 peripheral neuropathy • Baseline characteristics: ◦ Median age: 72.5 ◦ Male/female: n.r. ◦ ISS: I, II, III ◦ ECOG performance status: 0-4 ◦ Country: Italy
Interventions	• Experimental arm: thalidomide was administered at 100 mg per day continuously, plus oral administration of melphalan at 4 mg/m2 and oral prednisone at a dose of 40 mg/m2 on days 1-7. • Control arm: oral administration of melphalan at 4 mg/m2 and oral prednisone at a dose of 40 mg/m2 on days 1-7. • Additional treatments: In the TMP arm, no anticoagulation prophylaxis was given until December, 2003, when the protocol was amended, and enoxaparin at 40 mg per day was delivered subcutaneously during the first four cycles of therapy
Outcomes	• Primary: RR, PFS, EFS • Secondary: AEs, OS
Notes	• Sponsor/ Funding: Pharmion supplied free thalidomide for this study • Type of publication (full text or abstract only): full text • Abbreviations: ◦ RR: response rate ◦ PFS: progression-free survival ◦ EFS: event free survival ◦ AEs: adverse events/ safety ◦ OS: overall survival

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation sequence was generated by a centralised computer"
Allocation concealment (selection bias)	Low risk	Quote: "patients were randomly allocated to treatments by use of an automated assignment procedure concealed from the investigators"
Blinding of participants and personnel (performance bias)	High risk	Quote: "Open Label"
Blinding of overall survival assessment (detection bias)	Low risk	Comment: patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Quote: "Open Label"
Blinding of safety assessment (detection bias)	High risk	Quote: "Open Label"
Incomplete survival data (attrition bias)	Low risk	Comment: Kaplan Meier curves
Incomplete safety data (attrition bias)	Low risk	Comment: all reported patients received at least one study drug
Selective reporting (reporting bias)	Low risk	Comment: protocol and results for all pre-specified primary and secondary outcomes available
Other bias	Low risk	Comment: no information to suggest other sources of bias

Palumbo 2012

Methods	• Design: randomised, double-blind, placebo-controlled, phase III trial; conducted at 82 centres in Europe, Australia, and Israel • Sample size: n = 459 patients; Arm 1 (RMPc) n = 152, Arm 2 (RMP) n = 153, Arm 3 (MP) n = 154 • Duration of treatment: nine 18-day cycles, followed by maintenance • Median follow-up: 30 months • Ongoing: no • Trial registration Nr: NCT00405756
Participants	• Patient population: patients with NDMM who were ineligible for stem cell transplant • Inclusion criteria: symptomatic, measurable, NDMM patients who were not candidates for transplantation (≥ 65 years of age) • Exclusion criteria: absolute neutrophil count of less than 1500 per mm^3, a platelet count of less than 75,000 per mm^3, a haemoglobin level of less than 8.0 g per dL, renal insufficiency (a serum creatinine level of > 2.5 mg per dL (>221 µmol L)), and peripheral neuropathy of grade 2 or higher • Baseline characteristics: ◦ Median age: 71 years ◦ Male/female: 47% to 54% male ◦ ISS: I, II, III ◦ ECOG performance status: n.r. ◦ Country: Europe, Australia, Israel
Interventions	• Arm 1: nine 28-day cycles of melphalan (at a dose of 0.18 mg per kg of body weight on days 1 through 4), prednisone (2 mg per kg on days 1 through 4), and lenalidomide (10 mg on days 1 through 21), followed by lenalidomide maintenance (10 mg on days 1 through 21 of each 28-day cycle) until disease progression or the development of unacceptable rates of adverse effects • Arm 2: nine 28-day cycles of melphalan (at a dose of 0.18 mg per kg of body weight on days 1 through 4), prednisone (2 mg per kg on days 1 through 4), and lenalidomide (10 mg on days 1 through 21), followed by placebo maintenance • Arm 3: nine 28-day cycles of melphalan (at a dose of 0.18 mg per kg of body weight on days 1 through 4), prednisone (2 mg per kg on days 1 through 4), and placebo during induction and maintenance • Additional treatments: all patients received aspirin thromboprophylaxis (75 to 100 mg daily) during induction; thromboprophylaxis could be continued during maintenance at the treating physician's discretion
Outcomes	• Primary: PFS • Secondary: OS, RR, TTR, DR, RQ, AEs
Notes	• Sponsor/ Funding: Celgene Coporation • Type of publication (fullt ext or abstract only): full text • Abbreviations: ◦ n.r.: not reported ◦ PFS: progression-free survival ◦ OS: overall survival ◦ RR: response rate ◦ TTR: time to response ◦ DR: duration of response ◦ RQ: response quality ◦ AEs: adverse events

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "procedure utilising a validated interactive voice response system"
Allocation concealment (selection bias)	Low risk	Quote: "procedure utilising a validated interactive voice response system"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Patients and treating physicians were unaware of the treatment assignments"
Blinding of overall survival assessment (detection bias)	Low risk	Comment: patients are dead or alive
Blinding of progression free survival assessment (detection bias)	Low risk	
Blinding of safety assessment (detection bias)	Low risk	Quote: "Patients and treating physicians were unaware of the treatment assignments"
Incomplete survival data (attrition bias)	Low risk	Comment: censored Kaplan Meier curves
Incomplete safety data (attrition bias)	Low risk	Comment: all reported patients received at least one study drug
Selective reporting (reporting bias)	Low risk	Comment: all pre-specified outcomes reported
Other bias	Low risk	Comment: no information to suggest other sources of bias

Palumbo 2014

Methods	• Design: randomised, open-label, phase III trial; conducted at 61 centres in Italy • Sample size: n = 511 patients; experimental arm (VTMP-VT) n = 254, control arm (VMP) n = 257 • Duration of treatment: nine 6-week cycles • Median follow-up: 54 months • Ongoing: no • Trial registration Nr: NCT01063179
Participants	• Patient population: patients with NDMM who were ineligible for stem cell transplant • Inclusion criteria: measurable disease and Karnofsky performance status >60% • Exclusion criteria: renal insufficiency (creatinine level > 25 mg/L), uncontrolled or severe cardiovascular disease, psychiatric disease, any grade 2 peripheral neuropathy, and other malignancy within the past 5 years • Baseline characteristics: ◦ Median age: 71 years ◦ Male/female ◦ ISS: I, II, III ◦ ECOG performance status: n.r. ◦ Country: Italy
Interventions	• Experimental arm: nine 6-week cycles of oral melphalan 9 mg/m2 on days 1 to 4; oral prednisone 60 mg/m2 on days 1 to 4; intravenous bortezomib 1.3 mg/m2 on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1 to 4 and on days 1, 8, 22, and 29 during cycles 5 to 9; and thalidomide 50mgper day continuously. After the last VMPTcourse, patients received maintenance therapy with bortezomib 1.3 mg/m2 every 14 days and thalidomide 50mgper day for 2 years or until progression or relapse • Control arm: nine 6-week cycles of oral melphalan 9 mg/m2 on days 1 to 4; oral prednisone 60 mg/m2 on days 1 to 4; intravenous bortezomib 1.3 mg/m2 on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1 to 4 and on days 1, 8, 22, and 29 during cycles 5 to 9 • Additional treatments:aAll VMPT-VT patients received antithrombotic prophylaxis during induction at physician discretion or were allowed to participate in a randomised substudy comparing subcutaneous low-molecular-weight heparin (enoxaparin, 40 mg daily) with oral aspirin (100 mg daily) or oral warfarin (1.25 mg daily).
Outcomes	• Primary: PFS • Secondary: RR, TTR, OS, Grade 3 or higher AEs
Notes	• Sponsor/ Funding: The study was sponsored by Fondazione Neoplasie Sangue Onlus and supported by Janssen-Cilag and Celgene • Type of publication (full text or abstract only): full text • Abbreviations: ◦ n.r.: not reported ◦ PFS: progression-free survival ◦ RR: response rate ◦ TTR: time to first evidence of response ◦ OS: overall survival ◦ AEs: adverse events

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not described
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias)	High risk	Quote: "OPEN LABEL"
Blinding of overall survival assessment (detection bias)	Low risk	Comment: Patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Quote: "OPEN LABEL"
Blinding of safety assessment (detection bias)	High risk	Quote: "OPEN LABEL"
Incomplete survival data (attrition bias)	Low risk	Comment: Kaplan Meier curves
Incomplete safety data (attrition bias)	Low risk	Comment: all reported patients received at least one study drug
Selective reporting (reporting bias)	Low risk	Comment: protocol and results for all pre-specified primary and secondary outcomes available
Other bias	Low risk	Comment: no information to suggest other sources of bias

Pawlyn 2017

Methods	• Design: randomised, controlled trial; conducted in the UK • Sample size: n = 1852 patients; experimental arm (TCD) n = 924, control arm (RCD) n = 928 • Duration of treatment: n.r. • Median follow-up: 34.8 months • Ongoing: yes • Trial registration Nr: NCT01554852
Participants	• Patient population: patients with NDMM who were ineligible for stem cell transplant • Inclusion criteria: n.r. • Exclusion criteria: n.r. • Baseline characteristics: ◦ Median age: 74 years ◦ Male/female: n.r. ◦ ISS: n.r. ◦ ECOG performance status: n.r. ◦ Country: UK
Interventions	• Experimental arm: TCD • Control arm: RCD • Additional treatments: n.r.
Outcomes	• Primary: n.r. • Secondary: n.r.
Notes	• Sponsor/ Funding: n.r. • Type of publication (full text or abstract only): abstracts only • Abbreviations: ◦ n.r.: not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient information, only abstracts available
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information, only abstracts available
Blinding of participants and personnel (performance bias)	High risk	Comment: insufficient information, only abstracts available, probably unblinded
Blinding of overall survival assessment (detection bias)	Low risk	Comment: patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Comment: insufficient information, only abstracts available, probably unblinded
Blinding of safety assessment (detection bias)	High risk	Comment: insufficient information, only abstracts available, probably unblinded
Incomplete survival data (attrition bias)	Low risk	Comment: Kaplan Meier curves
Incomplete safety data (attrition bias)	Unclear risk	Comment: insufficient information, only abstracts available
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient information, only abstracts available
Other bias	Low risk	Comment: no information to suggest other sources of bias

Sacchi 2011

Methods	• Design: randomised, open-label, phase II trial; conducted at 10 centres in Italy • Sample size: n = 135 patients; experimental arm (TMP) n =70, control arm (MP) n = 65 • Duration of treatment: six to-12, 28-day cycles • Median follow-up: 30 months • Ongoing: no • Trial registration Nr: NCT01274403
Participants	• Patient population: patients with NDMM who were ineligible for stem cell transplant • Inclusion criteria: patients over age 65 years and younger patients who were ineligible for high-dose treatment with newly diagnosed stage II or III MM and ECOG performance status of 3 or less • Exclusion criteria: primary amyloidosis, polyneuropathy, severe cardiac, hepatic, or pulmonary dysfunction, a diagnosis of human immunodeficiency virus (HIV), hepatitis C virus (HCV), or positive serum hepatitis B surface antigen (HBsAg), renal failure with dialysis dependency, history of other malignancy, female of childbearing age, and diagnosis of psychiatric disease • Baseline characteristics: ◦ Median age: 77 years ◦ Male/female: 45% to 48% male ◦ ISS: I, II, III ◦ ECOG performance status: 0-4 ◦ Country: Italy
Interventions	• Experimental arm: thalidomide at a dose of 100 mg per day continuously, plus melphalan (0.25 mg/kg) and prednisone (60 mg/m2) were given orally for 4 days for a maximum of 48 weeks • Control arm: melphalan (0.25 mg/kg) and prednisone (60 mg/m2) were given orally for 4 days for a maximum of 48 weeks. • Additional treatments:n.r.
Outcomes	• Primary: RR, AEs • Secondary: OS, DR
Notes	• Sponsor/ Funding: Gruppo Italiano Studio Linfomi and in part by the Associazione Angela Serra per la Ricerca sul Cancro, Modena, Italy. • Type of publication (full text or abstract only): full text • Abbreviations: ◦ n.r.: not reported ◦ RR: response rates ◦ AEs: adverse events/ safety ◦ OS: overall survival ◦ DR: duration of response

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "centrally randomised"
Allocation concealment (selection bias)	Low risk	Quote "centrally randomised"
Blinding of participants and personnel (performance bias)	High risk	Quote: "open label"
Blinding of overall survival assessment (detection bias)	Low risk	Comment: Patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Quote: "open label"
Blinding of safety assessment (detection bias)	High risk	Quote: "open label"
Incomplete survival data (attrition bias)	Low risk	Comment: Kaplan Meier curves
Incomplete safety data (attrition bias)	Low risk	Comment: all reported patients received at least one study drug
Selective reporting (reporting bias)	Low risk	Comment: protocol available; pre-specified primary and most secondary outcomes reported; pre-specified outcome DR not reported
Other bias	Low risk	Comment: no information to suggest other sources of bias

San Miguel 2008

Methods	• Design: randomised, open-label, phase III trial; conducted at 151 centres in 22 countries in Europe, North and South America, and Asia • Sample size: n = 682 patients; experimental arm (VMP) n = 344, control arm (MP) n = 338 • Duration of treatment: nine 6-week cycles • Median follow-up: 25.9 months • Ongoing: no • Trial registration Nr: NCT00111319
Participants	• Patient population: patients with NDMM who were ineligible for stem cell transplant • Inclusion criteria: patients with newly diagnosed, untreated, symptomatic, measurable myeloma who were not candidates for high-dose therapy plus stem-cell transplantation because of age (≥ 65 years) or coexisting condition • Exclusion criteria: n.r. • Baseline characteristics: ◦ Median age: 71 years ◦ Male/female: 49% to 51% male ◦ ISS: I, II, III ◦ ECOG performance status: n.r. ◦ Country: Europe, North and South America, and Asia
Interventions	• Experimental arm: bortezomib (at a dose of 1.3 mg per m^2), by i.v. bolus on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1 to 4 and on days 1, 8, 22, and 29 during cycles 5 to 9, melphalan (at a dose of 9 mg per m^2 of body-surface area) and prednisone (at a dose of 60 mg per m^2) on days 1 to 4 • Control arm: melphalan (at a dose of 9 mg per m^2 of body-surface area) and prednisone (at a dose of 60 mg per m^2) on days 1 to 4 • Additional treatments: patients with myeloma-associated bone disease received bisphosphonates, unless such therapy was contraindicated
Outcomes	• Primary: TTP • Secondary: CR, DR, TTNT, OS
Notes	• Sponsor/ Funding: Millennium Pharmaceuticals, Inc. • Type of publication (full text or abstract only): full text • Abbreviations: ◦ n.r.: not reported ◦ TTP: time to progression ◦ CR: complete response ◦ DR: duration of response ◦ TTNT: time to next treatment ◦ OS: overall survival

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not described
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias)	High risk	Quote: " open-label"
Blinding of overall survival assessment (detection bias)	Low risk	Comment: patients are death or alive
Blinding of progression free survival assessment (detection bias)	High risk	Quote: " open-label"
Blinding of safety assessment (detection bias)	High risk	Quote: " open-label"
Incomplete survival data (attrition bias)	Low risk	Comment: censored Kaplan Meier curves
Incomplete safety data (attrition bias)	Low risk	Comment: all reported patients received study drug
Selective reporting (reporting bias)	High risk	Comment: protocol available; not all pre-specified primary and secondary endpoints are reported; missing: ORR, QoL
Other bias	Low risk	Comment: no information to suggest other sources of bias

Stewart 2015

Methods	• Design: randomised, open-label, phase III trial; conducted in Israel and the USA • Sample size: n = 306 patients; experimental arm (TMP) n = 154, control arm (RMP) n = 152 • Duration of treatment: 12, 28-day cycles • Median follow-up: 40.7 months • Ongoing: no • Trial registration Nr: NCT00602641
Participants	• Patient population: patients with NDMM who were ineligible for stem cell transplant • Inclusion criteria: confirmed diagnosis ofMM as well as evidence of end-organ damage at the time of diagnosis. Patients were > 65 years and had declined alternative treatment or were 65 years and were not candidates for autologous stem cell transplantation or had declined transplant. ECOG performance status < 2 was required. Eligibility laboratory values included haemoglobin .7 g/dL, platelet count 75, 000 cells/mm3, absolute neutrophil count .1000 cells/mm3, creatinine ,2.5 mg/dL, creatinine clearance > 60 mL/min, total bilirubin < 1.5 mg/dL, and ASP and ALT < 2.5 times the upper limit of normal. Patients must have been previously untreated for MM, although prior treatment with prednisone or dexamethasone for ,4 weeks total dosing alone or in combination with thalidomide or lenalidomide for 2 weeks total dosing was allowed. Patients could be receiving bisphosphonates or growth factors (erythropoietin). Patients had to be willing and able to take antithrombotic prophylaxis. • Exclusion criteria: n.r. • Baseline characteristics: ◦ Median age: 75.7 years ◦ Male/female: 53% to 56% male ◦ ISS: I, II, III ◦ ECOG performance status: 0-2 ◦ Country: Israel, USA
Interventions	• Experimental arm: 9 mg/m2 melphalan and 100 mg prednisone by mouth on days 1 to 4 with 100 mg thalidomide daily • Control arm: 5 mg/m2 melphalan and 100 mg prednisone po on days 1 to 4 with 10 mg lenalidomide by mouth on days 1 -21 • Additional treatments: aspirin prophylaxis was required. Full anticoagulation was implemented for patients at higher risk for deep vein thrombosis.
Outcomes	• Primary: PFS • Secondary: n.r.
Notes	• Sponsor/ Funding: National Cancer Institute (NCI) • Type of publication (full text or abstract only): full text • Abbreviations: ◦ n.r.: not reported ◦ PFS: progression-free survival

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Treatments were assigned using permuted blocks within strata with dynamic balancing within main institution and their affiliate networks"
Allocation concealment (selection bias)	Low risk	Quote: "Treatments were assigned using permuted blocks within strata with dynamic balancing within main institution and their affiliate networks"
Blinding of participants and personnel (performance bias)	High risk	Quote: "open label"
Blinding of overall survival assessment (detection bias)	Low risk	Comment: Patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Quote: "open label"
Blinding of safety assessment (detection bias)	High risk	Quote: "open label"
Incomplete survival data (attrition bias)	Low risk	Comment: Kaplan Meier curves
Incomplete safety data (attrition bias)	Low risk	Comment: all reported patients received at least one study drug
Selective reporting (reporting bias)	Low risk	Comment: protocol and results for all pre-specified primary and secondary outcomes available
Other bias	Low risk	Comment: no information to suggest other sources of bias

Waage 2010

Methods	• Design: randomised, double-blind, phase III trial; conducted at 48 centres in Norway, Sweden, and Denmark • Sample size: n = 363 patients; experimental arm (TMP) n = 182, control arm (MP) n = 175 • Duration of treatment: until disease progression • Median follow-up: 42 months • Ongoing: no • Trial registration Nr: NCT00218855
Participants	• Patient population: patients with NDMM who were ineligible for stem cell transplant • Inclusion criteria: previously untreated symptomatic, measurable MM in patients who were not eligible for high-dose treatment with autologous stem cell support • Exclusion criteria: previous treatment against MM, need of high-dose chemotherapy with autologous stem cell support, women in fertile age, psychiatric disease or mental reduction leading to lack of co-operation, lack of consent, life expectancy below 3 months, active cancer of other aetiology • Baseline characteristics: ◦ Median age: 74.4 years ◦ Male/female: 51% to 61% male ◦ ISS: I, II, III ◦ ECOG performance status: 0-4 ◦ Country: Norway, Sweden, Denmark
Interventions	• Experimental arm: thalidomide 200 mg daily for one week and thereafter 400 mg daily, plus melphalan 0.25 mg/kg, and prednisone 100 mg daily for 4 days every 6 weeks • Control arm: placebo, plus melphalan 0.25 mg/kg, and prednisone 100 mg daily for 4 days every 6 weeks • Additional treatments: no routine prophylaxis for venous thrombosis was recommended
Outcomes	• Primary: OS • Secondary: QoL, TTR, FoR, TTP, AEs
Notes	• Sponsor/ Funding: This work was supported by the Norwegian Cancer Society and the Norwegian Research Council (grant 160388/V50). • Type of publication (full text or abstract only): full text • Abbreviations: ◦ OS: overall survival ◦ QoL: quality of life ◦ TTR: time to response ◦ FoR: frequency of response ◦ TTP: time to progression ◦ AEs: Adverse Events/Toxicity

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote:"centralized and performed by telephone call or fax"
Allocation concealment (selection bias)	Low risk	Quote:"centralized and performed by telephone call or fax"
Blinding of participants and personnel (performance bias)	Low risk	Quote:"neither patient nor doctor know which of these are given"; Comment: double-blind
Blinding of overall survival assessment (detection bias)	Low risk	Comment: patients are dead or alive
Blinding of progression free survival assessment (detection bias)	Low risk	Quote:"neither patient nor doctor know which of these are given"; Comment: double-blind
Blinding of safety assessment (detection bias)	Low risk	Quote:"neither patient nor doctor know which of these are given"; Comment: double-blind
Incomplete survival data (attrition bias)	Low risk	Comment: Kaplan Meier curves
Incomplete safety data (attrition bias)	Low risk	Comment: all reported patients received at least one study drug
Selective reporting (reporting bias)	Low risk	Comment: protocol available; 2-phase study. Pre-specified objectives regarding maintenance therapy (Time to 2. response, Frequency of 2. response, Time to 2. progression) not reported in this publication; not sure whether frequency of response stands for PR, VGPR, PR, MR, NR
Other bias	Low risk	Comment: no information to suggest other sources of bias

Wijermans 2010

Methods	• Design: randomised, open-label, phase III trial; conducted in the Netherlands • Sample size: n = 333 patients; experimental arm (TMP) n = 165, control arm (MP) n = 168 • Duration of treatment: eight 4-week cycles planned; in case on ongoing response, treatment continuation until plateau in response was reached • Median follow-up: 39 months • Ongoing: no • Trial registration Nr: N/A
Participants	• Patient population: patients with NDMM who were ineligible for stem cell transplant • Inclusion criteria: patients older than age 65 years with a newly diagnosed stage IB, II, or IIIMM, a WHO performance status of 0 to 3, and a measurable tumour parameter • Exclusion criteria: presence of amyloid light-chain amyloidosis; polyneuropathy; severe cardiac, pulmonary,and hepatic dysfunction; renal failure with dependency on dialysis; uncontrolled infection of any kind or HIV positivity; and other malignancies. Pretreatment with chemotherapy or corticosteroids was not allowed • Baseline characteristics: ◦ Median age: 72.6 years ◦ Male/female: 55% to 57% male ◦ ISS: I, II, III ◦ ECOG performance status: 0-3 ◦ Country: the Netherlands
Interventions	• Experimental arm: melphalan 0.25 mg/kg and prednisone 1 mg/kg were administered daily for 5 days every 4 weeks, plus thalidomide 200 mg/day was administered continuously until 4 weeks after the last MP-T cycle • Control arm: melphalan 0.25 mg/kg and prednisone 1 mg/kg were administered daily for 5 days every 4 weeks • Additional treatments: treatment with bisphosphonates was recommended using either pamidronate or clodronate. From 2005, low molecular weight heparin (nadroparin 2,850 U anti-Xa or 5,700 U anti-Xa in case of weight > 90 kg) was recommended as standard prophylaxis during TMP
Outcomes	• Primary: EFS • Secondary: RR, OS, PFS, AEs, QoL
Notes	• Sponsor/ Funding: n.r. • Type of publication (full text or abstract only): full text • Abbreviations: ◦ EFS: event-free survival ◦ RR: response rate ◦ OS: overall survival ◦ PFS: progression-free survival ◦ AEs: adverse events/ toxicity/ safety ◦ QoL: quality of life ◦ n.r.: not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not described
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias)	High risk	Quote: " open-label"
Blinding of overall survival assessment (detection bias)	Low risk	Comment: Patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Quote: " open-label"
Blinding of safety assessment (detection bias)	High risk	Quote: " open-label"
Incomplete survival data (attrition bias)	Low risk	Comment: Kaplan Meier curves
Incomplete safety data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	Comment: protocol and results for all pre-specified primary and secondary outcomes available
Other bias	Low risk	Comment: no information to suggest other sources of bias

Zweegman 2016

Methods	• Design: randomised, open-label, phase III trial; conducted in Europe • Sample size: n = 637 patients; experimental arm (TMP) n = 318, control arm (RMP) n = 319 • Duration of treatment:nine 28-day cycles • Median follow-up: 36 months • Ongoing: no • Trial registration Nr: EudraCT number 2007-004007-34

Participants	• Patient population: patients with NDMM who were ineligible for stem cell transplant • Inclusion criteria: previously untreated patients with a confirmed diagnosis of symptomatic MM according to IMWG criteria, Age > 65 years or patients <65 not eligible for high dose chemotherapy and peripheral stem cell transplantation, WHO performance status 0-3 for patients < 75 years and WHO performance status 0-2 for patients > 75 years, Measurable disease as defined by the presence of M-protein in serum or urine or proven plasmacytoma by biopsy; • Exclusion criteria: non-secretory MM, known hypersensitivity to thalidomide, systemic AL amyloidosis, polyneuropathy, grade 2 or higher, severe cardiac dysfunction (NYHA classification II-IV), severe pulmonary dysfunction, significant hepatic dysfunction (total bilirubin ≥ 30 µmol/L or transaminases ≥3 times normal level), unless related to myeloma, creatinine clearance < 30 mL/minute, patients with active, uncontrolled infections, pre-treatment with cytostatic drug, IMIDs or proteasome inhibitors, radiotherapy or a short course of steroids (e.g. 4-day treatment of dexamethasone 40 mg/day or equivalent) are allowed, patients known to be HIV-positive History of active malignancy during the past 5 years, except basal carcinoma of the skin or stage 0 cervical carcinoma, not able and/or not willing to use adequate contraception. • Baseline characteristics: ◦ Median age: 72-73 years ◦ Male/female: 51% 58% male ◦ ISS: I, II, III ◦ ECOG performance status: 0-3 ◦ Country: Europe
Interventions	• Experimental arm: 9 cycles of melphalan 0.18 mg/kg on days 1 to 4, prednisone 2 mg/kg on days 1 to 4, and thalidomide 200 mg/day until 4 weeks after the last cycle of MP • Control arm: 9 cycles of oral treatment with melphalan 0.18 mg/kg on days 1 to 4, prednisone 2 mg/kg on days 1 to 4, and lenalidomide 10 mg on days 1 to 21, independent of age • Additional treatments: thrombosis prophylaxis during induction therapy consisted of acetylsalicylic acid 75 mg or 80 mg or carbasalate calcium 100 mg daily. In patients with a history of venous thrombotic events, low-molecular-weight heparin was given instead. Bisphosphonate therapy and prophylactic antibiotics were given at the discretion of the physician. In case of an infectious event that required admission during induction therapy, prophylactic antibiotics (type of antibiotics according to local protocols: e.g. quinolone, trimethoprim-sulfamethoxazole, or penicillin) were mandatory during the following courses of induction therapy
Outcomes	• Primary: PFS, RR • Secondary: OS,TTMR, QoL
Notes	• Sponsor/ Funding: This study was supported by Dutch Cancer Society grant 20084246, the Norwegian Cancer Society, and Celgene. • Type of publication (full text or abstract only): full text • Abbreviations: ◦ PFS: progression-free survival ◦ RR: response rates ◦ OS: overall survival ◦ TTMR: time to maximum response ◦ QoL: quality of life

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not described
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias)	High risk	Quote: " open-label"
Blinding of overall survival assessment (detection bias)	Low risk	Comment: Patients are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Quote: " open-label"
Blinding of safety assessment (detection bias)	High risk	Quote: " open-label"
Incomplete survival data (attrition bias)	Low risk	Comment: Kaplan Meier curves
Incomplete safety data (attrition bias)	Low risk	Comment: all reported patients received at least one study drug
Selective reporting (reporting bias)	Low risk	Comment: protocol available; study ongoing. Pre-specified objectives regarding maintenance therapy not yet reported
Other bias	Low risk	Comment: no information to suggest other sources of bias

Footnotes

ECOG: Eastern Cooperative Oncology Group
i.v.: intravenous
MM: multiple myeloma
NCI: National Cancer Institute
NDMM: newly diagnosed multiple myeloma
s.c.subcutaneous
SGOT: serum glutamic-oxaloacetic transaminase (AST - aspartate aminotransferase)
SGPT: Serum glutamic pyruvic transaminase (ALT, - alanine aminotransferase)
WHO: Worlsd Health Organization

Units
dL: decilitre
kg: kilogram
mg: milligram
m^2: square metre
mm3: cubic millimetre
µL: microlitre

Characteristics of excluded studies

Anonymous 2003

Reason for exclusion	Comparator not of interest, dexamethasone alone

Barlogie 2004

Reason for exclusion	Patients with relapsed or progressive disease after at least one autologous transplant

Brioli 2014

Reason for exclusion	Patients who are candidates to receive double autologous transplantation

Facon 2006

Reason for exclusion	Comparator not of interest, dexamethasone alone

Facon 2017

Reason for exclusion	Includes a novel agent, which was excluded from our review

Facon 2018

Reason for exclusion	Includes a novel agent, which was excluded from our review

Foa 2007

Reason for exclusion	Relapsed/refractory multiple myeloma patients

Harousseau 2003

Reason for exclusion	Transplant setting

Hejlova 2000

Reason for exclusion	The protocol consisted of 4 cycles of induction therapy using VAD followed by autologous transplantation. Patients were then randomised into two groups receiving interferon-alpha or interferon-alpha plus dexamethasone as maintenance treatment.

Hernández 2004

Reason for exclusion	Comparator not of interest, dexamethasone combined with melphalan

Kumar 2012

Reason for exclusion	A total of 150 patients were included in the study, out of which 75 received a stem cell mobilisation after cycle 2 and 59 received a stem cell transplantation after cycle 4.

Ludwig 2017a

Reason for exclusion	Includes a novel agent, which was excluded from our review

Mateos 2016

Reason for exclusion	Sequential versus alternating VMP/Rd: no results after first cycle

Mateos 2018

Reason for exclusion	Includes a novel agent, which was excluded from our review

Merz 2015

Reason for exclusion	Comparator not of interest, bortezomib+doxorubicin+dexamethasone

Montefusco 2013

Reason for exclusion	Non-randomised trial

Morgan 2002

Reason for exclusion	Standard conventional-dose combination chemotherapy with adriamycin, carmustine, cyclophosphamide, and melphalan (ABCM) or a sequence of treatment of cyclophospamide, vincristine, adriamycin, and methyl-prednisolone (C-VAMP) followed by high-dose therapy (HDT)

NCT00522392

Reason for exclusion	Consolidation therapy, patients received 1-6 prior cycles of dexamethasone-based regimens

NCT00734877

Reason for exclusion	Transplant-setting

NCT01850524

Reason for exclusion	Includes a novel agent, which was excluded from our review

NCT01863550

Reason for exclusion	Includes a novel agent, which was excluded from our review

NCT02586038

Reason for exclusion	Includes a novel agent, which was excluded from our review

NCT03710603

Reason for exclusion	Includes a novel agent, which was excluded from our review

Niesvizky 2003

Reason for exclusion	Comparator not of interest, dexamethasone alone

Offidani 2004

Reason for exclusion	Relapsed/refractory multiple myeloma patients

Palumbo 2016

Reason for exclusion	Includes a novel agent, which was excluded from our review

Rajkumar 2006b

Reason for exclusion	Comparator not of interest, dexamethasone alone

Rajkumar 2008

Reason for exclusion	Comparator not of interest, dexamethasone alone

San Miguel 2014

Reason for exclusion	includes a novel agent, which was excluded from our review

Takezako 2017

Reason for exclusion	Includes a novel agent, which was excluded from our review

Usmani 2014

Reason for exclusion	Includes a novel agent, which was excluded from our review

White 2007

Reason for exclusion	Non-randomised trial

Zonder 2010

Reason for exclusion	Comparator not of interest, dexamethasone alone

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

1 Summary of findings

Multiple drug combinations of bortezomib, lenalidomide, and thalidomide for first-line treatment in transplant-ineligible multiple myeloma patients

Patient or population: newly diagnosed, transplant-ineligible adults with symptomatic multiple myeloma

Settings: mostly outpatient; mostly multi-centre studies across Europe, Asia, North- and South America, Australia, and the Pacific region

Intervention: lenalidomide plus dexamethasone (RD), thalidomide plus melphalan and prednisone (TMP), bortezomib plus melphalan and prednisone (VMP), continuous bortezomib plus lenalidomide plus dexamethasone (VRDc)

Comparison: melphalan and prednisone (MP)

Outcomes	Effects and 95% confidence intervals in the effects. Main comparator is MP*				
	Risk with MP	**Risk with RD**	**Risk with TMP**	**Risk with VMP**	**Risk with VRDc**
Overall survival	Median overall survival over all studies in the network[1]: 34.8 months	NMA-median OS: 55.2 (35.2 to 87.0) months	NMA-median OS: 46.4 (35.9 to 60.0) months	NMA-median OS: 49.7 (32.5 to 77.3) months	NMA-median OS: 71.0 (37.8 to 133.8) months
		NMA-HR: 0.63 (95% CI 0.40 to 0.99)	NMA-HR: 0.75 (95% CI 0.58 to 0.97)	NMA-HR: 0.70 (95% CI 0.45 to 1.07)	NMA-HR: 0.49 (95% CI 0.26 to 0.92)
		⊕⊕⊕⊖ **moderate** confidence in estimates due to inconsistency of I^2 = 53.9% (downgrade minus 1)	⊕⊕⊕⊖ **moderate** confidence in estimates due to inconsistency of I^2 = 53.9% (downgrade minus 1)	⊕⊕⊖⊖ **low** confidence in estimates due to inconsistency of I^2 = 53.9% (downgrade minus 1), imprecision (downgrade minus 1)	⊕⊕⊕⊖ **moderate** confidence in estimates due to inconsistency of I^2 = 53.9% (downgrade minus 1)

Progression-free survival	Median progression-free survival over all studies included in the network[1]: 16.2 months	NMA-median PFS: 24.9 (16.9 to 36.8) months	NMA-median PFS: 25.7 (20.8 to 32.4) months	NMA-median PFS: 28.9 (18.0 to 46.3) months	NMA-median PFS: 47.6 (27.9 to 81.0) months
		NMA-HR: 0.65 (95% CI 0.44 to 0.96)	NMA-HR: 0.63 (95% CI 0.50 to 0.78)	NMA-HR: 0.56 (95% CI 0.35 to 0.90)	NMA-HR: 0.34 (95% CI 0.20 to 0.58)
		⊕⊕⊖⊖ **low** confidence in estimates due to high risk of bias (downgrade minus 1) and inconsistency of I^2 = 55.3% (downgrade minus 1).	⊕⊕⊖⊖ **low** confidence in estimates due to high risk of bias (downgrade minus 1) and inconsistency of I^2 = 55.3% (downgrade minus 1).	⊕⊕⊖⊖ **low** confidence in estimates due to high risk of bias (downgrade minus 1) and inconsistency of I^2=55.3% (downgrade minus 1).	⊕⊕⊖⊖ **low** confidence in estimates due to high risk of bias (downgrade minus 1) and inconsistency of I^2 = 55.3% (downgrade minus 1).
Polyneuropathies	Mean risk over all studies included in the network[2]: 0.9% (10/1074)	NMA-risk: 0.5% (0.1 to 1.8)	NMA-risk: 4.0% (1.6 to 10.0)	NMA-risk: 79.4% (4.8 to 1306.0)	No study reported the amount of participants with grade ≥ 3 polyneuropathies for treatment with VRDc.
		NMA-RR: 0.57 (95% CI 0.16 to 1.99)	NMA-RR: 4.44 (95% C: 1.77 to 11.11)	NMA-RR: 88.22 (95% CI 5.36 to 1451.11)	
		⊕⊕⊖⊖ **low** confidence in estimates. Downgrade minus 1 for imprecision and minus 1 for high risk of bias.	⊕⊕⊕⊖ **moderate** confidence in estimates. Downgrade minus 1 for high risk of bias.	⊕⊕⊕⊖ **moderate** confidence in estimates. Downgrade minus 1 for high risk of bias.	
Serious adverse events	Mean risk over all studies included in the network[2]: 36.1% (177/490)	Risk not available, because RD is not connected to MP in the network.	Risk not available, because TMP is not connected to MP in the network.	NMA-risk: 46.2% (38.3 to 55.6)	Risk not available, because VRDc is not connected to MP in the network.
		NMA-RR not available, because RD is not connected to MP in the network.	NMA-RR not available, because TMP is not connected to MP in the network.	NMA-RR: 1.28 (95% CI 1.06 to 1.54)	NMA-RR not available, because VRDc is not connected to MP in the network.
		Confidence in estimates can not be assessed, because RD is not connected to MP in the network.	Confidence in estimates can not be assessed, because TMP is not connected to MP in the network.	⊕⊕⊕⊖ **moderate** confidence in estimates. Downgrade minus 1 for high risk of bias.	Confidence in estimates can not be assessed, because VRDc is not connected to MP in the network.

Withdrawals due to adverse events	Mean risk over all studies included in the network[2]: 9.2% (77/837)	NMA-risk: 38.5% (19.6 to 75.4)	NMA-risk: 37.7% (22.1 to 64.5)	NMA-risk: 9.75% (5.8 to 16.7)	NMA-risk: 82.1% (35.1 to 191.7)
		NMA-RR: 4.18 (95% CI 2.13 to 8.20)	NMA-RR: 4.10 (95% CI 2.40 to 7.01)	NMA-RR: 1.06 (95% CI 0.63 to 1.81)	NMA-RR: 8.92 (95% CI 3.82 to 20.84)
		⊕⊕⊕⊕ **high** confidence in estimates.	⊕⊕⊕⊕ **high** confidence in estimates.	⊕⊕⊕⊖ **moderate** confidence in estimates. Downgrade minus 1 for imprecision.	⊕⊕⊕⊕ **high** confidence in estimates.
Quality of life	One study reported that health-related QoL scores increased steadily from baseline until completion of cycle 10	One study reported that global health status of patients improved from baseline over the duration of the study and disease symptoms decreased	One study reported that global health status of patients improved from baseline over the duration of the study and disease symptoms decreased	No study reported the outcome QoL for treatment with VMP.	No study reported the outcome QoL for treatment with VRDc.
		RD was not compared to MP in this study	TMP was not compared to MP in this study		

*Basis for the assumed risks:

1: Median OS/PFS over all studies in the network were estimated, calculating the mean of all available MP-medians (OS and PFS, respectively).

2: mean risk over all studies included in the network was estimated, dividing the total events under MP-therapy by the total of patients treated with MP.

The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk Ratio; **MP:** Melphalan and Prednisone; **RD:** Lenalidomide and Dexamethasone; **TMP:** Thalidomide, Melphalan and Prednisone; **VMP:** Bortezomib, Melphalan and Prednisone; **VRDc:** continuous Bortezomib, Lenalidomide and Dexamethasone

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes

Additional tables

1 Myeloma defining events

Myeloma defining events (Rajkumar 2014)	
CRAB criteria	
Hypercalcaemia	> 2.75 mmol/L (> 11 mg/dL)
Renal insufficiency	creatine clearance < 40 mL per min or serum creatine > 177 µmol/L (> 2 mg/dL)
Anaemia	haemoglobin value < 100 g/L
Bone lesions	1 or more oseolytic lesions on skeletal radiography, computer tomography, or positron emission tomography–computer tomography
Biomarkers of malignancy (SLiM criteria)	
clonal bone marrow plasma cell %–age	≧ 60 (Sixty)%
Involved to uninvolved serum free Light chain ratio	≧ 100
focal lesions on Magnetic resonance imaging (MRI) studies	< 1

Footnotes

2 Results of NMA for the outcome OS.

League tables for the outcome overall survival. Direct and network estimates with 95% CIs are given. Treatments are ordered by P score (descending). The treatment with the highest probability of being the best is in the upper left corner.

Direct estimates are presented in the upper triangle; network estimates are presented in the lower triangle

Global approach to check inconsistency/heterogeneity: Q-statistics, I^2.

OS- Subnetwork 1

No. of studies: 19. No. of treatments: 15. No. of pairwise comparisons: 25. No. of designs: 14

Q_{total}= 17.36, df = 8, P = 0.027 / Q_{within}= 7.54, df = 5, P = 0.18 / $Q_{between}$= 12.35, df = 3, P = 0.006; I^2 = 53.9%, Tau^2 = 0.0381

Treatment Effects:

VRDc	.	.	0.71 (0.44, 1.15)	.	.	.	.	.	.	.	.	.	.	.
1.01 (0.41, 2.48)	**VTMPc**	.	.	0.70 (0.43, 1.13)	.	.	.	.	.	.	.	.	.	.
0.79 (0.42, 1.48)	0.78 (0.35, 1.71)	**RD**	0.98 (0.65, 1.49)	.	.	0.77 (0.51, 1.16)	.	.	.	.	.	.	.	.
0.71 (0.44, 1.15)	0.70 (0.33, 1.50)	0.90 (0.60, 1.35)	**RDc**	.	1.07 (0.70, 1.63)	0.78 (0.52, 1.18)	0.98 (0.59, 1.64)	.	.	.	.	.	.	.
0.71 (0.33, 1.51)	0.70 (0.43, 1.13)	0.90 (0.48, 1.69)	1.00 (0.55, 1.79)	**VMP**	.	.	.	.	.	.	0.70 (0.45, 1.07)	.	.	.
0.67 (0.35, 1.26)	0.66 (0.29, 1.50)	0.85 (0.49, 1.48)	0.94 (0.63, 1.41)	0.94 (0.48, 1.84)	**RCPc**	.	1.16 (0.69, 1.95)	.	.	.	.	.	.	.
0.65 (0.36, 1.20)	0.65 (0.32, 1.30)	0.83 (0.56, 1.24)	0.92 (0.64, 1.32)	0.93 (0.56, 1.53)	0.98 (0.59, 1.62)	**TMP**	.	.	.	1.08 (0.49, 2.40)	0.66 (0.49, 0.88)	.	.	.
0.59 (0.31, 1.11)	0.59 (0.28, 1.23)	0.75 (0.45, 1.25)	0.84 (0.56, 1.25)	0.84 (0.48, 1.47)	0.89 (0.55, 1.42)	0.91 (0.61, 1.35)	**RMPc**	0.95 (0.67, 1.33)	.	.	0.95 (0.54, 1.67)	.	0.79 (0.45, 1.38)	.

0.53 (0.27, 1.03)	0.52 (0.25, 1.10)	0.67 (0.39, 1.16)	0.75 (0.47, 1.18)	0.75 (0.42, 1.33)	0.79 (0.46, 1.35)	0.81 (0.53, 1.24)	0.89 (0.66, 1.21)	**TMPc**	0.92 (0.66, 1.28)	.	1.06 (0.64, 1.75)	.	.	.
0.49 (0.23, 1.03)	0.48 (0.21, 1.09)	0.62 (0.33, 1.17)	0.68 (0.39, 1.21)	0.69 (0.35, 1.33)	0.73 (0.39, 1.37)	0.74 (0.43, 1.28)	0.82 (0.52, 1.29)	0.92 (0.66, 1.28)	**MPc**	.	.	.	.	0.65 (0.38, 1.11)
0.49 (0.24, 1.00)	0.48 (0.23, 1.02)	0.62 (0.35, 1.10)	0.69 (0.40, 1.17)	0.69 (0.39, 1.22)	0.73 (0.39, 1.36)	0.74 (0.48, 1.14)	0.82 (0.49, 1.37)	0.92 (0.54, 1.56)	1.00 (0.54, 1.87)	**TCD**	1.12 (0.73, 1.72)	0.92 (0.61, 1.39)	.	.
0.49 (0.26, 0.92)	0.49 (0.26, 0.93)	0.63 (0.40, 0.99)	0.69 (0.47, 1.03)	0.70 (0.45, 1.07)	0.74 (0.44, 1.23)	0.75 (0.58, 0.97)	0.83 (0.58, 1.19)	0.93 (0.64, 1.35)	1.01 (0.61, 1.67)	1.01 (0.69, 1.48)	**MP**	.	0.82 (0.47, 1.44)	.
0.45 (0.20, 1.02)	0.44 (0.19, 1.04)	0.57 (0.28, 1.15)	0.63 (0.32, 1.23)	0.63 (0.31, 1.28)	0.67 (0.32, 1.42)	0.68 (0.38, 1.24)	0.75 (0.39, 1.46)	0.85 (0.43, 1.65)	0.92 (0.44, 1.95)	0.92 (0.61, 1.39)	0.91 (0.52, 1.60)	**RCD**	.	.
0.43 (0.20, 0.94)	0.43 (0.19, 0.98)	0.55 (0.29, 1.07)	0.61 (0.34, 1.12)	0.62 (0.31, 1.21)	0.65 (0.34, 1.27)	0.67 (0.38, 1.16)	0.73 (0.44, 1.22)	0.82 (0.47, 1.44)	0.90 (0.47, 1.72)	0.89 (0.47, 1.69)	0.89 (0.53, 1.48)	0.97 (0.46, 2.08)	**RMP**	.
0.31 (0.12, 0.79)	0.31 (0.12, 0.83)	0.40 (0.17, 0.92)	0.44 (0.20, 0.97)	0.44 (0.19, 1.04)	0.47 (0.20, 1.08)	0.48 (0.22, 1.03)	0.53 (0.26, 1.07)	0.59 (0.31, 1.12)	0.65 (0.38, 1.11)	0.64 (0.28, 1.47)	0.64 (0.31, 1.33)	0.70 (0.28, 1.76)	0.72 (0.31, 1.68)	**TDc**

OS- Subnetwork 2

No. of studies: 2. No. of treatments: 4. No. of pairwise comparisons: 4. No. of designs: 2

Q_{total}=0, df = 0, p = n.a./ Q_{within}= 0, df = 0, p = n.a./ $Q_{between}$=0, df = 0, p = n.a.; I^2 = n.a., Tau^2 = n.a.

Treatment Effects:

VMPc	0.92 (0.65, 1.29)	0.89 (0.64, 1.25)	0.67 (0.49, 0.91)
0.92 (0.65, 1.29)	**VTDc**	0.98 (0.70, 1.38)	.
0.89 (0.64, 1.25)	0.98 (0.69, 1.38)	**VDc**	.
0.67 (0.49, 0.91)	0.73 (0.46, 1.16)	0.75 (0.47, 1.18)	**VTPc**

Footnotes

c: continuous; **C**: cyclophosphamide; **CI**: confidence interval; **df**: degrees of freedom; **D**: dexamethasone; **M**: melphalan; **NMA**: network meta-analysis; **n.a.**: not applicable; **OS**: overall survival; **P**: prednisone; **R**: revlimid (lenalidomide); **T**: thalidomide; **V**: velcade (bortezomib)

3 Results of NMA for the outcome PFS.

League tables for the outcome progression-free survival. Direct and network estimates with 95% CIs are given. Treatments are ordered by P score (descending). The treatment with the highest probability of being the best is in the upper left corner.

Direct estimates are presented in the upper triangle; network estimates are presented in the lower triangle

Global approach to check inconsistency/heterogeneity: Q-statistics, I^2.

PFS- Subnetwork 1

No. of studies: 19. No. of treatments: 15. No. of pairwise comparisons: 25. No. of designs: 14

Q_{total}=17.89, df=8, P = 0.022 / Q_{within}= 6.06, df = 5, P = 0.30 / $Q_{between}$=11.80, df = 3, P = 0.008; I^2 = 55.3%, Tau^2 = 0.0269

Treatment Effects:

VRDc	.	.	0.71 (0.48, 1.06)	.	.	.	.	.	.	.	.	.	.	.
1.06 (0.48, 2.36)	**VTMPc**	.	.	.	.	0.58 (0.40, 0.85)	.	.	.	.	.	.	.	.

0.77 (0.46, 1.29)	0.73 (0.37, 1.44)	**RMPc**	0.80 (0.54, 1.20)	1.00 (0.76, 1.32)	0.80 (0.53, 1.19)	.	.	.	.	.	0.49 (0.31, 0.80)	0.40 (0.25, 0.64)	.	.
0.71 (0.48, 1.06)	0.67 (0.34, 1.34)	0.92 (0.67, 1.27)	**RDc**	.	1.00 (0.71, 1.40)	.	.	0.69 (0.48, 0.98)	0.70 (0.49, 1.00)	.	.	.	.	.
0.70 (0.40, 1.20)	0.66 (0.33, 1.30)	0.90 (0.70, 1.15)	0.98 (0.67, 1.42)	**TMPc**	.	.	0.84 (0.63, 1.11)	.	.	.	.	0.62 (0.41, 0.93)	.	.
0.67 (0.40, 1.13)	0.64 (0.30, 1.33)	0.87 (0.60, 1.26)	0.95 (0.68, 1.32)	0.97 (0.63, 1.49)	**RCPc**	.	.	.	.	.	.	.	.	.
0.61 (0.30, 1.24)	0.58 (0.40, 0.85)	0.79 (0.45, 1.39)	0.86 (0.48, 1.54)	0.88 (0.50, 1.55)	0.91 (0.49, 1.71)	**VMP**	.	.	.	.	.	0.56 (0.35, 0.90)	.	.
0.58 (0.31, 1.08)	0.55 (0.26, 1.15)	0.75 (0.52, 1.10)	0.82 (0.51, 1.31)	0.84 (0.63, 1.11)	0.87 (0.52, 1.45)	0.95 (0.51, 1.78)	**MPc**	.	.	0.77 (0.49, 1.21)	.	.	.	.
0.55 (0.33, 0.90)	0.52 (0.27, 0.99)	0.71 (0.51, 0.98)	0.77 (0.57, 1.04)	0.79 (0.55, 1.12)	0.81 (0.54, 1.22)	0.89 (0.53, 1.50)	0.94 (0.60, 1.47)	**TMP**	1.01 (0.71, 1.43)	.	.	0.56 (0.44, 0.72)	0.89 (0.44, 1.78)	.
0.53 (0.31, 0.89)	0.50 (0.24, 1.02)	0.68 (0.45, 1.04)	0.74 (0.52, 1.04)	0.76 (0.48, 1.18)	0.78 (0.49, 1.23)	0.86 (0.46, 1.58)	0.90 (0.53, 1.53)	0.96 (0.68, 1.35)	**RD**	.	.	.	.	.
0.45 (0.21, 0.96)	0.42 (0.18, 1.00)	0.58 (0.32, 1.04)	0.63 (0.33, 1.21)	0.64 (0.38, 1.10)	0.67 (0.34, 1.32)	0.73 (0.34, 1.58)	0.77 (0.49, 1.21)	0.82 (0.43, 1.55)	0.85 (0.43, 1.71)	**TDc**	.	.	.	.
0.41 (0.22, 0.77)	0.39 (0.19, 0.80)	0.53 (0.35, 0.81)	0.57 (0.35, 0.94)	0.59 (0.37, 0.93)	0.61 (0.35, 1.04)	0.67 (0.36, 1.25)	0.70 (0.41, 1.20)	0.75 (0.48, 1.18)	0.78 (0.45, 1.34)	0.91 (0.45, 1.84)	**RMP**	0.80 (0.51, 1.24)	.	.
0.34 (0.20, 0.58)	0.32 (0.18, 0.59)	0.44 (0.33, 0.60)	0.48 (0.35, 0.67)	0.49 (0.36, 0.67)	0.51 (0.34, 0.77)	0.56 (0.35, 0.90)	0.59 (0.39, 0.89)	0.63 (0.50, 0.78)	0.65 (0.44, 0.96)	0.76 (0.41, 1.41)	0.84 (0.56, 1.26)	**MP**	0.82 (0.57, 1.17)	.
0.32 (0.17, 0.57)	0.30 (0.15, 0.59)	0.41 (0.27, 0.63)	0.44 (0.28, 0.69)	0.45 (0.29, 0.70)	0.47 (0.28, 0.78)	0.51 (0.29, 0.91)	0.54 (0.32, 0.91)	0.58 (0.40, 0.83)	0.60 (0.37, 0.98)	0.70 (0.35, 1.40)	0.77 (0.46, 1.30)	0.92 (0.67, 1.27)	**TCD**	0.96 (0.68, 1.35)
0.30 (0.15, 0.60)	0.29 (0.13, 0.62)	0.39 (0.23, 0.68)	0.43 (0.24, 0.74)	0.44 (0.25, 0.76)	0.45 (0.24, 0.83)	0.49 (0.25, 0.96)	0.52 (0.28, 0.97)	0.55 (0.34, 0.91)	0.58 (0.32, 1.04)	0.68 (0.31, 1.46)	0.74 (0.40, 1.38)	0.88 (0.55, 1.41)	0.96 (0.68, 1.35)	**RCD**

PFS- Subnetwork 2

No. of studies: 2. No. of treatments: 4. No. of pairwise comparisons: 4. No. of designs: 2

Q_{total}= 0, df = 0, P = n.a./ Q_{within}= 0, d f= 0, P = n.a./ $Q_{between}$= 0, df=0, P = n.a.; I^2 = n.a., Tau^2 = n.a.

Treatment Effects:

VTPc	.	0.83 (0.61, 1.15)	.
0.87 (0.56, 1.34)	**VTDc**	0.96 (0.72, 1.28)	0.89 (0.67, 1.19)
0.83 (0.61, 1.15)	0.96 (0.72, 1.28)	**VMPc**	0.93 (0.71, 1.23)
0.78 (0.51, 1.19)	0.89 (0.67, 1.19)	0.93 (0.71, 1.23)	**VDc**

Footnotes

c: continuous; **C**: cyclophosphamide; **CI**: confidence interval; **df**: degrees of freedom; **D**: dexamethasone; **M**: melphalan; **NMA**: network meta-analysis; **n.a.**: not applicable; **OS**: overall survival; **P**: prednisone; **R**: revlimid (lenalidomide); **T**: thalidomide; **V**: velcade (bortezomib)

4 Results of NMA for the outcome polyneuropathy.

League tables for the outcome polyneuropathy. Direct and network estimates with 95% CIs are given. Treatments are ordered by P score (descending). The treatment with the highest probability of being the best is in the upper left corner.

Direct estimates are presented in the upper triangle; network estimates are presented in the lower triangle

Global approach to check inconsistency/heterogeneity: Q-statistics, I^2.

Polyneuropathy-subnetwork 1

No. of studies: 16. No. of treatments: 15. No. of pairwise comparisons: 24. No. of designs: 12

Q_{total}= 6.21, df = 6, P = 0.40/ Q_{within}= 4.10, df = 4, p=0.39/ $Q_{between}$= 2.11, df = 2, P = 0.35; I^2 = 3.4%, Tau^2 = 0.0248

Treatment Effects:

RCD	.	.	0.38 (0.23, 0.62)	.	.	.	.	.	.	.	.	.	.	.
0.50 (0.05, 5.07)	**RD**	0.99 (0.31, 3.16)	.	.	.	.	.	.	.	0.12 (0.05, 0.30)	.	.	.	.
0.39 (0.04, 3.85)	0.78 (0.26, 2.40)	**RDc**	.	.	0.86 (0.26, 2.90)	.	.	0.83 (0.25, 2.79)	.	0.12 (0.05, 0.30)	.	.	.	.
0.38 (0.23, 0.62)	0.77 (0.08, 7.38)	0.98 (0.10, 9.13)	**TCD**	.	.	.	.	.	0.19 (0.02, 1.71)	0.17 (0.02, 1.34)	.	.	.	.
0.28 (0.03, 2.90)	0.57 (0.16, 1.99)	0.72 (0.26, 2.04)	0.74 (0.08, 7.20)	**MP**	.	.	0.66 (0.23, 1.90)	0.53 (0.19, 1.48)	.	0.33 (0.11, 0.96)	0.05 (0.00, 0.83)	0.01 (0.00, 0.19)	.	.
0.26 (0.02, 3.16)	0.52 (0.11, 2.38)	0.66 (0.21, 2.09)	0.68 (0.06, 7.85)	0.91 (0.25, 3.34)	**RCPc**	.	.	0.96 (0.30, 3.05)	.	.	.	.	.	.
0.25 (0.01, 6.67)	0.51 (0.04, 6.88)	0.65 (0.06, 7.55)	0.67 (0.03, 16.79)	0.90 (0.08, 9.76)	0.98 (0.08, 12.13)	**MPc**	.	.	.	.	0.10 (0.01, 0.80)	.	.	.
0.22 (0.02, 2.63)	0.45 (0.10, 1.98)	0.57 (0.17, 1.96)	0.58 (0.05, 6.54)	0.79 (0.29, 2.12)	0.86 (0.22, 3.43)	0.87 (0.08, 9.79)	**RMP**	0.81 (0.33, 2.00)	.	.	.	.	.	.
0.20 (0.02, 2.14)	0.40 (0.10, 1.50)	0.51 (0.19, 1.36)	0.52 (0.05, 5.31)	0.70 (0.30, 1.64)	0.77 (0.25, 2.33)	0.78 (0.08, 7.45)	0.89 (0.37, 2.15)	**RMPc**	.	.	0.14 (0.05, 0.36)	.	.	.
0.07 (0.01, 0.69)	0.14 (0.03, 0.69)	0.18 (0.04, 0.85)	0.19 (0.02, 1.71)	0.25 (0.05, 1.24)	0.28 (0.04, 1.74)	0.28 (0.02, 4.58)	0.32 (0.05, 1.93)	0.36 (0.07, 1.91)	**TD**	0.89 (0.24, 3.25)	.	.	.	.
0.06 (0.01, 0.54)	0.13 (0.05, 0.31)	0.16 (0.07, 0.37)	0.17 (0.02, 1.34)	0.23 (0.09, 0.56)	0.25 (0.07, 0.90)	0.25 (0.02, 2.95)	0.29 (0.08, 0.98)	0.32 (0.11, 0.91)	0.89 (0.24, 3.25)	**TMP**	.	.	.	.
0.03 (0.00, 0.32)	0.05 (0.01, 0.25)	0.07 (0.02, 0.24)	0.07 (0.01, 0.80)	0.09 (0.03, 0.30)	0.10 (0.02, 0.41)	0.10 (0.01, 0.80)	0.11 (0.03, 0.40)	0.13 (0.05, 0.32)	0.36 (0.06, 2.31)	0.40 (0.10, 1.54)	**TMPc**	.	.	.
0.00 (0.00, 0.12)	0.01 (0.00, 0.14)	0.01 (0.00, 0.16)	0.01 (0.00, 0.31)	0.01 (0.00, 0.19)	0.01 (0.00, 0.27)	0.01 (0.00, 0.50)	0.01 (0.00, 0.28)	0.02 (0.00, 0.30)	0.04 (0.00, 1.12)	0.05 (0.00, 0.96)	0.13 (0.01, 2.62)	**VMP**	0.48 (0.23, 0.97)	0.20 (0.01, 3.70)
0.00 (0.00, 0.06)	0.00 (0.00, 0.07)	0.00 (0.00, 0.08)	0.00 (0.00, 0.16)	0.01 (0.00, 0.10)	0.01 (0.00, 0.14)	0.01 (0.00, 0.25)	0.01 (0.00, 0.15)	0.01 (0.00, 0.16)	0.02 (0.00, 0.57)	0.02 (0.00, 0.50)	0.06 (0.00, 1.35)	0.48 (0.23, 0.97)	**VTMPc**	.

0.00 (0.00, 0.07)	0.00 (0.00, 0.09)	0.00 (0.00, 0.11)	0.00 (0.00, 0.17)	0.00 (0.00, 0.13)	0.00 (0.00, 0.17)	0.00 (0.00, 0.28)	0.00 (0.00, 0.19)	0.00 (0.00, 0.20)	0.01 (0.00, 0.69)	0.01 (0.00, 0.64)	0.03 (0.00, 1.69)	0.20 (0.01, 3.70)	0.42 (0.02, 8.45)	**VD**

Polyneuropathy-subnetwork 2

No. of studies: 2. No. of treatments: 4. No. of pairwise comparisons: 4. No. of designs: 2

Q_{total}= 0, df =n0, P = n.a./ Q_{within}=0, df = 0,P = n.a./ $Q_{between}$= 0, df = 0, P = n.a.; I^2 = n.a., Tau^2 = n.a.

Treatment Effects:

VMPc	0.88 (0.57, 1.33)	0.75 (0.33, 1.72)	0.72 (0.48, 1.08)
0.88 (0.57, 1.33)	**VDc**	.	0.82 (0.56, 1.21)
0.75 (0.33, 1.72)	0.86 (0.34, 2.17)	**VTPc**	.
0.72 (0.48, 1.08)	0.82 (0.56, 1.21)	0.96 (0.38, 2.42)	**VTDc**

Footnotes

c: continuous; **C**: cyclophosphamide; **CI**: confidence interval; **df**: degrees of freedom; **D**: dexamethasone; **M**: melphalan; **NMA**: network meta-analysis; **n.a.**: not applicable; **OS**: overall survival; **P**: prednisone; **R**: revlimid (lenalidomide); **T**: thalidomide; **V**: velcade (bortezomib)

5 Results of NMA for the outcome neutropenia.

League tables for the outcome neutropenia. Direct and network estimates with 95% CIs are given. Treatments are ordered by P score (descending). The treatment with the highest probability of being the best is in the upper left corner.

Direct estimates are presented in the upper triangle; network estimates are presented in the lower triangle

Global approach to check inconsistency/heterogeneity: Q-statistics, I^2.

Neutropenia-subnetwork 1

No. of studies: 12. No. of treatments: 12. No. of pairwise comparisons: 18. No. of designs: 9

Q_{total}= 6.67, df = 4, P = 0.15/ Q_{within}= 4.53, df = 3, P = 0.21/ $Q_{between}$= 2.14, df = 1, P = 0.14; I^2 = 40%, Tau^2 = 0.0465

Treatment Effects:

TD	.	.	.	0.30 (0.04, 2.37)	.	.	.	.	.	0.16 (0.02, 1.20)	.
0.31 (0.04, 2.39)	**MP**	0.95 (0.60, 1.51)	.	.	.	1.07 (0.53, 2.15)	.	.	.	0.48 (0.33, 0.72)	.
0.29 (0.04, 2.39)	0.95 (0.60, 1.51)	**VMP**	.	.	.	.	.	0.73 (0.45, 1.20)	.	.	.
0.29 (0.04, 2.29)	0.94 (0.54, 1.65)	0.99 (0.48, 2.05)	**RD**	.	0.87 (0.55, 1.38)	.	.	.	.	0.58 (0.37, 0.91)	.
0.30 (0.04, 2.37)	0.96 (0.34, 2.68)	1.01 (0.32, 3.12)	1.01 (0.35, 2.93)	**TCD**	.	.	.	.	0.63 (0.40, 0.98)	0.55 (0.21, 1.43)	.
0.27 (0.03, 2.08)	0.86 (0.52, 1.44)	0.91 (0.46, 1.81)	0.91 (0.58, 1.44)	0.90 (0.32, 2.58)	**RDc**	.	0.85 (0.49, 1.49)	.	.	0.67 (0.42, 1.05)	0.35 (0.21, 0.58)
0.26 (0.03, 2.11)	0.84 (0.48, 1.46)	0.88 (0.43, 1.82)	0.89 (0.46, 1.72)	0.88 (0.29, 2.70)	0.97 (0.56, 1.69)	**TMPc**	.	.	.	.	0.45 (0.29, 0.72)
0.25 (0.03, 2.04)	0.80 (0.40, 1.58)	0.84 (0.37, 1.92)	0.85 (0.43, 1.68)	0.84 (0.26, 2.66)	0.93 (0.54, 1.59)	0.95 (0.51, 1.77)	**RCPc**	.	.	.	0.41 (0.25, 0.67)

0.22 (0.03, 1.85)	0.69 (0.35, 1.36)	0.73 (0.45, 1.20)	0.73 (0.31, 1.77)	0.73 (0.21, 2.49)	0.80 (0.34, 1.87)	0.83 (0.34, 1.98)	0.87 (0.33, 2.27)	**VTMPc**	.	.	.
0.19 (0.02, 1.56)	0.60 (0.19, 1.85)	0.63 (0.19, 2.13)	0.64 (0.20, 2.01)	0.63 (0.40, 0.98)	0.70 (0.22, 2.18)	0.71 (0.21, 2.39)	0.75 (0.22, 2.60)	0.86 (0.23, 3.21)	**RCD**	.	.
0.16 (0.02, 1.20)	0.52 (0.36, 0.75)	0.55 (0.30, 0.99)	0.55 (0.35, 0.86)	0.55 (0.21, 1.43)	0.60 (0.40, 0.91)	0.62 (0.35, 1.10)	0.65 (0.34, 1.24)	0.75 (0.35, 1.62)	0.87 (0.30, 2.51)	**TMP**	.
0.11 (0.01, 0.85)	0.34 (0.19, 0.61)	0.36 (0.17, 0.75)	0.36 (0.20, 0.67)	0.36 (0.12, 1.09)	0.40 (0.25, 0.63)	0.41 (0.27, 0.62)	0.43 (0.26, 0.70)	0.49 (0.20, 1.20)	0.57 (0.17, 1.89)	0.66 (0.38, 1.14)	**RMPc**

Neutropenia-subnetwork 2

No. of studies: 2. No. of treatments: 4. No. of pairwise comparisons: 4. No. of designs: 2

Q_{total}= 0, df = 0, P = n.a./ Q_{within}= 0, df = 0,P = n.a./ $Q_{between}$= 0, df = 0, P = n.a.; I^2 = n.a., Tau^2 = n.a.
Treatment Effects:

VDc	0.72 (0.16, 3.16)	.	0.10 (0.03, 0.31)
0.72 (0.16, 3.16)	**VTDc**	.	0.13 (0.05, 0.37)
0.17 (0.05, 0.57)	0.23 (0.08, 0.70)	**VTPc**	0.57 (0.39, 0.84)
0.10 (0.03, 0.31)	0.13 (0.05, 0.37)	0.57 (0.39, 0.84)	**VMPc**

Footnotes

c: continuous; **C**: cyclophosphamide; **CI**: confidence interval; **df**: degrees of freedom; **D**: dexamethasone; **M**: melphalan; **NMA**: network meta-analysis; **n.a.**: not applicable; **OS**: overall survival; **P**: prednisone; **R**: revlimid (lenalidomide); **T**: thalidomide; **V**: velcade (bortezomib)

6 Results of NMA for the outcome anaemia.

League tables for the outcome anaemia. Direct and network estimates with 95% CIs are given. Treatments are ordered by P score (descending). The treatment with the highest probability of being the best is in the upper left corner.

Direct estimates are presented in the upper triangle; network estimates are presented in the lower triangle

Global approach to check inconsistency/heterogeneity: Q-statistics, I^2.

Anaemia-subnetwork 1

No. of studies: 11. No. of treatments: 13. No. of pairwise comparisons: 19. No. of designs: 10

Q_{total}=7.31, df = 3, P = 0.063/ Q_{within}=5.38, df = 1, P = 0.020/ $Q_{between}$= 1.93, df = 2, P = 0.38; I^2 = 59%, Tau^2 = 0.1287
Treatment Effects:

VRD	0.31 (0.01, 8.11)	.	.	.	.	.	.	.	.	.	.	.
0.31 (0.01, 8.11)	**RD**	.	0.84 (0.40, 1.78)	.	0.84 (0.40, 1.77)	.	.	.	.	.	.	.
0.29 (0.01, 9.54)	0.94 (0.27, 3.24)	**VMP**	.	0.99 (0.41, 2.38)	.	.	.	0.67 (0.31, 1.43)	.	.	.	.
0.28 (0.01, 7.90)	0.90 (0.43, 1.87)	0.96 (0.31, 3.01)	**RDc**	.	1.00 (0.47, 2.10)	0.67 (0.23, 1.96)	.	.	.	.	.	0.28 (0.10, 0.76)
0.29 (0.01, 10.51)	0.93 (0.20, 4.24)	0.99 (0.41, 2.38)	1.03 (0.24, 4.34)	**VTMPc**	.	.	.	.	.	.	.	.

0.24 (0.01, 6.86)	0.78 (0.38, 1.62)	0.83 (0.28, 2.45)	0.87 (0.44, 1.70)	0.84 (0.21, 3.39)	**TMP**	.	.	0.98 (0.40, 2.41)	0.33 (0.03, 3.39)	0.28 (0.02, 3.21)	.	.
0.22 (0.01, 7.07)	0.71 (0.21, 2.33)	0.75 (0.20, 2.78)	0.79 (0.29, 2.15)	0.76 (0.16, 3.68)	0.90 (0.30, 2.72)	**RCPc**	.	.	.	.	.	0.42 (0.17, 1.06)
0.19 (0.01, 5.93)	0.61 (0.20, 1.86)	0.65 (0.21, 1.95)	0.67 (0.26, 1.77)	0.66 (0.16, 2.69)	0.78 (0.29, 2.08)	0.86 (0.30, 2.47)	**TMPc**	0.79 (0.18, 3.44)	.	.	.	0.56 (0.30, 1.03)
0.19 (0.01, 5.86)	0.63 (0.23, 1.67)	0.67 (0.31, 1.43)	0.70 (0.30, 1.63)	0.68 (0.21, 2.16)	0.80 (0.37, 1.72)	0.89 (0.31, 2.56)	1.03 (0.46, 2.30)	**MP**	.	.	0.52 (0.23, 1.20)	0.56 (0.24, 1.31)
0.08 (0.00, 4.73)	0.26 (0.02, 2.96)	0.28 (0.02, 3.59)	0.29 (0.03, 3.24)	0.28 (0.02, 4.20)	0.33 (0.03, 3.39)	0.37 (0.03, 4.80)	0.43 (0.03, 5.33)	0.42 (0.04, 4.78)	**TCD**	0.84 (0.13, 5.28)	.	.
0.07 (0.00, 4.26)	0.22 (0.02, 2.79)	0.23 (0.02, 3.36)	0.24 (0.02, 3.05)	0.24 (0.01, 3.91)	0.28 (0.02, 3.21)	0.31 (0.02, 4.50)	0.36 (0.03, 5.00)	0.35 (0.03, 4.50)	0.84 (0.13, 5.28)	**TD**	.	.
0.10 (0.00, 3.07)	0.31 (0.10, 0.99)	0.33 (0.11, 0.99)	0.34 (0.12, 0.97)	0.33 (0.08, 1.36)	0.40 (0.14, 1.10)	0.44 (0.14, 1.39)	0.51 (0.20, 1.28)	0.49 (0.23, 1.09)	1.19 (0.09, 14.97)	1.41 (0.10, 19.72)	**RMP**	1.09 (0.49, 2.40)
0.10 (0.00, 3.04)	0.32 (0.12, 0.88)	0.35 (0.13, 0.95)	0.36 (0.16, 0.81)	0.35 (0.09, 1.33)	0.41 (0.18, 0.97)	0.46 (0.19, 1.13)	0.53 (0.30, 0.94)	0.52 (0.26, 1.01)	1.24 (0.10, 14.68)	1.47 (0.11, 19.39)	1.04 (0.49, 2.23)	**RMPc**

Anaemia-subnetwork 2

No. of studies: 2. No. of treatments: 4. No. of pairwise comparisons: 4. No. of designs: 2

Q_{total}= 0, df = 0, P = n.a./ Q_{within}=0, df =0, P = n.a./ $Q_{between}$= 0, df = 0, P = n.a.; I^2 = n.a., Tau^2 = n.a.

Treatment Effects:

VDc	.	0.29 (0.08, 1.02)	0.25 (0.07, 0.86)
0.37 (0.09, 1.60)	**VTPc**	.	0.67 (0.31, 1.43)
0.29 (0.08, 1.02)	0.78 (0.25, 2.36)	**VTDc**	0.86 (0.38, 1.93)
0.25 (0.07, 0.86)	0.67 (0.31, 1.43)	0.86 (0.38, 1.93)	**VMPc**

Footnotes

c: continuous; **C**: cyclophosphamide; **CI**: confidence interval; **df**: degrees of freedom; **D**: dexamethasone; **M**: melphalan; **NMA**: network meta-analysis; **n.a.**: not applicable; **OS**: overall survival; **P**: prednisone; **R**: revlimid (lenalidomide); **T**: thalidomide; **V**: velcade (bortezomib)

7 Results of NMA for the outcome thrombocytopenia.

League tables for the outcome thrombocytopenia. Direct and network estimates with 95% CIs are given. Treatments are ordered by P score (descending). The treatment with the highest probability of being the best is in the upper left corner.

Direct estimates are presented in the upper triangle; network estimates are presented in the lower triangle

Global approach to check inconsistency/heterogeneity: Q-statistics, I².

Thrombocytopenia-subnetwork 1

No. of studies: 8. No. of treatments: 10. No. of pairwise comparisons: 14. No. of designs: 8

Q_{total}= 0.01, df = 2, P = 0.99/ Q_{within}= 0.00, df = 0, Pm=mnot available/ $Q_{between}$=m0.01, df = 2, P = 0.99; I^2 = 0%, Tau^2 = 0.0

Treatment Effects:

TMPc	0.79 (0.21, 2.87)	.	.	.	.	.	.	0.26 (0.17, 0.39)	.
0.77 (0.46, 1.29)	**MP**	.	.	0.82 (0.66, 1.01)	.	.	0.72 (0.39, 1.33)	0.34 (0.22, 0.50)	0.31 (0.21, 0.46)
0.75 (0.38, 1.49)	0.97 (0.55, 1.72)	**RD**	0.88 (0.60, 1.31)	.	.	.	0.72 (0.49, 1.04)	.	.
0.66 (0.36, 1.21)	0.86 (0.52, 1.40)	0.88 (0.60, 1.29)	**RDc**	.	.	0.82 (0.43, 1.57)	0.81 (0.57, 1.17)	0.40 (0.23, 0.71)	.
0.63 (0.36, 1.10)	0.82 (0.66, 1.01)	0.84 (0.46, 1.54)	0.95 (0.56, 1.64)	**VMP**	0.90 (0.64, 1.26)	.	.	.	.
0.57 (0.30, 1.08)	0.73 (0.49, 1.10)	0.75 (0.37, 1.51)	0.86 (0.45, 1.62)	0.90 (0.64, 1.26)	**VTMPc**	.	.	.	.
0.53 (0.28, 1.02)	0.69 (0.38, 1.26)	0.71 (0.36, 1.42)	0.81 (0.44, 1.48)	0.85 (0.45, 1.61)	0.94 (0.46, 1.95)	**RCPc**	.	0.49 (0.29, 0.83)	.
0.54 (0.29, 1.01)	0.70 (0.43, 1.14)	0.72 (0.50, 1.04)	0.82 (0.59, 1.15)	0.86 (0.51, 1.46)	0.96 (0.51, 1.79)	1.02 (0.53, 1.93)	**TMP**	.	.
0.26 (0.18, 0.39)	0.34 (0.24, 0.48)	0.35 (0.20, 0.61)	0.40 (0.25, 0.63)	0.41 (0.27, 0.63)	0.46 (0.27, 0.79)	0.49 (0.29, 0.82)	0.48 (0.29, 0.79)	**RMPc**	0.92 (0.73, 1.16)
0.24 (0.15, 0.38)	0.31 (0.22, 0.45)	0.32 (0.18, 0.58)	0.36 (0.22, 0.60)	0.38 (0.25, 0.58)	0.42 (0.25, 0.73)	0.45 (0.26, 0.79)	0.44 (0.26, 0.75)	0.92 (0.73, 1.16)	**RMP**

Thrombocytopenia-subnetwork 2

No. of studies: 2. No. of treatments: 4. No. of pairwise comparisons: 4. No. of designs: 2

Q_{total}= 0, df = 0, P = n.a./ Q_{within}= 0, df = 0,P = n.a./ $Q_{between}$= 0, df = 0, P = n.a.; I^2 = n.a., Tau^2 = n.a.

Treatment Effects:

VDc	0.64 (0.18, 2.22)	.	0.16 (0.06, 0.46)
0.64 (0.18, 2.22)	**VTDc**	.	0.26 (0.11, 0.61)
0.36 (0.11, 1.16)	0.56 (0.20, 1.57)	**VTPc**	0.46 (0.27, 0.78)
0.16 (0.06, 0.46)	0.26 (0.11, 0.61)	0.46 (0.27, 0.78)	**VMPc**

Footnotes

c: continuous; **C**: cyclophosphamide; **CI**: confidence interval; **df**: degrees of freedom; **D**: dexamethasone; **M**: melphalan; **NMA**: network meta-analysis; **n.a.**: not applicable; **OS**: overall survival; **P**: prednisone; **R**: revlimid (lenalidomide); **T**: thalidomide; **V**: velcade (bortezomib)

8 Results of NMA for the outcome thromboembolism.

League table for the outcome thromboembolism. Direct and network estimates with 95% CIs are given. Treatments are ordered by P score (descending). The treatment with the highest probability of being the best is in the upper left corner.

Direct estimates are presented in the upper triangle; network estimates are presented in the lower triangle

Global approach to check inconsistency/heterogeneity: Q-statistics, I^2.

Thromboembolism-subnetwork 1

No. of studies: 11. No. of treatments: 9. No. of pairwise comparisons: 13. No. of designs: 7

Heterogeneity / inconsistency: Q = 5.47, df = 4, P = 0.24; I^2 = 26.9%, Tau^2 = 0.1107
Treatment Effects:

MP	0.67 (0.10, 4.49)	0.36 (0.16, 0.81)	.	.	.	0.14 (0.03, 0.67)	.	.
0.67 (0.10, 4.49)	**VMP**	.	0.38 (0.11, 1.27)	.	.	.	.	.
0.36 (0.16, 0.81)	0.54 (0.07, 4.23)	**TMP**	.	.	.	.	.	.
0.26 (0.03, 2.43)	0.38 (0.11, 1.27)	0.71 (0.06, 7.69)	**VTMPc**	.	.	.	.	.
0.19 (0.03, 1.17)	0.28 (0.02, 3.90)	0.52 (0.07, 3.83)	0.73 (0.04, 13.36)	**MPc**	.	0.73 (0.29, 1.80)	.	.
0.15 (0.03, 0.87)	0.23 (0.02, 2.98)	0.43 (0.06, 2.86)	0.60 (0.04, 10.29)	0.83 (0.27, 2.53)	**RMPc**	0.88 (0.46, 1.69)	.	.
0.14 (0.03, 0.67)	0.20 (0.02, 2.41)	0.37 (0.06, 2.24)	0.53 (0.03, 8.39)	0.73 (0.29, 1.80)	0.88 (0.46, 1.69)	**TMPc**	0.67 (0.11, 4.20)	0.56 (0.08, 4.09)
0.09 (0.01, 1.04)	0.13 (0.01, 2.96)	0.25 (0.02, 3.25)	0.35 (0.01, 9.77)	0.48 (0.06, 3.77)	0.59 (0.08, 4.14)	0.67 (0.11, 4.20)	**TCDc**	0.84 (0.14, 5.18)
0.08 (0.01, 0.98)	0.11 (0.00, 2.72)	0.21 (0.01, 3.05)	0.30 (0.01, 8.94)	0.41 (0.05, 3.62)	0.50 (0.06, 4.00)	0.56 (0.08, 4.09)	0.84 (0.14, 5.18)	**TDc**

Footnotes

c: continuous; **C**: cyclophosphamide; **CI**: confidence interval; **df**: degrees of freedom; **D**: dexamethasone; **M**: melphalan; **NMA**: network meta-analysis; **n.a.**: not applicable; **OS**: overall survival; **P**: prednisone; **R**: revlimid (lenalidomide); **T**: thalidomide; **V**: velcade (bortezomib)

9 Results of NMA for outcome infections.

League tables for the outcome infections. Direct and network estimates with 95% CIs are given. Treatments are ordered by P score (descending). The treatment with the highest probability of being the best is in the upper left corner.

Direct estimates are presented in the upper triangle; network estimates are presented in the lower triangle

Global approach to check inconsistency/heterogeneity: Q-statistics, I^2.

Infections-subnetwork 1

No. of studies: 12. No. of treatments: 11. No. of pairwise comparisons: 18. No. of designs: 9

Q_{total}= 7.67, df = 5, P = 0.18/ Q_{within}= 2.72, df=3, P = 0.44/ $Q_{between}$= 4.95, df = 2, P = 0.08; I^2 = 34.8%, Tau^2 = 0.0713

Treatment Effects:

MP	0.50 (0.26, 0.96)	.	0.57 (0.29, 1.11)	.	.	0.72 (0.29, 1.79)	.	.	0.48 (0.20, 1.12)	0.17 (0.04, 0.82)
0.60 (0.34, 1.07)	**TMP**	.	.	.	0.77 (0.43, 1.37)	.	0.53 (0.30, 0.94)	.	.	.
0.60 (0.23, 1.54)	1.00 (0.40, 2.48)	**RCPc**	.	.	.	0.58 (0.26, 1.33)	0.71 (0.30, 1.65)	.	.	.
0.57 (0.29, 1.11)	0.94 (0.39, 2.27)	0.94 (0.30, 3.00)	**TCD**	.	.	.	.	.	.	.
0.50 (0.19, 1.30)	0.83 (0.31, 2.26)	0.84 (0.28, 2.49)	0.89 (0.28, 2.84)	**MPc**	.	.	.	.	.	0.65 (0.39, 1.08)
0.50 (0.24, 1.07)	0.83 (0.47, 1.46)	0.83 (0.32, 2.17)	0.89 (0.32, 2.44)	1.00 (0.34, 2.92)	**RD**	.	0.69 (0.39, 1.21)	.	.	.
0.40 (0.21, 0.77)	0.66 (0.33, 1.34)	0.66 (0.30, 1.47)	0.70 (0.27, 1.80)	0.79 (0.37, 1.70)	0.79 (0.36, 1.76)	**RMPc**	1.22 (0.56, 2.65)	.	0.66 (0.30, 1.48)	0.91 (0.49, 1.67)
0.37 (0.19, 0.73)	0.61 (0.37, 1.03)	0.62 (0.27, 1.39)	0.65 (0.25, 1.70)	0.74 (0.28, 1.95)	0.74 (0.43, 1.28)	0.93 (0.49, 1.78)	**RDc**	0.95 (0.48, 1.88)	.	.
0.35 (0.13, 0.92)	0.58 (0.25, 1.38)	0.58 (0.20, 1.69)	0.62 (0.19, 2.01)	0.70 (0.21, 2.30)	0.70 (0.29, 1.68)	0.88 (0.34, 2.26)	0.95 (0.48, 1.88)	**VRDc**	.	.
0.34 (0.16, 0.75)	0.57 (0.23, 1.39)	0.57 (0.20, 1.64)	0.60 (0.21, 1.69)	0.68 (0.24, 1.94)	0.68 (0.25, 1.84)	0.86 (0.40, 1.82)	0.92 (0.37, 2.28)	0.98 (0.31, 3.04)	**RMP**	.
0.33 (0.15, 0.73)	0.54 (0.23, 1.29)	0.54 (0.21, 1.44)	0.58 (0.20, 1.65)	0.65 (0.39, 1.08)	0.65 (0.25, 1.68)	0.82 (0.46, 1.46)	0.88 (0.38, 2.04)	0.94 (0.32, 2.76)	0.96 (0.38, 2.41)	**TMPc**

Infections-subnetwork 2

No. of studies: 2. No. of treatments: 4. No. of pairwise comparisons: 4. No. of designs: 2

Q_{total}= 0, df = 0, P = n.a./ Q_{within}= 0, df = 0, P = n.a./ $Q_{between}$= 0, df = 0, P = n.a.; I^2 = n.a., Tau^2 = n.a.

Treatment Effects:

VTPc	.	0.11 (0.01, 0.86)	.
0.12 (0.02, 1.03)	**VTDc**	0.89 (0.55, 1.45)	0.75 (0.47, 1.19)
0.11 (0.01, 0.86)	0.89 (0.55, 1.45)	**VMPc**	0.84 (0.54, 1.30)
0.09 (0.01, 0.76)	0.75 (0.47, 1.19)	0.84 (0.54, 1.30)	**VDc**

Footnotes

c: continuous; **C**: cyclophosphamide; **CI**: confidence interval; **df**: degrees of freedom; **D**: dexamethasone; **M**: melphalan; **NMA**: network meta-analysis; **n.a.**: not applicable; **OS**: overall survival; **P**: prednisone; **R**: revlimid (lenalidomide); **T**: thalidomide; **V**: velcade (bortezomib)

10 Results of NMA for the outcome SAEs.

League tables for the outcome serious adverse events. Direct and network estimates with 95% CIs are given. Treatments are ordered by P-Score (descending). The treatment with the highest probability of being the best is in the upper left corner.

Direct estimates are presented in the upper triangle; network estimates are presented in the lower triangle

Global approach to check inconsistency/heterogeneity: Q-statistics, I^2.

SAE-subnetwork 1

No. of studies: 3. No. of treatments: 5. No. of pairwise comparisons: 5. No. of designs: 3

Q_{total}= 0, df = 0, P = n.a./ Q_{within}= 0, df = 0, P = n.a./ $Q_{between}$= 0, d f= 0, P = n.a.; I^2 = n.a., Tau^2 = n.a.
Treatment Effects:

TMP	0.88 (0.78, 0.98)	.	0.70 (0.64, 0.78)	.
0.88 (0.78, 0.98)	**RD**	0.98 (0.65, 1.49)	0.80 (0.73, 0.88)	.
0.86 (0.56, 1.32)	0.98 (0.65, 1.49)	**VRD**	.	.
0.70 (0.64, 0.78)	0.80 (0.73, 0.88)	0.82 (0.53, 1.26)	**RDc**	0.90 (0.75, 1.09)
0.63 (0.51, 0.78)	0.73 (0.59, 0.89)	0.74 (0.46, 1.18)	0.90 (0.75, 1.09)	**VRDc**

SAE-subnetwork 2

No. of studies: 2. No. of treatments: 4. No. of pairwise comparisons: 4. No. of designs: 2

Q_{total}= 0, df = 0, P = n.a./ Q_{within}= 0, df = 0, P = n.a./ $Q_{between}$= 0, df = 0, P = n.a.; I^2 = n.a., Tau^2 = n.a.
Treatment Effects:

VMPc	0.95 (0.78, 1.18)	0.87 (0.72, 1.07)	0.50 (0.31, 0.81)	VMPc
0.95 (0.78, 1.18)	**VDc**	0.92 (0.75, 1.11)	.	0.95 (0.78, 1.18)
0.87 (0.72, 1.07)	0.92 (0.75, 1.11)	**VTDc**	.	0.87 (0.72, 1.07)
0.50 (0.31, 0.81)	0.52 (0.31, 0.88)	0.57 (0.34, 0.96)	**VTPc**	0.50 (0.31, 0.81)

SAE-subnetwork 3

No. of studies: 3. No. of treatments: 5. No. of pairwise comparisons: 5. No. of designs: 3

Q_{total}= 0, df = 0, P = n.a./ Q_{within}= 0, df=0, P = n.a./ $Q_{between}$= 0, df = 0, P = n.a.; I^2 = n.a., Tau^2 = n.a.
Treatment Effects:

MP	0.90 (0.68, 1.19)	0.83 (0.63, 1.10)	0.78 (0.65, 0.94)	.
0.90 (0.68, 1.19)	**RMP**	0.93 (0.71, 1.21)	.	.
0.83 (0.63, 1.10)	0.93 (0.71, 1.21)	**RMPc**	.	0.79 (0.67, 0.93)
0.78 (0.65, 0.94)	0.87 (0.62, 1.22)	0.94 (0.68, 1.31)	**VMP**	.
0.66 (0.48, 0.91)	0.73 (0.54, 1.00)	0.79 (0.67, 0.93)	0.84 (0.58, 1.21)	**TMPc**

Footnotes

c: continuous; **C**: cyclophosphamide; **CI**: confidence interval; **df**: degrees of freedom; **D**: dexamethasone; **M**: melphalan; **NMA**: network meta-analysis; **n.a.**: not applicable; **OS**: overall survival; **P**: prednisone; **R**: revlimid (lenalidomide); **T**: thalidomide; **V**: velcade (bortezomib)

11 Results of NMA for the outcome withdrawals due to AEs.

League tables for the outcome withdrawals due to adverse events. Direct and network estimates with 95% CIs are given. Treatments are ordered by P score (descending). The treatment with the highest probability of being the best is in the upper left corner.

Direct estimates are presented in the upper triangle; network estimates are presented in the lower triangle

Global approach to check inconsistency/heterogeneity: Q-statistics, I^2.

Withdrawals due to AEs- Subnetwork 1

No. of studies: 14. No. of treatments: 15. No. of pairwise comparisons: 22. No. of designs: 12

Q_{total}= 5.37, df= 4, P = 0.25/ Q_{within}= 0.93, df = 2, P = 0.62/ $Q_{between}$= 4.44, df = 2, P = 0.11; I^2 = 25.5%, Tau^2 = 0.0392

Treatment Effects:

MPc	.	.	0.76 (0.16, 3.48)	.	.	.	.	0.29 (0.18, 0.48)	.	.	.	.	.	.
0.83 (0.37, 1.85)	**MP**	0.94 (0.55, 1.60)	.	.	0.38 (0.16, 0.91)	0.33 (0.14, 0.78)	.	0.25 (0.09, 0.71)	.	.	.	0.32 (0.17, 0.61)	.	.
0.78 (0.30, 2.04)	0.94 (0.55, 1.60)	**VMP**	.	0.82 (0.48, 1.39)	.	.	.	.	.	.	.	.	.	.
0.76 (0.16, 3.48)	0.91 (0.16, 5.10)	0.97 (0.16, 5.88)	**TDc**	.	.	.	.	.	.	.	.	.	.	.
0.64 (0.21, 1.92)	0.77 (0.36, 1.63)	0.82 (0.48, 1.39)	0.85 (0.13, 5.56)	**VTMPc**	.	.	.	.	.	.	.	.	.	.
0.39 (0.16, 0.97)	0.47 (0.22, 0.99)	0.50 (0.20, 1.25)	0.52 (0.09, 3.06)	0.61 (0.21, 1.76)	**RMP**	0.87 (0.45, 1.69)	.	.	.	.	.	.	.	.
0.37 (0.19, 0.72)	0.45 (0.25, 0.78)	0.48 (0.22, 1.03)	0.49 (0.09, 2.60)	0.58 (0.23, 1.49)	0.95 (0.50, 1.80)	**RMPc**	.	0.85 (0.52, 1.39)	0.59 (0.33, 1.05)	.	0.47 (0.27, 0.83)	.	.	.
0.30 (0.07, 1.38)	0.37 (0.09, 1.43)	0.39 (0.09, 1.69)	0.40 (0.05, 3.47)	0.48 (0.10, 2.27)	0.78 (0.17, 3.45)	0.82 (0.20, 3.28)	**TD**	.	.	0.76 (0.21, 2.75)	.	0.67 (0.19, 2.34)	.	.
0.29 (0.18, 0.48)	0.35 (0.19, 0.67)	0.38 (0.16, 0.86)	0.39 (0.08, 1.94)	0.46 (0.17, 1.23)	0.75 (0.35, 1.61)	0.79 (0.50, 1.24)	0.97 (0.23, 4.06)	**TMPc**	.	.	.	.	.	.
0.25 (0.11, 0.59)	0.30 (0.15, 0.61)	0.32 (0.13, 0.78)	0.33 (0.06, 1.92)	0.40 (0.14, 1.11)	0.65 (0.28, 1.47)	0.68 (0.39, 1.18)	0.83 (0.20, 3.41)	0.86 (0.43, 1.72)	**RCPc**	.	0.80 (0.48, 1.34)	.	.	.
0.23 (0.06, 0.84)	0.28 (0.09, 0.84)	0.30 (0.09, 1.01)	0.31 (0.04, 2.27)	0.36 (0.10, 1.38)	0.59 (0.17, 2.09)	0.62 (0.20, 1.94)	0.76 (0.21, 2.75)	0.79 (0.24, 2.59)	0.92 (0.29, 2.94)	**TCD**	.	0.88 (0.33, 2.31)	.	.
0.22 (0.10, 0.50)	0.27 (0.15, 0.48)	0.28 (0.13, 0.63)	0.29 (0.05, 1.65)	0.35 (0.13, 0.91)	0.57 (0.26, 1.22)	0.60 (0.36, 0.98)	0.73 (0.19, 2.77)	0.75 (0.40, 1.43)	0.88 (0.53, 1.45)	0.96 (0.33, 2.79)	**RDc**	0.76 (0.46, 1.26)	0.81 (0.49, 1.35)	0.42 (0.23, 0.77)
0.20 (0.09, 0.47)	0.24 (0.14, 0.42)	0.26 (0.12, 0.55)	0.27 (0.05, 1.54)	0.32 (0.13, 0.80)	0.52 (0.23, 1.16)	0.55 (0.30, 0.98)	0.67 (0.19, 2.34)	0.69 (0.34, 1.38)	0.80 (0.42, 1.53)	0.87 (0.33, 2.31)	0.92 (0.58, 1.45)	**TMP**	1.07 (0.65, 1.75)	.
0.20 (0.08, 0.49)	0.24 (0.12, 0.47)	0.25 (0.11, 0.60)	0.26 (0.04, 1.56)	0.31 (0.11, 0.85)	0.51 (0.21, 1.21)	0.54 (0.28, 1.03)	0.65 (0.17, 2.51)	0.68 (0.32, 1.45)	0.79 (0.40, 1.57)	0.86 (0.29, 2.53)	0.90 (0.55, 1.47)	0.98 (0.61, 1.59)	**RD**	.

0.09 (0.03, 0.25)	0.11 (0.05, 0.26)	0.12 (0.04, 0.32)	0.12 (0.02, 0.77)	0.15 (0.05, 0.45)	0.24 (0.09, 0.63)	0.25 (0.11, 0.55)	0.31 (0.07, 1.33)	0.32 (0.13, 0.76)	0.37 (0.17, 0.81)	0.40 (0.12, 1.37)	0.42 (0.23, 0.77)	0.46 (0.22, 0.98)	0.47 (0.21, 1.02)	**VRDc**
Withdrawals due to AEs- Subnetwork 2 No. of studies: 2. No. of treatments: 4. No. of pairwise comparisons: 4. No. of designs: 2 Q_{total}= 0, df = 0, P = n.a./ Q_{within}= 0, df=0, P = n.a./ $Q_{between}$= 0, df = 0, P = n.a.; I^2 = n.a., Tau^2 = n.a. Treatment Effects:														
VDc				0.89 (0.67, 1.18)				0.86 (0.65, 1.14)				.		
0.89 (0.67, 1.18)				VMPc				0.97 (0.74, 1.27)				0.68 (0.37, 1.25)		
0.86 (0.65, 1.14)				0.97 (0.74, 1.27)				VTDc				.		
0.60 (0.31, 1.18)				0.68 (0.37, 1.25)				0.70 (0.36, 1.37)				VTPc		

Footnotes

c: continuous; **C**: cyclophosphamide; **CI**: confidence interval; **df**: degrees of freedom; **D**: dexamethasone; **M**: melphalan; **NMA**: network meta-analysis; **n.a.**: not applicable; **OS**: overall survival; **P**: prednisone; **R**: revlimid (lenalidomide); **T**: thalidomide; **V**: velcade (bortezomib)

References to studies

Included studies

Bahlis 2017

[CRSSTD: 12308382]

Avet-Loiseau H, Hulin C, Benboubker L, Dimopoulos MA, Belch A, Reece D, et al. Impact of cytogenetics on outcomes of transplant-ineligible patients with newly diagnosed multiple myeloma treated with continuous lenalidomide plus low-dose dexamethasone in the first (MM-020) trial. In: Blood. Vol. 126. 2015:730. [CRSREF: 12308383]

Bahlis N, Corso A, Mugge LO, Shen ZX, Desjardins P, Stoppa AM, et al. Impact of response in patients (pts) with stem cell transplant (SCT)-ineligible newly diagnosed multiple myeloma (NDMM) treated with continuous lenalidomide + low-dose dexamethasone (Rd) in the first trial. In: Clinical Lymphoma, Myeloma and Leukemia. Vol. 15. 2015:e56. [CRSREF: 12308384]

Bahlis N, Corso A, Mugge Lo, Shen ZX, Desjardins P, Stoppa AM, et al. Assessing the benefit of continuous treatment in the first trial (MM-020): impact of response in patients with transplant-ineligible newly diagnosed multiple myeloma. In: Haematologica. Vol. 100. 2015:85-6. [CRSREF: 12308385]

* Bahlis NJ, Corso A, Mugge LO, Shen ZX, Desjardins P, Stoppa AM, et al. Benefit of continuous treatment for responders with newly diagnosed multiple myeloma in the randomized FIRST trial. Leukemia 2017; 31(11):2435-42. [CRSREF: 12308386]

Benboubker L, Dimopoulos MA, Dispenzieri A, Catalano J, Belch AR, Cavo M, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. New England Journal of Medicine 2014; 371(10):906-17. [CRSREF: 12308387]

Delforge M, Minuk L, Eisenmann JC, Arnulf B, Canepa L, Fragasso A, et al. Health-related quality of life (HRQOL) in patients (pts) with newly diagnosed multiple myeloma (NDMM): the first trial. In: Haematologica. Vol. 99. 2014:109-10. [CRSREF: 12308388]

Delforge M, Minuk L, Eisenmann JC, Arnulf B, Canepa L, Fragasso A, et al. Health-related quality-of-life in patients with newly diagnosed multiple myeloma in the FIRST trial: lenalidomide plus low-dose dexamethasone versus melphalan, prednisone, thalidomide. Haematologica 2015;100(6):826-33. [CRSREF: 12308389]

Dimopoulos M, Cheung M, Roussel M, Liu T, Gamberi B, Kolb B, et al. Impact of renal impairment on outcomes after treatment with lenalidomide and low-dose dexamethasone in patients with newly diagnosed multiple myeloma: first trial results. In: Haematologica. Vol. 100. 2015:83-4. [CRSREF: 12308390]

Dimopoulos MA, Cheung MC, Roussel M, Liu T, Gamberi B, Kolb B, et al. Impact of renal impairment on outcomes with lenalidomide and dexamethasone treatment in the FIRST trial, a randomized, open-label phase 3 trial in transplant-ineligible patients with multiple myeloma. Haematologica 2016;101(3):363-70. [CRSREF: 12308391]

Facon T, Dimopoulos MA, Dispenzieri A, Catalano JV, Belch A, Cavo M, et al. Final analysis of overall survival from the first trial. In: Blood. Vol. 128. 2016. [CRSREF: 12308392]

Facon T, Dimopoulos MA, Dispenzieri A, Catalano JV, Belch A, Cavo M, et al. Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. Blood 2018;131(3):301-10. [CRSREF: 12308393]

Facon T, Dimopoulos MA, Dispenzieri A, Catalano JV, Belch A, Hulin C, et al. Lenalidomide+low-dose

dexamethasone (RD) VS. melphalanprednisone-thalidomide (MPT) in newly diagnosed multiple myeloma (NDMM) patients (PTS): the first trial. In: Haematologica. Vol. 99. 2014:220-1. [CRSREF: 12308394]

Facon T, Dimopoulos MA, Hulin C, Benboubker L, Belch A, Ludwig H, et al. Updated overall survival (OS) analysis of the FIRST study: lenalidomide plus low-dose dexamethasone (Rd) continuous vs melphalan, prednisone, and thalidomide (MPT) in patients (Pts) With newly diagnosed multiple myeloma (NDMM). In: Clinical Lymphoma, Myeloma and Leukemia. Vol. 15. 2015:e134. [CRSREF: 12308395]

Facon T, Dimopoulos MA, Hulin C, Benboubker L, Belch A, Ludwig H, et al. Updated overall survival analysis of the first study: continuous lenalidomide plus low-dose dexamethasone vs melphalan, prednisone, and thalidomide in patients with newly diagnosed multiple myeloma. In: Haematologica. Vol. 100. 2015:3. [CRSREF: 12308396]

Facon T, Hulin C, Dimopoulos MA, Belch A, Meuleman N, Mohty M, et al. A frailty scale predicts outcomes in transplant-ineligible patients with newly diagnosed multiple myeloma treated with continuous lenalidomide plus low-dose dexamethasone in the first (MM-020) trial. In: Haematologica. Vol. 101. 2016:258-9. [CRSREF: 12308397]

Facon T, Hulin C, Dimopoulos MA, Belch A, Meuleman N, Mohty M, et al. A frailty scale predicts outcomes of patients with newly diagnosed multiple myeloma who are ineligible for transplant treated with continuous lenalidomide plus low-dose dexamethasone on the first trial. In: Blood. Vol. 126. 2015:4239. [CRSREF: 12308398]

Facon T, Hulin C, Dimopoulos MA, Belch A, Reece DE, Catalano JV, et al. FIRST study: updated overall survival (OS) in stem cell transplant (SCT)-ineligible newly diagnosed multiple myeloma (NDMM) patients (pts) treated with continuous lenalidomide plus low-dose dexamethasone (Rd) vs melphalan, prednisone, and thalidomide (MPT). In: Journal of Clinical Oncology. Vol. 33. 2015. [CRSREF: 12308399]

Facon T. Continuous therapy for elderly newly diagnosed multiple myeloma. In: Clinical Lymphoma, Myeloma and Leukemia. Vol. 15. 2015:e28. [CRSREF: 12308400]

Hulin C, Belch A, Shustik C, Petrucci MT, Dührsen U, Lu J, et al. Updated outcomes and impact of age with lenalidomide and low-dose dexamethasone or melphalan, prednisone, and thalidomide in the randomized, phase III FIRST trial. Journal of Clinical Oncology 2016;34(30):3609-17. [CRSREF: 12308401]

Hulin C, Shustik C, Belch A, Petrucci M, Duhrsen U, Lu J, et al. Effect of age on efficacy and safety outcomes in patients with newly diagnosed multiple myeloma receiving lenalidomide and low-dose dexamethasone (RD): the first trial. In: Haematologica. Vol. 100. 2015:152-3. [CRSREF: 12308402]

Hulin C, Shustik C, Belch A, Petrucci MT, Duhrsen U, Lu J, et al. Continuous treatment with lenalidomide and low-dose dexamethasone for patients with transplant-ineligible newly diagnosed multiple myeloma in the first trial: impact of age. In: Clinical Lymphoma, Myeloma and Leukemia. Vol. 15. 2015:e130-1. [CRSREF: 12308403]

Lu J, Lee JH, Huang SY, Qiu L, Lee JJ, Liu T, et al. Continuous treatment with lenalidomide and low-dose dexamethasone in transplant-ineligible patients with newly diagnosed multiple myeloma in Asia: subanalysis of the first trial. In: Blood. Vol. 126. 2015:4240. [CRSREF: 12308404]

Lu J, Lee JH, Huang SY, Qiu L, Lee JJ, Liu T, et al. The first trial: analysis of the Asian subgroup of transplant-ineligible patients with newly diagnosed multiple myeloma treated with continuous lenalidomide and low-dose dexamethasone. In: Haematologica. Vol. 101. 2016:548-9. [CRSREF: 12308405]

Weisel K, Vogl D, Corso A, Delforge M, Song K, Dimopoulos MA, et al. Health resource utilization with continuous lenalidomide treatment (TX) in elderly patients with newly diagnosed multiple myeloma (NDMM). In: Haematologica. Vol. 100. 2015:24-5. [CRSREF: 12308406]

Beksac 2011

[CRSSTD: 12308407]

Beksac M, Haznedar R, Firatli-Tuglular T, Ozdogu H, Aydogdu I, Konuk N, et al. Addition of thalidomide to oral melphalan/prednisone in patients with multiple myeloma not eligible for transplantation: results of a randomized trial from the Turkish Myeloma Study Group. European Journal of Haematology 2011;86(1):16-22. [CRSREF: 12308408]

Durie 2017

[CRSSTD: 12308409]

Durie B, Hoering A, Rajkumar SV, Abidi MH, Epstein J, Kahanic SP, et al. Bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (PTS) with previously untreated multiple myeloma without an intent for immediate Autologous Stem Cell Transplant (ASCT): results of the randomized phase III trial SWOG S0777. In: Blood. Vol. 126. 2015:25. [CRSREF: 12308410]

* Durie BG, Hoering A Abidi MH, Rajkumar SV, Epstein J, Kahanic SP, 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;389:519-27. [CRSREF: 12308411]

Facon 2007

[CRSSTD: 12308412]

Facon T, Mary JY, Hulin C, Benboubker L, Attal M, Harousseau JL, et al. Randomized clinical trial comparing melphalan-prednisone (MP), MP-thalidomide (MP-THAL) and high-dose therapy using melphalan 100 MG/Mý (MEL100) for newly diagnosed myeloma patients Aged 65-75 years. Interim analysis of the IFM 99-06 Trial on 350 patients. In: Blood. Vol. 104. 2004:63. [CRSREF: 12308413]

* Facon T, Mary JY, Hulin C, Benboubker L, Attal M, Pegourie B, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet 2007;370(9594):1209-18. [CRSREF: 12308414]

Hulin 2009

[CRSSTD: 12308415]

* Hulin C, Facon T, Rodon P, Pegourie B, Benboubker L, Doyen C, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. Journal of Clinical Oncology 2009;27(22):3664-70. [CRSREF: 12308416]

Hulin C, Facon T, Rodon P, Pegourie B, Benboubker L, Doyen C, et al. Melphalan-prednisone-thalidomide (MP-T) demonstrates a significant survival advantage in elderly patients >=75 years with multiple myeloma compared with melphalan-pPrednisone (MP) in a randomized, double-blind, placebo-controlled trial, IFM 01/01. In: Blood. Vol. 110. 2007. [CRSREF: 12308417]

Hulin C, Virion J, Leleu X, Rodon P, Pegourie B, Benboubker L, et al. Comparison of melphalan-prednisone-thalidomide (MP-T) to melphalan-prednisone (MP) in patients 75 years of age or older with untreated multiple myeloma (MM). Preliminary results of the randomized, double-blind, placebo controlled IFM 01-01 trial. In: Journal of Clinical Oncology. Vol. 25. 2007:441. [CRSREF: 12308418]

Hungria 2016

[CRSSTD: 12308419]

Anonymous. Iberoamerican protocol with thalidomide in patients with symptomatic newly diagnosed multiple myeloma over 65 years. available at: https://clinicaltrials.gov/show/nct01532856 (Accessed 06 May 2019). [CRSREF: 12308420]

Crusoe E, Maiolino A, Bittencourt R, Fantl DB, MacIel J, Sampaio M, et al. A phase III study comparing thalidomide/cyclophosphamide/dexa vs thalidomide/dexa vs thalidomide/melphalan/prednisone in de novo multiple myeloma patients not eligible for ASCT. In: Blood. Vol. 118. 2011. [CRSREF: 12308421]

Hungria V, Crusoe E, Maiolino A, Bittencourt R, Fantl D, Quero A, et al. A phase III study comparing thalidomide/cyclophosphamide/ dexa vs thalidomide/dexa vs thalidomide/melphalan/prednisone in de novo multiple myeloma patients not eligible for ASCT: preliminary analysis. In: Haematologica. Vol. 92. 2010:148. [CRSREF: 12308422]

* Hungria VT, Crusoe EQ, Maiolino A, Bittencourt R, Fantl D, Maciel JF, et al. Phase 3 trial of three thalidomide-containing regimens in patients with newly diagnosed multiple myeloma not transplant-eligible. Annals of Hematology 2016;95(2):271-8. [CRSREF: 12308423]

Jacobus 2016

[CRSSTD: 12308424]

Fonseca R, Rajkumar SV. Consolidation therapy with bortezomib/lenalidomide/ dexamethasone versus bortezomib/dexamethasone after a dexamethasone-based induction regimen in patients with multiple myeloma: a randomized phase III trial. Clinical Lymphoma and Myeloma 2008;8(5):315-7. [CRSREF: 12308425]

* Jacobus SJ, Rajkumar SV, Weiss M, Stewart AK, Stadtmauer EA, Callander NS, et al. Randomized phase III trial of consolidation therapy with bortezomib-lenalidomide-Dexamethasone (VRd) vs bortezomib-dexamethasone (Vd) for patients with multiple myeloma who have completed a dexamethasone based induction regimen. Blood Cancer Journal 2016;6(7):e448. [CRSREF: 12308426]

Katsuoka 2013

[CRSSTD: 12308427]

Katsuoka Y, Kato Y, Omoto E, Sasaki O, Kimura H, Meguro K, et al. Phase ii trial of bortezomib based regimen for transplant-ineligible multiple myeloma-tomato study. In: Clinical Lymphoma, Myeloma and Leukemia. Vol. 13. 2013:S148. [CRSREF: 12308428]

Kim 2007

[CRSSTD: 12308429]

Kim YK, Lee JJ, Sohn SK, Shin HJ, Lee SR, Shim HJ, et al. Efficacy and safety of thalidomide and dexamethasone combination with or without cyclophosphamide in patients with newly diagnosed multiple myeloma. In: Haematologica. Vol. 92. 2007:411-2. [CRSREF: 12308430]

Ludwig 2009

[CRSSTD: 12308431]

Ludwig H, Drach J, Tothova E, Gisslinger H, Linkesch W, Jaksic B, et al. Thalidomide-dexamethasone (TD) versus melphalan-prednisolone (MP) as first line treatment in elderly patients with multiple myeloma (MM): an interim analysis. In: Onkologie. Vol. 28. 2005:14-5. [CRSREF: 12308432]

* Ludwig H, Hajek R, Tóthová E, Drach J, Adam Z, Labar B, et al. Thalidomide-dexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma. Blood 2009;113(15):3435-42. [CRSREF: 12308433]

Ludwig H, Tothova E, Hajek R, Drach J, Adam Z, Labar B, et al. Thalidomide-dexamethasone vs. melphalan-prednisone as first line treatment and thalidomide-interferon vs. interferon maintenance therapy in elderly patients with multiple myeloma. In: Blood. Vol. 110. 2007:163a. [CRSREF: 12308434]

Ludwig H, Tothova E, Hajek R, Drach J, Labar B, Egyed M, et al. Thalidomide-dexamethasone versus melphalan-prednisolone as first line treatment in elderly patients with multiple myeloma: second interim analysis. In: Haematologica. Vol. 92. 2007:166. [CRSREF: 12308435]

Ludwig HL, Drach J, Tothova E, Gisslinger H, Linkesch W, Jaksic B, et al. Thalidomide-dexamethasone versus melphalan-prednisolone as first line treatment in elderly patients with multiple myeloma: an interim analysis. In: European Hematology Association. 2005. [CRSREF: 12308436]

Ludwig HL, Drach J, Tothova E, Gisslinger H, Linkesch W, Jaksic B, et al. Thalidomide-dexamethasone versus melphalan-prednisolone as first line treatment in elderly patients with multiple myeloma: an interim analysis. In: Haematologica. Vol. 90. 2005:158. [CRSREF: 12308437]

Magarotto 2016

[CRSSTD: 12308438]

Bringhen S, Offidani M, Musto P, Liberati AM, Benevolo G, Cascavilla N, et al. Long term outcome of lenalidomide-dexamethasone (RD) vs melphalan-lenalidomide-prednisone (MPR) vs cyclophosphamide-prednisone-lenalidomide (CPR) as induction followed by. In: Blood. Vol. 130. 2017. [CRSREF: 12308439]

Gay F, Bringhen S, Offidani M, Liberati A, Cellini C, Magarotto V, et al. Efficacy and safety of 3 lenalidomide-based combinations in elderly newly diagnosed multiple myeloma patients: results from the phase 3 community based emn01 trial. In: Haematologica. Vol. 98. 2013:95-6. [CRSREF: 12308440]

Gentile M, Magarotto V, Offidani M, Musto P, Bringhen S, Teresa Petrucci M, et al. Lenalidomide and low-dose dexamethasone (Rd) versus bortezomib, melphalan, prednisone (VMP) in elderly newly diagnosed multiple myeloma patients: A comparison of two prospective trials. American Journal of Hematology 2017;92(3):244-50. [CRSREF: 12308441]

Larocca A, Bringhen S, Petrucci MT, Offidani M, Benevolo G, Galli M, et al. Early death in elderly patients with newly diagnosed multiple myeloma treated with new drugs: a pooled analysis of two randomized phase 3 trials. In: Haematologica. Vol. 100. 2015:51-2. [CRSREF: 12308442]

Larocca A, Bringhen S, Petrucci MT, Offidani M, Paoli L, Pietrantuono G, et al. Early mortality in elderly newly diagnosed multiple myeloma patients treated with novel agents: a pooled analysis of two large randomized phase III trials. In: Haematologica. Vol. 100. 2015:81-2. [CRSREF: 12308443]

Larocca A, Magarotto V, Offidani M, Pour L, Liberati AM, Benevolo G, et al. Lenalidomide-dexamethasone vs melphalan-prednisone-lenalidomide vs cyclophosphamide-prednisone-lenalidomide in ndmm. In: Clinical Lymphoma, Myeloma and Leukemia. Vol. 13. 2013:S113-s114. [CRSREF: 12308444]

Larocca A, Offidani M, Ciccone G, Guglielmelli T, Cangialosi C, Salvini M, et al. Impact of bortezomib-or lenalidomide-based induction treatment on high risk cytogenetic transplant-ineligible patients with newly diagnosed multiple myeloma enrolled in the gimema-MM-03-05 and EMN01 trials. In: Blood. Vol. 130. 2017. [CRSREF: 12308445]

Magarotto V, Bringhen S, Hajek R, Musto P, Goldaniga MC, Ledda A, et al. Lenalidomide-dexamethsone (RD) vs melphalan-lenalidomide-prednisone (MPR) vs cyclophosphamide-prednisone-lenalidomide (CPR) in elderly community-based newly diagnosed myeloma patients. In: Haematologica. Vol. 99. 2014:103-4. [CRSREF: 12308446]

Magarotto V, Bringhen S, Musto P, Benevolo G, Ledda A, Genuardi M, et al. Feasibility of lenalidomide maintenance therapy in frail patients with multiple myeloma: subgroup analysis of a randomized phase 3 trial. In: Haematologica. Vol. 100. 2015:100-1. [CRSREF: 12308447]

Magarotto V, Bringhen S, Musto P, Benevolo G, Ledda A, Genuardi M, et al. Lenalidomide-dexamethasone or melphalan-lenalidomide-prednisone (MPR) or cyclophosphamide-prednisone-lenalidomide (CPR) for initial treatment of real life elderly patients with newly diagnosed multiple myeloma. In: Clinical Lymphoma, Myeloma and Leukemia. Vol. 15. 2015:e69. [CRSREF: 12308448]

* Magarotto V, Bringhen S, Offidani M, Benevolo G, Patriarca F, Mina R, et al. Triplet vs doublet lenalidomide-containing regimens for the treatment of elderly patients with newly diagnosed multiple myeloma. Blood 2016;

127(9):1102-8. [CRSREF: 12308449]

Magarotto V, Bringhen S, Offidani M, Benevolo G, Patriarca F, Palladino C, et al. Maintenance therapy with lenalidomide in elderly patients with newly diagnosed multiple myeloma: a Post-HOC analysis of the EMN01 trial. In: Haematologica. Vol. 100. 2015:82. [CRSREF: 12308450]

Magarotto V, Bringhen S, Offidani M, Liberati AM, Benevolo G, Patriarca F, et al. Lenalidomide plus dexamethasone (RD) vs melphalan-lenalidomide-prednisone (MPR) or cyclophosphamide-prednisone-lenalidomide (CPR) in elderly comunity-based newly diagnosed multiple myeloma patients: efficacy and safety results from a phase 3 trial. In: Haematologica. Vol. 98. 2013:50. [CRSREF: 12308451]

Mateos 2014

[CRSSTD: 12308452]

Mateos MV, Oriol A, Martínez-López J, Gutiérrez N, Teruel AI, López de la Guía A, et al. Maintenance therapy with bortezomib plus thalidomide or bortezomib plus prednisone in elderly multiple myeloma patients included in the GEM2005MAS65 trial. In: Blood. Vol. 120. 2012:2581-8. [CRSREF: 12308453]

Mateos MV, Oriol A, Martínez-López J, Gutiérrez N, Teruel AI, Paz R, et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. Lancet Oncology 2010;11(10):934-41. [CRSREF: 12308454]

* Mateos MV, Oriol A, Martínez-López J, Teruel AI, López de la Guía A, 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. [CRSREF: 12308455]

Mateos MV, Oriol A, Martinez-Lopez J, Gutierrez N, Teruel AI, de Paz R, et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. Lancet Oncology 2010;11(10):934-41. [CRSREF: 12308456]

Mateos MV, Oriol A, Martinez-Lopez J, Teruel AI, Lopez de la Guia A, Blanchard MJ, et al. Do we still need the alkylators as part of the up front treatment of elderly newly diagnosed multiple myeloma patients? Updated follow-up of GEM2005MAS65 Spanish trial comparing VMP vs VTP as induction. In: Haematologica. Vol. 99. 2014:221. [CRSREF: 12308457]

Mookerjee 2017

[CRSSTD: 12308458]

Mookerjee A, Gupta R, Jasrotia S, Sahoo R, Kumar R, Thulkar 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. In: Blood. Vol. 130. 2017. [CRSREF: 12308459]

Morgan 2011

[CRSSTD: 12308460]

Morgan GJ, Davies FE, Gregory WM, Russell NH, Bell SE, Szubert AJ, et al. Cyclophosphamide, thalidomide, and dexamethasone (CTD) as initial therapy for patients with multiple myeloma unsuitable for autologous transplantation. Blood 2011;118(5):1231-8. [CRSREF: 12308461]

Niesvizky 2015

[CRSSTD: 12308462]

Moon MA. Triple therapy added toxicity without survival benefit in multiple myeloma. Journal of Clinical Oncology 2015;11(7):3-4. [CRSREF: 12308463]

Niesvizky R, Flinn I, Rifkin R, Charu V, Essell J, Gaffar Y, et al. Efficacy and safety of three bortezomib-based induction regimens followed by weekly bortezomib maintenance therapy in newly diagnosed multiple myeloma (MM) patients (PTS) ineligible for transplant: results of the phase 3B upfront study. In: Haematologica. Vol. 96. 2011:S98. [CRSREF: 12308464]

Niesvizky R, Flinn I, Rifkin R, Gabrail N, Charu V, Clowney B, et al. Patient-reported quality of life (QOL) in previously untreated, elderly multiple myeloma (MM) patients treated with bortezomib-based regimens: results from the phase 3B upfront study. In: Haematologica. Vol. 96. 2011:123-4. [CRSREF: 12308465]

* Niesvizky R, Flinn IW, Rifkin R, Gabrail N, Charu V, Clowney B, et al. Community-based phase IIIB trial of three UPFRONT bortezomib-based myeloma regimens. Journal of Clinical Oncology 2015;33(33):3921-9. [CRSREF: 12308466]

Niesvizky R, Flinn IW, Rifkin R, Gabrail N, Charu V, Clowney B. Patient-reported quality of life (QOL) in elderly, newly diagnosed multiple myeloma (MM) patients receiving bortezomib-based combinations: results from all randomized patients in the community-based, phase 3b UPFRONT study. In: Blood. Vol. 118. 2011. [CRSREF: 12308467]

Niesvizky R, Flinn IW, Rifkin RM, Gabrail N, Charu V, Gaffar Y, et al. Impact of baseline characteristics on efficacy

and safety after bortezomib-based induction and maintenance in newly diagnosed multiple myeloma (MM) patients ineligible for transplant in the phase IIIb UPFRONT study. In: Journal of Clinical Oncology. Vol. 29. 2011. [CRSREF: 12308468]

Niesvizky R, Flinn IW, Rifkin RM, Gabrail NY, Charu V, Clowney B, et al. Phase 3b UPFRONT study: safety and efficacy of weekly bortezomib maintenance therapy after bortezomib-based induction regimens in elderly, newly diagnosed multiple myeloma patients. In: Blood. Vol. 116. 2010. [CRSREF: 12308469]

Niesvizky R, Reeves J, Flinn I, Gabrail N, Rifkin R, Charu V, et al. Phase 3b upfront study: interim results from a community based prospective randomized trial evaluating three bortezomib-based regimens in elderly, newly diagnosed multiple myeloma patients. In: Haematologica. Vol. 92. 2010:144. [CRSREF: 12308470]

Palumbo 2006

[CRSSTD: 12308471]

Palumbo A, Bringhen S, Caravita T, Callea V, Zambello R, Pregno P, et al. A prospective randomized controlled trial of oral melphalan, prednisone, thalidomide versus oral melphalan, prednisone in elderly newly diagnosed myeloma patients. In: Haematologica. Vol. 91. 2006. [CRSREF: 12308472]

Palumbo A, Bringhen S, Caravita T, Falcone A, Callea V, Cangialosi C, et al. Oral melphalan, prednisone, thalidomide versus oral melphalan, prednisone in elderly newly diagnosed myeloma patients. In: Haematologica. Vol. 92. 2007:147. [CRSREF: 12308473]

* Palumbo A, Bringhen S, Caravita T, Merla E, Capparella V, Callea V, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet 2006;367(9513):825-31. [CRSREF: 12308474]

Palumbo A, Bringhen S, Liberati AM, Caravita T, Falcone A, Callea V, et al. Oral melphalan, prednisone and thalidomide in elderly multiple myeloma patients: updated results of a randomized controlled trial. In: Haematologica. Vol. 93. 2008:363-5. [CRSREF: 12308475]

Palumbo A, Bringhen S, Liberati AM, Caravita T, Falcone A, Callea V, et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. In: Blood. Vol. 112. 2008:3107-14. [CRSREF: 12308476]

Palumbo 2012

[CRSSTD: 12308477]

Cavo M, Dimopoulos M, Palumbo A, Weisel K, Delforge M, Blade J, et al. Impact of renal impairment on the efficacy and safety of melphalan-prednisone-lenalidomide (LEN) induction followed by LEN maintenance in newly diagnosed multiple myeloma: mM-015 post-hoc analysis. In: Haematologica. Vol. 98. 2013:330-1. [CRSREF: 12308478]

Dimopoulos MA, Delforge M, Hájek R, Kropff M, Petrucci MT, Lewis P, et al. Lenalidomide, melphalan, and prednisone, followed by lenalidomide maintenance, improves health-related quality of life in newly diagnosed multiple myeloma patients aged 65 years or older: results of a randomized phase III trial. Haematologica 2013; 98(5):784-8. [CRSREF: 12308479]

Dimopoulos MA, Palumbo A, Hajek R, Kropff M, Petrucci MT, Lewis P, et al. Factors that influence health-related quality of life in newly diagnosed patients with multiple myeloma aged ? 65 years treated with melphalan, prednisone and lenalidomide followed by lenalidomide maintenance: results of a randomized trial. Leukemia and Lymphoma 2014;55(7):1489-97. [CRSREF: 12308480]

Gay F, Cavallo F, Raimondo F, Hardan I, Nagler A, Petrucci MT, et al. Impact of continuous treatment vs fixed duration of therapy in newly diagnosed myeloma patients: pFS1, PFS2, OS endpoints. In: Haematologica. Vol. 99. 2014:519. [CRSREF: 12308481]

Palumbo A, Adam Z, Kropff M, Foa R, Catalano J, Gisslinger H. A phase 3 study evaluating the efficacy and safety of lenalidomide (len) combined with melphalan and prednisone followed by continuous lenalidomide maintenance (MPR-R) in patients (pts) = 65 Years (yrs) with newly diagnosed multiple myeloma (NDMM): updated results for pts aged 65-75 yrs enrolled in MM-015. In: Blood. Vol. 118. 2011. [CRSREF: 12308482]

Palumbo A, Delforge M, Catalano J, Hajek R, Kropff M, Petrucci MT, et al. A phase 3 study evaluating the efficacy and safety of lenalidomide combined with melphalan and prednisone in patients 65 years with newly diagnosed multiple myeloma (NDMM): continuous use of lenalidomide vs fixed-duration regimens. In: Blood. Vol. 116. 2010. [CRSREF: 12308483]

Palumbo A, Dimopoulos M, Delforge M, Hajek R, Kropff M, Petrucci M, et al. A phase 3 study to determine the efficacy and safety of lenalidomide combined with melphalan and prednisone in patients = 65 years with newly diagnosed multiple myeloma (NDMM). In: Haematologica. Vol. 92. 2010:234-5. [CRSREF: 12308484]

Palumbo A, Gay F, Cavallo F, Di Raimondo F, Larocca A, Hardan I, et al. Continuous therapy versus fixed duration of therapy in patients with newly diagnosed multiple myeloma. Journal of Clinical Oncology 2015; 33(30):3459-66. [CRSREF: 12308485]

* Palumbo A, Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J, et al. Continuous lenalidomide treatment for

newly diagnosed multiple myeloma.. New England Journal of Medicine 2012;366(19):1759-69. [CRSREF: 12308486]

Palumbo A, Kropff M, Hajek R, Delforge M, Catalano J, Petrucci MT, et al. Incidence of second primary malignancy (SPM) in melphalan-prednisone-lenalidomide combination followed by lenalidomide maintenance (MPR-R) in newly diagnosed multiple myeloma (MM) patients=65 years. In: Haematologica. Vol. 96. 2011:218. [CRSREF: 12308487]

Palumbo 2014

[CRSSTD: 12308488]

Bringhen S, Larocca A, Rossi D, Cavalli M, Genuardi M, Ria R, et al. Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. Blood 2010;116(23):4745-53. [CRSREF: 12308489]

Bringhen S, Larocca A, Rossi D, Romano A, Genuardi M, Ria R, et al. Efficacy and safety of once weekly bortezomib in multiple myeloma patients. In: Blood. Vol. 116. 2010. [CRSREF: 12308490]

Bringhen S, Magarotto V, Rossi D, Ria R, Offidani M, Patriarca F, et al. Bortezomib, melphalan, prednisone and thalidomide followed by maintenance with bortezomib and thalidomide (VMPT-VT) vs bortezomib, melphalan, prednisone (VMP) alone as first line treatment of multiple myeloma: updated follow-up and impact of prognostic factors. In: Haematologica. Vol. 96. 2011:67-8. [CRSREF: 12308491]

Corso A, Raimondo F, Mangiacavalli S, Ria R, Offidani M, Pascutto C, et al. Bortezomib-based therapy overcomes the prognostic role of ISS score in multiple myeloma patients not eligible for transplant. In: Haematologica. Vol. 96. 2011:128. [CRSREF: 12308492]

Gay F, Cavallo F, Raimondo F, Hardan I, Nagler A, Petrucci MT, et al. Impact of continuous treatment vs fixed duration of therapy in newly diagnosed myeloma patients: pFS1, PFS2, OS endpoints. In: Haematologica. Vol. 99. 2014:519. [CRSREF: 12308493]

Gay F, Larocca A, Petrucci MT, Musto P, Liberati AM, Callea V, et al. Achievement of complete remission is a strong prognostic factor in 895 elderly myeloma patients treated with melphalan-prednisone based-regimens: results of 3 multicenter Italian trials. In: Haematologica. Vol. 92. 2010:236. [CRSREF: 12308494]

Gentile M, Magarotto V, Offidani M, Musto P, Bringhen S, Petrucci MT, et al. Lenalidomide and low-dose dexamethasone (Rd) versus bortezomib, melphalan, prednisone (VMP) in elderly newly diagnosed multiple myeloma patients: A comparison of two prospective trials. American Journal of Hematology 2017;92(3):244-50. [CRSREF: 12308495]

Genuardi M, Bringhen S, Rossi D, Spadano A, Pisani F, Nozza A, et al. Evaluation of the efficacy and safety of weekly infusion bortezomib in elderly patients with newly diagnosed multiple myeloma. In: Haematologica. Vol. 95. 2010:S104-s105. [CRSREF: 12308496]

Larocca A, Bringhen S, Petrucci MT, Offidani M, Paoli L, Pietrantuono G, et al. Early mortality in elderly newly diagnosed multiple myeloma patients treated with novel agents: a pooled analysis of two large randomized phase III trials. In: Haematologica. Vol. 100. 2015:81-2. [CRSREF: 12308497]

Larocca A, Bringhen S, Petrucci Mt, Offidani M, Benevolo G, Galli M, et al. Early death in elderly patients with newly diagnosed multiple myeloma treated with new drugs: a pooled analysis of two randomized phase 3 trials. In: Haematologica. Vol. 100. 2015:51-2. [CRSREF: 12308498]

Larocca A, Offidani M, Ciccone G, Guglielmelli T, Cangialosi C, Salvini M, et al. Impact of bortezomib-or lenalidomide-based induction treatment on high risk cytogenetic transplant-ineligible patients with newly diagnosed multiple myeloma enrolled in the gimema-MM-03-05 and EMN01 trials. In: Blood. Vol. 130. 2017. [CRSREF: 12308499]

Morabito F, Gentile M, Mazzone C, Rossi D, Di Raimondo F, Bringhen S, et al. Safety and efficacy of bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide maintenance (VMPT-VT) versus bortezomib-melphalan-prednisone (VMP) in untreated multiple myeloma patients with renal impairment. Blood 2011;118(22):5759-66. [CRSREF: 12308500]

Morabito F, Gentile M, Mazzone C, Rossi D, Ria R, Offidani M, et al. VMPT (bortezomib, melphalan, prednisone and thalidomide) followed by maintenance with bortezomib-thalidomide (VT) is active and well tolerated in newly diagnosed patients with multiple myeloma (MM) with moderate renal impairment (RI) ineligible for autologous stem cell transplantation: results from a cohort analysis of a phase III randomized controlled trial. In: Haematologica. Vol. 96. 2011:S98-s99. [CRSREF: 12308501]

Palumbo A, Bringhen S, Cavalli M, Ria R, Offidani M, Patriarca F, et al. Bortezomib, melphalan, prednisone and thalidomide followed by maintenance with bortezomib and thalidomide (VMPT-VT) for initial treatment of elderly multiple myeloma patients: updated follow-up and impact of prognostic factors. In: Blood. Vol. 116. 2010. [CRSREF: 12308502]

* Palumbo A, Bringhen S, Larocca A, Rossi D, Di Raimondo F, Magarotto V, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: updated follow-up and improved survival. Journal of Clinical Oncology 2014;32(7):634-40. [CRSREF: 12308503]

Palumbo A, Bringhen S, Rossi D, Cavalli M, Larocca A, Ria R, et al. Bortezomib-melphalan-prednisone-thalidomide followed by continuous bortezomib-thalidomide for initial therapy of elderly multiple myeloma patients: a prospective randomized trial. Journal of Clinical Oncology 2010;95:S101-s102. [CRSREF: 12308504]

Palumbo A, Bringhen S, Rossi D, Cavalli M, Larocca A, Ria R, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. Journal of Clinical Oncology 2010;28(34):5101-9. [CRSREF: 12308505]

Palumbo A, Bringhen S, Rossi D, Cavalli M, Larocca A, Ria R, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. Journal of Clinical Oncology 2010;28(34):5101-9. [CRSREF: 12308506]

Palumbo A, Bringhen S, Rossi D, Cavalli M, Ria R, Gentilini S, et al. Overall survival benefit for bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide (VMPT-VT) versus bortezomib-melphalan-prednisone (VMP) in newly diagnosed multiple myeloma patients. In: Blood. Vol. 120. 2012. [CRSREF: 12308507]

Palumbo A, Bringhen S, Rossi D, Cavalli M, Ria R, Offidani M, et al. A prospective randomized trial of bortezomib-melphalan-prednisone-thalidomide followed by continuous bortezomib-thalidomide for initial therapy of multiple myeloma: effect of age and co-morbidities. In: Haematologica. Vol. 92. 2010:235-6. [CRSREF: 12308508]

Palumbo A, Bringhen S, Rossi D, Magarotto V, Raimondo F, Ria R, et al. A prospective, randomized, phase iii study of bortezomib, melphalan, prednisone and thalidomide (VMPT) versus bortezomib, melphalan and prednisone (VMP) in elderly newly diagnosed myeloma patients. In: Blood. Vol. 112. 2009:243. [CRSREF: 12308509]

Palumbo A, Bringhen S, Rossi D, Ria R, Magarotto V, Offidani M, et al. Bortezomib, melphalan, prednisone and thalidomide followed by bortezomib and thalidomide (VMPT-VT) as initial treatment of multiple myeloma (MM) patients older than 65 years: updated follow-up and prognostic factors. In: Haematologica. Vol. 96. 2011:S80-s81. [CRSREF: 12308510]

Palumbo A, Bringhen S, Rossi D, Ria R, Magarotto V, Offidani M, et al. Prognostic factors in elderly myeloma patients receiving bortezomib, melphalan, prednisone and thalidomide followed by bortezomib and thalidomide (VMPT-VT) as first line treatment. In: Haematologica. Vol. 96. 2011:376. [CRSREF: 12308511]

Palumbo A, Gay F, Cavallo F, Di Raimondo F, Larocca A, Hardan I, et al. Continuous therapy versus fixed duration of therapy in patients with newly diagnosed multiple myeloma. Journal of Clinical Oncology 2015; 33(30):3459-66. [CRSREF: 12308512]

Palumbo AB, Bringhen S, Rossi D, Berretta S, Montefusco V, Peccatori J, et al. A phase III study of VMPT versus VMP in newly diagnosed elderly myeloma patients. In: Journal of Clinical Oncology. Vol. 27. 2009:437. [CRSREF: 12308513]

Pawlyn 2017

[CRSSTD: 12308514]

Brioli A, Davies F, Gregory W, Hinsley S, Marshall S, Pawlyn C, et al. Low rate of secondary primary malignancies (SPMs) in newly diagnosed multiple myeloma (MM) patients treated with lenalidomide: first results from the MRC MM XI trial. In: Haematologica. Vol. 98. 2013:104. [CRSREF: 12308515]

Jackson GH, Davies FE, Pawlyn C, Cairns DA, Striha A, Collett C, et al. Lenalidomide is a highly effective maintenance therapy in myeloma patients of all ages; Results of the phase III myeloma XI study. In: Blood. Vol. 128. 2016. [CRSREF: 12308516]

Jones JR, Cairns D, Gregory W, Sigsworth R, Collett C, Pawlyn C, et al. The NCRI Myeloma XI trial for newly diagnosed symptomatic multiple myeloma (NDMM); second primary malignancy (SPM) incidence when lenalidomide is used as an induction and maintenance treatment option. In: British Journal of Haematology. Vol. 173. 2016:86. [CRSREF: 12308517]

Jones JR, Cairns DA, Gregory WM, Collett C, Pawlyn C, Sigsworth R, et al. Second malignancies in the context of lenalidomide treatment: an analysis of 2732 myeloma patients enrolled to the Myeloma XI trial. Blood Cancer Journal 2016;6(12):e506. [CRSREF: 12308518]

Jones JR, Cairns DA, Sigsworth R, Collett C, Pawlyn C, Striha A, et al. Myeloma XI trial for newly diagnosed multiple myeloma (NDMM); a report of second primary malignancy (SPM) rates and the importance of review of reported cases. In: Blood. Vol. 126. 2015:1847. [CRSREF: 12308519]

* Pawlyn C, Davies FE, Cairns D, Striha A, Best P, Sigsworth R, et al. Continuous treatment with lenalidomide improves outcomes in newly diagnosed myeloma patients not eligible for autologous stem cell transplant: results of the myeloma xi trial. In: Blood. Vol. 130. 2017. [CRSREF: 12308520]

Pawlyn C, Davies FE, Gregory WM, Szubert AJ, Bell SE, Ouzman J, et al. Sequential immunomodulatory drug (IMID) and proteosome inhibitor therapy improves response rates in newly diagnosed multiple myeloma: preliminary

results from the myeloma XI trial. In: Blood. Vol. 120. 2012. [CRSREF: 12308521]

Pawlyn C, Kaiser MF, Cairns D, Striha A, Jones JR, Shah V, et al. Factors predicting poor outcomes for myeloma patients at different ages: results from 3894 patients in the myeloma XI trial. In: Blood. Vol. 130. 2017. [CRSREF: 12308522]

Tute RM, Rawstron AC, Cairns D, Pawlyn C, Davies F, Collett C, et al. Minimal residual disease predicts outcome in transplant ineligible myeloma patients: results from the UK NCRI Myeloma XI trial. In: British Journal of Haematology. Vol. 173. 2016:105. [CRSREF: 12308523]

Tute RM, Rawstron AC, Cairns DA, Pawlyn C, Davies FE, Collett C, et al. Impact of minimal residual disease in transplant ineligible myeloma patients: results from the UK NCRI myeloma XI trial. In: Blood. Vol. 128. 2016. [CRSREF: 12308524]

Sacchi 2011

[CRSSTD: 12308525]

Sacchi S, Marcheselli R, Lazzaro A, Morabito F, Fragasso A, Di Renzo N, et al. A randomized trial with melphalan and prednisone versus melphalan and prednisone plus thalidomide in newly diagnosed multiple myeloma patients not eligible for autologous stem cell transplant. Leukemia and Lymphoma 2011;52(10):1942-8. [CRSREF: 12308526]

San Miguel 2008

[CRSSTD: 12308527]

Delforge M, Terpos E, Richardson PG, Shpilberg O, Khuageva NK, Schlag R, et al. Fewer bone disease events, improvement in bone remodeling, and evidence of bone healing with bortezomib plus melphalan-prednisone vs. melphalan-prednisone in the phase III VISTA trial in multiple myeloma. European Journal of Haematology 2011; 86(5):372-84. [CRSREF: 12308528]

Dimopoulos MA, Mateos MV, Richardson PG, Schlag R, Khuageva NK, Shpilberg O, et al. Risk factors for, and reversibility of, peripheral neuropathy associated with bortezomib-melphalan-prednisone in newly diagnosed patients with multiple myeloma: subanalysis of the phase 3 VISTA study. European Journal of Haematology 2011; 86(1):23-31. [CRSREF: 12308529]

Dimopoulos MA, Richardson PG, Schlag R, Khuageva NK, Shpilberg O, Kastritis E, et al. VMP (Bortezomib, Melphalan, and Prednisone) is active and well tolerated in newly diagnosed patients with multiple myeloma with moderately impaired renal function, and results in reversal of renal impairment: cohort analysis of the phase III VISTA study. Journal of Clinical Oncology 2009;27(36):6086-93. [CRSREF: 12308530]

Harousseau JL, Palumbo A, Richardson PG, Schlag R, Dimopoulos MA, Shpilberg O, et al. Superior outcomes associated with complete response in newly diagnosed multiple myeloma patients treated with nonintensive therapy: analysis of the phase 3 VISTA study of bortezomib plus melphalan-prednisone versus melphalan-prednisone. Blood 2010;116(19):3743-3750. [CRSREF: 12308531]

Mateos MV, Richardson PG, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. Journal of Clinical Oncology 2010;28(13):2259-66. [CRSREF: 12308532]

Palumbo A, Schlag R, Khuageva N, Dimopoulos M, Kropff M, Spicka I, et al. Prolonged therapy with bortezomib plus melphalan-prednisone (VMP) results in improved quality and duration of response in the phase III vista study in previously untreated multiple myeloma (MM). In: Haematologica. Vol. 93. 2008. [CRSREF: 12308533]

Richardson P, Schlag R, Khuageva N, Dimopoulos M, Shpilberg O, Kropff M, et al. Characterization of haematological parameters with bortezomib-melphalan-prednisone versus melphalan-prednisone in newly diagnosed myeloma, with evaluation of long-term outcomes and risk of thromboembolic events with use of erythropoiesis-stimulating agents: analysis of the VISTA trial. British Journal of Haematology 2011;153:212-21. [CRSREF: 12308534]

San Miguel JF, Schlag R, Khuageva N, Shpilberg O, Dimopoulos M, Kropff M, et al. MMY-3002: a phase 3 study comparing Bortezomib-Melphalan-Prednisone (VMP) with Melphalan-Prednisone (MP) in newly diagnosed multiple myeloma. In: Blood. Vol. 110. 2007. [CRSREF: 12308535]

* San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. New England Journal of Medicine 2008;359(9):906-17. [CRSREF: 12308536]

San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M. Continued overall survival benefit after 5 years' follow-up with bortezomib-melphalan-prednisone (VMP) versus melphalan-prednisone (MP) in patients with previously untreated multiple myeloma, and no increased risk of second primary malignancies: final results of the phase 3 VISTA trial. In: Blood. Vol. 118. 2011. [CRSREF: 12308537]

San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M. Superior efficacy with bortezomib plus melphalan-prednisone (VMP) versus melphalan-prednisone (MP) alone in previously untreated multiple

myeloma (MM): results of the phase III MMY-3002 VISTA study. In: Haematologica. Vol. 93. 2008. [CRSREF: 12308538]

San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M. Updated follow-up and results of subsequent therapy in the phase III vista trial: bortezomib plus melphalan-prednisone versus melphalan-prednisone in newly diagnosed multiple myeloma. In: Blood. Vol. 112. 2009:242. [CRSREF: 12308539]

Spicka I, Mateos MV, Redman K, Dimopoulos MA, Richardson PG. An overview of the VISTA trial: newly diagnosed, untreated patients with multiple myeloma ineligible for stem cell transplantation. Immunotherapy 2011; 3(9):1033-40. [CRSREF: 12308540]

Stewart 2015

[CRSSTD: 12308541]

Stewart AK, Jacobus S, Fonseca R, Weiss M, Callander NS, Chanan Khan AA, et al. E1A06: a phase III trial comparing melphalan, prednisone, and thalidomide (MPT) versus melphalan, prednisone, and lenalidomide (MPR) in newly diagnosed multiple myeloma MM). In: Haematologica. Vol. 99. 2014:220. [CRSREF: 12308542]

* Stewart AK, Jacobus S, Fonseca R, Weiss M, Callander NS, Chanan-Khan AA, et al. Melphalan, prednisone, and thalidomide vs melphalan, prednisone, and lenalidomide (ECOG E1A06) in untreated multiple myeloma. Blood 2015;126(11):1294-301. [CRSREF: 12308543]

Waage 2010

[CRSSTD: 12308544]

* Waage A, Gimsing P, Fayers P, Abildgaard N, Ahlberg L, Björkstrand B, et al. Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. Blood 2010;116(9):1405-12. [CRSREF: 12308545]

Waage A, Gimsing P, Juliusson G, Turesson I, Fayers P. Melphalan-prednisone-thalidomide to newly diagnosed patients with multiple myeloma: a placebo controlled randomised phase 3 trial. In: Blood. Vol. 110. 2007:32a. [CRSREF: 12308546]

Wijermans 2010

[CRSSTD: 12308547]

Beurden-Tan C, Blommestein H, Zweegman S, Sonneveld P. The relationship of response on time to next treatment based on evidence from two RCTs in newly diagnosed stem cell transplantation ineligible multiple myeloma patients. In: Blood. Vol. 128. 2016:(no pagination). [CRSREF: 12308548]

Verelst S, Termorshuizen F, Uyl-De Groot C, Sonneveld P, Wijermans P. Effect of thalidomide with melphalan and prednisone on health-related quality of life (HRQOL) in elderly patients with newly diagnosed multiple myeloma: a prospective analysis in a randomized trial (HOVON 49). In: Haematologica. Vol. 96. 2011:S135. [CRSREF: 12308549]

Verelst S, Termorshuizen F, Uyl-de Groot C, Schaafsma MR, Ammerlaan R, Wittebol S. Effect of thalidomide with melphalan and prednisone on health-related quality of life (HRQOL) in elderly patients with newly diagnosed multiple myeloma: a prospective analysis in a randomized trial. In: Blood. Vol. 116. 2010. [CRSREF: 12308550]

Verelst SG, Termorshuizen F, Uyl-de Groot CA, Schaafsma MR, Ammerlaan AH, Wittebol S, et al. Effect of thalidomide with melphalan and prednisone on health-related quality of life (HRQoL) in elderly patients with newly diagnosed multiple myeloma: a prospective analysis in a randomized trial. Annals of Hematology 2011; 90(12):1427-39. [CRSREF: 12308551]

Wijermans P, Schaafsma M, Norden Y, Ammerlaan R, Sonneveld P, Wittebol S, et al. Melphalan + prednisone vs melphalan + prednisone + thalidomide in induction therapy for multiple myeloma in elderly patients: first interim results of the Dutch cooperative group HOVON. In: Haematologica. Vol. 93. 2008:177. [CRSREF: 12308552]

Wijermans P, Schaafsma M, Norden Y, Ammerlaan R, Wittebol S, Sinnige H, et al. Melphalan + prednisone versus melphalan + prednisone + thalidomide in induction therapy for multiple myeloma in elderly patients: final analysis of the Dutch Cooperative Group HOVON 49 study. Blood 2009;112(11):241-2. [CRSREF: 12308553]

* Wijermans P, Schaafsma M, Termorshuizen F, Ammerlaan R, Wittebol S, Sinnige H, et al. Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 Study. Journal of Clinical Oncology 2010;28(19):3160-6. [CRSREF: 12308554]

Zweegman 2016

[CRSSTD: 12308555]

Beurden-Tan C, Blommestein H, Zweegman S, Sonneveld P. The relationship of response on time to next treatment based on evidence from two RCTs in newly diagnosed stem cell transplantation ineligible multiple myeloma patients. In: Blood. Vol. 128. 2016:(no pagination). [CRSREF: 12308556]

Kongsgaard Nielsen L, Stege C, Witte B, Holt B, Mellqvist UH, Salomo M, et al. Health-related quality of life in non-transplant eligible newly diagnosed multiple myeloma patients treated with melphalan/prednisolone plus

either thalidomide or lenalidomide; results of the HOVON87/NMSG18 study. In: Quality of Life Research. Vol. 26. 2017:56-7. [CRSREF: 12308557]

Stege C, Holt B, Mellqvist UH, Levin MD, Salomo M, Abildgaard N, et al. Frailty predicts survival and toxicity in newly diagnosed multiple myeloma patients ineligible for autologous stem cell transplantation; report of the HOVON-87/NMSG-18 study group. In: Blood. Vol. 130. 2017:(no pagination). [CRSREF: 12308558]

Stege C, Kongsgaard Nielsen L, Witte B, Holt B, Mellqvist UH, Salomo M, et al. Quality of life with melphalan/prednisone plus either thalidomide (MPT-T) or lenalidomide (MPR-R) in non-transplant eligible newly diagnosed multiple myeloma; Results of the Hovon87/NMSG18 study. In: Haematologica. Vol. 102. 2017:190. [CRSREF: 12308559]

* Zweegman S, Holt B, Mellqvist UH, Salomo M, Bos GM, Levin MD, et al. Melphalan, prednisone, and lenalidomide versus melphalan, prednisone, and thalidomide in untreated multiple myeloma. Blood 2016;127(9):1109-16. [CRSREF: 12308560]

Excluded studies

Anonymous 2003

[CRSSTD: 12308561]

Anonymous. A multicenter parallel-group, placebo controlled, randomized, double-blind study of combination thalidomide plus glucocorticoid therapy versus glucocorticoid therapy alone as induction therapy for previously untreated subjects with multiple myeloma. available at: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00500364/full (accessed 06 May 2019). [CRSREF: 12308562]

Barlogie 2004

[CRSSTD: 12308563]

Anonymous. Study of bortezomib and Revlimid ™ for patients relapsing or progressing on total therapy II. available at: https://clinicaltrials.gov/show/nct00093028 (Accessed 28 May 2019). [CRSREF: 12308564]

* Barlogie B, Rasmussen E, Tricot G, Crowley J. Management of patients with multiple myeloma (MM) failing total therapy 2 (TT 2) according to thalidomide (THAL) randomization. In: Blood. Vol. 104. 2004:414a. [CRSREF: 12308565]

Brioli 2014

[CRSSTD: 12308566]

Brioli A, Galli M, Tacchetti P, Crippa C, Spadano T, Pezzi A, et al. A combination therapy with bortezomib (BOR) and thalidomide in newly diagnosed myeloma patients is associated with a low incidence of second primary malignancies (SPMS). In: Haematologica. Vol. 99. 2014:373. [CRSREF: 12308567]

Facon 2006

[CRSSTD: 12308568]

Facon T, Mary JY, Attal M, Pegourie B, Harousseau JL, Sadoun A. Melphalan-prednisone versus dexamethasone-based regimens for newly diagnosed myeloma patients aged 65-75 years. Final analysis of the IFM 95-01 trial on 489 patients. In: Blood. Vol. 102. 2003:147a. [CRSREF: 12308569]

* Facon T, Mary JY, Pégourie B, Attal M, Renaud M, Sadoun A, et al. Dexamethasone-based regimens versus melphalan-prednisone for elderly multiple myeloma patients ineligible for high-dose therapy. Blood 2006; 107(4):1292-8. [CRSREF: 12308570]

Facon 2017

[CRSSTD: 12308571]

Anonymous. Phase 3 study of carfilzomib, melphalan, prednisone vs bortezomib, melphalan, prednisone in newly diagnosed multiple myeloma. available at: ttps://clinicaltrials.gov/show/nct01818752 (accessed 03 July 2019). [CRSREF: 12308572]

* Facon T, Lee JH, Moreau P, Niesvizky R, Dimopoulos MA, Hajek R, et al. Phase 3 Study (CLARION) of carfilzomib, melphalan, prednisone (KMP) v bortezomib, melphalan, prednisone (VMP) in newly diagnosed multiple myeloma (NDMM). Clinical Lymphoma, Myeloma and Leukemia 2017;17(1):e26-7. [CRSREF: 12308573]

Facon 2018

[CRSSTD: 12308574]

Facon T, Kumar SK, Plesner T, Orlowski RZ, Moreau P, Bahlis N, et al. LBA-2 phase 3 randomized study of daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) in patients with newly diagnosed multiple myeloma (NDMM) ineligible for transplant (MAIA). In: Blood. Vol. 132. 2018:LBA-2. [CRSREF: 12308575]

Foa 2007

[CRSSTD: 12308576]

Foa R, Weber D, Dimopoulos M, Olesnyckyj M, Yu Z, Zeldis J, et al. Lenalidomide/dexamethasone improves response and prolongs time to progression, even in patients with IgA multiple myeloma: a sub-analysis of the MM-009/010 studies. In: Blood. Vol. 110. 2007:284b. [CRSREF: 12308577]

Harousseau 2003

[CRSSTD: 12308578]

Harousseau JL, Attal M. The IFM-90 trial. In: Hematology Journal. Vol. 4. 2003:S55. [CRSREF: 12308579]

Hejlova 2000

[CRSSTD: 12308580]

Hejlova N, Hajek R, Adam Z, Scudla Z, Bacovsky J, Koza V, et al. Report of the "4W" trial of the Czech myeloma group. In: Hematology Journal. Vol. 1. 2000:168-9. [CRSREF: 12308581]

Hernández 2004

[CRSSTD: 12308582]

Hernández JM, García-Sanz R, Golvano E, Bladé J, Fernandez-Calvo J, Trujillo J, et al. Randomized comparison of dexamethasone combined with melphalan versus melphalan with prednisone in the treatment of elderly patients with multiple myeloma. British Journal of Heamatology 2004;127(2):159-64. [CRSREF: 12308583]

Kumar 2012

[CRSSTD: 12308584]

Kumar S, Flinn I, Richardson PG, Hari P, Callander N, Noga SJ, 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. [CRSREF: 12308585]

Ludwig 2017a

[CRSSTD: 12308586]

Anonymous. Patients with newly diagnosed multiple myeloma comparing KTd vs. KRd induction therapy and investigating a K-mono maintenance strategy. Available at: https://clinicaltrials.gov/show/nct02891811 (accessed 03 July 2019). [CRSREF: 12308587]

* Ludwig H. AGMT-MM2 A randomized phase II study in transplant ineligible patients with newly diagnosed multiple myeloma (NDMM) comparing Carfilzomib + Thalidomide + Dexamethasone(KTd) with Carfilzomib + Lenalidomide + Dexamethasone (KRd) induction therapy followed by Carfilzomib (K) maintenance or control. In: Magazine of European Medical Oncology. Vol. 10. 2017:S44-s45. [CRSREF: 12308588]

Mateos 2016

[CRSSTD: 12308589]

Mateos MV, Gutierrez NC, Martin ML, Martinez-Lopez J, Hernandez MT, Martinez R, et al. Bortezomib plus melphalan and prednisone (VMP) followed by lenalidomide and dexamethasone (RD) in newly diagnosed elderly myeloma patients overcome the poor prognosis of high-risk cytogenetic abnormalities (CA) detected by fluorescence in situ hibridization (FISH). In: Blood. Vol. 126. 2015:4243. [CRSREF: 12308590]

* Mateos MV, Martínez-López J, Hernández MT, Ocio EM, Rosiñol L, Martínez R, et al. Sequential vs alternating administration of VMP and Rd in elderly patients with newly diagnosed MM. Blood 2016;127(4):420-5. [CRSREF: 12308591]

Mateos MV, Martinez-Lopez J, Hernandez M, Martinez R, Rosinol L, Ocio EM, et al. Depth of response as surrogate marker for progression-free survival and overall survival in elderly newly diagnosed myeloma patients treated with VMP and Rd: gEM2010MAS65. In: Haematologica. Vol. 102. 2017:143. [CRSREF: 12308592]

Mateos MV, Martinez-Lopez J, Hernandez MT, Ocio EM, Rosinol L, Martinez R, et al. Bortezomib, melphalan, prednisone (VMP) and lenalidomide plus dexamethasone (RD) is the optimal combination for patients with newly diagnosed multiple myeloma (MM) patients between 65 and 80 years. In: Blood. Vol. 126. 2015:1848. [CRSREF: 12308593]

Mateos 2018

[CRSSTD: 12308594]

Facon T, Cavo M, Jakubowiak A, San Miguel J, Kumar S, Orlowski RZ, et al. Two randomized open-label studies of daratumumab (DARA) plus standard of care treatment versus standard of care alone in patients with previously untreated multiple myeloma (MM) ineligible for high-dose therapy: 54767414MMY3007 (Alcyone) and 54767414MMY3008 (Maia). In: Clinical Lymphoma, Myeloma and Leukemia. Vol. 15. 2015:e294-5. [CRSREF: 12308595]

Mateos MV, Cavo M, Jakubowiak AJ, Carson RL, Qi M, Bandekar R, et al. A randomized open-label study of bortezomib, melphalan, and prednisone (VMP) versus daratumumab (DARA) plus VMP in patients with previously

untreated multiple myeloma (MM) who are ineligible for high-dose therapy: 54767414MMY3007 (Alcyone). In: Journal of Clinical Oncology. Vol. 33. 2015:supplement 1 (no pagination). [CRSREF: 12308596]

Mateos MV, Dimopoulos MA, Cavo M, Suzuki K, Jakubowiak A, Knop S, et al. Daratumumab plus bortezomib, melphalan, and prednisone (D-VMP) versus bortezomib, melphalan, and prednisone (VMP) in newly diagnosed multiple myeloma (NDMM) patients (PTS) ineligible for transplant: a phase 3 ran-domized study (alcyone). In: Haematologica. Vol. 103. 2018:22. [CRSREF: 12308597]

* Mateos MV, Dimopoulos MA, Cavo M, Suzuki K, Jakubowiak A, Knop S, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. New England Journal of Medicine 2018;378(6):518-28. [CRSREF: 12308598]

Mateos MV, Dimopoulos MA, Cavo M, Suzuki K, Jakubowiak AJ, Knop S, et al. Phase 3 randomized study of daratumumab plus bortezomib, melphalan, and prednisone (D-VMP) versus bortezomib, melphalan, and prednisone (VMP) in newly diagnosed multiple myeloma (NDMM) patients (Pts) ineligible for transplant (ALCYONE). In: Blood. Vol. 130. 2017:Supplement 1 (no pagination). [CRSREF: 12308599]

Stirrups R. Daratumumab for untreated multiple myeloma. Lancet Oncology 2018;19(2):e80. [CRSREF: 12308600]

Merz 2015

[CRSSTD: 12308601]

Merz M, Salwender HJ, Haenel M, Bertsch U, Kunz C, Hielscher T, et al. Clinical risk factors for peripheral neuropathy in patients treated with subcutaneous or intravenous bortezomib for newly diagnosed multiple myeloma. In: BLood. Vol. 126. 2015:4233. [CRSREF: 12308602]

Montefusco 2013

[CRSSTD: 12308603]

Montefusco V. First-line treatment in elderly patients. In: European journal of cancer. Vol. 49. 2013:S19. [CRSREF: 12308604]

Morgan 2002

[CRSSTD: 12308605]

Morgan G, Davies FE, Hawkins K, Brown J, Drayson MT. The MRC Myeloma VII Trial of standard versus intensive treatment in patients <65 years of age with multiple myeloma. In: Blood. Vol. 100. 2002:178a. [CRSREF: 12308606]

NCT00522392

[CRSSTD: 12308607]

Anonymous. Bortezomib and dexamethasone with or without lenalidomide in treating patients with multiple myeloma previously treated with dexamethasone. available at: https://clinicaltrials.gov/show/nct00522392 (accessed 06 May 2019). [CRSREF: 12308608]

NCT00734877

[CRSSTD: 12308609]

Anonymous. UARK 2013-13, Total Therapy 4B - Formerly 2008-01 - A phase III trial for low risk myeloma. available at: https://clinicaltrials.gov/show/nct00734877 (accessed 06 May 2019). [CRSREF: 12308610]

NCT01850524

[CRSSTD: 12308611]

Anonymous. IXAZOMIB plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with newly diagnosed multiple myeloma. available at: https://clinicaltrials.gov/show/nct01850524 (accessed 03 July 2019). [CRSREF: 12308612]

NCT01863550

[CRSSTD: 12308613]

Anonymous. Bortezomib or carfilzomib With lenalidomide and dexamethasone in treating patients with newly diagnosed multiple myeloma. available at: https://clinicaltrials.gov/show/nct01863550 (accessed 03 July 2019). [CRSREF: 12308614]

NCT02586038

[CRSSTD: 12308615]

Anonymous. Study that compares 3 arm: MLN9708 dexamethasone, MLN9708 cyclophosphamide and dexamethasone, MLN9708 thalidomide and dexamethasone followed by maintenance with MLN9708 in newly diagnosed elderly multiple myeloma patients. available at: https://clinicaltrials.gov/show/nct02586038 (accessed 03 July 2019). [CRSREF: 12308616]

NCT03710603

[CRSSTD: 12308617]

Anonymous. A study comparing daratumumab, VELCADE (bortezomib), lenalidomide, and dexamethasone (D-VRd) with VELCADE, lenalidomide, and dexamethasone (VRd) in participants with untreated multiple myeloma and for whom hematopoietic stem cell transplant is not planned as initial therapy. available at: https://clinicaltrials.gov/show/nct03652064 (accessed 03 July 2019). [CRSREF: 12308618]

Anonymous. Daratumumab, VELCADE (bortezomib), lenalidomide and dexamethasone compared to VELCADE, lenalidomide and dexamethasone in subjects with previously untreated multiple myeloma. available at: https://clinicaltrials.gov/show/nct03710603 (accessed 03 July 2019). [CRSREF: 12308619]

Niesvizky 2003

[CRSSTD: 12308620]

Niesvizky R, Pekle K, Lyons L, Pearse RN, Bergsagel PL, Schuster MW. Dexamethsone alone, or in combination with low-dose thalidomide as induction therapy for advanced multiple myeloma, and the effect of the addition of clarithromycin (Biaxin?) on response rate. Interim results of a prospective, sequential, randomized trial. In: Blood. Vol. 102. 2003:237a. [CRSREF: 12308621]

Offidani 2004

[CRSSTD: 12308622]

Offidani M, Corvatta L, Marconi M, Olivieri A, Catarini M, Mele A, et al. Thalidomide plus oral melphalan compared with thalidomide alone for advanced multiple myeloma. Hematology Journal 2004;5(4):312-7. [CRSREF: 12308623]

Palumbo 2016

[CRSSTD: 12308624]

Lonial S, Ribeiro De Oliveira M, Yimer H, Mateos MV, Rifkin R, Schjesvold F, et al. KEYNOTE-185: a randomized, open-label phase 3 study of pembrolizumab in combination with lenalidomide and lowdose dexamethasone in newly diagnosed and treatmentnaive multiple myeloma (MM). In: Annals of Oncology. Vol. 27. 2016:viii16. [CRSREF: 12308625]

* Palumbo A, Mateos MV, San Miguel J, Shah J, Thompson S, Marinello P, et al. Pembrolizumab in combination with lenalidomide and low-dose dexamethasone in newly diagnosed and treatment-naive multiple myeloma (MM): randomized, phase 3 KEYNOTE-185 study. In: Annals of Oncology. Vol. 27. 2016:(no pagination). [CRSREF: 12308626]

Shah J, Lonial S, Oliveira MR, Yimer H, Mateos MV, Rifkin R, et al. KEYNOTE-185: randomized, open-label, phase III study of pembrolizumab in combination with lenalidomide and low-dose dexamethasone in patients with newly diagnosed and treatment-naive multiple myeloma (MM). In: Journal for Immunotherapy of Cancer. Vol. 4. 2016. [CRSREF: 12308627]

Rajkumar 2006b

[CRSSTD: 12308628]

Greipp PR. Eastern Cooperative Oncology Group E1A00: phase III randomized study of dexamethasone with or without thalidomide in patients with newly diagnosed multiple myeloma. Clinical Advances in Hematology & Ooncology 2003;1(3):188-9. [CRSREF: 12308629]

* Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR, Eastern Cooperative Oncology Group. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. Journal of Clinical Oncology 2006;24(3):431-6. [CRSREF: 12308630]

Rajkumar SV, Vesole DH, Shepard PR, Greipp PR. A randomised phase III trial of thalidomide plus dexamethasone versus dexamethasone in newly diagnosed multiple myeloma (E1A00): a trial coordinated by the Eastern Cooperative Oncology Group. In: Journal of Clinical Oncology. Vol. 22. 2004:558. [CRSREF: 12308631]

Rajkumar SV, Vesole DH, Shepard R, Greipp PR. Thalidomide plus dexamethasone versus dexamethasone alone in newly diagnosed multiplemMyeloma (E1A00): results of a phase III trial coordinated by the Eastern Cooperative Oncology Group. In: Blood. Vol. 104. 2004:63. [CRSREF: 12308632]

Rajkumar 2008

[CRSSTD: 12308633]

Rajkumar SV, Hussein M, Catalano J, Jedrzejcak W, Sirkovich S, Olesnyckyj M, et al. A multicenter, randomized, double-blind, placebo-controlled trial of thalidomide plus dexamethasone versus dexamethasone alone as initial therapy for newly diagnosed multiple myeloma. In: Journal of Clinical Oncology. Vol. 24. 2006:426. [CRSREF: 12308634]

Rajkumar SV, Hussein M, Catalano J, Jedrzejczak W, Sirkovich S, Olesnyckyj M, et al. A randomized, double-blind, placebo-controlled trial of thalidomide plus dexamethasone versus dexamethasone alone as primary therapy for newly diagnosed multiple myeloma. In: Blood. Vol. 108. 2006:238. [CRSREF: 12308635]

* Rajkumar SV, Rosiñol L, Hussein M, Catalano J, Jedrzejczak W, Lucy L, et al. Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. Journal of Clinical Oncology 2008;26(13):2171-7. [CRSREF: 12308636]

San Miguel 2014

[CRSSTD: 12308637]

San Miguel J, Blade J, Samoilova O, Shpilberg O, Grosicki S, Maloisel F, et al. Randomized, open-label, phase 2 study of siltuximab (an anti-il-6 mab) and bortezomib-melphalan-prednisone versus bortezomib-melphalan-prednisone in patients with previously untreated multiple myeloma. In: Haematologica. Vol. 98. 2013:97. [CRSREF: 12308638]

* San Miguel J, Blade J, Shpilberg O, Grosicki S, Maloisel F, Min CK, et al. Phase 2 randomized study of bortezomib-melphalan-prednisone with or without siltuximab (anti-IL-6) in multiple myeloma. Blood 2014; 123(26):4136-42. [CRSREF: 12308639]

Takezako 2017

[CRSSTD: 12308640]

Anonymous. PH III study of lenalidomide and dexamethasone with or without elotuzumab to treat peviously untreated multiple myeloma (ELO 1 substudy). available at: https://clinicaltrials.gov/show/nct01891643 (accessed 03 July 2019). [CRSREF: 12308641]

Anonymous. Phase III study of lenalidomide and dexamethasone with or without elotuzumab to treat newly diagnosed, previously untreated multiple myeloma. available at: https://clinicaltrials.gov/show/nct01335399 (accessed 03 July 2019). [CRSREF: 12308642]

* Takezako N, Ohta K, Handa H, Hori M, Kinoshita G, Shelat S, et al. Elotuzumab plus lenalidomide/dexamethasone (ELD) vs LD in patients with newly diagnosed multiple myeloma: phase 2, randomized, open-label study in Japan. In: Blood. Vol. 130. 2017:supplement 1 (no pagination). [CRSREF: 12308643]

Usmani 2014

[CRSSTD: 12308644]

Anonymous. S1211 Bortezomib, Dexamethasone, and Lenalidomide With or Without Elotuzumab in Treating Patients With Newly Diagnosed High-Risk Multiple Myeloma. available at: https://clinicaltrials.gov/show/nct01668719 (accessed 03 July 2019). [CRSREF: 12308645]

* Usmani SZ, Hoering A, Sexton R, Ailawadhi S, Shah JJ, Fredette S, et al. SWOG 1211: a randomized phase I/II study of optimal induction therapy for newly diagnosed high-risk multiple myeloma (HRMM). In: Journal of Clinical Oncology. Vol. 32. 2014:15 suppl.1 (no pagination). [CRSREF: 12308646]

White 2007

[CRSSTD: 12308647]

White DJ, Kovacs MJ, Belch A, Stewart K, Chen C, Rubin S, et al. Phase II testing of lenalidomide plus melphalan for previously untreated older patients with multiple myeloma: toxicity data from the NCIC CTG MY.11 trial. In: Blood. Vol. 110. 2007:63a. [CRSREF: 12308648]

* White DJ, Paul N, Macdonald DA, Meyer RM, Shepherd LE. Addition of lenalidomide to melphalan in the treatment of newly diagnosed multiple myeloma: the National Cancer Institute of Canada Clinical Trials Group MY.11 trial. Current Oncology 2007;14(2):61-5. [CRSREF: 12308649]

Zonder 2010

[CRSSTD: 12308650]

* Zonder JA, Crowley J, Hussein MA, Bolejack V, Moore DF, Whittenberger BF, 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. [CRSREF: 12308651]

Zonder JA, Crowley J, Hussein MA, Bolejack V, Moore DF, Whittenberger BF, et al. Superiority of lenalidomide (Len) plus high-dose dexamethasone (HD) compared to HD alone as treatment of newly-diagnosed multiple myeloma (NDMM): results of the randomized, double-blinded, placebo-controlled SWOG trial S0232. In: Blood. Vol. 110. 2007:32a. [CRSREF: 12308652]

Zonder JA, Crowley JJ, Bolejack V, Hussein MA, Moore DF, Whittenberger BF. A randomized Southwest Oncology Group study comparing dexamethasone (D) to lenalidomide + dexamethasone (LD) as treatment of newly-diagnosed multiple myeloma (NDMM): impact of cytogenetic abnormalities on efficacy of LD, and updated overall study results. In: Journal of Clinical Oncology. Vol. 26. 2008:459. [CRSREF: 12308653]

Zonder JA. Phase III randomized study of dexamethasone with or without CC-5013 in patients with newly diagnosed multiple myeloma. http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/578/CN-00501578/frame.html 2003. [CRSREF: 12308654]

Studies awaiting classification

Ongoing studies

Other references

Additional references

Ailawadhi 2018

Ailawadhi S, Jacobus S, Sexton R, Stewart AK, Dispenzieri A, Hussein MA, et al. Disease and outcome disparities in multiple myeloma: exploring the role of race/ethnicity in the Cooperative Group clinical trials. Blood Cancer Journal 2018;8(7):67.

Anderson 2011

Anderson KC, Carrasco RD. Pathogenesis of myeloma. Annual Review of Pathology 2011;6:249-74.

Anderson 2015

Anderson KC, Alsina M, Atanackovic D, Biermann JS, Chandler JC, Costello C, et al. Multiple Myeloma, version 2.2016: Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network 2015; 13(11):1398-435.

Argyriou 2008

Argyriou AA, Iconomou G, Kalofonos HP. Bortezomib-induced peripheral neuropathy in multiple myeloma: a comprehensive review of the literature. Blood 2008;112(5):1593-9.

Asatsuma-Okumura 2019

Asatsuma-Okumura T, Ito T, Handa H. Molecular mechanisms of cereblon-based drugs. Pharmacology and Therapeutics 2019;202:132-9.

Bianchi 2015

Bianchi G, Richardson PG, Anderson KC. Promising therapies in multiple myeloma. Blood 2015;126(3):300-10.

Blommestein 2019

Blommestein HM, van Beurden-Tan CHY, Franken MG, Uyl-de Groot CA, Sonneveld P, Zweegman S. Efficacy of first-line treatments for multiple myeloma patients not eligible for stem cell transplantation - A Network Meta-analysis. Haematologica 2019;104(5):1026-35.

Cancer Research UK 2018

Cancer Research UK. Myeloma statistics. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma (accessed 27 August 2018).

Chaimani 2017

Chaimani A, Caldwell DM, Li T, Higgins JP, Salanti G. Additional considerations are required when preparing a protocol for a systematic review with multiple interventions. Journal of Clinical Epidemiology 2017;83:65-74.

Covidence systematic review software

Covidence systematic review software [Computer program]. Melbourne, Australia: Veritas Health Innovation, Available at www.covidence.org.

Cowan 2018

Cowan AJ, Allen C, Barac A, Basaleem H, Bensenor I, Curado MP, et al. Global burden of multiple myeloma: a systematic analysis for the global burden of disease study 2016. JAMA Oncology 2018;4(9):1221-7. [DOI: 10.1001/jamaoncol.2018.2128]

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses on behalf of the Cochrane Statistical Methods Group. In: Higgins JP Green S (editors). Cochrane Handbook of Systematic Reviews of Intervention. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Dias 2010

Dias S, Welten NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis.. Statistics in Medicine 2010;29(7-8):932-44. [PubMed: 20213715]

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629-34.

Fayers 2011

Fayers P M, Palumbo A, Hulin C, Waage A, Wijermans P, Beksac M, et al. Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials. Blood 2011;118(5):1239-47.

Fink 2015

Fink EC, Ebert BL. The novel mechanism of lenalidomide activity. Blood 2015;126(21):2366-9.

Gandolfi 2017

Gandolfi S, Laubach JP, Hideshima T, Chauhan D, Anderson KC, Richardson PG. The proteasome and proteasome inhibitors in multiple myeloma. Cancer and Metastasis Reviews 2017;36(4):561-84.

Higgins 2011a

Higgins JP, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JP Green S (editors). Cochrane Handbook of Systematic Reviews of Intervention. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011b

Higgins JP, Altman DG, Sterne JA (editors. Chapter 8: Assessing risk of bias in included studies. In: Higgins JP Green S (editors). Cochrane Handbook of Systematic Reviews of Intervention. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org..

Higgins 2011c

Higgins JP, Deeks JJ, Altman DG (editors. Chapter 16: Special topics in statistics. In: Higgins JP Green S (editors). Cochrane Handbook of Systematic Reviews of Intervention. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Holstein 2017

Holstein SA, McCarthy PL. Immunomodulatory drugs in multiple myeloma: mechanisms of action and clinical experience. Drugs 2017;77(5):505-20.

IMS Institute for Healthcare Informatics 2015

IMS Institute for Healthcare Informatics. Understanding the Role and Use of Essential Medicines Lists,. Available at: http://apps.who.int/medicinedocs/documents/s21980en/s21980en.pdf (accessed 30 August 2019) 2015.

Key 2019

Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. Journal of Clinical Oncology 2019; [Epub ahead of print]. [DOI: 10.1200/JCO.19.01461]

Kimpton 2016

Kimpton M, Buyting R, Corsi DJ, Rupani N, Carrier M, McCurdy A. Incidence and risk factors of venous thromboembolism in patients with multiple myeloma receiving immunomodulatory agents. Blood 2016; 128(22):2624.

Kirtane 2017

Kirtane K, Lee SJ. Racial and ethnic disparities in hematologic malignancies. Blood 2017;130(15):1699.

Kuehl 2012

Kuehl WM, Bergsagel PL. Molecular pathogenesis of multiple myeloma and its premalignant precursor. Journal of Clinical Investigation 2012;122(10):3456-63.

Kuhr 2016

Kuhr K, Wirth D, Srivastava K, Lehmacher W, Hellmich M. First-line therapy for non-transplant eligible patients with multiple myeloma: direct and adjusted indirect comparison of treatment regimens on the existing market in Germany. European Journal of Clinical Pharmacology 2016;72(3):257-65.

Kumar 2018

Kumar SK, Callander NS, Alsina M, Atanackovic D, Biermann JS, Castillo J, et al. NCCN guidelines insights: multiple myeloma, version 3.2018. Journal of the National Comprehensive Cancer Network 2018;16(1):11-20.

Liu 2017

Liu X, Chen J, He YA, Meng X, Li K, He CK, et al. Comparing efficacy and survivals of initial treatments for elderly patients with newly diagnosed multiple myeloma: a network meta-analysis of randomized controlled trials. OncoTargets and Therapy 2017;10:121-8.

Lu 2014

Lu G, Middleton RE, Sun H, Naniong M, Ott C J, Mitsiades CS, et al. The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. Science 2014;343(6168):305-9.

Ludwig 2017b

Ludwig H, Zojer N. Fixed duration vs continuous therapy in multiple myeloma. ASH Education Program 2017; Hematology 2017(1):212-22.

McMaster 2015

GRADEpro Guideline Development Tool [Computer program]. McMaster University (developed by Evidence Prime, Inc). Available from www.gradepro.org, 2015.

Miceli 2008

Miceli T, Colson K, Gavino M, Lilleby K. Myelosuppression associated with novel therapies in patients with multiple myeloma: consensus statement of the IMF Nurse Leadership Board. Clinical Journal of Oncology Nursing 2008;12(Supplement 3):13-20.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLOS Medicine 2009;6(7):e1000097.

Moreau 2012

Moreau P, Richardson PG, Cavo M, Orlowski RZ, San Miguel JF, Palumbo A, et al. Proteasome inhibitors in multiple myeloma: 10 years later. Blood 2012;120(5):947-59.

Moreau 2017

Moreau P, San Miguel J, Sonneveld P, Mateos MV, Zamagni E, Avet-Loiseau H, et al. Multiple myeloma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2017;28 Suppl 4:iv52-61.

National Cancer Institute 2018

National Cancer Institute. Cancer stat facts: myeloma. https://seer.cancer.gov/statfacts/html/mulmy.html (accessed 27 August 2018).

Nwabuko 2017

Nwabuko OC, Igbigbi EE, Chukwuonye II, Nnoli MA. Multiple myeloma in Niger Delta, Nigeria: complications and the outcome of palliative interventions. Cancer Management and Research 2017;9:189-96.

Palumbo 2004

Palumbo A, Bringhen S, Petrucci MT, Musto P, Rossini F, Nunzi M, et al. Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial. Blood 2004; 104(10):3052-7.

Palumbo 2008

Palumbo A, Rajkumar SV, Dimopoulos MA, Richardson PG, San Miguel J, Barlogie B, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia 2008;22(2):414-23.

Palumbo 2011

Palumbo A, Anderson K. Multiple myeloma. New England Journal of Medicine 2011;364(11):1046-60.

Palumbo 2013

Palumbo A, Waage A, Hulin C, Beksac M, Zweegman S, Gay F, et al. Safety of thalidomide in newly diagnosed elderly myeloma patients: a meta-analysis of data from individual patients in six randomized trials. Haematologica 2013;98(1):87-94.

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Statistics in Medicine 1998;17(24):2815-34.

Puhan 2014

Puhan MA, Schunemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ (Clinical research ed.) 2014;349:g5630.

Quach 2010

Quach H, Ritchie D, Stewart AK, Neeson P, Harrison S, Smyth MJ, et al. Mechanism of action of immunomodulatory drugs (IMiDS) in multiple myeloma. Leukemia 2010;24(1):22-32.

R 2018

R: A language and environment for statistical computing [Computer program]. R Core Team. Vienna, Austria: R Foundation for Statistical Computing, 2018.

Rajkumar 2014

Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncology 2014;15(12):e538-48.

RevMan 2014

Review Manager [Computer program]. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Richardson 2018

Richardson PG, Laubach J, Gandolfi S, Facon T, Weisel K, O'Gorman P. Maintenance and continuous therapy for multiple myeloma. Expert Review of Anticancer Therapy 2018;18(8):751-64.

Rücker 2012

Rücker G. Network meta-analysis, electrical networks and graph theory. Research Synthesis Methods 2012; 3(4):312-24.

Rücker 2014

Rücker G, Schwarzer G. Reduce dimension or reduce weights? Comparing two approaches to multi-arm studies in network meta-analysis. Statistics in Medicine 2014;33(25):4353-69.

Rücker 2015

Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Medical Research Methodology 2015;15:58.

Rücker 2018

netmeta: Network Meta-Analysis using Frequentist Methods. R package version 0.9-8 [Computer program]. Rücker G, Schwarzer G, Krahn U, König J. http://CRAN.R-project.org/package=netmeta, 2018. [Other:]

San Miguel 2013

San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma. Journal of Clinical Oncology 2013; 31(4):448-55.

Schwarzer 2015

Schwarzer G, Carpenter JR, Rücker G. Chapter 8: Network Meta-Analysis. In: netmeta: Network Meta-Analysis using Frequentist Methods. Springer International Publishing Switzerland, 2015.

Schwarzer 2018

meta: General Package for Meta-Analysis. R package version 4.9-2 [Computer program]. Schwarzer G. http://CRAN.R-project.org/package=meta, 2018.

Schünemann 2011

Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings tables'. In: Higgins JP Green S (editors). Cochrane Handbook of Systematic Reviews of Intervention. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Schünemann 2011a

Schünemann HJ, Oxman AD, Vist GE, Higgins JP, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JP, Green S editor(s). Cochrane Handbook of Systematic Reviews of Intervention. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Schünemann 2019

Schünemann HJ, Higgins JPT, Vist GE, Glasziou P, Akl AE, Skoetz N, Guyatt GH. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions. London: Cochrane, Draft Version (29 January 2019).

Singhal 1999

Singhal S, Mehta J, Desikan R, Ayers D, Roberson P, Eddlemon P, et al. Antitumor activity of thalidomide in refractory multiple myeloma. New England Journal of Medicine 1999;341(21):1565-71.

Sterne 2011

Sterne JA, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JP, Green S, editor(s). Cochrane Handbook of Systematic Reviews of Intervention. Version 5.1.0 (updated March 2011). The Cochrane

Collaboration, 2011. Available from handbook.cochrane.org.

Taplitz 2018

Taplitz RA, Kennedy EB, Bow EJ, Crews J, Gleason C, Hawley DK, et al. Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression: ASCO and IDSA Clinical Practice Guideline Update. Journal of Clinical Oncology 2018;36(30):3043-54.

The American Cancer Society 2018

The American Cancer Society. Signs and symptoms of multiple myeloma. https://www.cancer.org/cancer/multiple-myeloma/detection-diagnosis-staging/signs-symptoms.html (accessed 27 August 2018).

Tierney 2007

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.

Waxman 2010

Waxman AJ, Mink PJ, Devesa SS, Anderson WF, Weiss BM, Kristinsson SY, et al.. Racial disparities in incidence and outcome in multiple myeloma: a population-based study. Blood 2010;116(25):5501-6.

Weisel 2017

Weisel K, Doyen C, Dimopoulos M, Yee A, Lahuerta JJ, Martin A, et al. A systematic literature review and network meta-analysis of treatments for patients with untreated multiple myeloma not eligible for stem cell transplantation. Leukemia & Lymphoma 2017;58(1):153-61.

Windebank 2008

Windebank AJ, Grisold W. Chemotherapy-induced neuropathy. Journal of the Peripheral Nervous System 2008; 13(1):27-46.

World Health Organization 2019

World Health Organization. WHO updates global guidance on medicines and diagnostic tests to address health challenges, prioritize highly effective therapeutics, and improve affordable access.. Available at: https://www.who.int/news-room/detail/09-07-2019-who-updates-global-guidance-on-medicines-and-diagnostic-tests-to-address-health-challenges-prioritize-highly-effective-therapeutics-and-improve-affordable-access (accessed: 30 August 2019) 2019.

World Health Organization 2019a

World Health Organization. Executive Summary. The Selection and Use of Essential Medicines 2019. Report of the 22nd WHO Expert Committee on the 2019 Selection and Use of Essential Medicines.. Available at: https://apps.who.int/iris/bitstream/handle/10665/325773/WHO-MVP-EMP-IAU-2019.05-eng.pdf?ua=1 (accessed 30 August 2019).

Other published versions of this review

Piechotta 2018

Piechotta V, Jakob T, Scheckel B, Langer P, Monsef I, Scheid, C, et al. Multiple drug combinations of bortezomib, lenalidomide, and thalidomide for first-line treatment in adults with transplant-ineligible multiple myeloma: a network meta-analysis. PROSPERO 2018 CRD42018118092 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018118092. [Other:]

Classification pending references

Ades 2013

Ades AE, Caldwell DM, Reken S, Welton NJ, Sutton AJ, Dias S. Evidence synthesis for decision making 7: a reviewer's checklist. Medical Decision Making 2013;33(5):679-91.

Bucher 1997

Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of Clinical Epidemiology 1997;50(6):683-91.

Chaimani 2014

Chaimani A, Salanti G, Becker L, Caldwell D, Higgins J, Li T. Protocol template for a Cochrane intervention review that compares multiple interventions. 2014.

Dias 2013

Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Medical Decision Making 2013;33(5):641-56.

Furukawa 2006

Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. Journal of Clinical Epidemiology 2006;59(1):7-10.

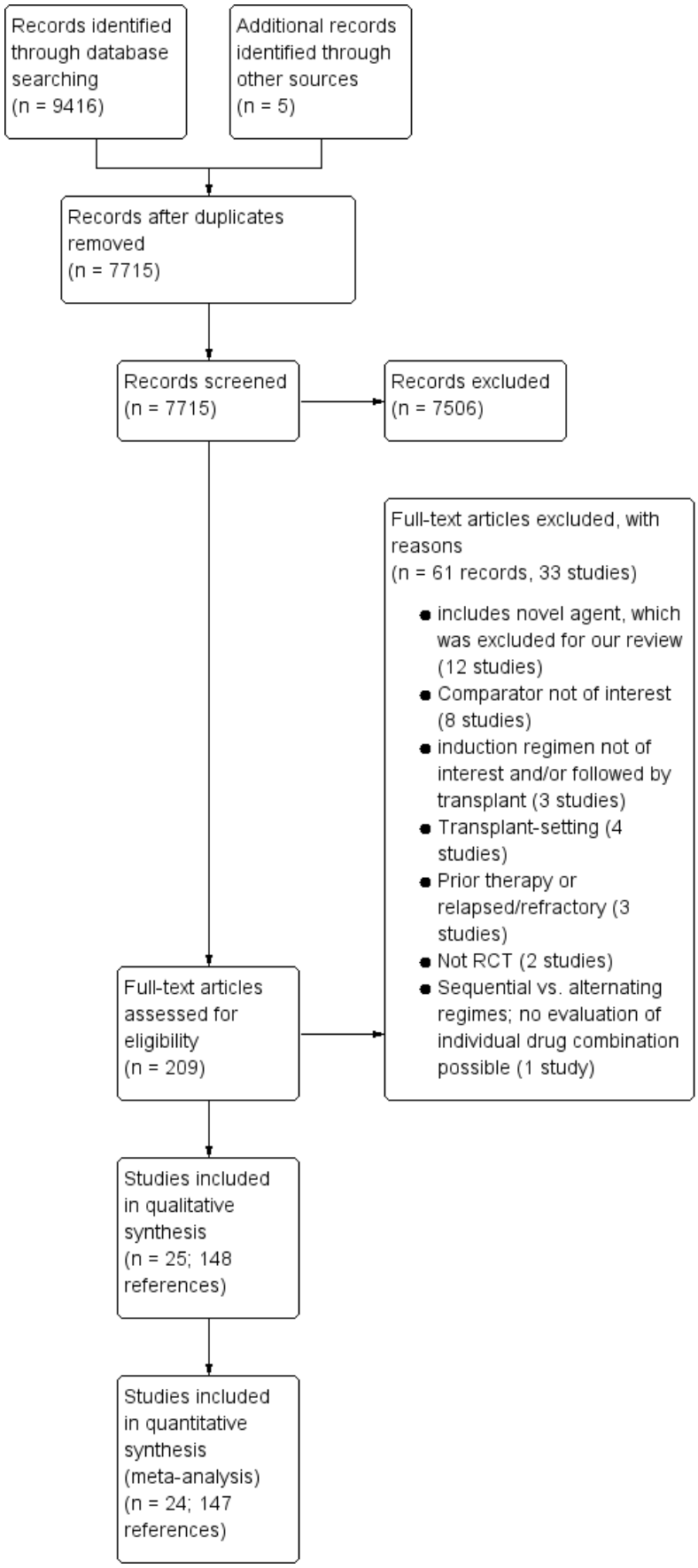
Krahn 2013

Krahn U, Binder H, König J. A graphical tool for locating inconsistency in network meta-analyses. BMC Medical Research Methodology 2013;13:35.

Data and analyses

Figures

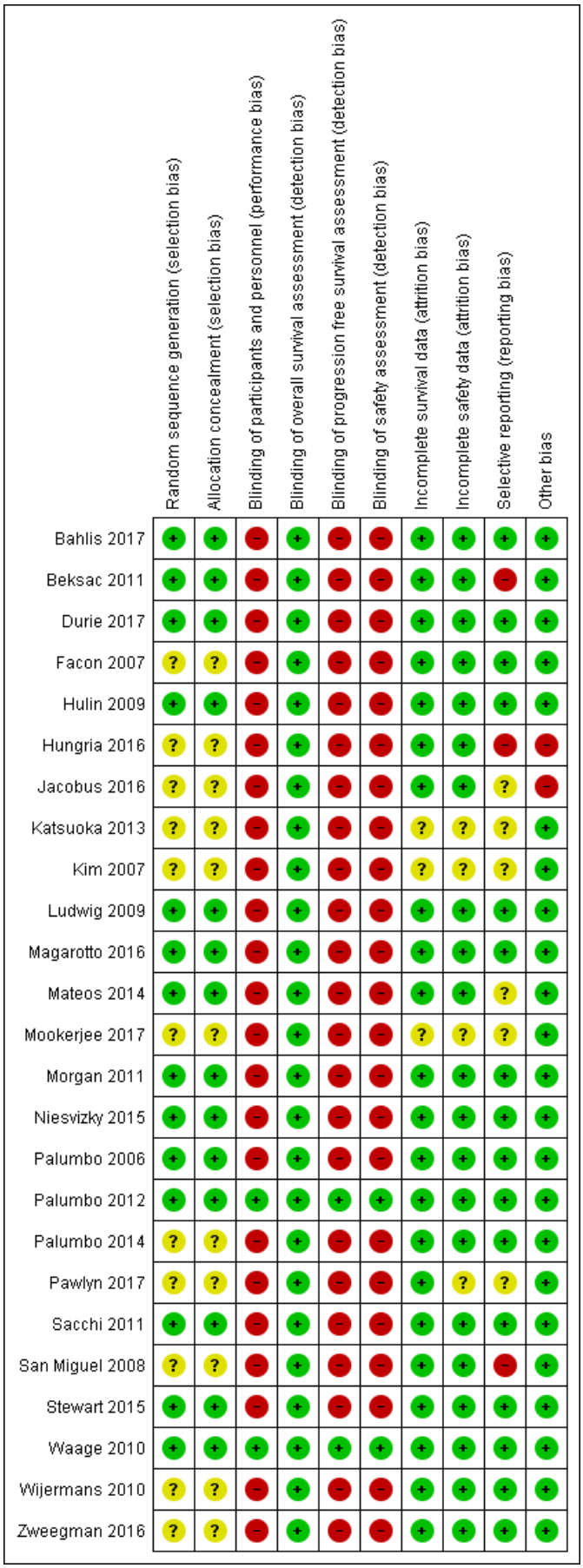
Figure 1



Caption

Study flow diagram.

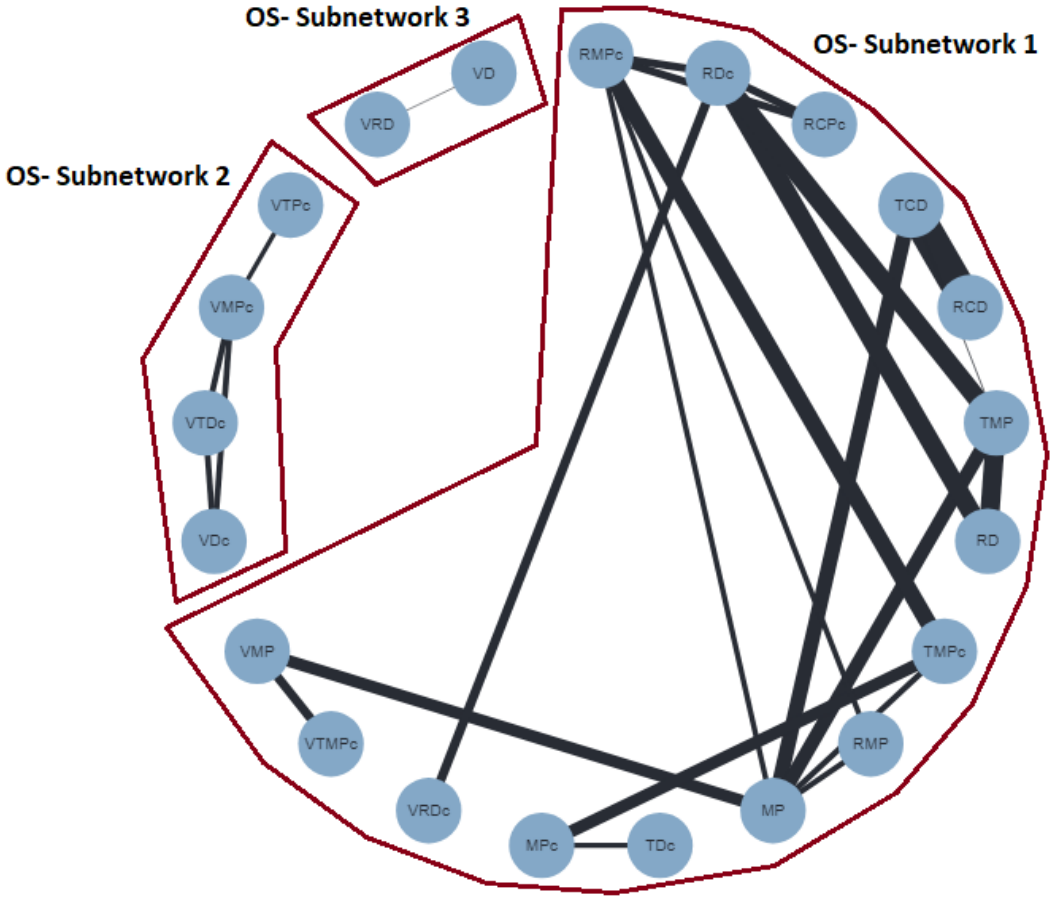
Figure 2



Caption

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

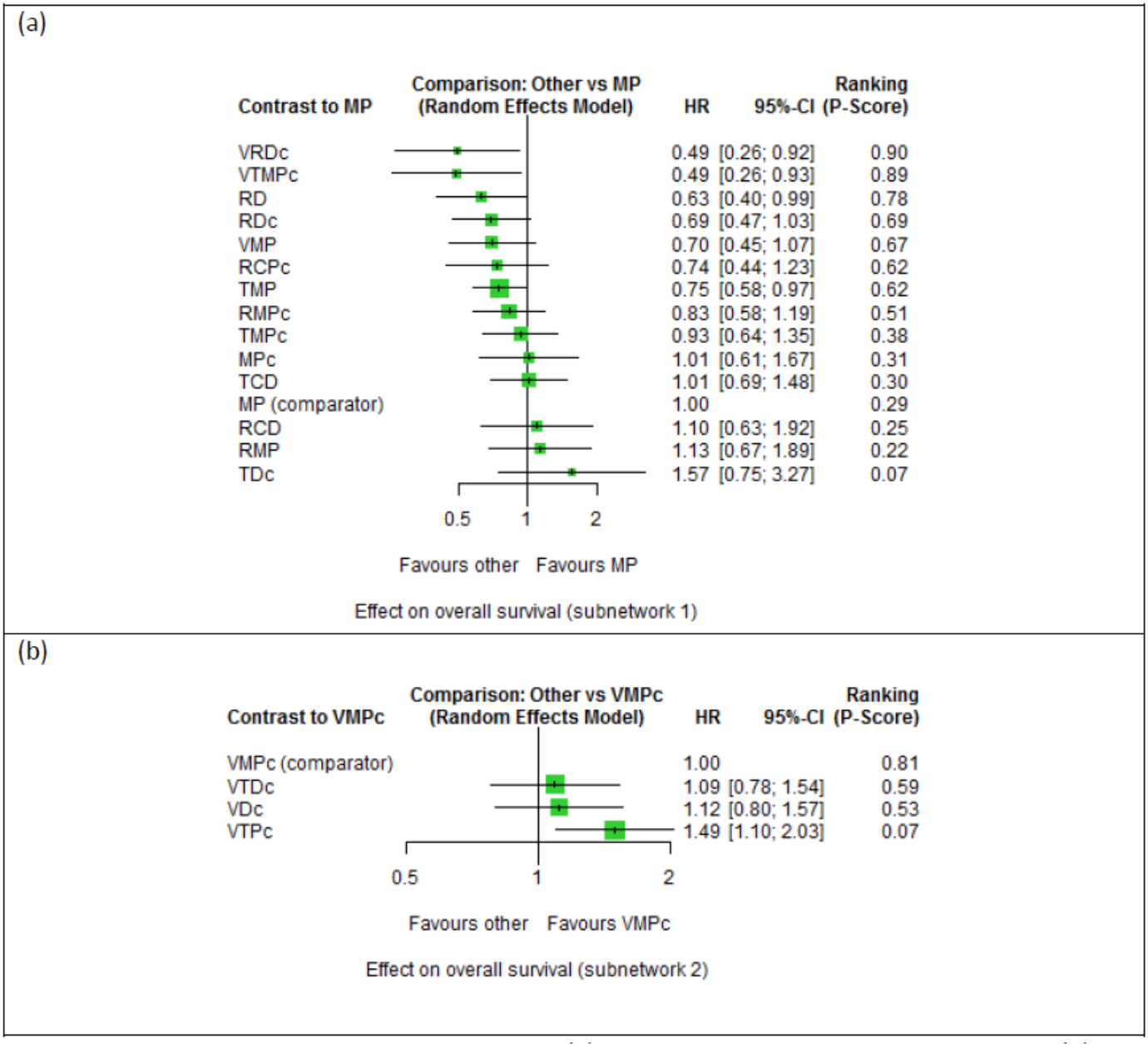
Figure 3



Caption

Network graph for outcome overall survival. Any two treatments are connected by a line when there is at least one study comparing the two treatments. Line width: number of patients

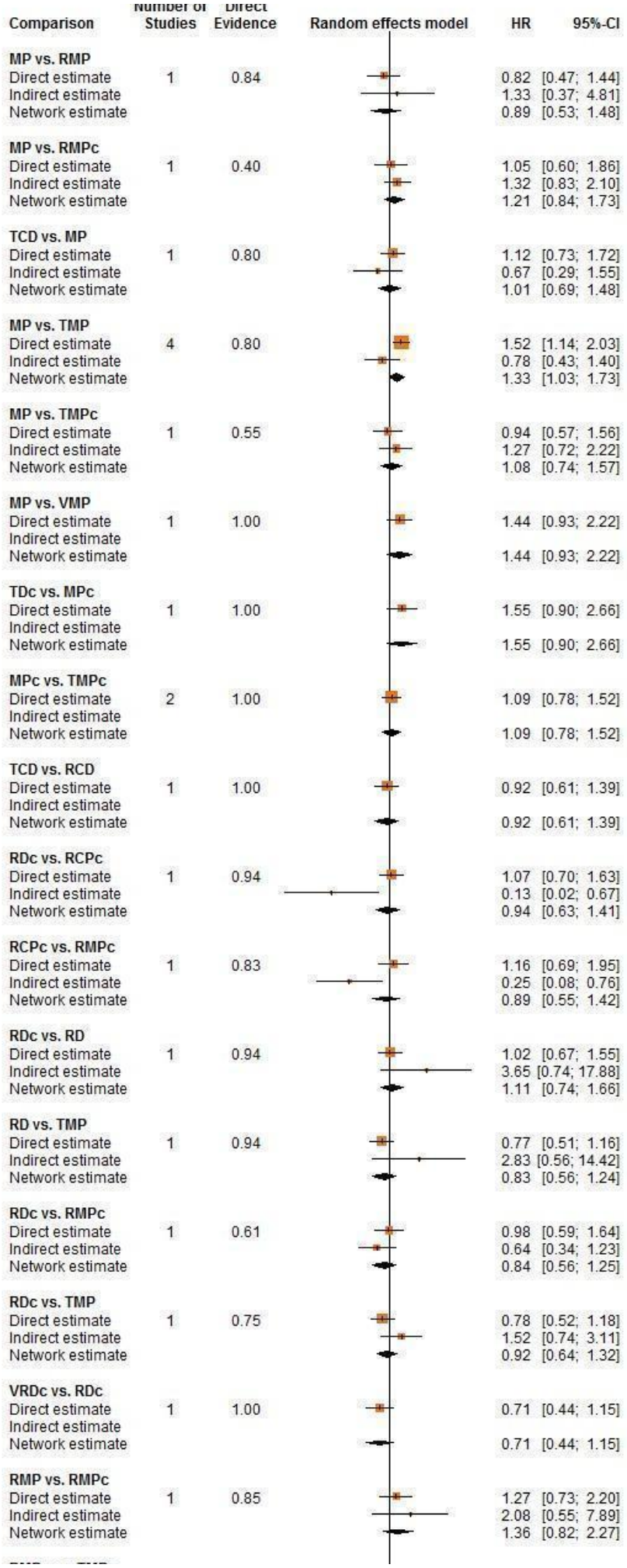
Figure 4

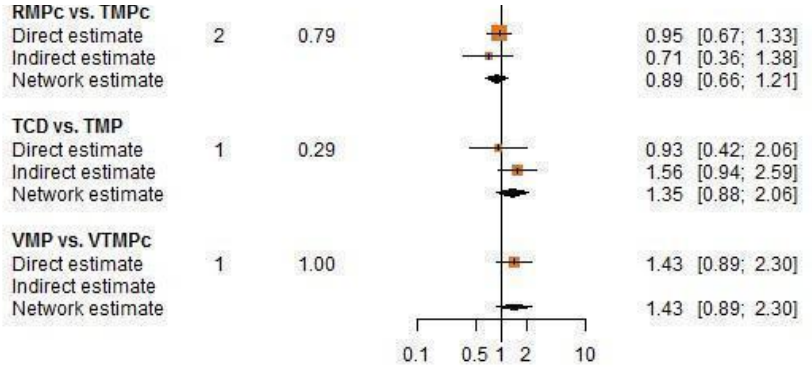


Caption

Forest plot for the outcome OS. (a) OS- Subnetwork 1. Reference treatment: MP. (b) OS- Subnetwork 2. Reference treatment: VMPc. Treatments are ordered by P-Score (descending)

Figure 5

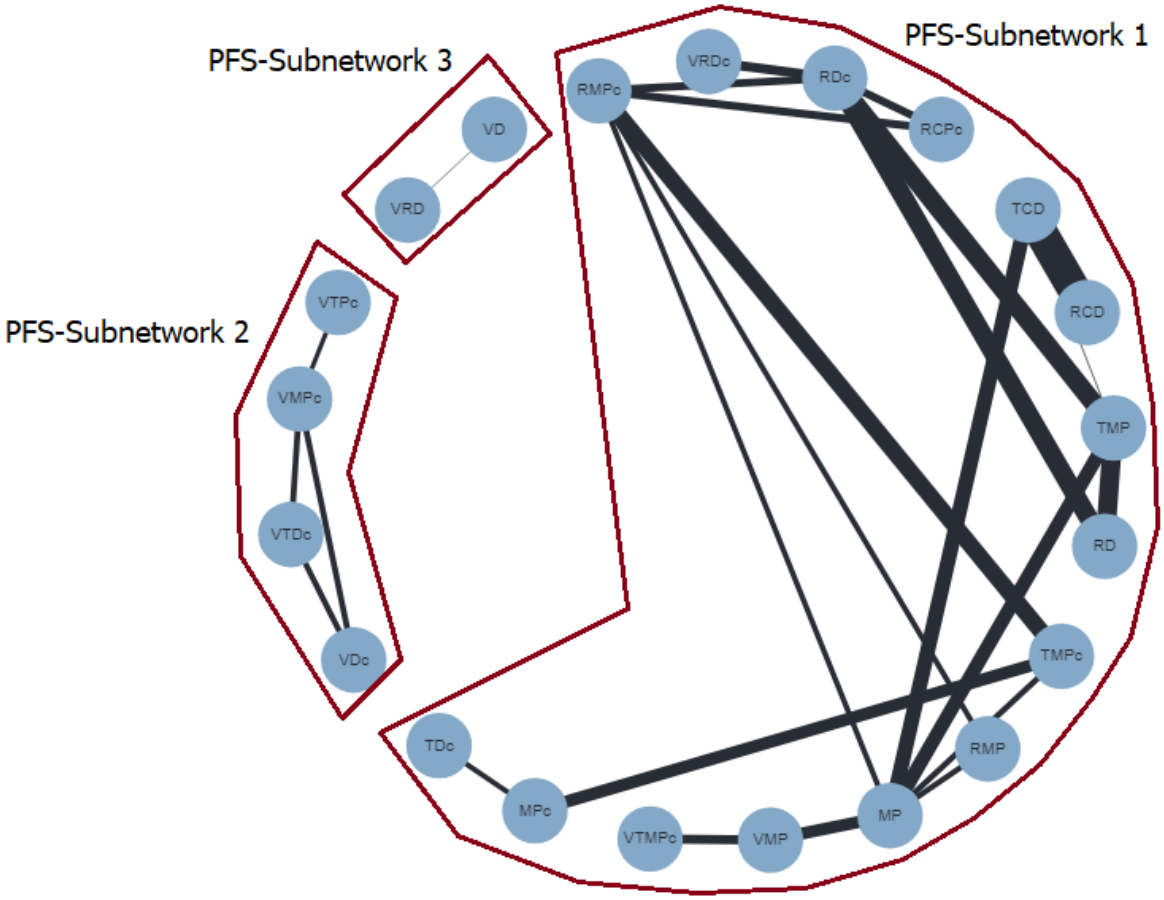

Comparison
Number of Studies
Direct Evidence
Random effects model
HR
95%-CI
MP vs. RMP
Direct estimate 1 0.84 0.82 [0.47; 1.44]
Indirect estimate 1.33 [0.37; 4.81]
Network estimate 0.89 [0.53; 1.48]
MP vs. RMPc
Direct estimate 1 0.40 1.05 [0.60; 1.86]
Indirect estimate 1.32 [0.83; 2.10]
Network estimate 1.21 [0.84; 1.73]
TCD vs. MP
Direct estimate 1 0.80 1.12 [0.73; 1.72]
Indirect estimate 0.67 [0.29; 1.55]
Network estimate 1.01 [0.69; 1.48]
MP vs. TMP
Direct estimate 4 0.80 1.52 [1.14; 2.03]
Indirect estimate 0.78 [0.43; 1.40]
Network estimate 1.33 [1.03; 1.73]
MP vs. TMPc
Direct estimate 1 0.55 0.94 [0.57; 1.56]
Indirect estimate 1.27 [0.72; 2.22]
Network estimate 1.08 [0.74; 1.57]
MP vs. VMP
Direct estimate 1 1.00 1.44 [0.93; 2.22]
Indirect estimate
Network estimate 1.44 [0.93; 2.22]
TDc vs. MPc
Direct estimate 1 1.00 1.55 [0.90; 2.66]
Indirect estimate
Network estimate 1.55 [0.90; 2.66]
MPc vs. TMPc
Direct estimate 2 1.00 1.09 [0.78; 1.52]
Indirect estimate
Network estimate 1.09 [0.78; 1.52]
TCD vs. RCD
Direct estimate 1 1.00 0.92 [0.61; 1.39]
Indirect estimate
Network estimate 0.92 [0.61; 1.39]
RDc vs. RCPc
Direct estimate 1 0.94 1.07 [0.70; 1.63]
Indirect estimate 0.13 [0.02; 0.67]
Network estimate 0.94 [0.63; 1.41]
RCPc vs. RMPc
Direct estimate 1 0.83 1.16 [0.69; 1.95]
Indirect estimate 0.25 [0.08; 0.76]
Network estimate 0.89 [0.55; 1.42]
RDc vs. RD
Direct estimate 1 0.94 1.02 [0.67; 1.55]
Indirect estimate 3.65 [0.74; 17.88]
Network estimate 1.11 [0.74; 1.66]
RD vs. TMP
Direct estimate 1 0.94 0.77 [0.51; 1.16]
Indirect estimate 2.83 [0.56; 14.42]
Network estimate 0.83 [0.56; 1.24]
RDc vs. RMPc
Direct estimate 1 0.61 0.98 [0.59; 1.64]
Indirect estimate 0.64 [0.34; 1.23]
Network estimate 0.84 [0.56; 1.25]
RDc vs. TMP
Direct estimate 1 0.75 0.78 [0.52; 1.18]
Indirect estimate 1.52 [0.74; 3.11]
Network estimate 0.92 [0.64; 1.32]
VRDc vs. RDc
Direct estimate 1 1.00 0.71 [0.44; 1.15]
Indirect estimate
Network estimate 0.71 [0.44; 1.15]
RMP vs. RMPc
Direct estimate 1 0.85 1.27 [0.73; 2.20]
Indirect estimate 2.08 [0.55; 7.89]
Network estimate 1.36 [0.82; 2.27]



Caption

Local approach to check inconsistency - comparison of direct and indirect estimate for closed loops in OS-Subnetwork 1

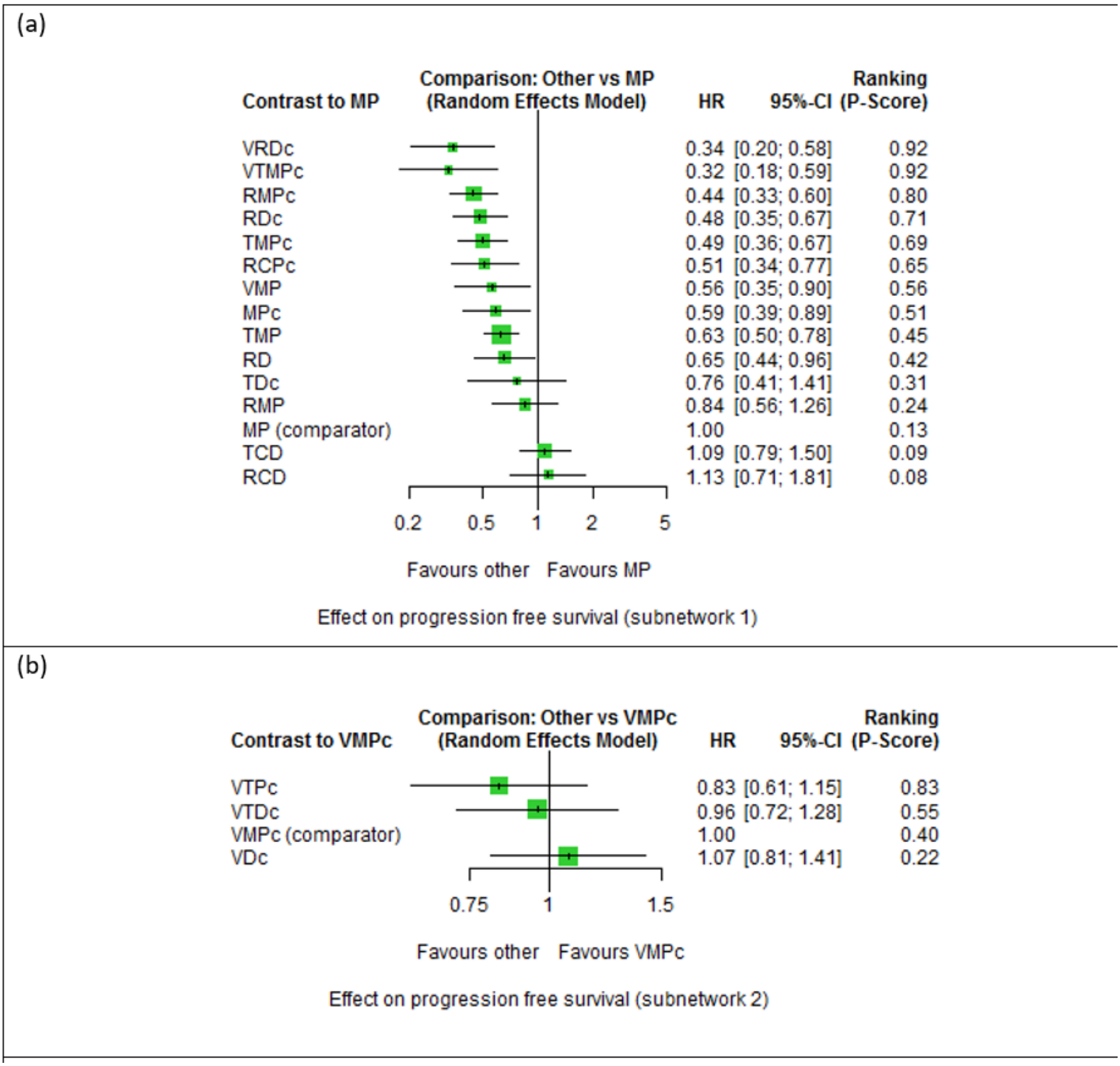
Figure 6



Caption

Network graph for the outcome PFS. Any two treatments are connected by a line when there is at least one study comparing the two treatments. Line width: number of patients

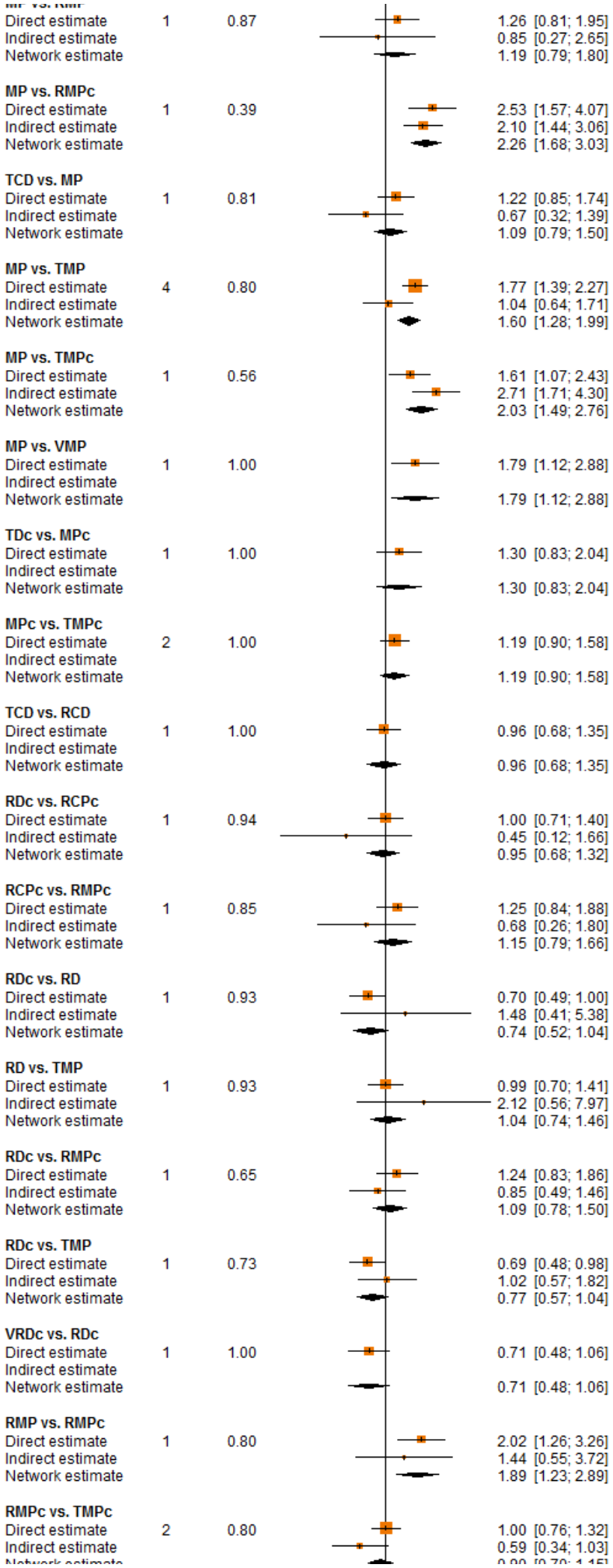
Figure 7

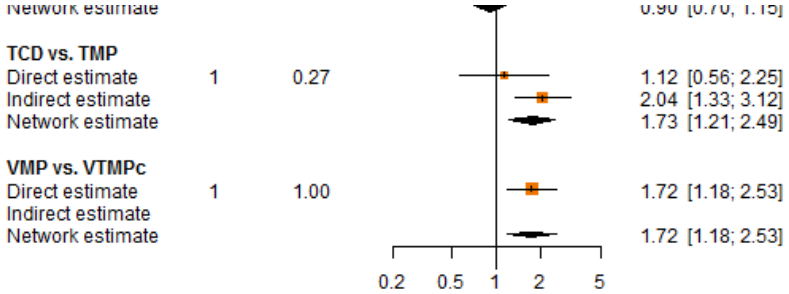


Caption

Forest plot for the outcome PFS. (a) PFS–subnetwork 1. Reference treatment: MP. (b) PFS–subnetwork 2. Reference treatment: VMPc. Treatments are ordered by P-Score (descending)

Figure 8

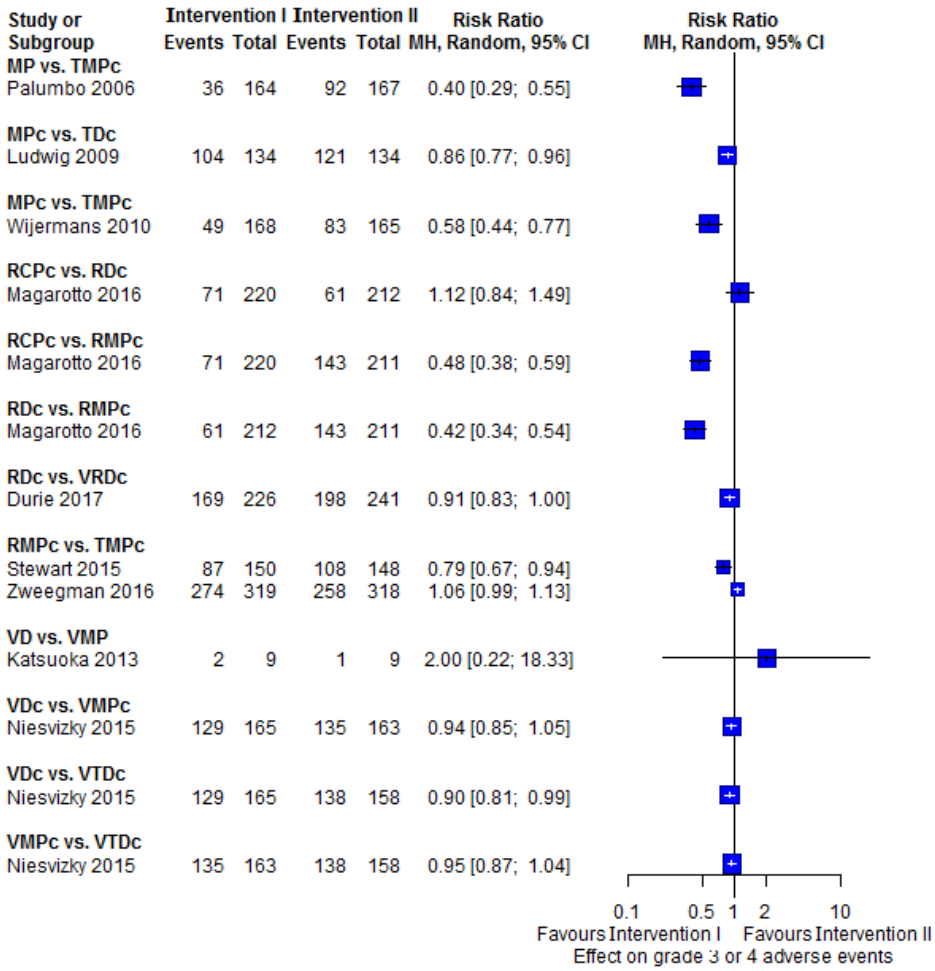

Direct estimate 1 0.87 1.26 [0.81; 1.95]
Indirect estimate 0.85 [0.27; 2.65]
Network estimate 1.19 [0.79; 1.80]
MP vs. RMPc
Direct estimate 1 0.39 2.53 [1.57; 4.07]
Indirect estimate 2.10 [1.44; 3.06]
Network estimate 2.26 [1.68; 3.03]
TCD vs. MP
Direct estimate 1 0.81 1.22 [0.85; 1.74]
Indirect estimate 0.67 [0.32; 1.39]
Network estimate 1.09 [0.79; 1.50]
MP vs. TMP
Direct estimate 4 0.80 1.77 [1.39; 2.27]
Indirect estimate 1.04 [0.64; 1.71]
Network estimate 1.60 [1.28; 1.99]
MP vs. TMPc
Direct estimate 1 0.56 1.61 [1.07; 2.43]
Indirect estimate 2.71 [1.71; 4.30]
Network estimate 2.03 [1.49; 2.76]
MP vs. VMP
Direct estimate 1 1.00 1.79 [1.12; 2.88]
Indirect estimate
Network estimate 1.79 [1.12; 2.88]
TDc vs. MPc
Direct estimate 1 1.00 1.30 [0.83; 2.04]
Indirect estimate
Network estimate 1.30 [0.83; 2.04]
MPc vs. TMPc
Direct estimate 2 1.00 1.19 [0.90; 1.58]
Indirect estimate
Network estimate 1.19 [0.90; 1.58]
TCD vs. RCD
Direct estimate 1 1.00 0.96 [0.68; 1.35]
Indirect estimate
Network estimate 0.96 [0.68; 1.35]
RDc vs. RCPc
Direct estimate 1 0.94 1.00 [0.71; 1.40]
Indirect estimate 0.45 [0.12; 1.66]
Network estimate 0.95 [0.68; 1.32]
RCPc vs. RMPc
Direct estimate 1 0.85 1.25 [0.84; 1.88]
Indirect estimate 0.68 [0.26; 1.80]
Network estimate 1.15 [0.79; 1.66]
RDc vs. RD
Direct estimate 1 0.93 0.70 [0.49; 1.00]
Indirect estimate 1.48 [0.41; 5.38]
Network estimate 0.74 [0.52; 1.04]
RD vs. TMP
Direct estimate 1 0.93 0.99 [0.70; 1.41]
Indirect estimate 2.12 [0.56; 7.97]
Network estimate 1.04 [0.74; 1.46]
RDc vs. RMPc
Direct estimate 1 0.65 1.24 [0.83; 1.86]
Indirect estimate 0.85 [0.49; 1.46]
Network estimate 1.09 [0.78; 1.50]
RDc vs. TMP
Direct estimate 1 0.73 0.69 [0.48; 0.98]
Indirect estimate 1.02 [0.57; 1.82]
Network estimate 0.77 [0.57; 1.04]
VRDc vs. RDc
Direct estimate 1 1.00 0.71 [0.48; 1.06]
Indirect estimate
Network estimate 0.71 [0.48; 1.06]
RMP vs. RMPc
Direct estimate 1 0.80 2.02 [1.26; 3.26]
Indirect estimate 1.44 [0.55; 3.72]
Network estimate 1.89 [1.23; 2.89]
RMPc vs. TMPc
Direct estimate 2 0.80 1.00 [0.76; 1.32]
Indirect estimate 0.59 [0.34; 1.03]



Caption

Local approach to check inconsistency – comparison of direct and indirect estimate for closed loops in PFS-subnetwork 1

Figure 9



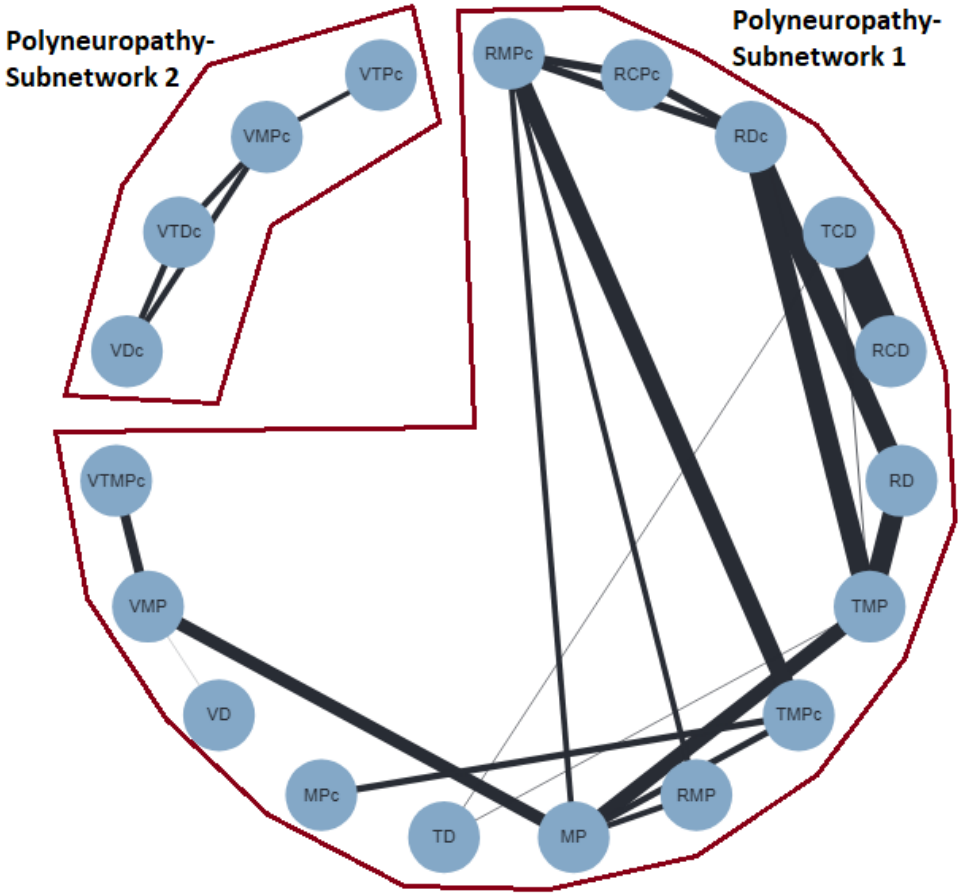
Caption

Pairwise comparisons for the outcome grade 3 or 4 adverse events.

The first-named interventions are referred to as "intervention I". The last-named interventions are referred to as "intervention II".

A RR < 1 indicates an advantage for the experimental intervention and correspondingly a smaller risk for AEs grade 3 or 4.

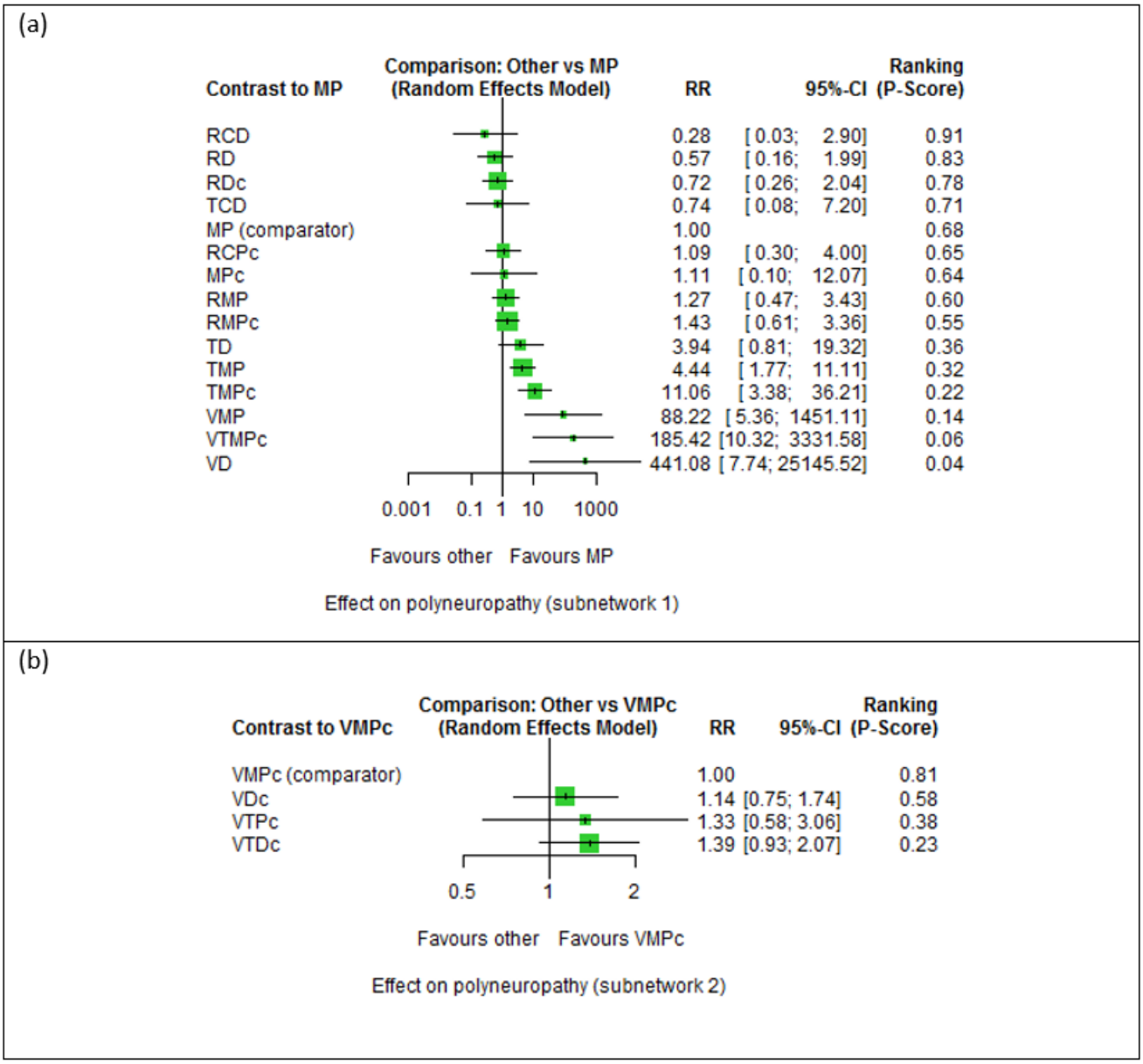
Figure 10



Caption

Network graph for the outcome polyneuropathy. A line connects any two treatments when there is at least one study comparing the two treatments. Line width: number of patients

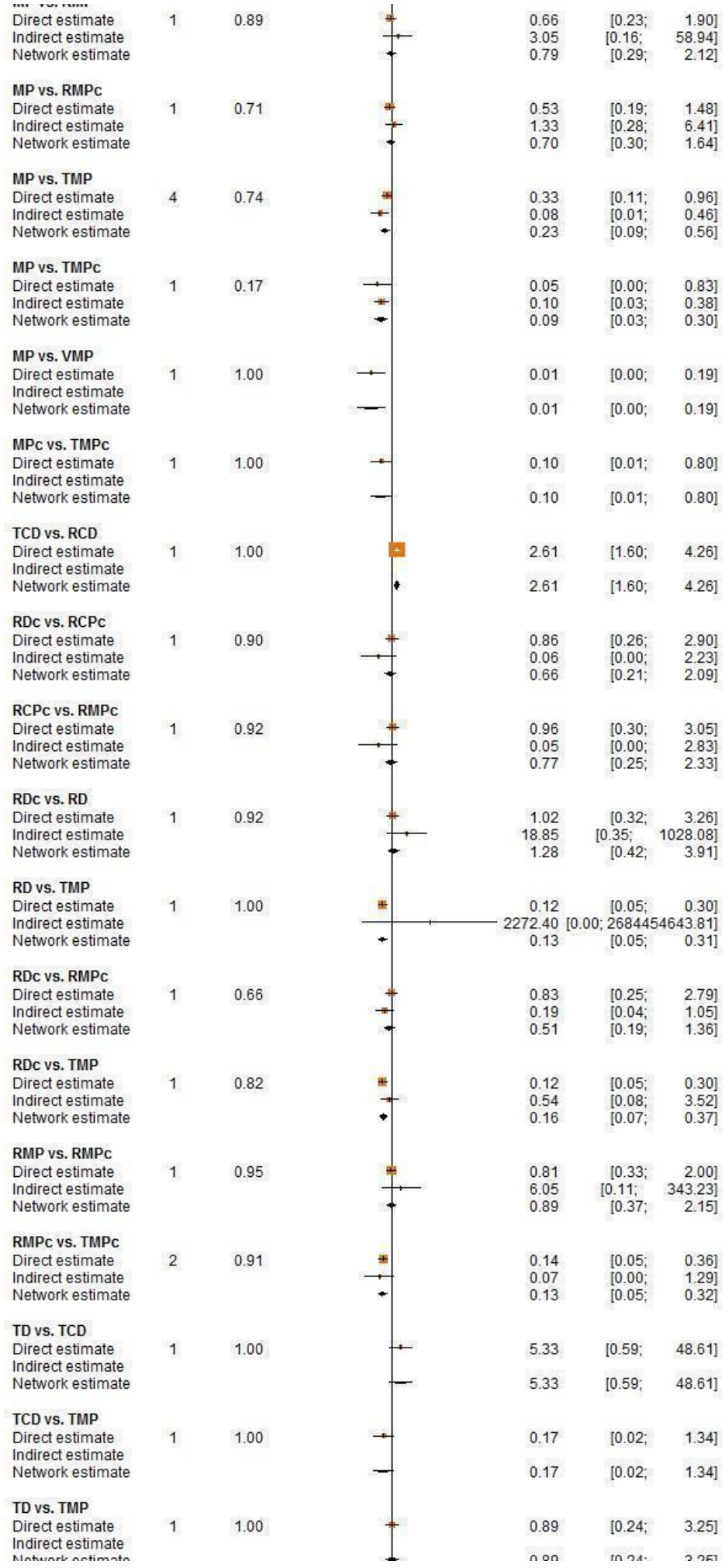
Figure 11



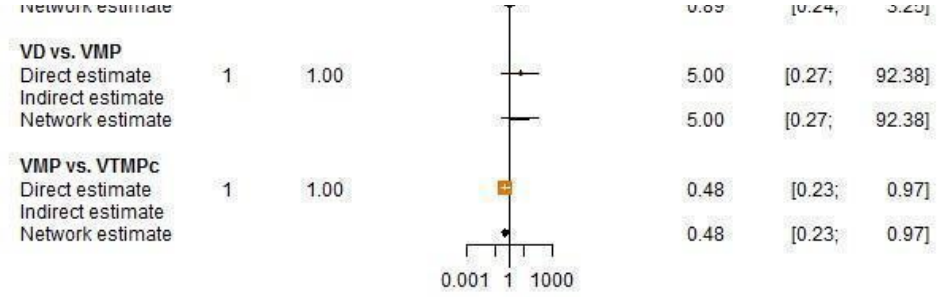
Caption

Forest plot for outcome polyneuropathy. (a) polyneuropathy- sSubnetwork 1. Reference treatment: MP. (b) polyneuropathy-subnetwork 2. Reference treatment: VMPc. Treatments are ordered by P-Score (descending).

Figure 12



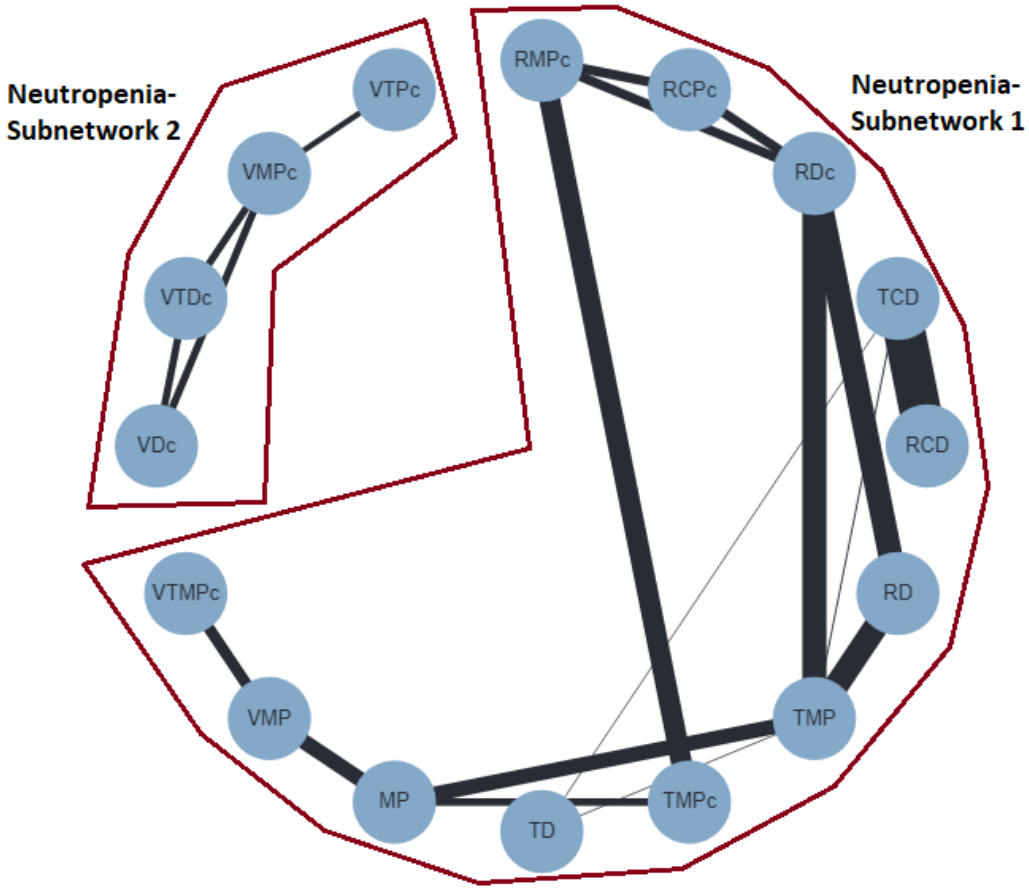
Direct estimate	1	0.89	0.66	[0.23;	1.90]
Indirect estimate			3.05	[0.16;	58.94]
Network estimate			0.79	[0.29;	2.12]
MP vs. RMPc					
Direct estimate	1	0.71	0.53	[0.19;	1.48]
Indirect estimate			1.33	[0.28;	6.41]
Network estimate			0.70	[0.30;	1.64]
MP vs. TMP					
Direct estimate	4	0.74	0.33	[0.11;	0.96]
Indirect estimate			0.08	[0.01;	0.46]
Network estimate			0.23	[0.09;	0.56]
MP vs. TMPc					
Direct estimate	1	0.17	0.05	[0.00;	0.83]
Indirect estimate			0.10	[0.03;	0.38]
Network estimate			0.09	[0.03;	0.30]
MP vs. VMP					
Direct estimate	1	1.00	0.01	[0.00;	0.19]
Indirect estimate					
Network estimate			0.01	[0.00;	0.19]
MPc vs. TMPc					
Direct estimate	1	1.00	0.10	[0.01;	0.80]
Indirect estimate					
Network estimate			0.10	[0.01;	0.80]
TCD vs. RCD					
Direct estimate	1	1.00	2.61	[1.60;	4.26]
Indirect estimate					
Network estimate			2.61	[1.60;	4.26]
RDc vs. RCPc					
Direct estimate	1	0.90	0.86	[0.26;	2.90]
Indirect estimate			0.06	[0.00;	2.23]
Network estimate			0.66	[0.21;	2.09]
RCPc vs. RMPc					
Direct estimate	1	0.92	0.96	[0.30;	3.05]
Indirect estimate			0.05	[0.00;	2.83]
Network estimate			0.77	[0.25;	2.33]
RDc vs. RD					
Direct estimate	1	0.92	1.02	[0.32;	3.26]
Indirect estimate			18.85	[0.35;	1028.08]
Network estimate			1.28	[0.42;	3.91]
RD vs. TMP					
Direct estimate	1	1.00	0.12	[0.05;	0.30]
Indirect estimate			2272.40	[0.00;	2684454643.81]
Network estimate			0.13	[0.05;	0.31]
RDc vs. RMPc					
Direct estimate	1	0.66	0.83	[0.25;	2.79]
Indirect estimate			0.19	[0.04;	1.05]
Network estimate			0.51	[0.19;	1.36]
RDc vs. TMP					
Direct estimate	1	0.82	0.12	[0.05;	0.30]
Indirect estimate			0.54	[0.08;	3.52]
Network estimate			0.16	[0.07;	0.37]
RMP vs. RMPc					
Direct estimate	1	0.95	0.81	[0.33;	2.00]
Indirect estimate			6.05	[0.11;	343.23]
Network estimate			0.89	[0.37;	2.15]
RMPc vs. TMPc					
Direct estimate	2	0.91	0.14	[0.05;	0.36]
Indirect estimate			0.07	[0.00;	1.29]
Network estimate			0.13	[0.05;	0.32]
TD vs. TCD					
Direct estimate	1	1.00	5.33	[0.59;	48.61]
Indirect estimate					
Network estimate			5.33	[0.59;	48.61]
TCD vs. TMP					
Direct estimate	1	1.00	0.17	[0.02;	1.34]
Indirect estimate					
Network estimate			0.17	[0.02;	1.34]
TD vs. TMP					
Direct estimate	1	1.00	0.89	[0.24;	3.25]
Indirect estimate					
Network estimate			0.89	[0.24;	3.25]



Caption

Local approach to check inconsistency – comparison of direct and indirect estimate for closed loops in polyneuropathy–subnetwork 1

Figure 13

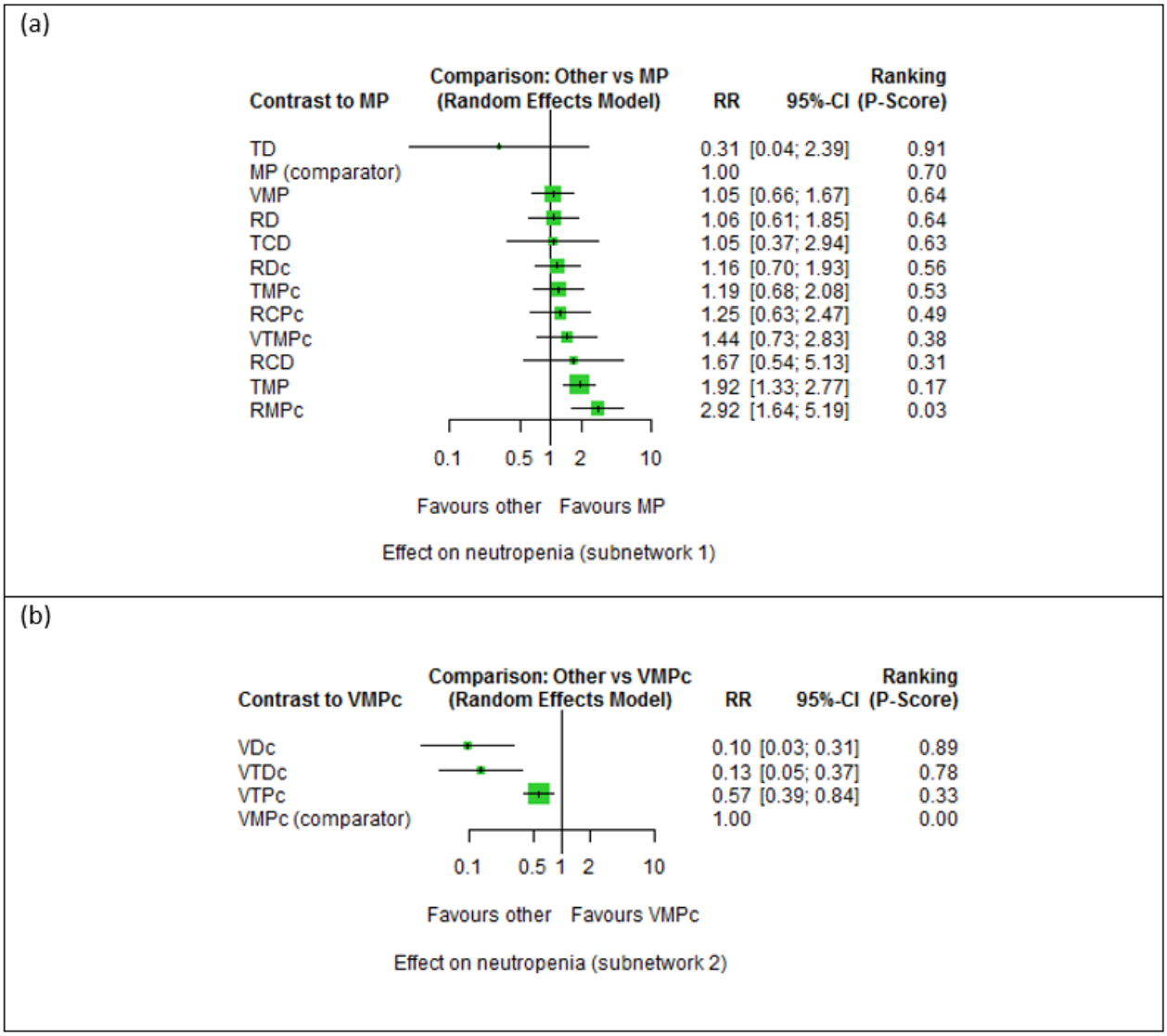


Caption

Network graph for the outcome neutropenia. A line connects any two treatments when there is at least one study

comparing the two treatments. Line width: number of patients

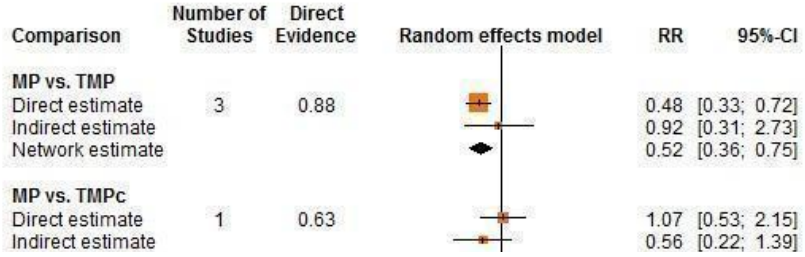
Figure 14

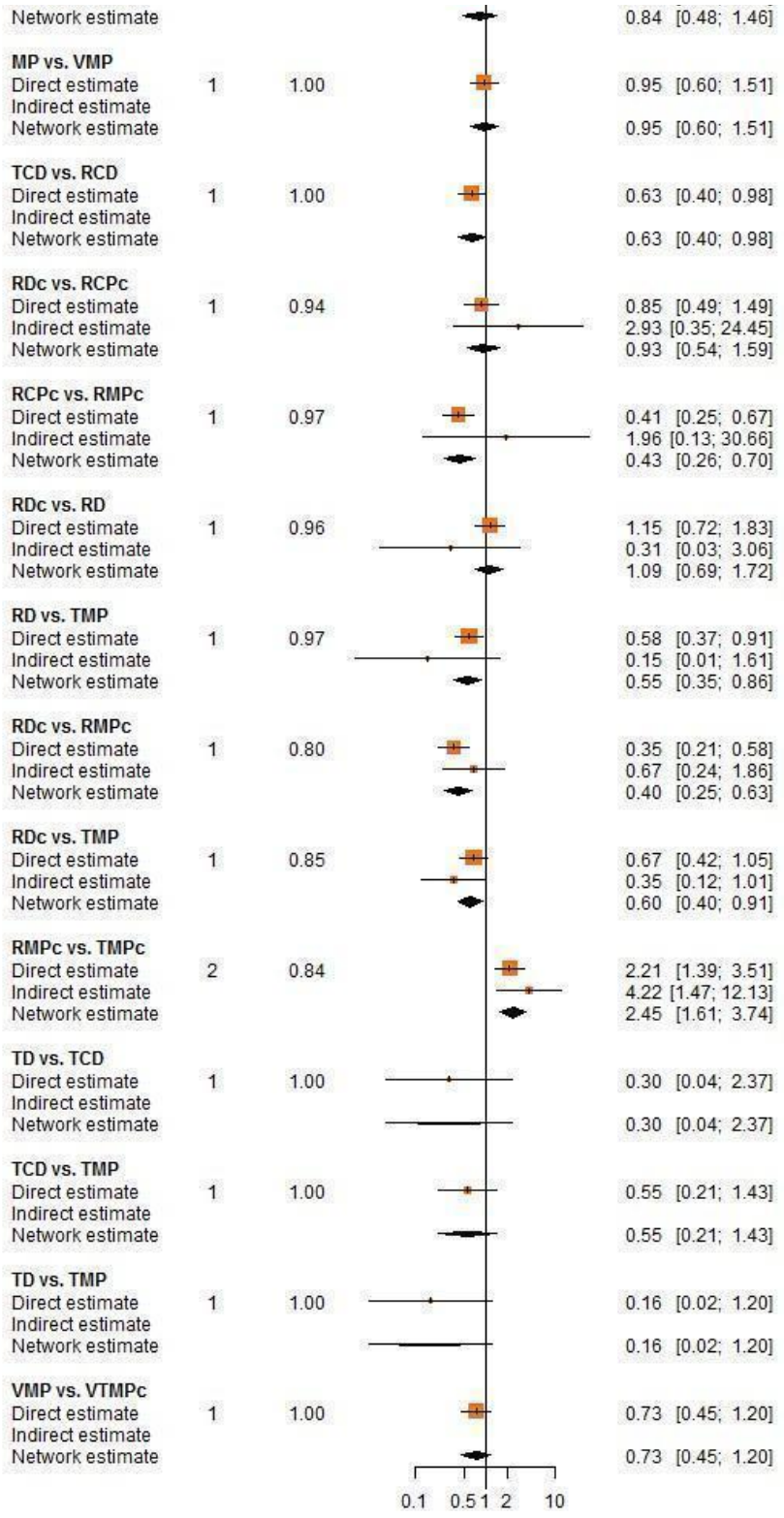


Caption

Forest plot for outcome neutropenia. (a) neutropenia–subnetwork 1. Reference treatment: MP. (b) neutropenia–subnetwork 2. Reference treatment: VMPc. Treatments are ordered by P-Score (descending).

Figure 15



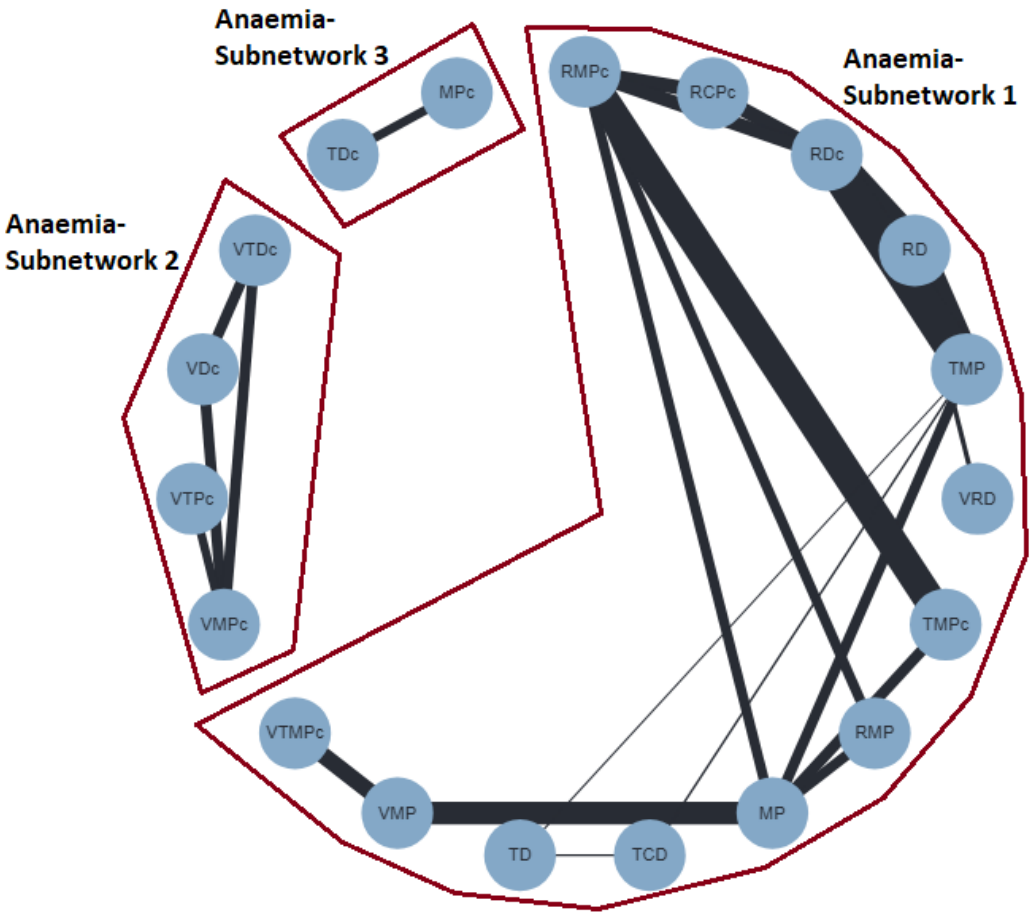


Caption

Local approach to check inconsistency – comparison of direct and indirect estimate for closed loops in

neutropenia-subnetwork 1

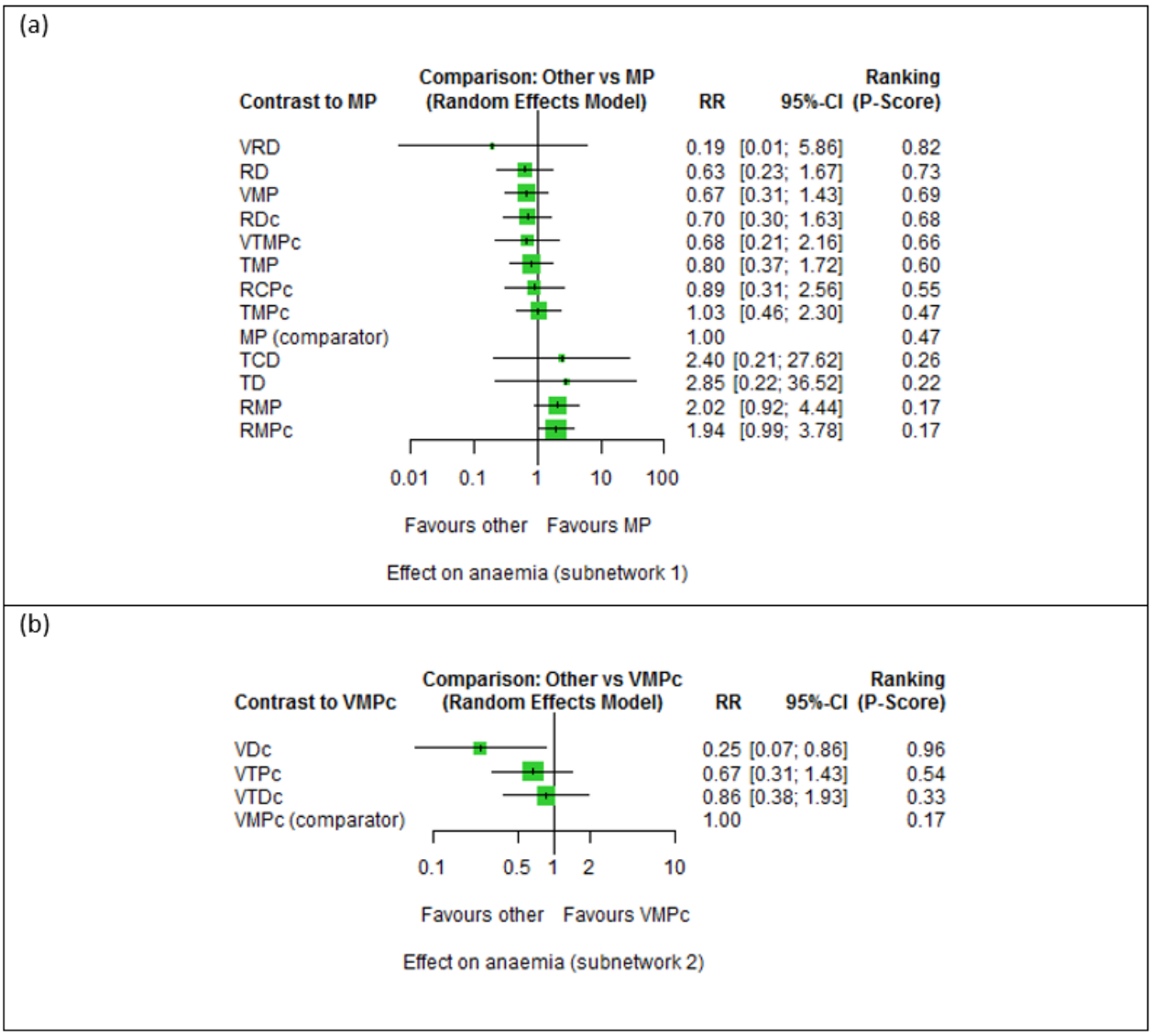
Figure 16



Caption

Network graph for the outcome anaemia. A line connects any two treatments when there is at least one study comparing the two treatments. Line width: number of patients

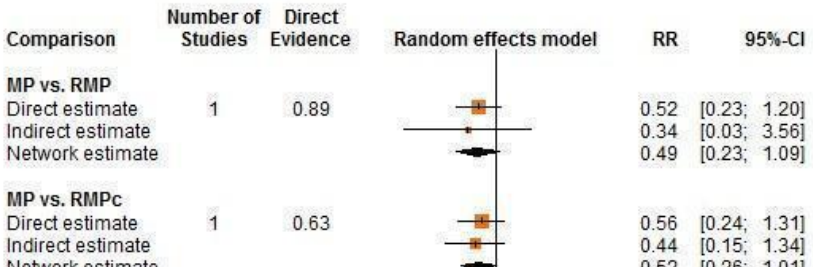
Figure 17

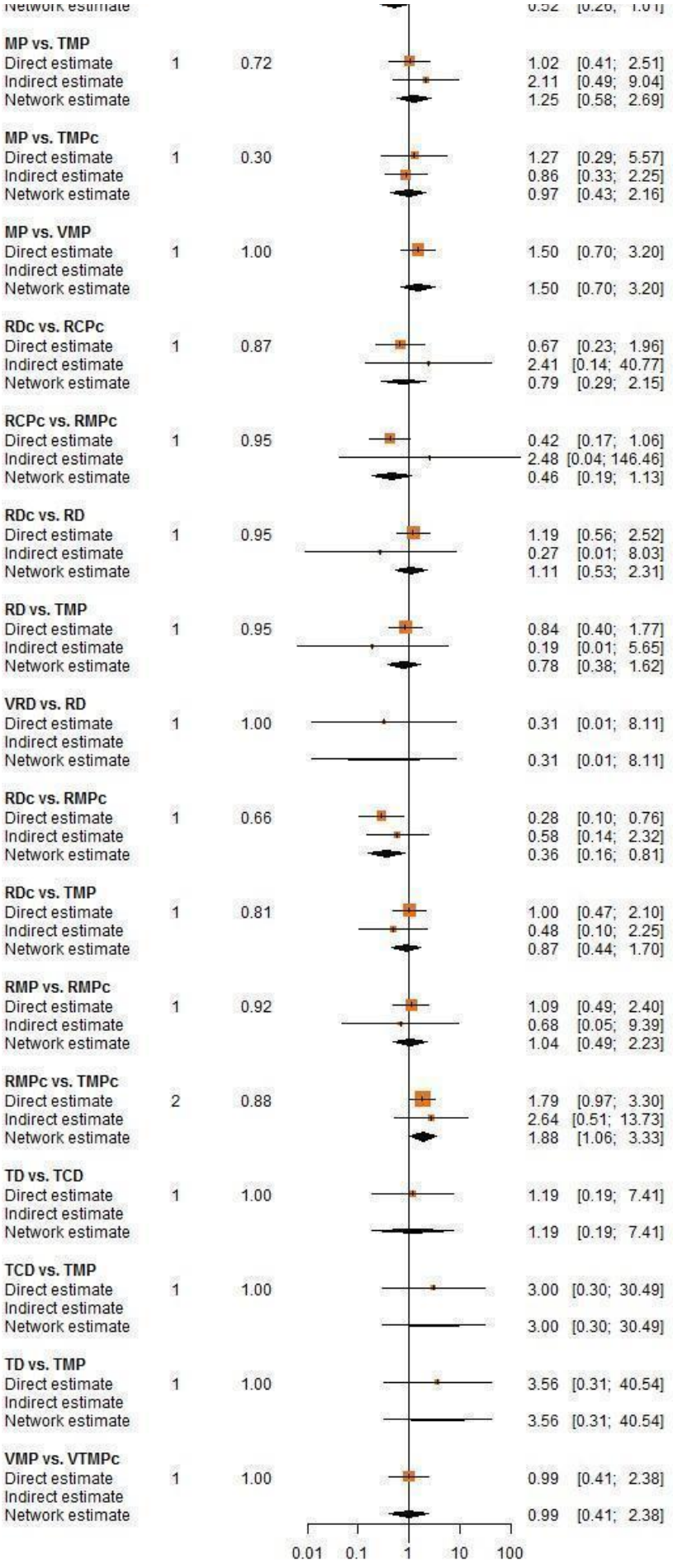


Caption

Forest plot for outcome anaemia. (a) anaemia–subnetwork 1. Reference treatment: MP. (b) anaemia–subnetwork 2. Reference treatment: VMPc. Treatments are ordered by P-Score (descending).

Figure 18

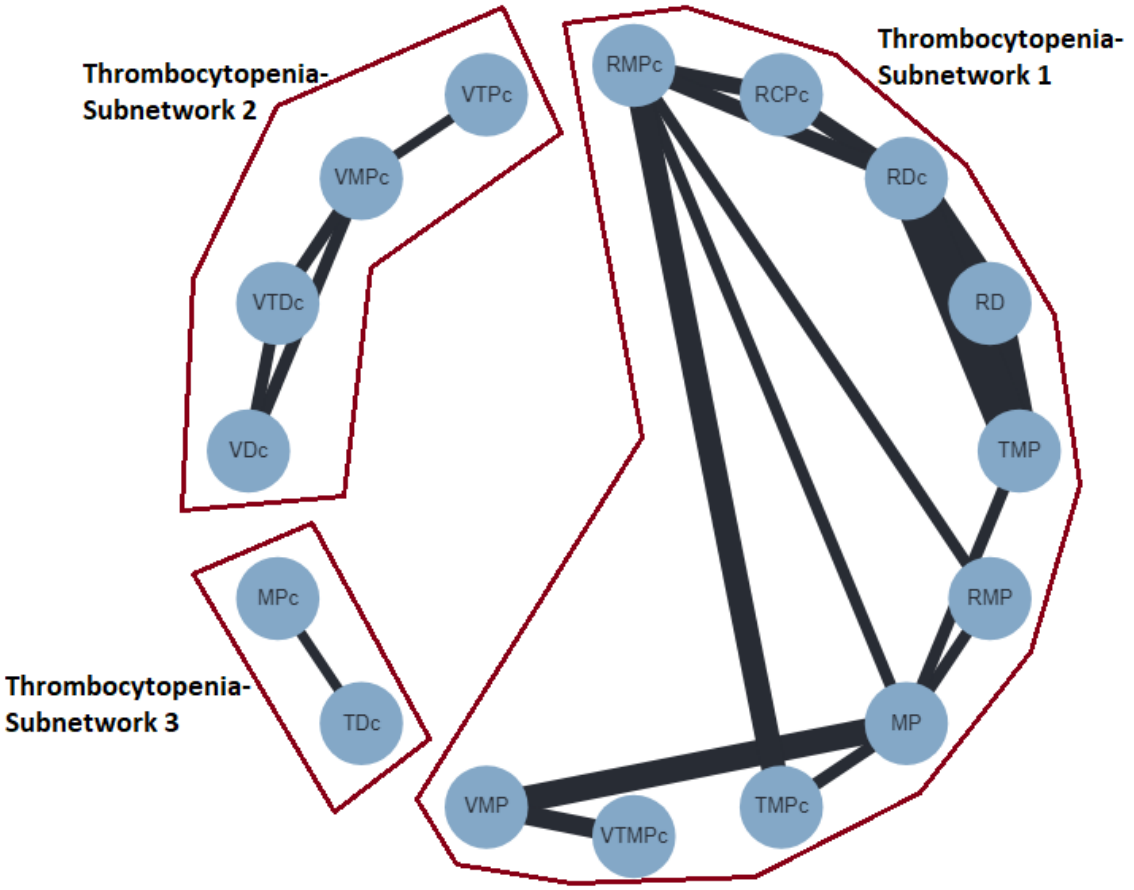



Network estimate 0.52 [0.26; 1.01]
MP vs. TMP
Direct estimate 1 0.72 1.02 [0.41; 2.51]
Indirect estimate 2.11 [0.49; 9.04]
Network estimate 1.25 [0.58; 2.69]
MP vs. TMPc
Direct estimate 1 0.30 1.27 [0.29; 5.57]
Indirect estimate 0.86 [0.33; 2.25]
Network estimate 0.97 [0.43; 2.16]
MP vs. VMP
Direct estimate 1 1.00 1.50 [0.70; 3.20]
Indirect estimate
Network estimate 1.50 [0.70; 3.20]
RDc vs. RCPc
Direct estimate 1 0.87 0.67 [0.23; 1.96]
Indirect estimate 2.41 [0.14; 40.77]
Network estimate 0.79 [0.29; 2.15]
RCPc vs. RMPc
Direct estimate 1 0.95 0.42 [0.17; 1.06]
Indirect estimate 2.48 [0.04; 146.46]
Network estimate 0.46 [0.19; 1.13]
RDc vs. RD
Direct estimate 1 0.95 1.19 [0.56; 2.52]
Indirect estimate 0.27 [0.01; 8.03]
Network estimate 1.11 [0.53; 2.31]
RD vs. TMP
Direct estimate 1 0.95 0.84 [0.40; 1.77]
Indirect estimate 0.19 [0.01; 5.65]
Network estimate 0.78 [0.38; 1.62]
VRD vs. RD
Direct estimate 1 1.00 0.31 [0.01; 8.11]
Indirect estimate
Network estimate 0.31 [0.01; 8.11]
RDc vs. RMPc
Direct estimate 1 0.66 0.28 [0.10; 0.76]
Indirect estimate 0.58 [0.14; 2.32]
Network estimate 0.36 [0.16; 0.81]
RDc vs. TMP
Direct estimate 1 0.81 1.00 [0.47; 2.10]
Indirect estimate 0.48 [0.10; 2.25]
Network estimate 0.87 [0.44; 1.70]
RMP vs. RMPc
Direct estimate 1 0.92 1.09 [0.49; 2.40]
Indirect estimate 0.68 [0.05; 9.39]
Network estimate 1.04 [0.49; 2.23]
RMPc vs. TMPc
Direct estimate 2 0.88 1.79 [0.97; 3.30]
Indirect estimate 2.64 [0.51; 13.73]
Network estimate 1.88 [1.06; 3.33]
TD vs. TCD
Direct estimate 1 1.00 1.19 [0.19; 7.41]
Indirect estimate
Network estimate 1.19 [0.19; 7.41]
TCD vs. TMP
Direct estimate 1 1.00 3.00 [0.30; 30.49]
Indirect estimate
Network estimate 3.00 [0.30; 30.49]
TD vs. TMP
Direct estimate 1 1.00 3.56 [0.31; 40.54]
Indirect estimate
Network estimate 3.56 [0.31; 40.54]
VMP vs. VTMPc
Direct estimate 1 1.00 0.99 [0.41; 2.38]
Indirect estimate
Network estimate 0.99 [0.41; 2.38]
0.01 0.1 1 10 100

Caption

Local approach to check inconsistency – comparison of direct and indirect estimate for closed loops in anaemia–subnetwork 1

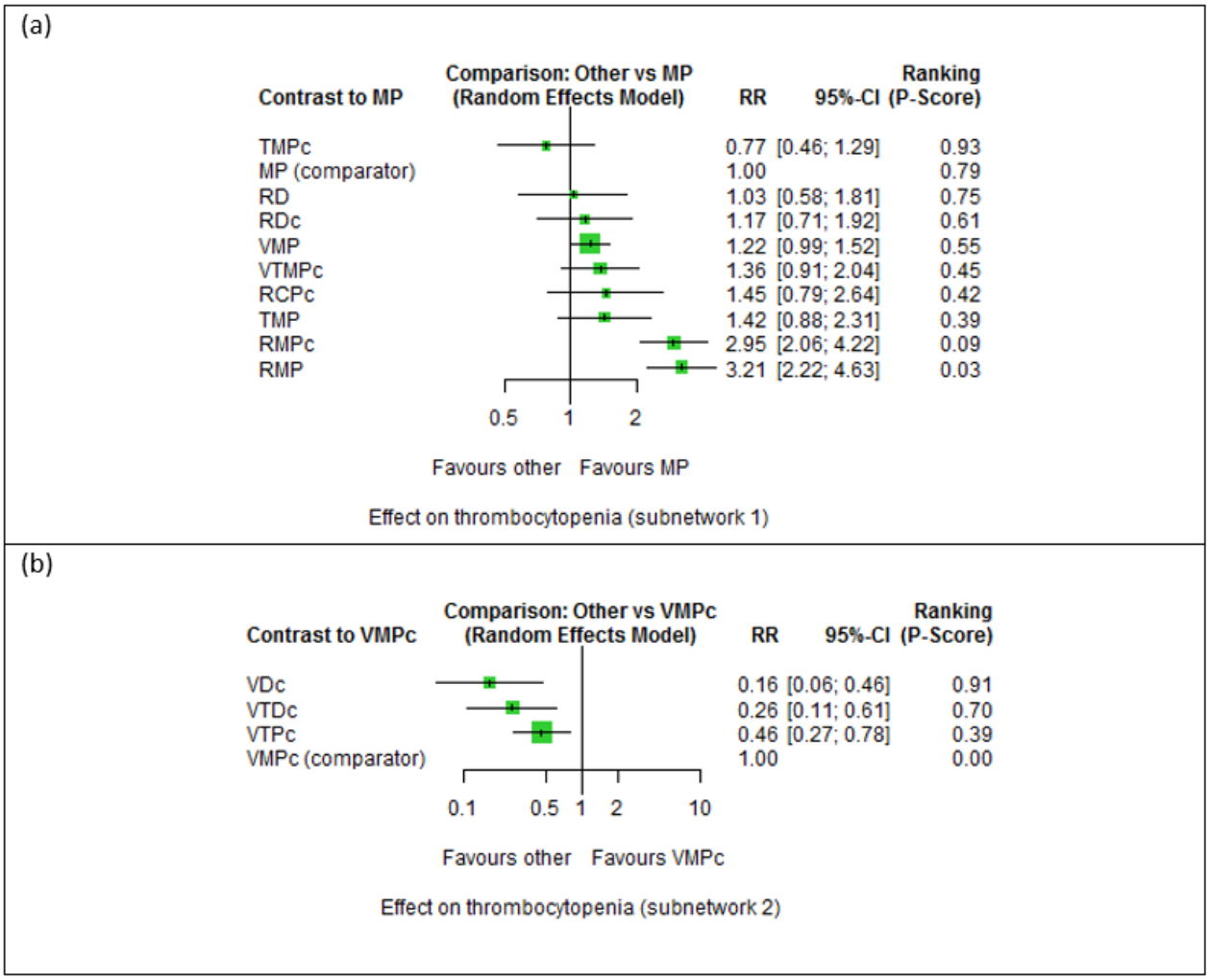
Figure 19



Caption

Network graph for the outcome thrombocytopenia. A line connects any two treatments when there is at least one study comparing the two treatments. Line width: number of patients

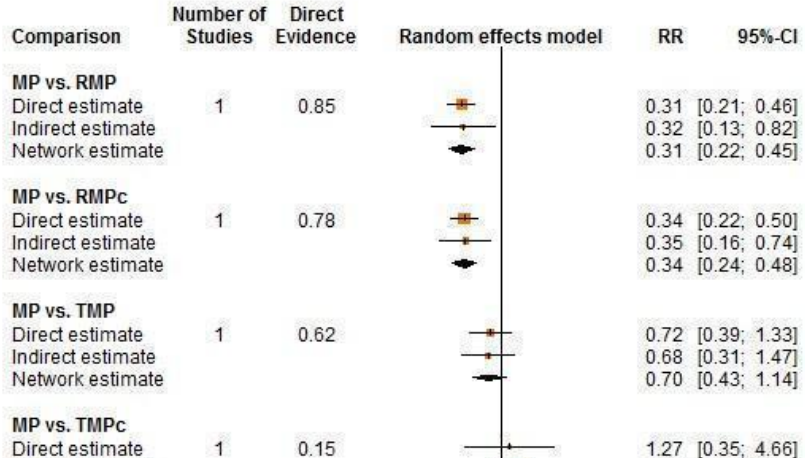
Figure 20

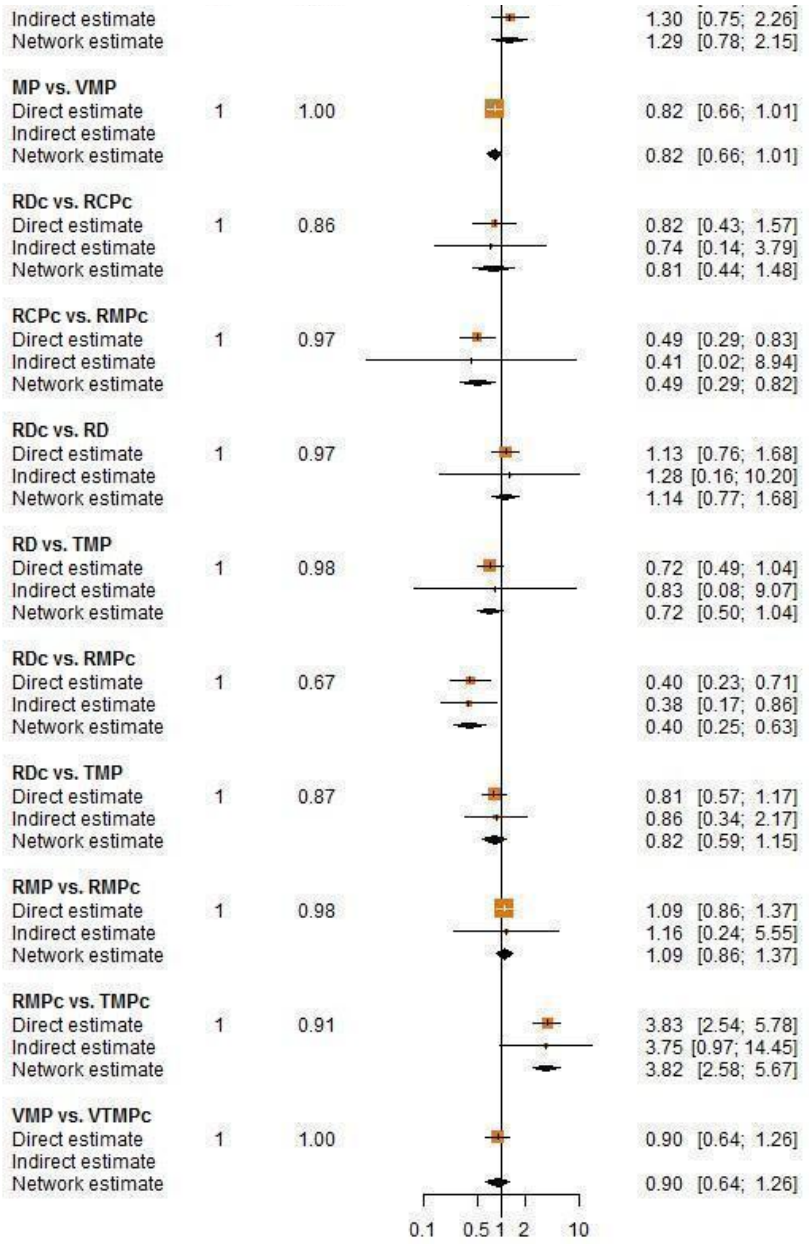


Caption

Forest plot for outcome thrombocytopenia. (a) thrombocytopenia–subnetwork 1. Reference treatment: MP. (b) thrombocytopenia–subnetwork 2. Reference treatment: VMPc. Treatments are ordered by P-Score (descending).

Figure 21

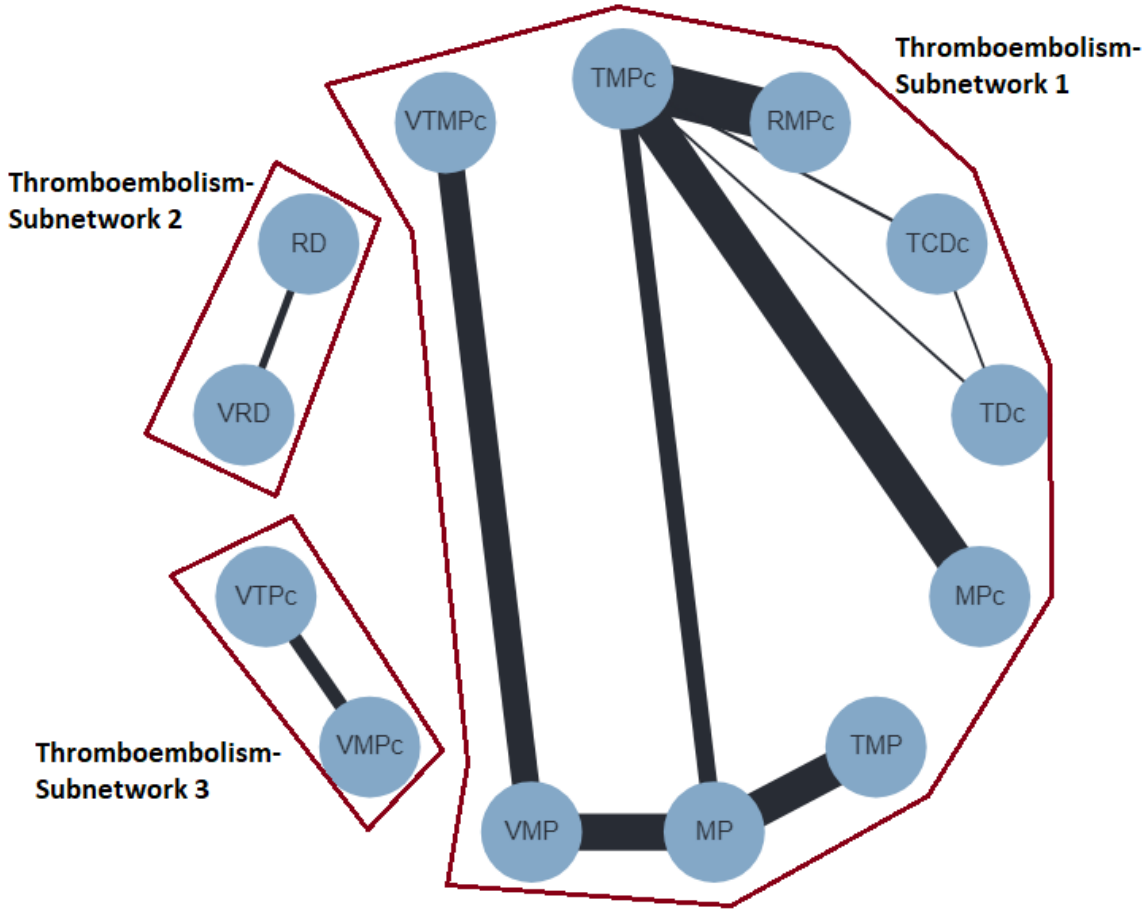




Caption

Local approach to check inconsistency - comparison of direct and indirect estimate for closed loops in thrombocytopenia-subnetwork 1

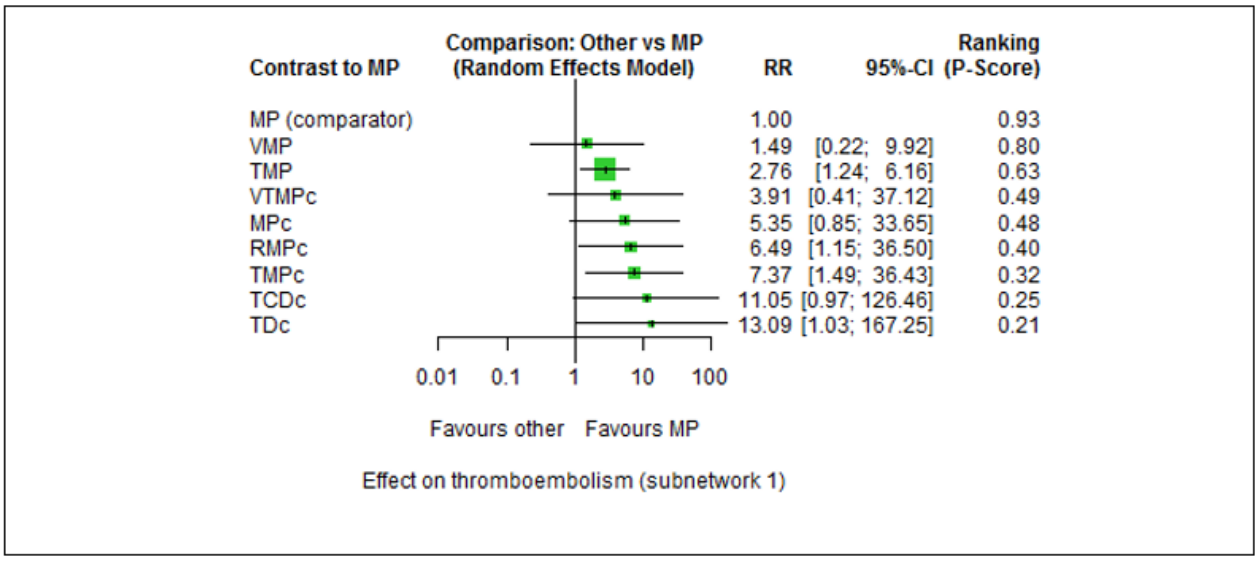
Figure 22



Caption

Network graph for the outcome thromboembolism. A line connects any two treatments when there is at least one study comparing the two treatments. Line width: number of patients

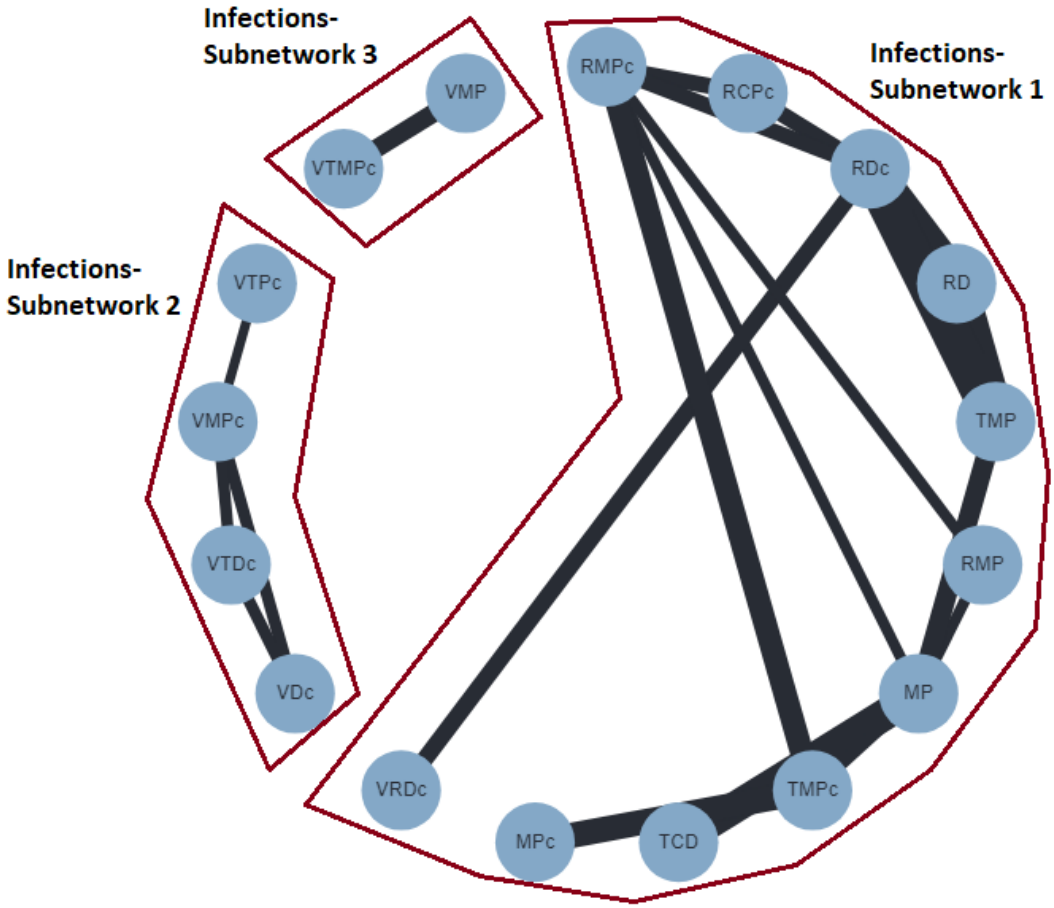
Figure 23



Caption

Forest plot for outcome thromboembolism. thromboembolism-subnetwork 1. Reference treatment: MP. Treatments are ordered by P-Score (descending).

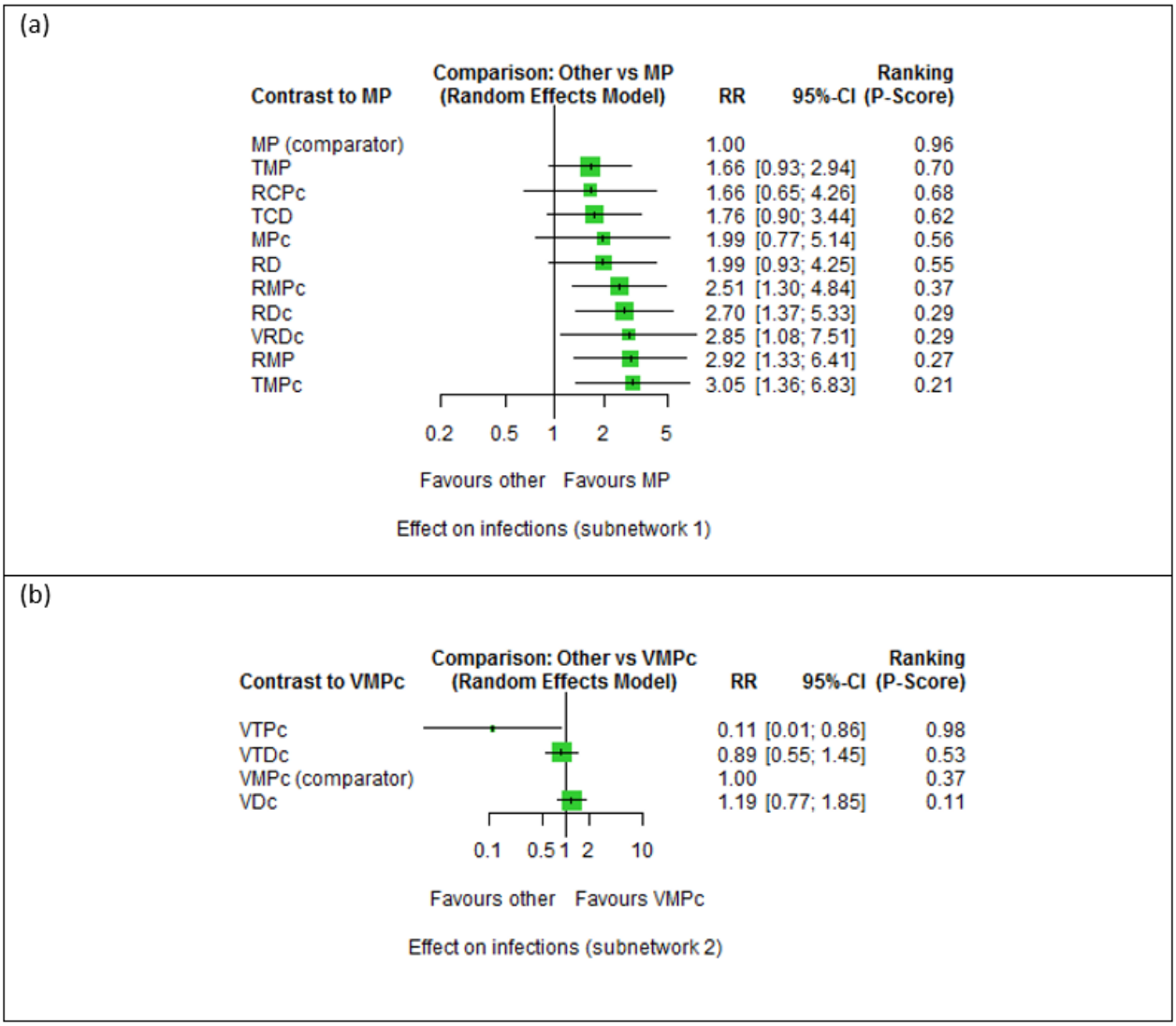
Figure 24



Caption

Network graph for the outcome infections. A line connects any two treatments when there is at least one study comparing the two treatments. Line width: number of patients

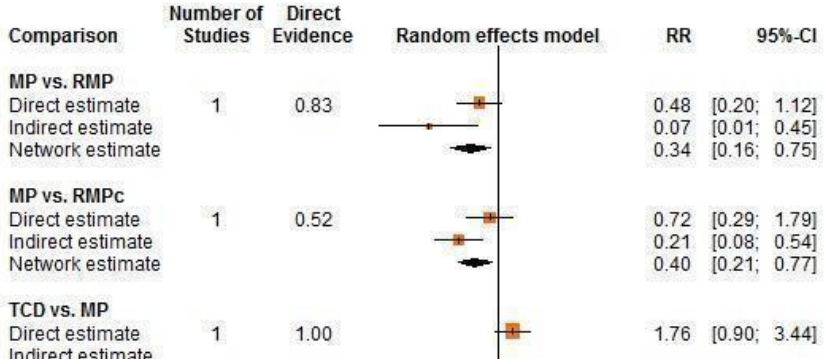
Figure 25

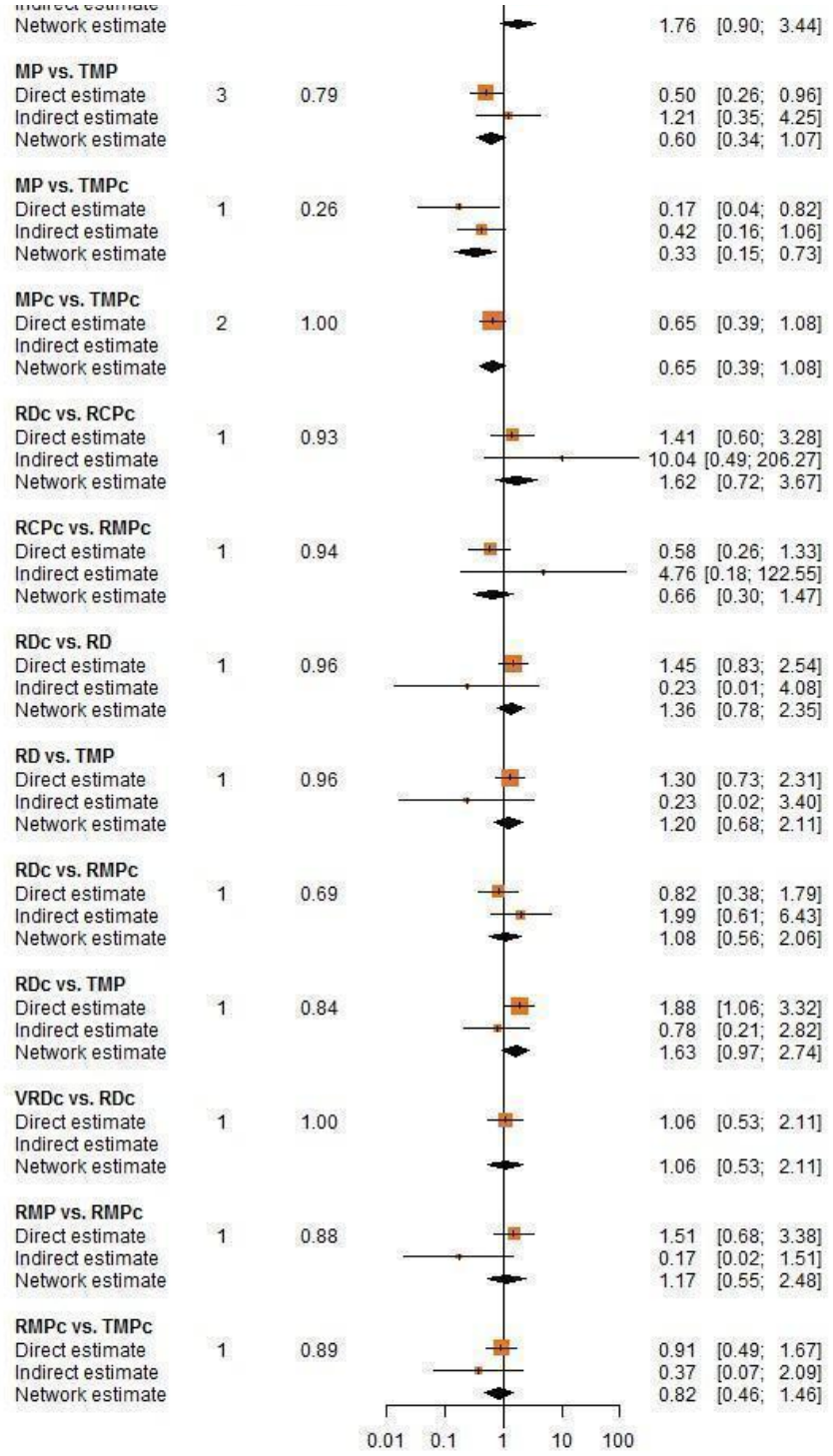


Caption

Forest plot for outcome infections. (a) infections–subnetwork 1. Reference treatment: MP. (b) infections–subnetwork 2. Reference treatment: VMPc. Treatments are ordered by P–Score (descending).

Figure 26

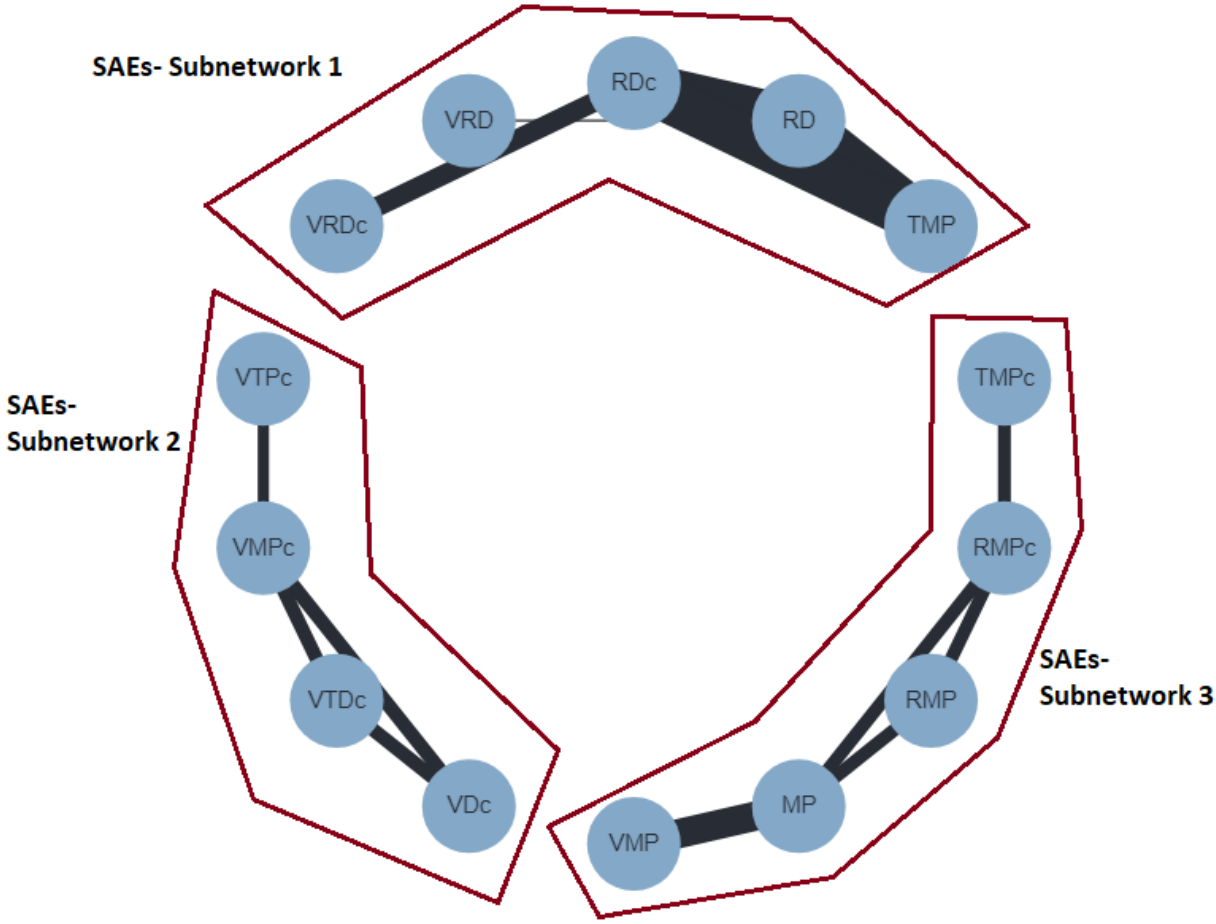




Caption

Local approach to check inconsistency - comparison of direct and indirect estimate for closed loops in infections-subnetwork 1

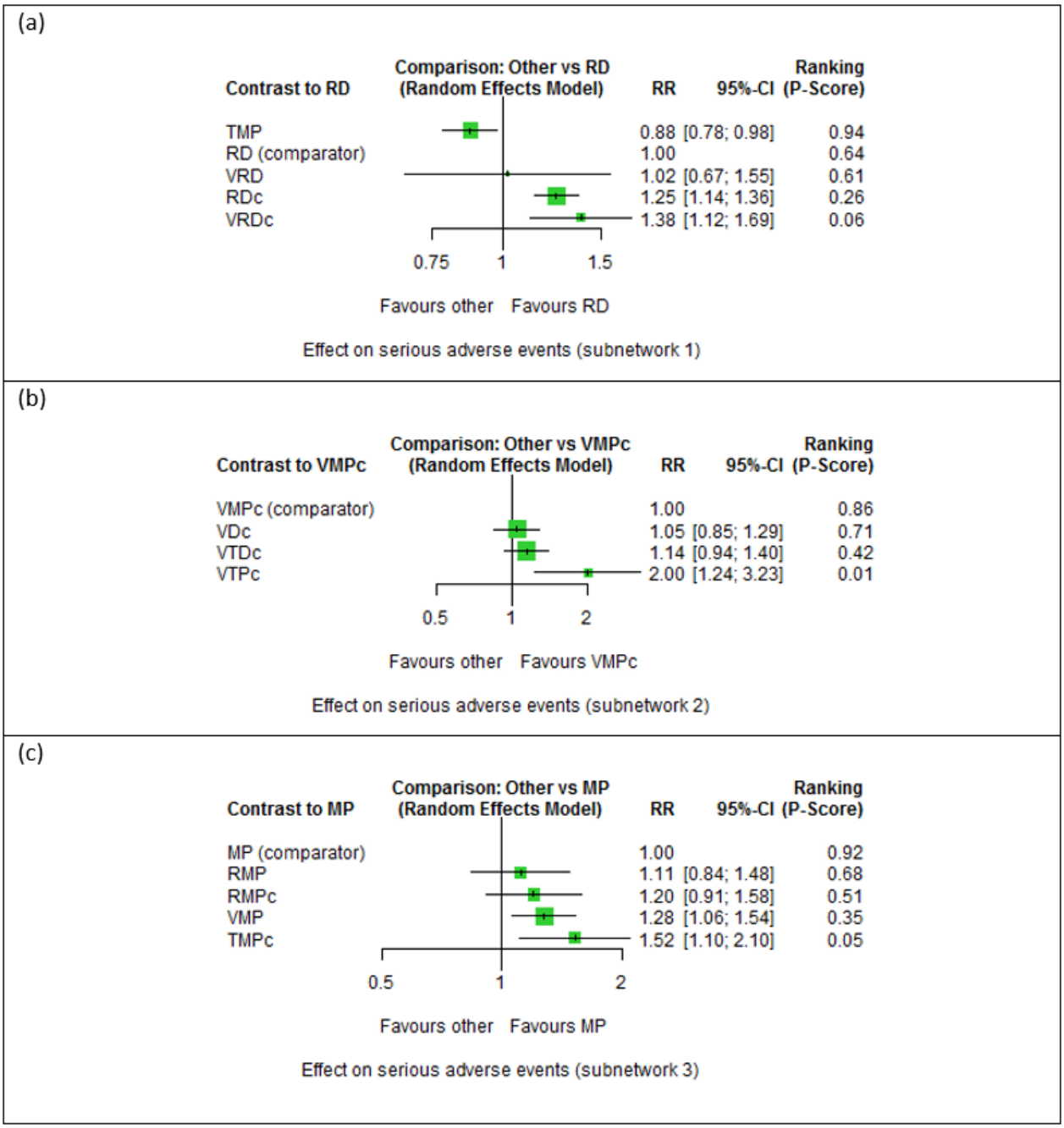
Figure 27



Caption

Network graph for the outcome SAEs. A line connects any two treatments when there is at least one study comparing the two treatments. Line width: number of patients

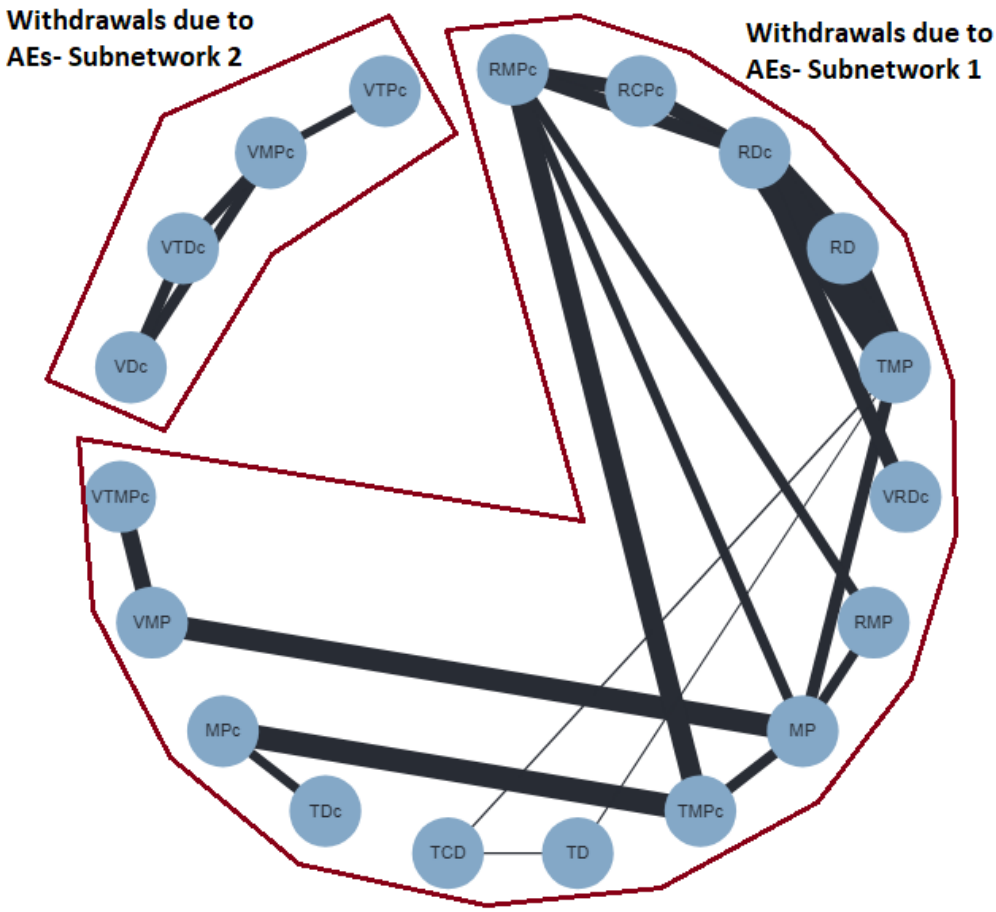
Figure 28



Caption

Forest plot for outcome serious adverse events. (a) SAE-subnetwork 1. Reference treatment: RD. (b) SAE-subnetwork 2. Reference treatment: VMPc. SAE-subnetwork 3. Reference treatment: MP. Treatments are ordered by P-Score (descending).

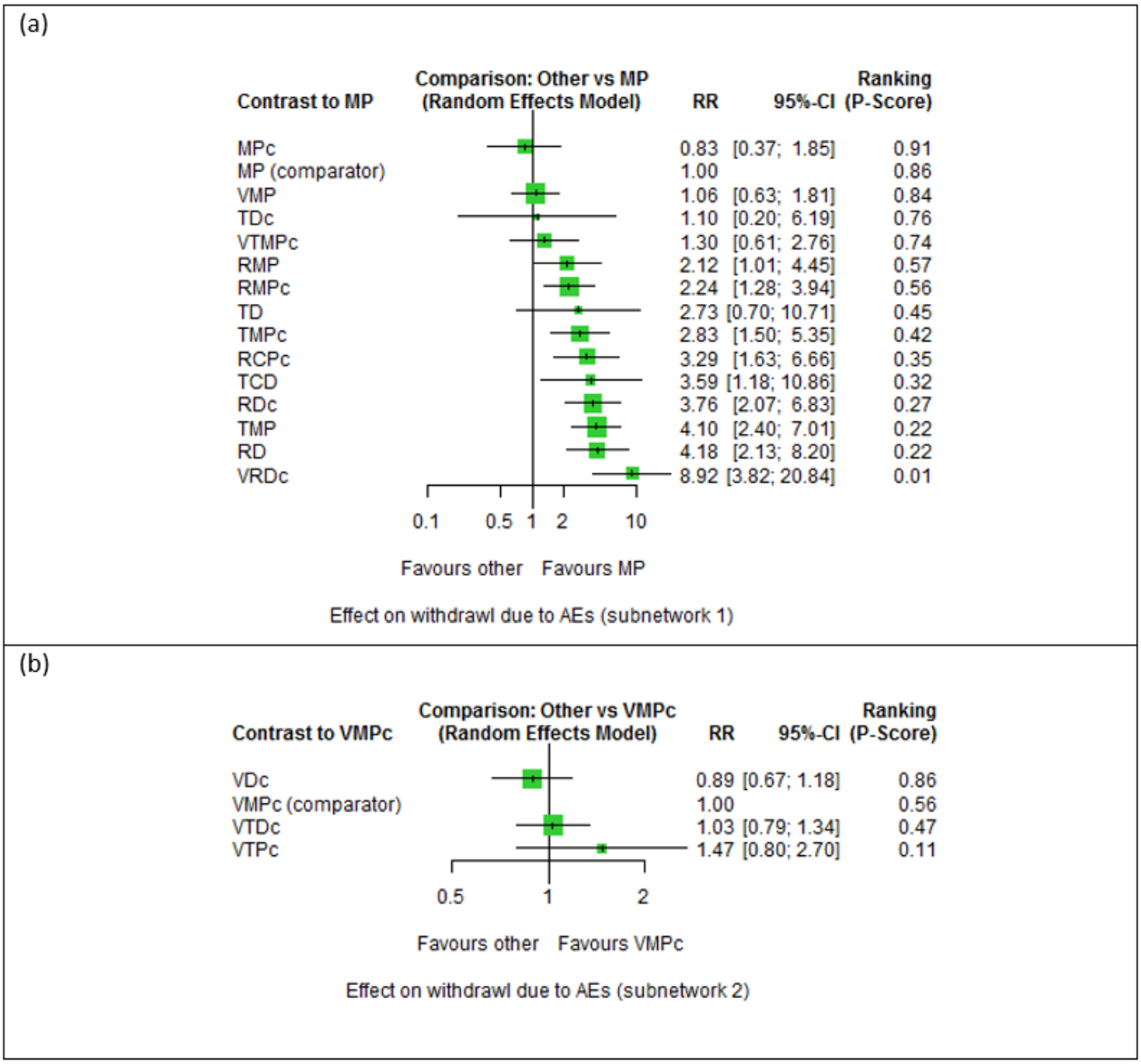
Figure 29



Caption

Network graph for the outcome withdrawals due to adverse events. A line connects any two treatments when there is at least one study comparing the two treatments. Line width: number of patients

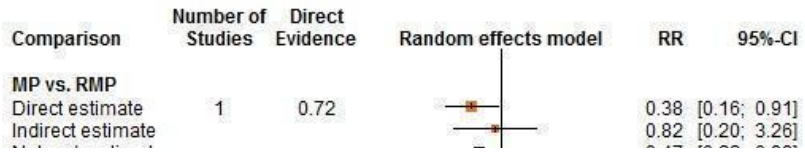
Figure 30

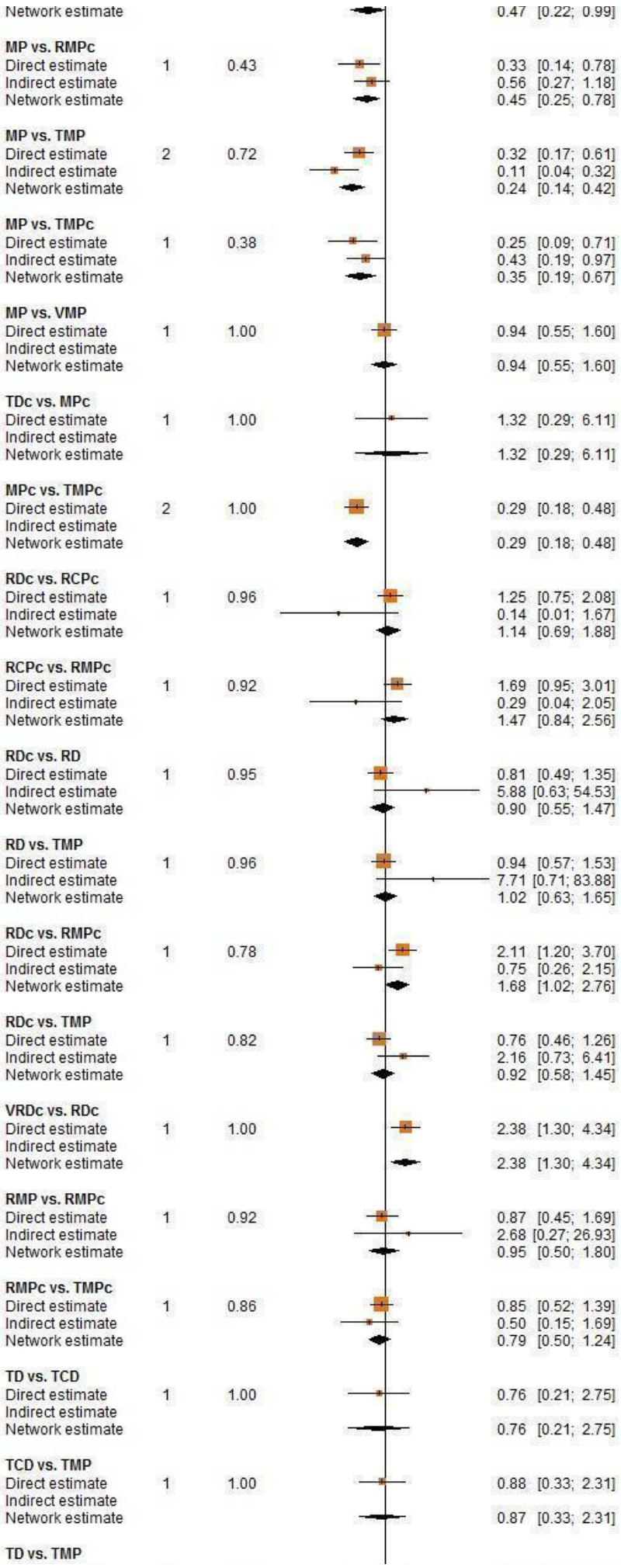


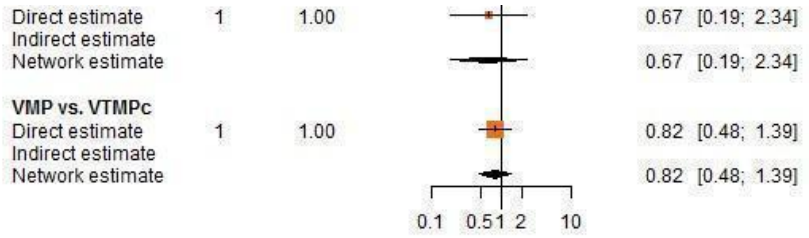
Caption

Forest plot for outcome withdrawals due to adverse events. (a) withdrawals due to AEs-subnetwork 1. Reference treatment: MP. (b) withdrawals due to AEs-subnetwork 2. Reference treatment: VMPc. Treatments are ordered by P-Score (descending).

Figure 31




Network estimate 0.47 [0.22; 0.99]
MP vs. RMPc
Direct estimate 1 0.43 0.33 [0.14; 0.78]
Indirect estimate 0.56 [0.27; 1.18]
Network estimate 0.45 [0.25; 0.78]
MP vs. TMP
Direct estimate 2 0.72 0.32 [0.17; 0.61]
Indirect estimate 0.11 [0.04; 0.32]
Network estimate 0.24 [0.14; 0.42]
MP vs. TMPc
Direct estimate 1 0.38 0.25 [0.09; 0.71]
Indirect estimate 0.43 [0.19; 0.97]
Network estimate 0.35 [0.19; 0.67]
MP vs. VMP
Direct estimate 1 1.00 0.94 [0.55; 1.60]
Indirect estimate
Network estimate 0.94 [0.55; 1.60]
TDc vs. MPc
Direct estimate 1 1.00 1.32 [0.29; 6.11]
Indirect estimate
Network estimate 1.32 [0.29; 6.11]
MPc vs. TMPc
Direct estimate 2 1.00 0.29 [0.18; 0.48]
Indirect estimate
Network estimate 0.29 [0.18; 0.48]
RDc vs. RCPc
Direct estimate 1 0.96 1.25 [0.75; 2.08]
Indirect estimate 0.14 [0.01; 1.67]
Network estimate 1.14 [0.69; 1.88]
RCPc vs. RMPc
Direct estimate 1 0.92 1.69 [0.95; 3.01]
Indirect estimate 0.29 [0.04; 2.05]
Network estimate 1.47 [0.84; 2.56]
RDc vs. RD
Direct estimate 1 0.95 0.81 [0.49; 1.35]
Indirect estimate 5.88 [0.63; 54.53]
Network estimate 0.90 [0.55; 1.47]
RD vs. TMP
Direct estimate 1 0.96 0.94 [0.57; 1.53]
Indirect estimate 7.71 [0.71; 83.88]
Network estimate 1.02 [0.63; 1.65]
RDc vs. RMPc
Direct estimate 1 0.78 2.11 [1.20; 3.70]
Indirect estimate 0.75 [0.26; 2.15]
Network estimate 1.68 [1.02; 2.76]
RDc vs. TMP
Direct estimate 1 0.82 0.76 [0.46; 1.26]
Indirect estimate 2.16 [0.73; 6.41]
Network estimate 0.92 [0.58; 1.45]
VRDc vs. RDc
Direct estimate 1 1.00 2.38 [1.30; 4.34]
Indirect estimate
Network estimate 2.38 [1.30; 4.34]
RMP vs. RMPc
Direct estimate 1 0.92 0.87 [0.45; 1.69]
Indirect estimate 2.68 [0.27; 26.93]
Network estimate 0.95 [0.50; 1.80]
RMPc vs. TMPc
Direct estimate 1 0.86 0.85 [0.52; 1.39]
Indirect estimate 0.50 [0.15; 1.69]
Network estimate 0.79 [0.50; 1.24]
TD vs. TCD
Direct estimate 1 1.00 0.76 [0.21; 2.75]
Indirect estimate
Network estimate 0.76 [0.21; 2.75]
TCD vs. TMP
Direct estimate 1 1.00 0.88 [0.33; 2.31]
Indirect estimate
Network estimate 0.87 [0.33; 2.31]
TD vs. TMP



Caption

Local approach to check inconsistency - comparison of direct and indirect estimate for closed loops in withdrawals due to AEs-subnetwork 1

Sources of support

Internal sources

- University Hospital Cologne, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Germany
  Provision of the offices, including technical equipment

External sources

- Cochrane, UK
  Cochrane Review Support Programme (Award of £5000 after publication of the review)

Feedback

Appendices

1 CENTRAL search strategy

ID Search

#1 MeSH descriptor: (Multiple Myeloma) explode all trees

#2 myelom*

#3 MeSH descriptor: (Plasmacytoma) explode all trees

#4 plasm*cytom*

#5 plasmozytom*

#6 plasm* cell myelom*

#7 myelomatosis

#8 MeSH descriptor: (Leukemia, Plasma Cell) explode all trees

#9 (plasma* near/3 neoplas*)

#10 kahler*

#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 with Cochrane Library publication date between Jan 1998 and Feb 2019

2 MEDLINE/Ovid search strategy

MEDLINE/Ovid search strategy for RCTs	
#	searches

1	exp MULTIPLE MYELOMA/
2	myelom$.tw,kf,ot.
3	exp PLASMACYTOMA/
4	plasm?cytom$.tw,kf,ot.
5	plasmozytom$.tw,kf,ot.
6	plasm$ cell myelom$.tw,kf,ot.
7	myelomatosis.tw,kf,ot.
8	LEUKEMIA, PLASMA CELL/
9	(plasma$ adj3 neoplas$).tw,kf,ot.
10	kahler*.tw,kf,ot.
11	or/1-10
12	randomized controlled trial.pt.
13	controlled clinical trial.pt.
14	randomi?ed.ab.
15	placebo.ab.
16	clinical trials as topic.sh.
17	randomly.ab.
18	trial.ti.
19	or/12-18
20	exp ANIMALS/ not HUMANS/
21	19 not 20
22	11 and 21
23	limit 22 to dt=19980101-20190214
MEDLINE/Ovid search strategy for Systematic Reviews	
#	**searches**
1	exp MULTIPLE MYELOMA/
2	myelom$.tw,kf,ot.
3	exp Plasmacytoma/
4	plasm?cytom$.tw,kf,ot.
5	plasmozytom$.tw,kf,ot.
6	plasm$ cell myelom$.tw,kf,ot.
7	myelomatosis.tw,kf,ot.
8	LEUKEMIA, PLASMA CELL/
9	(plasma$ adj3 neoplas$).tw,kf,ot.
10	kahler*.tw,kf,ot.
11	or/1-10
12	(MEDLINE or systematic review).tw. or meta analysis.pt.
13	11 and 12
14	limit 11 to systematic reviews
15	13 or 14
16	from 15 keep 1-818
17	limit 16 to dt=19980101-20190214

3 Search criteria study registries

We applied the following search criteria (adjusted according to available search options):

- phase: ≥ 2
- study type: interventional studies
- condition: multiple myeloma
- interventions: bortezomib, velcade, lenalidomide, revlimid, thalidomide
- date of registration or study start: as of 01 January 1998

4 Search criteria conference proceedings

We searched for the following keywords:

- multiple myeloma or plasmozytoma in combination with newly diagnosed, first-line or initial therapy
- transplant-ineligible, non transplant
- bortezomib, velcade, lenalidomide, revlimid, thalidomide
- random

5 Additional figures

Figure 6; Figure 7; Figure 8; Figure 9; Figure 10; Figure 11; Figure 12; Figure 13; Figure 14; Figure 15; Figure 16; Figure 17; Figure 18; Figure 19; Figure 20; Figure 21; Figure 22; Figure 23; Figure 24; Figure 25; Figure 26; Figure 27; Figure 28; Figure 29; Figure 30; Figure 31