EUROPEAN HEMATOLOGY ASSOCIATION
haematologica
Journal of the European Hematology Association

Efficacy of first-line treatments for multiple myeloma patients not eligible for stem cell transplantation - A Network Meta-analysis

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Haematologica 2019 [Epub ahead of print]

Citation: Hedwig M. Blommestein, Chrissy H.Y. van Beurden-Tan, Margreet G. Franken, Carin A. Uyl-de Groot, Pieter Sonneveld, and Sonja Zweegman . Efficacy of first-line treatments for multiple myeloma patients not eligible for stem cell transplantation - A Network Meta-analysis. Haematologica. 2019; 104:xxx
doi:10.3324/haematol.2018.206912

Title page

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Running title: Efficacy of MM treatments

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Presented elsewhere: This research is not presented elsewhere.

Word count: 3871

Abstract

Decision making for not transplant eligible patients with multiple myeloma is complicated by lacking head-to-head comparisons of standards of care, increasing treatment modalities and rapidly evolving promising results of studies with novel regimens. To support evidence-based decision making, we performed a network meta-analysis for not transplant-eligible multiple myeloma patients that synthesizes direct and indirect evidence and enable a comparison of all treatments. Relevant randomized clinical trials were identified by a systematic literature review in EMBASE®, MEDLINE®, MEDLINE®-in-Process and the Cochrane Central Register of Controlled Trials for January-1999 to March-2016. Efficacy outcomes (i.e. the hazard ratio and 95% confidence interval for progression-free survival) were extracted and synthesized in a random effects network-meta analysis. In total 24 studies were identified including 21 treatments. According to the network-meta analysis, the hazard ratio for progression-free survival was favorable for all not transplant-eligible myeloma treatments compared to dexamethasone (hazard ratios between 0.19-0.90). Daratumumab-bortezomib-melphalan-prednisone and bortezomib-melphalan-prednisone-thalidomide with bortezomib-thalidomide maintenance were identified as the most effective treatments (hazard ratio: 0.19 (95% confidence interval 0.08-0.45) and 0.22 (95% confidence interval 0.10-0.51), respectively). The hazard ratios and 95% confidence interval for currently recommended treatments, bortezomib-lenalidomide-dexamethasone, bortezomib-melphalan-prednisone, and lenalidomide-dexamethasone compared to dexamethasone, were 0.31 (0.16-0.59), 0.39 (0.20-0.75) and 0.44 (0.29-0.65), respectively. In addition to identifying the most effective treatment options, we illustrate the additional value and evidence of network meta-analysis in clinical practice. In the current treatment landscape, the results of network meta-analysis may support evidence based decisions and ultimately help to optimize treatment and outcomes of not transplant eligible multiple myeloma patients.

Ethics committee approval

Not applicable.

Introduction

Multiple myeloma (MM) is a hematological disease characterized by the proliferation of malignant plasma cells, causing disease-related symptoms such as anemia, hypercalcemia, renal and bone disease. The age standardized incidence rate is 4.5 per 100,000[1]. Incidence increases with age and two-thirds of the patients diagnosed with MM are above 65 years[2]. The treatment armamentarium greatly increased in the last decade, with novel proteasome inhibitors (PI's), immunomodulatory drugs (IMiD's), and monoclonal antibodies now being incorporated in first line treatment regimens, which considerably improved progression-free survival (PFS) and overall survival (OS) of MM. Given the median age of 70 years at diagnosis, the majority of newly diagnosed (ND) MM patients are not eligible for SCT (NTE). Current standards of care for NTE NDMM patients are bortezomib-melphalan-prednisone (VMP), lenalidomide-dexamethasone (Rd), and in the USA bortezomib-Rd (VRd)[3], supported by randomized phase III trials[4-6]. Recently, better PFS was demonstrated for Daratumumab-VMP (DaraVMP) compared to VMP[7].

Although randomized clinical trials (RCTs) remain the gold standard to define standards of care, we predict that in the current treatment landscape the role of network meta-analysis (NMA) will become increasingly important. Firstly, currently there is more than one standard of care, but a randomized study between two registered standards of care is highly unlikely to be performed, because of reluctance of pharmaceutical industries to support such studies[8]. Therefore, head-to-head comparisons of VMP versus Rd or VRd versus VMP are not likely to be initiated[9]. NMA can help to discriminate between efficacy of non-head-to-head compared regimens. Secondly, with the growing possibilities of treatment modalities, the number of smaller randomized phase II studies is expected to increase at the cost of phase III RCTs. NMA provide more solid estimates of treatment effects by combining RCTs that provide direct and indirect evidence for effectiveness and enable a ranking of competing treatments[10]. Thirdly, with the current high number of accruing studies, standard of care arms are expected to change within short times frames[8]. This hampers the development of classical phase III trials, as at the end of the study, it might appear the standard arm of the study does not reflect clinical reality anymore. Lastly, the heterogeneous biological characteristics of MM and clonal evolution of

the disease will lead to studies with a smaller sample size that will not allow randomization, increasing the need for indirect comparisons.

There are currently two systematic literature reviews (SLRs) and NMAs available for first-line NTE NDMM treatments[11,12]. Due to the timing of their searches and selection criteria, these reviews did not, however, include all currently available treatments (e.g. VRd, VMPT-VT, DaraVMP) and RCT evidence (e.g. HOVON87 comparing MPT-T and MPR-R[13]). To support evidence-based decision making in clinical practice, we performed a SLR and NMA synthesizing all direct and indirect evidence from phase III RCTs that is currently available and compared the outcome of all treatment options for NTE NDMM patients.

Methods

Systematic literature review

A SLR was conducted in the databases EMBASE®, MEDLINE®, MEDLINE®-in-Process and the Cochrane Central Register of Controlled Trials for the period 01 January 1999 to 01 March 2016 to identify relevant studies (Appendix 1). Studies were included if they described a phase III RCT among newly diagnosed adult patients with MM. Furthermore, one of the pre-specified treatments (Appendix 2) had to be part of the regimens of the RCT. After removing duplicates, citations were first screened on title and abstract and then screened on the contents of their full text. Citations were excluded due to the following reasons: non-English, review, study phase, intervention, disease, study design, meta-analysis, patient population, economic outcomes, meta-analysis, and other (for a detailed description of the exclusion categories see Appendix 2). To incorporate the latest clinical developments, the publication of the pre-specified interim analysis of the phase III ALCYONE RCT comparing DaraVMP to VMP[7], was added as additional record.

Data extraction

Data were extracted on trial details (i.e. publication source, trial ID, trial number, research, and comparator treatment(s), number of patients, median age, and primary outcome, and follow-up) and efficacy outcomes. Efficacy outcomes included PFS and OS. For OS we obtained median survival. For PFS we obtained the median survival, 95% confidence interval (CI) and hazard ratio (HR) and 95% CI of the HR. In case HRs and/or 95% CI for PFS were not reported, we estimated the missing data with the available Kaplan-Meier curves using the methods described by Tierney et al.[14] The most recent published PFS data were extracted in case multiple sources reported on one trial. Risk of bias in randomized trials was assessed using the Cochrane Collaboration's tool[15] (Appendix 3).

Network meta-analysis

A network was made from the identified treatment options in the SLR. It includes the HRs for PFS from the trials for treatments that were head-to-head compared. A comparison between all treatments can be made based on a common comparator (i.e. reference treatment). The choice of the reference treatment does not influence the outcomes of the study and final results can be presented relative to all included treatments. The oldest treatment (i.e. dexamethasone) was selected as a reference treatment from which the relative effectiveness of all treatments was estimated. We performed a similar analysis with MPT as reference treatment, concerning the fact that this regimen was used as (comparator) treatment in several RCTs. Treatments were sorted based on their P-score. This P-score measures the average proportion of treatments worse than the respective treatment where 1 means theoretically best and 0 means worst[16].

To conduct a NMA for two- and multi-arm studies, we used the netmeta package version 0.9-7 in R version 3.3.1 (Appendix 4). We ran a random effects model assuming that the included studies represent a random sample of effect sizes that could have been observed and that the effect can best be estimated by the mean of all available studies. A random effects model was deemed appropriate since there were multiple trials available for some comparisons (e.g. MPT with MP) and sampling error was not considered to be the most plausible explanation for the observed variation. With a random effects model we allow for differences in the patient population and implementations of interventions[17]. The netmeta package uses a frequentist approach based on the graph-theoretical

methods routinely applied in electrical networks[18,19]. In contrast to the Bayesian approach that produces credible intervals, analysis based on the frequentist approach produces 95% CIs and, as all CIs, these should be interpreted as follows; 95% of the produced CIs would contain the true value if the analysis would be repeated many times[20].

Face-validity of the NMA results was checked by comparing the computed HRs by the NMA with the HRs reported in the publications of the trials. To validate our outcomes to a previously reported NMA[12], we performed a scenario analysis with different treatment groups (separating MPT and MPT-T) and a scenario with a limited number of studies. In the third scenario analysis we used a fixed effect model instead of a random effects model. Heterogeneity and inconsistency were assessed by decomposing the Q statistic[21,22] and quantified by the I^2-statistic[23], which presents the percentage of the variability in effects due to heterogeneity rather than chance[24].

Results

Systematic literature review

Figure 1 presents the PRISMA flow diagram, the PRISMA checklist is presented in Appendix 3. The SLR identified in total 19,773 citations from the databases. One additional recent record was included (i.e. the ALCYONE trial[7]). After removing duplicates, 18,752 citations remained. Based on title and abstract, 17,741 citations were excluded for further analysis. The full text of 1,011 citations were reviewed and based on this assessment 944 citations were excluded. In the second full text review of the remaining 67 citations, 43 citations were excluded because these did not report the most recent results (e.g. extended follow-up results were available). After the entire assessment, 24 RCTs remained and were included for data extraction and the NMA. See Figure 1 for the detailed reasons for exclusion.

These 24 RCTs included 21 treatment options: 1) Dexamethasone (D), 2) Dexamethasone-Interferon alpha (DI), 3) Melphalan 100 (M100), 4) Melphalan-Dexamethasone (MD), 5) Melphalan-Prednisone (MP), 6) Thalidomide-Dexamethasone (TD), 7) Cyclophosphamide-Thalidomide-Dexamethasone

(CTD), 8) Cyclophosphamide-Thalidomide-Dexamethasone (attenuated) (CTD(a)), 9) Melphalan-Prednisone-Thalidomide / Melphalan-Prednisone-Thalidomide and Thalidomide maintenance (MPT/MPT-T), 10) Bortezomib-Dexamethasone (VD), 11) Bortezomib-Thalidomide-Dexamethasone (VTD), 12) Bortezomib-Melphalan-Prednisone (VMP), 13) Bortezomib-Thalidomide-Prednisone (VTP), 14) Bortezomib-Melphalan-Prednisone-Thalidomide and Bortezomib-Thalidomide (VMPT-VT), 15) Cyclophosphamide-Prednisone-Lenalidomide (CPR), 16) Lenalidomide-Dexamethasone (Rd), 17) 18 cycles Lenalidomide-Dexamethasone (Rd18), 18) Melphalan-Prednisone-Lenalidomide (MPR), 19) Melphalan-Prednisone-Lenalidomide and Lenalidomide maintenance (MPR-R), 20) Bortezomib-Lenalidomide-Dexamethasone (VRd), 21) Daratumumab-Bortezomib-Melphalan-Prednisone (DaraVMP),

Data Extraction

Table 1 provides the details, extracted, and calculated data of the included trials. Most trials (N=21 out of 24) investigated iMIDs-based regimens (thalidomide or lenalidomide). Since MP has been the standard treatment for decades[25], MP was the comparator in 12 trials. PFS was the primary endpoint for 13 trials. The median age of the patient population was reported by most trials and ranged from 64 to 79. While some trials included patients aged <65 years either because of choosing broader age limits or because of including patients who were not eligible for SCT independent of age, most trials only included patients aged ≥65 years. The IFM99-06[26] and IFM01/01[27] only focused on patients aged ≥70 and ≥75, respectively.

Network meta-analysis

Network

All identified RCTs (N=24) and treatments (N=21) were incorporated within one network (Figure 2). We combined MPT and MPT-T. The duration of induction therapy with thalidomide varied, leading to a clear overlap in planned thalidomide use between protocols with and without maintenance, preventing to clearly discriminate between MPT with and without thalidomide maintenance.

Figure 2 presents the obtained HR(s) from the trial(s) and the HR obtained from the NMA for each of the connections (i.e. treatment comparisons) in our network. In order to validate our data, we compared the HR from treatments for which only direct evidence from a single RCT was available. The HR obtained from the NMA should be equal to the HR obtained from the RCT. The HR from the NMA was indeed similar to the HR from the trials for six comparisons[5-7,28-30] (i.e. CTD(a) vs. MP, VMP vs. MP, DaraVMP vs. VMP, VRd vs Rd, VMPT-VT vs. VMP and VMP vs. VTP) (Appendix 5). In addition, our network includes several treatments for which both direct and indirect evidence were available. Appendix 5 presents the HRs based on direct and indirect evidence and shows that none of the p-values for disagreement was smaller than 0.05.

The percentage of the variability in effect estimates due to heterogeneity rather than sampling error ($=I^2$) was 72% indicating substantial between-study heterogeneity (i.e. within the 50%-90% range can be quantified as substantial heterogeneity[24]). We allowed for between-study heterogeneity by using the random effects model. Heterogeneity could be reduced by excluding some of the trials, however, because of a lack of valid reasons (e.g. patient characteristics, treatment dosing or follow-up) for excluding trials, we decided not to perform such analyses.

Results versus dexamethasone

Figure 3 presents the HRs with the corresponding 95% CI for PFS and the P-score of the NMA in which dexamethasone was used as comparator for the remaining 20 "other treatment" options. HRs above one indicate that the "other treatment" is less effective than the comparator treatment dexamethasone, HRs below one indicate that the "other treatment" is more effective than dexamethasone. All first-line NTE NDMM treatment options were better compared to the reference treatment dexamethasone (i.e. reduce the risk of progression or death compared to dexamethasone). HRs ranged between 0.19-0.90; however, not all treatments were statistically significantly different from dexamethasone, because of wide 95% CIs. DaraVMP and VMPT-VT were identified as the most effective treatment options as they had the highest and almost similar P-scores (i.e. a 96% and 93% certainty that this treatment is better than another treatment, averaged over all competing

treatments) and most favorable relative treatment effects compared to dexamethasone (i.e. HR: 0.19, 95% CI 0.08 to 0.45 and HR 0.22, 95% CI 0.10 to 0.51 for DaraVMP and VMPT-VT, respectively). The HRs and 95% CIs for currently recommended treatments, VRd, VMP and Rd compared to dexamethasone, were 0.31 (95% CI 0.16-0.59), 0.39 95% CI 0.20-0.75) and 0.44 (0.29-0.65), respectively. Selecting MPT as a reference treatment does not change the hierarchy of the treatments as the P-score values do not change if one considers a different reference treatment. Compared to MPT, only DaraVMP had a statistically lower HR for PFS (HR 0.41 95% CI 0.19-0.91, p-value <0.05) (Appendix 6).

Scenario analysis NMA

In order to rule out that grouping of MPT and MPT-T would affect the outcome of the analysis, we performed a scenario in which we grouped IFM 01/01, IFM 99/06 and Sacchi et al. 2011 as MPT and GIMEMA, HOVON49, TMSG and NMSG as MPT-T. The MPT-T group was connected in the network to the MPT-T arm from the HOVON87 trial and the ECOG E1A06 trial. Overall, the results were comparable to the base case (Appendix 7). We found similar results for MPT (HR 0.46 95% CI 0.30-0.71) and MPT-T (HR 0.47 95% CI 0.30-0.73) compared to D.

The second scenario, based on the trials included by Weisel et al.[12] showed lower HRs for PFS for Rd compared to VMP, MPT and MP but the 95% CI for VMP was overlapping with Rd (Rd vs. VMP HR 0.73, 95% CI 0.48-1.11 (Appendix 8)).

Results from the third scenario analysis (fixed effect model instead of random effects model) are presented in Appendix 9. While the HRs from the fixed effect model are rather similar, the 95% CIs are typically smaller for fixed effect models.

Discussion

Current clinical decision making in MM is complicated by lacking head-to-head comparisons of standards of care, an increasing number of treatment modalities and rapidly evolving promising results of studies with novel regimens (among smaller sub populations). In this treatment landscape,

we believe the role of NMA will become increasingly important, although it cannot replace RCTs that still remain the gold standard.

Firstly, NMAs are able to provide data where head-to-head comparisons are lacking[20,24]. For NTE NDMM, head-to-head comparisons from the current three standard of care regimens (i.e. VRd, VMP and Rd) are lacking. Only VRd has been head-to-head compared to Rd but there are no studies comparing VMP with VRd or Rd. With our NMA, we show that the HR of VRd was lower as compared to VMP and Rd, and VRd also had the highest P-Score. We present similar HRs and P-Scores for VMP and Rd. However, we also show considerable overlap of the 95% CIs of VRd, Rd and VMP. Our NMA does not support the use of one over the other regimens, leaving three valuable options for clinical practice. The choice of therapy will be guided by characteristics of the patient and the, such as a PI-based regimen in high risk cytogenetic disease and a preference for lenalidomide without bortezomib in patients with neuropathy[31-34].

According to the ranking based on their P-scores and comparative effectiveness estimates, DaraVMP and VMPT-VT were identified as the most effective treatments. Although there is a RCT already showing better PFS and OS[28] for VMPT-VT when compared with VMP, we now add data showing comparable efficacy to DaraVMP, which is expected to become an important standard of care. This finding is of importance given the pronounced differences in global access to costly treatment regimens. As all drugs in the VMPT-VT regimen will soon be available as generic compounds, this regimen is a valuable option in clinical practice as well. In addition, the pronounced efficacy of VMPT-VT highlights the use of maintenance therapy following PI-based induction regimens. Also the study of the PETHEMA group showed (in a non-head-to-head comparison with VMP) that maintenance therapy did result in a substantial longer PFS[35]. We now add further evidence for maintenance therapy with PIs by showing high efficacy of VMPT-VT as compared to VMP. This is of importance as currently EMA did not approve maintenance therapy with bortezomib, as head-to-head comparisons of maintenance versus no maintenance therapy are lacking.

Secondly, NMAs provide more solid and precise effectiveness estimates in case head-to-head data from multiple RCTs are available[20,24]. Our network included several trials investigating MPT/MPT-T vs. MP. Some of these trials showed MPT/MPT-T to be superior over MP[26,27,36], while other trials found no difference[37-40]. NMA enables synthesizing this evidence and according to our analysis, MPT/MPT-T was superior over MP (HR 0.67 95% CI 0.55-0.81).

Third, NMA calculates effectiveness estimates including direct and indirect evidence from RCTs providing additional evidence in case head-to-head data from a single RCT only are available. Due to the rapid evolvement of the treatment armamentarium, efficacy evidence is increasingly based on a single RCT, not seldom from only one institute or region in the world. There is increasing evidence for contradictory results of RCTs investigating a similar treatment comparison[41] and this may increase the interest in indirect evidence. Indirect evidence may confirm or alter the results from a single RCT as we showed for MPR-R compared to MPT. Although there was no statistically significant difference between MPR-R and MPT-T based on direct evidence from two RCTs, synthesizing direct and indirect evidence resulted in a statistically significant HR for MPR-R compared to MPT/MPT-T. Favorable indirect evidence for MPR-R compared to MPT-T was obtained through the comparison with MP. MPR-R compared more favorable to MP (according to the MM-15 HR MPR-R vs MP 0.4) than MPT (HR MPT vs MP 0.67 according to multiple trials). However, it should be noted that the direct evidence for MPR-R compared to MP was based on a single RCT while MPT/MPT-T vs MP was studied in seven RCTs and therefore the evidence for the latter comparison is believed to be more solid[24,41]. Indirect evidence is not always available, for example for the comparison VRd and Rd there is only direct evidence from a single study[6]. While a fixed effect NMA will produce similar results to the trial (HR 0.71 95% CI 0.57-0.9), a random effects NMA obtains larger 95% CIs (HR 0.71 95% CI 0.43-1.17), as it includes two levels of uncertainty; within and between study variances[17]. Hence, treatments are less likely to differ significantly.

Two other NMAs are available for newly diagnosed NTE NDMM patients. Our results align with the results from Kuhr et al.[11] in that VMP and MPT are more effective than MP. Our results also confirm the conclusion from Weisel et al.[12] that Rd is more favorable than MP (HR 0.63, 95% CI 0.44-0.89 (Appendix 5)). However in contrast to their findings, we found that Rd and VMP have comparable effectiveness outcomes (i.e., small difference in HR for PFS compared to D but largely overlapping CIs). The primary analysis of Weisel et al. included a limited number of treatments (i.e. VMP, MP, MPT and Rd) and RCTs (i.e. VISTA, IFM01/01, IFM 99/06, Sacchi, FIRST) as phase III trials not using dosing schemes in line with the summary of product characteristics (SmPC) were excluded. There are several arguments against this restriction. Firstly, although dosing schemes in line with the SmPC might be recommended in the selected trials by Weisel et al., it is debatable whether this ensures treatments are identical within a network, especially because of variation in clinical practice either due to physicians preference or patient-related factors such as age, co-morbidities and toxicities. For example, the trial of Sacchi et al. 2011 was grouped with MPT studies while maintenance was provided in a limited number of centers. Furthermore, the administered and planned dose may differ, as for example illustrated by the HOVON87 where relative dose intensity varied between 0.54-0.96[13]. Since there is a lack of evidence on the impact of dosing schemes, we believe that a more comprehensive network (i.e. our network included 19 additional trials) provides more solid evidence. The reason Weisel et al.[12] did not found overlap between VMP and Rd in their sensitivity analyses including six and twelve additional studies, is most likely because they used a fixed effect model for their analysis. A random effects model that was used in our analysis and by Kuhr et al.[11] is however, more appropriate as this model allows for the between study-heterogeneity in the added studies.

One might argue that while our NMA provides additional evidence in different circumstances, we had to make assumptions to conduct the analysis, which introduces a level of uncertainty. First, we grouped MPT and MPT-T studies since we could not make an unambiguous distinction between

them. For example, thalidomide was prescribed until disease progression in the HOVON49 and GIMEMA trial but prescribed "continuously" for up to a maximum of 12 months in the TMSG trial. In the NMSG trial it was even recommended to continue thalidomide maintenance until second relapse. However, most investigators discontinued thalidomide at first relapse. Prescription of thalidomide was also not consistent within a trial[38]. Sacchi et al.[38] described that, although planned, maintenance was only provided to 18% of the patients and in a limited number of centers. Their results however, showed that PFS did not differ between maintenance and no-maintenance[42]. Therefore, we believe that combining these trials, as performed previously[11,43] is appropriate, and the results of our sensitivity analysis confirm this assumption (see Appendix 7).

Secondly, the validity of the outcomes of NMA depend on the comparability between studies. Our analysis focused on treatments for NTE NDMM patients studied in phase III RCTs. Although, including non-randomized evidence in NMA is possible[45] and could have provided additional information regarding effectiveness in clinical practice[46-48] or treatments not analyzed in a phase III RCT (e.g. bortezomib-cyclophosphamide-dexamethasone; VCD[49]), we believe that limiting our analysis to the relative effectiveness of RCT evidence, reduces the risk of bias and systematic errors[44]. Further research to improve methodologies for conducting, evaluating and interpreting non-randomized evidence is recommended.[44] We focused on NTE NDMM treatment to increase homogeneity between the patient populations in the study We observed between-study heterogeneity comparable to the proportions previously reported by Kuhr et al. By using a random effects instead of a fixed effect model we allow for this heterogeneity. As a consequence we obtain however, larger 95% CIs.

A potential limitation of our search strategy is that we only included English publication. To the best of our knowledge this does however not lead to the exclusion of relevant studies or treatments. Furthermore, our NMA was limited to the intermediate outcome PFS and did not include other outcomes of interest such as OS, adverse events, quality of life, costs, and cost-effectiveness. While OS may even be the most important subject of investigation for patients and health care decision makers, we believe a comparison of OS for first-line therapies with the currently available data is

prone to bias due to cross-over, different and limited follow-up (e.g. especially for DaraVMP median OS was not reached at 16.5 months follow-up) and subsequent treatment lines[50,51]. Also cost-effectiveness, in the context of increasing health care expenditures another relevant and important outcome, remains subject for further research. Several treatment options showed comparable effectiveness outcomes but costs could very well differ due to drug prices, treatment duration, and route of administration. Our study facilitates cost-effectiveness research of first-line NTE treatments.

As the treatment armamentarium is rapidly increasing and evolving for NTE NDMM patients NMAs will become increasingly important. We illustrate the additional value and evidence that can be provided. NMAs support evidence based decision making and may help to optimize treatment and outcomes of NTE NDMM patients in clinical practice.

Acknowledgement of research support

This work was supported by a grant from ZonMw, the Netherlands Organisation for Health Research and Development, project number 152001020, project title “Treatment Sequencing in Multiple Myeloma: modeling the disease and evaluating cost-efficacy vs. cost-effectiveness”. The funding source had no role in writing the manuscript or decision to submit for publication.

References

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in europe: Estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-1403.

2. Mateos MV, San Miguel JF. How should we treat newly diagnosed multiple myeloma patients? Hematology Am Soc Hematol Educ Program. 2013;2013:488-495.

3. Moreau P, San Miguel J, Sonneveld P, et al. Multiple myeloma: ESMO clinical practice guidelines for diagnosis, treatment and follow-updagger. Ann Oncol. 2017128(suppl_4):iv52-iv61.

4. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014;371(10):906-917.

5. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359(9):906-917.

6. Durie BG, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): A randomised, open-label, phase 3 trial. Lancet. 2017;389(10068):519-527.

7. Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. N Engl J Med. 2018;378(6):518-528.

8. Bothwell LE, Greene JA, Podolsky SH, Jones DS. Assessing the gold standard--lessons from the history of RCTs. N Engl J Med. 2016;374(22):2175-2181.

9. Gentile M, Magarotto V, Offidani 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. Am J Hematol. 2017;92(3):244-250.

10. Neupane B, Richer D, Bonner AJ, Kibret T, Beyene J. Network meta-analysis using R: A review of currently available automated packages. PLoS One. 2014;9(12):e115065.

11. 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. Eur J Clin Pharmacol. 2016;72(3):257-265.

12. Weisel K, Doyen C, Dimopoulos M, et al. A systematic literature review and network meta-analysis of treatments for patients with untreated multiple myeloma not eligible for stem cell transplantation. Leuk Lymphoma. 2017;58(1):153-161.

13. Zweegman S, van der Holt B, Mellqvist UH, et al. Melphalan, prednisone, and lenalidomide versus melphalan, prednisone, and thalidomide in untreated multiple myeloma. Blood. 2016;127(9):1109-1116.

14. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16.

15. Higgins JP, Altman DG, Gotzsche PC, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

16. Rucker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol. 2015;15:58.

17. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods. 2010;1(2):97-111.

18. Rucker G. Network meta-analysis, electrical networks and graph theory. Res Synth Methods. 2012;3(4):312-324.

19. Rucker G, Schwarzer G. Reduce dimension or reduce weights? comparing two approaches to multi-arm studies in network meta-analysis. Stat Med. 2014;33(25):4353-4369.

20. Bhatnagar N, Lakshmi PV, Jeyashree K. Multiple treatment and indirect treatment comparisons: An overview of network meta-analysis. Perspect Clin Res. 2014;5(4):154-158.

21. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: Concepts and models for multi-arm studies. Res Synth Methods. 2012;3(2):98-110.

22. Krahn U, Binder H, Konig J. A graphical tool for locating inconsistency in network meta-analyses. BMC Med Res Methodol. 2013;13:35.

23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-560.

24. Higgins JP, Green S, eds. Cochrane handbook for systematic reviews of interventions version 5.1.0. [updated March 2011] ed. The Cochrane Collaboration; 2011. Available from www.handbook.cochrane.org. Available from www.handbook.cochrane.org.

25. Alexanian R, Haut A, Khan AU, et al. Treatment for multiple myeloma. combination chemotherapy with different melphalan dose regimens. JAMA. 1969;208(9):1680-1685.

26. Facon T, Mary JY, Hulin C, 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):1209-1218.

27. Hulin C, Facon T, Rodon P, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. J Clin Oncol. 2009;27(22):3664-3670.

28. Palumbo A, Bringhen S, Larocca A, 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. J Clin Oncol. 2014;32(7):634-640.

29. Morgan GJ, Davies FE, Gregory WM, et al. Long-term follow-up of MRC myeloma IX trial: Survival outcomes with bisphosphonate and thalidomide treatment. Clin Cancer Res. 2013;19(21):6030-6038.

30. Mateos MV, Richardson PG, Schlag R, 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. J Clin Oncol. 2010;28(13):2259-2266.

31. Dimopoulos MA, Terpos E, Chanan-Khan A, et al. Renal impairment in patients with multiple myeloma: A consensus statement on behalf of the international myeloma working group. J Clin Oncol. 2010;28(33):4976-4984.

32. Larocca A, Offidani M, Musto P, et al. 744 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. Blood. 2017;130(Suppl 1):744.

33. Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: A consensus of the international myeloma working group. Blood. 2016;127(24):2955-2962.

34. Terpos E, Kleber M, Engelhardt M, et al. European myeloma network guidelines for the management of multiple myeloma-related complications. Haematologica. 2015;100(10):1254-1266.

35. Mateos MV, Oriol A, Martinez-Lopez J, et al. Outcomes with two different schedules of bortezomib, melphalan, and prednisone (VMP) for previously untreated multiple myeloma: Matched pair analysis using long-term follow-up data from the phase 3 VISTA and PETHEMA/GEM05 trials. Ann Hematol. 2016;95(12):2033-2041.

36. Palumbo A, Bringhen S, Liberati AM, et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: Updated results of a randomized controlled trial. Blood. 2008;112(8):3107-3114.

37. Wijermans P, Schaafsma M, Termorshuizen F, 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. J Clin Oncol. 2010;28(19):3160-3166.

38. Sacchi S, Marcheselli R, Lazzaro A, 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. Leuk Lymphoma. 2011;52(10):1942-1948.

39. Beksac M, Haznedar R, Firatli-Tuglular T, 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. Eur J Haematol. 2011;86(1):16-22.

40. Waage A, Gimsing P, Fayers P, et al. Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. Blood. 2010;116(9):1405-1412.

41. Ioannidis JP. Why most published research findings are false. PLoS Med. 2005;2(8):e124.

42. Mateos MV, Oriol A, Martinez-Lopez J, 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 Oncol. 2010;11(10):934-941.

43. Fayers PM, Palumbo A, Hulin C, 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):1239-1247.

44. Efthimiou O, Mavridis D, Debray TP, et al. Combining randomized and non-randomized evidence in network meta-analysis. Stat Med. 2017;36(8):1210-1226.

45. Mohty M, Terpos E, Mateos MV, et al. Multiple myeloma treatment in real-world clinical practice: Results of a prospective, multinational, noninterventional study. Clin Lymphoma Myeloma Leuk. 2018;18(10):e401-e419.

46. Schmitz S, Maguire A, Morris J, et al. The use of single armed observational data to closing the gap in otherwise disconnected evidence networks: A network meta-analysis in multiple myeloma. BMC Med Res Methodol. 2018;18(1):66.

47. Verelst SGR, Blommestein HM, de Groot S, et al. Long-term outcomes in patients with multiple myeloma: A retrospective analysis of the dutch population-based HAematological regustry for observational studies (PHAROS). HemaSphere. 2018;2(4):1.

48. Jimenez-Zepeda VH, Duggan P, Neri P, Tay J, Bahlis NJ. Bortezomib-containing regimens (BCR) for the treatment of non-transplant eligible multiple myeloma. Ann Hematol. 2017;96(3):431-439.

49. Arditi C, Burnand B, Peytremann-Bridevaux I. Adding non-randomised studies to a cochrane review brings complementary information for healthcare stakeholders: An augmented systematic review and meta-analysis. BMC Health Serv Res. 2016;16(1):598.

50. Blommestein HM, Verelst SG, de Groot S, Huijgens PC, Sonneveld P, Uyl-de Groot CA. A cost-effectiveness analysis of real-world treatment for elderly patients with multiple myeloma using a full disease model. Eur J Haematol. 2015;96(2):198-208.
51. Zheng Y, Pan F, Sorensen S. Modeling treatment sequences in pharmacoeconomic models. Pharmacoeconomics. 2017;35(1):15-24.

Table 1 Data extraction of the included trials

Trial reference Trial ID	NCT Number	Primary outcome	Randomised / enrolled patients	Treatment	Median age research treatment (range)	N itt	Median PFS	95% CI	HRs (95% CI) {research v comparator treatment}		Median OS	Median follow-up
Facon 2006	n/r	OS	500	D	70 (67-73)	127	12.2	(10.2-14.2)			33.4	82.8
IFM 95/01				MP	70 (68-72)	122	21.1	(17.8-24.4)	0.75 (0.62-0.91) {MP v D}	1.15 (0.93-1.42) {MP v MD}	34	82.8
				MD	69 (68-72)	118	22.9	(19.0-26.8)	0.66 (0.53-0.81) {MD v D}	1.45 (1.17-1.79) {DI v MD}	39.6	82.8
				DI	69 (67-72)	121	15.2	(9.9-20.5)	0.92 (0.76-1.11) {DI v D}	1.26 (1.04-1.53) {DI v MP}	32	82.8
Facon 2007	NCT00367185	OS	447	MPT	n/r (65-75[1])	125	27.5	(23.4-31.6)	0.59 (0.44-0.78) {MPT v M100}		51.6	51.5
IFM 99–06				MP	n/r (65-75[2])	196	17.8	(15.1-20.5)	0.51 (0.39-0.66) {MPT v MP}		33.2	51.5
				M100	n/r (65-75[3])	126	19.4	(17.4-21.4)	0.87 (0.68-1.1) {M100 v MP}		38.3	51.5
Morgan 2013	ISRCTN68454111	PFS, OS	856	MP	73 (57-89)	423	12	n/r	0.81 (0.69-0.94) {CTD(a) v MP}		32	70.8
MRC M IX				CTDa	73 (58-87)	426	13	n/r			34	70.8
Rajkumar 2008	NCT00057564	TTP	470	TD	64 (39-86)	235	14.9	n/r	0.5 (0.38-0.64) {TD v D}		NR	17
MM-003				D	64 (31-84)	235	6.5	n/r			30	18
Ludwig 2009	NCT00205751	PFS, tolerance	289	TD	72 (54-86)	145	16.7	n/r	1.3 (0.95-1.78) {TD v MP}		41.5	28.1
				MP	72 (55-86)	144	20.7	n/r			49.4	28.1
Palumbo 2008	NCT00232934	RR, PFS	331	MPT-T	72	167	21.8	(19.6-26.1)	0.63 (0.48-0.81) {MPT v MP}		45	38.4
GIMEMA				MP	72	164	14.5	(12.2-17)			47.6	37.7
Hulin 2009	n/r	OS	232	MPT	79 (75-89)	115	24.1	(19.4-29)	0.61 (0.46-0.82) {MPT v MP}		44	47.5
IFM 01/01 Trial				MP		117	18.5	(14.6-21.3)			29.1	47.5
Waage 2010	NCT00218855	OS	363	MPT-T	75	184	15	(12-19)	0.89 (0.7-1.13) {MPT v MP}		29	42
NMSG				MP	74	179	14	(11-18)			32	42
Beksac 2010	NCT00934154	Treatment response, toxicities	122	MPT	69	60	n/r	n/r	0.7 (0.42-1.17) {MPT v MP}		26	35
TMSG				MP	72	62	n/r	n/r			28	23
Wijermans 2010	ISRCTN90692740	EFS	344	MPT-T	72 (65-87)	171	15	n/r	0.79 (0.62-1) {MPT v MP}		40	39
HOVON-49				MP	73 (65-84)	173	11	n/r			31	39
Sacchi 2011	n/r	n/r	135	MPT	76 (66–89)	70	33	n/r	0.67 (0.38-1.18) {MPT v MP}		52	30
				MP	79 (68–88)	65	22	n/r			32	30
Hungria 2016	NCT01532856	ORR	82	CTD	70	32	25.9	n/r	0.89 (0.48-1.64) {MPT v CTD}		32.4	37.5
				TD	72	18	21.5	n/r	1.1 (0.53-2.31) {TD v CTD}		54.6	37.5

				MPT	72	32	38.5	n/r	0.73 (0.34-1.59) {MPT vs TD}	42	37.5
San Miguel 2008	NCT00111319	TTP	682	VMP	71 (57–90)	344	21.7	n/r	0.56 (0.4-0.79) {VMP v MP}	56.4	60.1
VISTA				MP	71 (48–91)	338	15.2	n/r		43.1	60.1
Mateos 2014	NCT00443235	n/r	260	VTP	73 (69–76)	130	23	n/r	0.8 (0.61-1.04) {VMP v VTP}	43	72
GEM2005				VMP	73 (68–77)	130	32	n/r		63	72
Niesvizky 2015	NCT00507416	PFS	502	VD	75 (67-79)	168	14.7	(12-18.6)	1.12 (0.83-1.51) {VD v VTD}	49.8	44.3
UPFRONT				VTD	73 (66-77)	167	15.4	(12.6-24.2)	0.89 (0.66-1.21) {VTD v VMP}	51.5	41.3
				VMP	72 (68-77)	167	17.3	(14.8-20.3)	1.11 (0.84-1.48) {VD v VMP}	53.1	43.4
Palumbo 2014	NCT01063179	PFS	511	VMPT-VT	71 (68-75)	254	35.3	n/r	0.58 (0.47-0.71) {VMPT-VT v VMP}	NR	54
GIMEMA0305				VMP	71 (68-75)	257	24.8	n/r		60.6	54
Zonder 2011	NCT00064038	PFS	198	RD	n/r[4]	99	39	(26-53)	0.56 (0.39-0.79) {RD v D}	NR	45.4
S0232				D	n/r[5]	99	15	(8-23)		NR	45.4
Benboubkher 2014	NCT00689936	PFS	1623	Rd	73 (44–91)	535	25.5	n/r	0.97 (0.83-1.12) {MPT v RD18}	58.9	45.5
FIRST/MM-020				Rd18	73 (40–89)	541	20.7	n/r	1.43 (1.22-1.67) {RD18 v RD}	56.7	45.5
				MPT	73 (51–92)	547	21.2	n/r	1.39 (1.18-1.64) {MPT v RD}	48.5	45.5
Zweegman 2016	EUDRACT 2007-004007-34	PFS	568	MPT-T	72 (60-91)	280	20	(18-23)	0.87 (0.72-1.04) {MPR-R vs MPT-T}	49	32.6
HOVON-87				MPR-R	73 (60-87)	280	22	(19-27)		50	32.6
Stewart 2015	NCT00602641	PFS	306	MPT-T	76 (54-92)	154	21	(18-27)	0.84 (0.64-1.09) {MPT-T v MPR-R}	52.6	40.7•
ECOG E1A06				MPR-R	77 (63-92)	152	18.7	(16-22)		47.7	
Magarotto 2016	NCT01093196	PFS	654	MPR-R	74 (63-91)	218	24	n/r	0.81 (0.63-1.03) {MPR-R v RD}	NR	39
EMN01				CPR	73 (63-87)	222	20	n/r	1.01 (0.9-1.13) {CPR v RD}	NR	39
				Rd	73 (50-89)	222	21	n/r	0.8 (0.63-1.02) {MPR-R v CPR}	NR	39
Palumbo 2012	NCT00405756	PFS	459	MPR-R	71 (65–87)	152	31	n/r	0.49 (0.35-0.69) {MPR-R v MPR}	56	53
MM-015				MP	72 (65–91)	154	13	n/r	1.19 (0.94-1.5) {MP v MPR}	52	53
				MPR	71 (65–86)	153	14	n/r	0.4 (0.29-0.54) {MPR-R v MP}	54	53
Durie 2017	NCT00644228	PFS	525	VRd	n/r (≥18[6])	264	43	(39-52)	0.71 (0.56-0.91) {VRd v Rd}	52	54
SWOG S0777				Rd	n/r (≥18[7])	261	30	(25-39)		38	56
Mateos 2018	NCT02195479	PFS	706	DaraVMP	71 (40-93)	350	NR		0.50 (0.38-0.65) {DaraVMP v VMP}	NR	16.5
ALCYONE				VMP	71 (50-91)	356	18.1	(16.5-19.9)		NR	

Legend Table 1

"□ Mean instead of median; n/r: not reported; NR: not reached; PFS: progression-free survival; OS: overall survival; TTP: time to progression; EFS: event-free survival; ORR: overall response rate; RR: repsonse rate, CI: confidence interval; C: cyclophosphamide; D/d: dexamethasone; Dara: daratumumab; M: melphalan; P: prednisone; R: lenalidomide; T: thalidomide; V: bortezomib"

□ Abstract identified from SLR, full text available from december 2016; • Median follow-up from survivors

[1]40% ≥70 years [2]43% ≥70 years [3]39% ≥70 years [4]49% ≥65 years [5]47% ≥65 years [6]38% ≥65 years [7]48% ≥65 years

Source HR: from published trial (MM-003, Ludwig 2009, GIMEMA, MRC-MIX, GIMEMA0305, HOVON87, S0777, E1A06, ALCYONE, IFM-99/06, EMN01, FIRST), obtained from a previous patient-level meta-analysis5 (IFM-01/01, NMSG, TMSG, HOVON49), from a previous NMA15 (Sacchi 2011) and data on file from investigators (Hungria 2016). Calculations were made using the published HR and P value (VISTA), Kaplan-Meier curves (IFM95/01 and the MM-15) and p-value and number of events (GEM2005, Upfront, s0232). Table 1 presents the extracted and calculated data.

Figure 1 PRISMA 2009 Flow Diagram – TNEMM phase III RCTs

Figure 2 Network of the included studies in the network meta-analysis

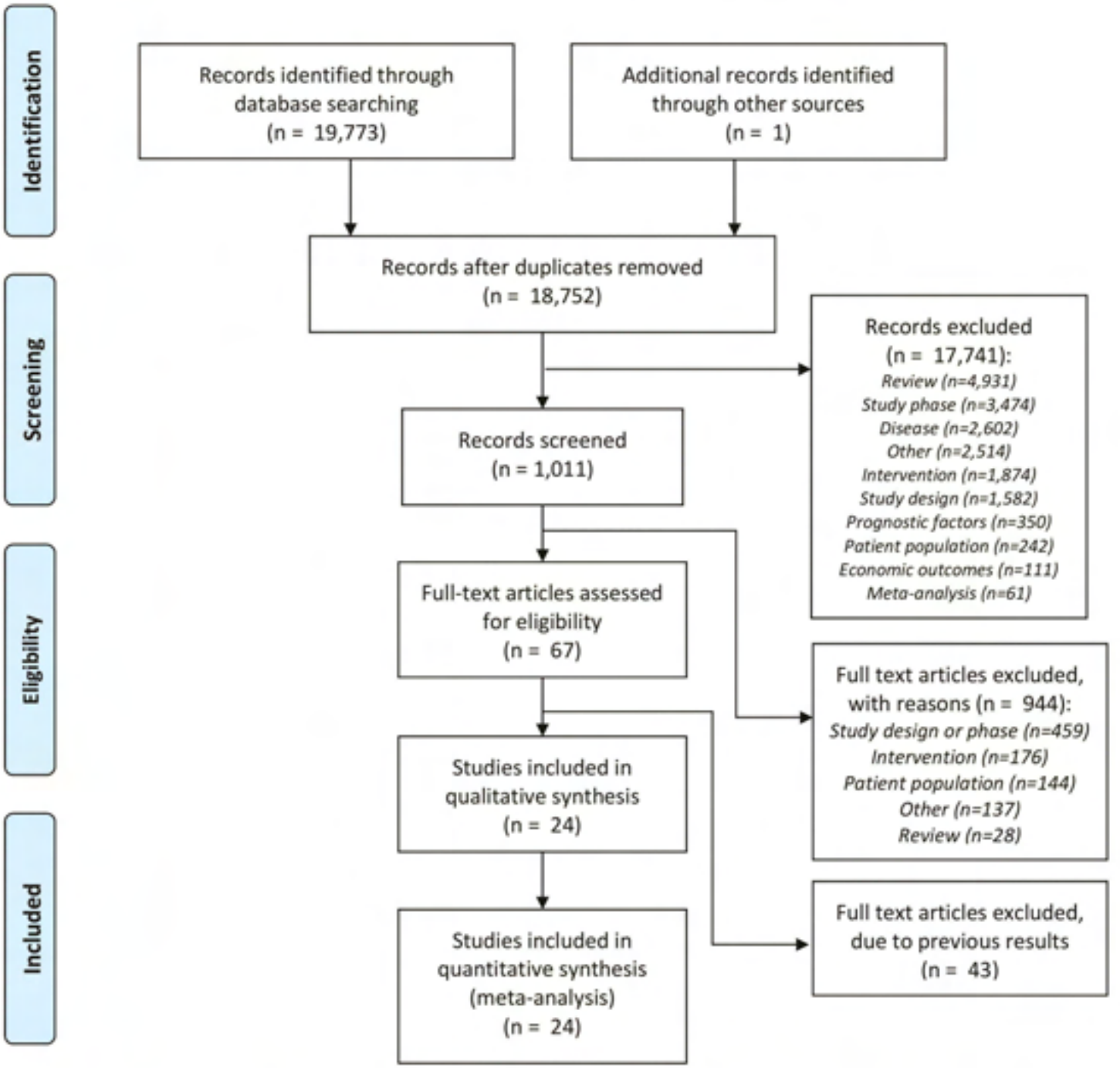
Legend:
White boxes represent treatments and reference numbers using the following abbreviations;

[1] Dexamethasone (D)
[2] Dexamethasone-Interferon alpha (DI)
[3] Melphalan 100 (M100)
[4] Melphalan-Dexamethasone (MD)
[5] Melphalan-Prednisone (MP)
[6] Thalidomide-Dexamethasone (TD)
[7] Cyclophosphamide-Thalidomide-Dexamethasone (CTD)
[8] Cyclophosphamide-Thalidomide-Dexamethasone (attenuated) (CTD(a))
[9] Melphalan-Prednisone-Thalidomide / Melphalan-Prednisone-Thalidomide and Thalidomide maintenance (MPT/MPT-T)
[10] Bortezomib-Dexamethasone (VD)
[11] Bortezomib-Thalidomide-Dexamethasone (VTD)
[12] Bortezomib-Melphalan-Prednisone (VMP)
[13] Bortezomib-Thalidomide-Prednisone (VTP)
[14] Bortezomib-Melphalan-Prednisone-Thalidomide and Bortezomib-Thalidomide (VMPT-VT)
[15] Cyclophosphamide-Prednisone-Lenalidomide (CPR)
[16] Lenalidomide-Dexamethasone (Rd)
[17] 18 cycles Lenalidomide-Dexamethasone (Rd18)
[18] Melphalan-Prednisone-Lenalidomide (MPR)
[19] Melphalan-Prednisone-Lenalidomide and Lenalidomide maintenance (MPR-R)
[20] Bortezomib-Lenalidomide-Dexamethasone (VRd)
[21] Daratumumab-Bortezomib-Melphalan-Prednisone (DaraVMP)

Black box represents the reference treatment in the network meta-analysis.
Grey boxes include the trial reference and hazard ratio for progression-free survival on the top row(s).
The bottom row shows the hazard ratio according to the network meta-analysis (NMA).
* (asterisk) indicates hazard ratio not statistically significant at 5%

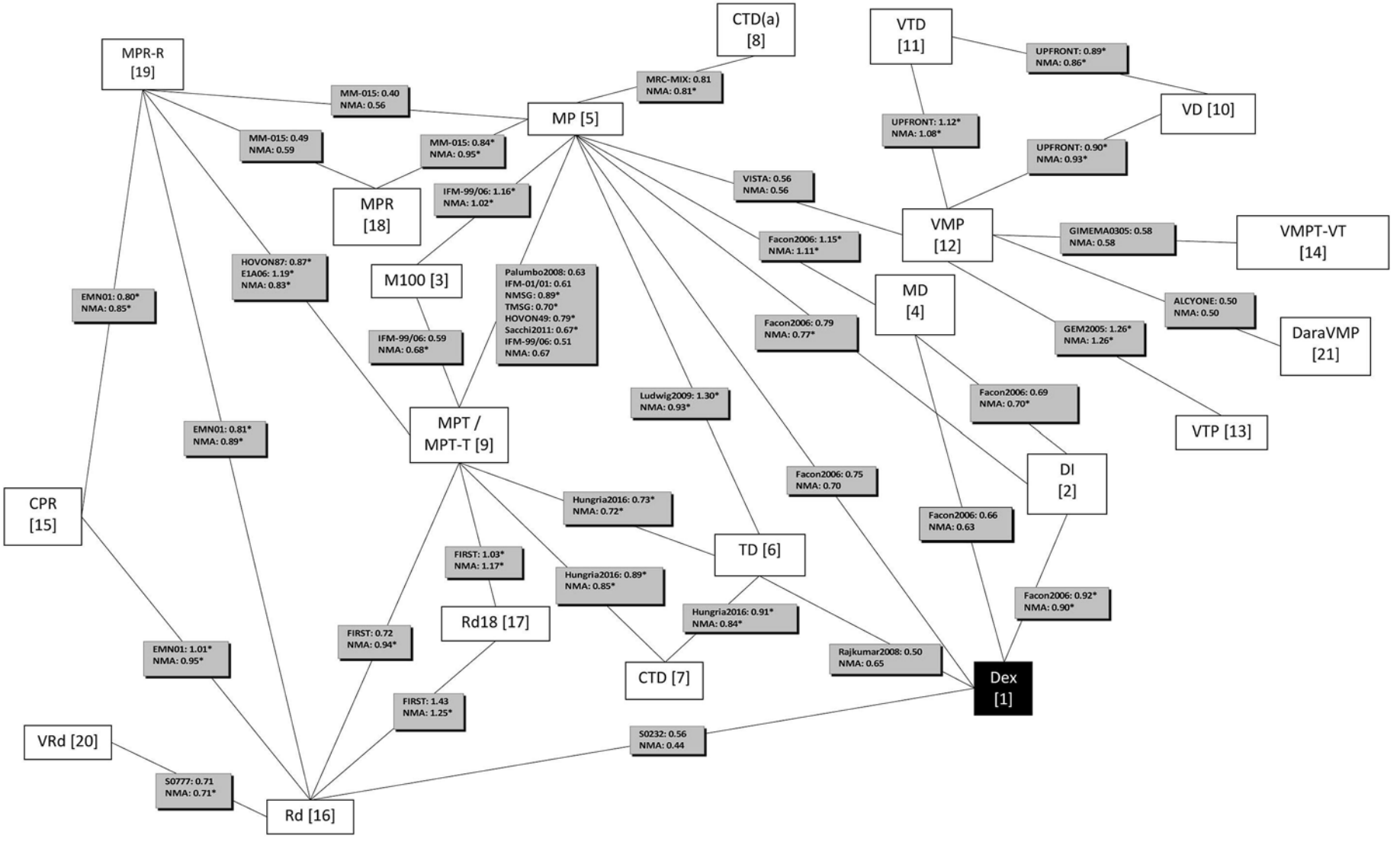
Figure 3 NMA results in which dexamethasone was used as comparator
Legend:
HR: Hazard ratio.
Abbreviations for treatments see legend Figure 2

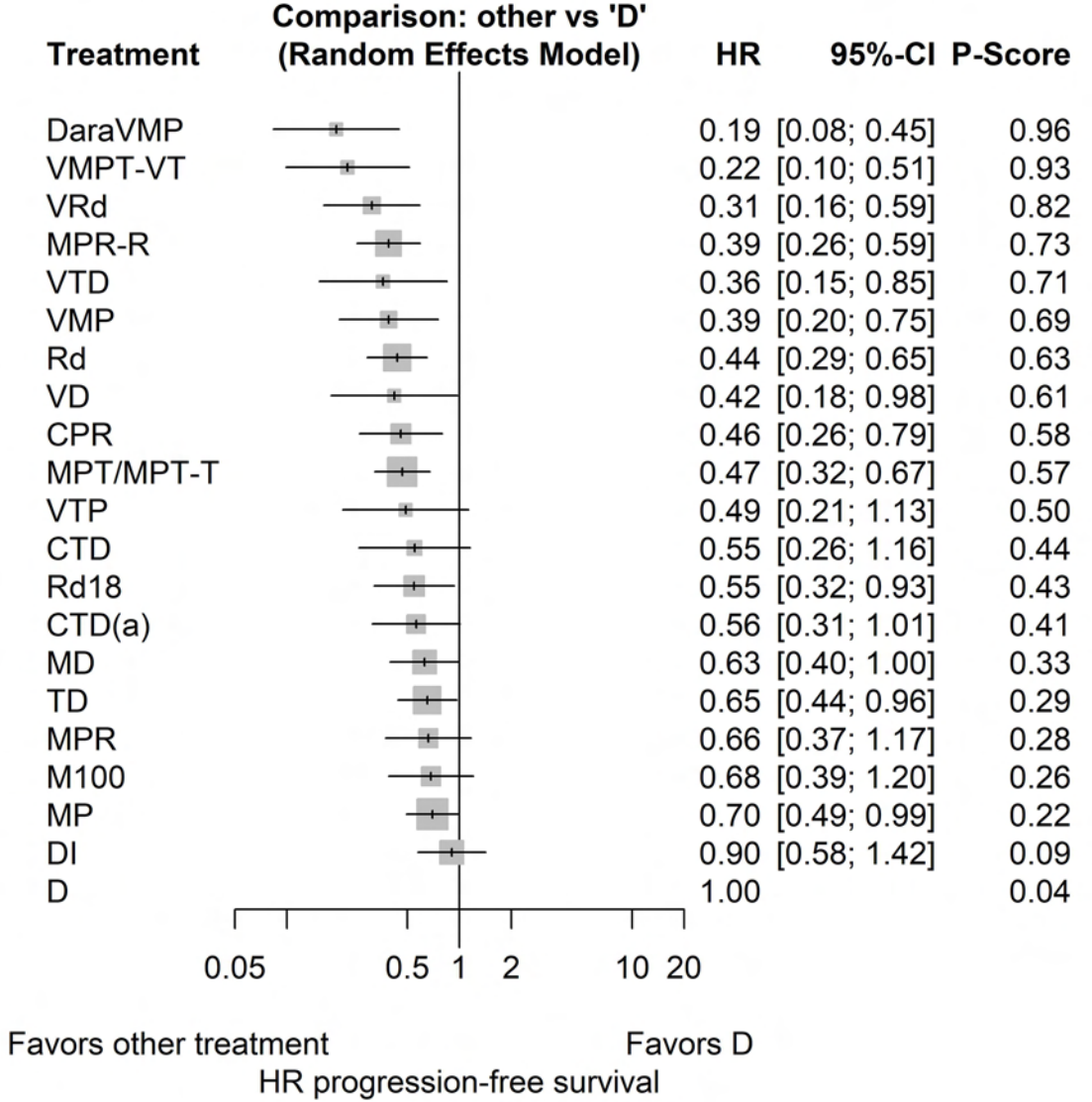
PRISMA 2009 Flow Diagram – TNEMM phase III RCTs



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.


MPR-R [19]
CTD(a) [8]
VTD [11]
MP [5]
MPR [18]
M100 [3]
MPT / MPT-T [9]
VMP [12]
MD [4]
VD [10]
VMPT-VT [14]
DaraVMP [21]
VTP [13]
DI [2]
TD [6]
CTD [7]
Rd18 [17]
Rd [16]
VRd [20]
CPR [15]
Dex [1]
MM-015: 0.40 NMA: 0.56
MRC-MIX: 0.81 NMA: 0.81*
UPFRONT: 0.89* NMA: 0.86*
MM-015: 0.49 NMA: 0.59
MM-015: 0.84* NMA: 0.95*
UPFRONT: 1.12* NMA: 1.08*
UPFRONT: 0.90* NMA: 0.93*
IFM-99/06: 1.16* NMA: 1.02*
VISTA: 0.56 NMA: 0.56
GIMEMA0305: 0.58 NMA: 0.58
HOVON87: 0.87* E1A06: 1.19* NMA: 0.83*
Palumbo2008: 0.63 IFM-01/01: 0.61 NMSG: 0.89* TMSG: 0.70* HOVON49: 0.79* Sacchi2011: 0.67* IFM-99/06: 0.51 NMA: 0.67
Facon2006: 1.15* NMA: 1.11*
ALCYONE: 0.50 NMA: 0.50
EMN01: 0.80* NMA: 0.85*
IFM-99/06: 0.59 NMA: 0.68*
Facon2006: 0.79 NMA: 0.77*
GEM2005: 1.26* NMA: 1.26*
Ludwig2009: 1.30* NMA: 0.93*
Facon2006: 0.69 NMA: 0.70*
EMN01: 0.81* NMA: 0.89*
Facon2006: 0.75 NMA: 0.70
Hungria2016: 0.73* NMA: 0.72*
Facon2006: 0.66 NMA: 0.63
FIRST: 1.03* NMA: 1.17*
Hungria2016: 0.89* NMA: 0.85*
Facon2006: 0.92* NMA: 0.90*
Hungria2016: 0.91* NMA: 0.84*
FIRST: 0.72 NMA: 0.94*
EMN01: 1.01* NMA: 0.95*
Rajkumar2008: 0.50 NMA: 0.65
FIRST: 1.43 NMA: 1.25*
S0232: 0.56 NMA: 0.44
S0777: 0.71 NMA: 0.71*


Comparison: other vs 'D'
Treatment
(Random Effects Model)
HR
95%-CI
P-Score
DaraVMP 0.19 [0.08; 0.45] 0.96
VMPT-VT 0.22 [0.10; 0.51] 0.93
VRd 0.31 [0.16; 0.59] 0.82
MPR-R 0.39 [0.26; 0.59] 0.73
VTD 0.36 [0.15; 0.85] 0.71
VMP 0.39 [0.20; 0.75] 0.69
Rd 0.44 [0.29; 0.65] 0.63
VD 0.42 [0.18; 0.98] 0.61
CPR 0.46 [0.26; 0.79] 0.58
MPT/MPT-T 0.47 [0.32; 0.67] 0.57
VTP 0.49 [0.21; 1.13] 0.50
CTD 0.55 [0.26; 1.16] 0.44
Rd18 0.55 [0.32; 0.93] 0.43
CTD(a) 0.56 [0.31; 1.01] 0.41
MD 0.63 [0.40; 1.00] 0.33
TD 0.65 [0.44; 0.96] 0.29
MPR 0.66 [0.37; 1.17] 0.28
M100 0.68 [0.39; 1.20] 0.26
MP 0.70 [0.49; 0.99] 0.22
DI 0.90 [0.58; 1.42] 0.09
D 1.00 0.04
0.05
0.5
1
2
10
20
Favors other treatment
Favors D
HR progression-free survival

Appendix 1 Search strategies

1.1 Embase® and MEDLINE®

Database name Embase®/MEDLINE®
Search interface http://www.embase.com
Date of search 5 March 2016
Time segment 16 June 2010 to 01 March 2016
Search filter -

Table Embase® and MEDLINE® search strategy for randomized controlled trials

#	Search term
1	'clinical trial'/exp
2	'randomization'/de
3	'controlled study'/de
4	'comparative study'/de
5	'single blind procedure'/de
6	'double blind procedure'/de
7	'crossover procedure'/de
8	'placebo'/de
9	'clinical trial' OR 'clinical trials'
10	'controlled clinical trial' OR 'controlled clinical trials'
11	'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials'
12	'randomisation' OR 'randomization'
13	rct
14	'random allocation'
15	'randomly allocated'
16	'allocated randomly'
17	allocated NEAR/2 random
18	(single OR double OR triple OR treble) NEAR/1 (blind* OR mask*)
19	placebo*
20	'prospective study'/de
21	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
22	'case study'/de
23	'case report'/de
24	'abstract report'/de
25	'letter'/de

#	Search term
26	#22 OR #23 OR #24 OR #25
27	#21 NOT #26
28	'cohort analysis'/exp
29	'longitudinal study'/exp
30	'prospective study'/exp
31	'follow up'/exp
32	'major clinical study'/exp
33	'clinical trial'/exp
34	'clinical article'/exp
35	'intervention study'/exp
36	'survival'/exp
37	cohort*:ab,ti
38	(('follow up' OR followup) NEXT/1 (study OR studies)):ab,ti
39	(clinical NEXT/1 trial*):ab,ti
40	'retrospective study'/exp
41	'case control study'/exp
42	(case* NEXT/1 control*):ab,ti
43	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42
44	#27 OR #43
45	'multiple myeloma'/de
46	'myeloma'/de
47	'myeloma cell'/de
48	myelom*
49	#45 OR #46 OR #47 OR #48
50	'bortezomib'/de
51	bortezomib:ab,ti OR velcade:ab,ti OR ps341:ab,ti OR 'ps-341':ab,ti OR (ps NEAR/1 '341'):ab,ti OR (proteasome NEXT/1 inhibit*):ab,ti
52	'lenalidomide'/de
53	lenalidomide:ab,ti OR revimid:ab,ti OR revlimid:ab,ti OR 'cc 5013':ab,ti OR cc5013:ab,ti OR 'cdc 501':ab,ti OR 'cdc 5013':ab,ti OR cdc501:ab,ti OR cdc5013:ab,ti OR 'enmd 0997':ab,ti OR enmd0997:ab,ti OR 'imid 3':ab,ti OR imid3:ab,ti
54	'thalidomide'/de
55	thalidomide:ab,ti OR thalidomid:ab,ti OR thalimodide:ab,ti OR thalomid:ab,ti OR contergan:ab,ti OR distaval:ab,ti OR isomin:ab,ti OR 'k-17':ab,ti OR kedavon:ab,ti OR kevadon:ab,ti OR neurosedin:ab,ti OR neurosedyne:ab,ti OR 'nsc 66847':ab,ti OR sedalis:ab,ti OR 'shin naito':ab,ti OR softenon:ab,ti OR synovir:ab,ti OR talimol:ab,ti OR talizer:ab,ti OR telagan:ab,ti OR telargan:ab,ti
56	'bendamustine'/de
57	bendamustine:ab,ti OR 'cimet 3393':ab,ti OR cytostasan:ab,ti OR cytostasane:ab,ti OR 'imet 3393':ab,ti OR ribomustin:ab,ti OR treanda:ab,ti

#	Search term
58	'dexamethasone'/de
59	'aeroseb dex':ab,ti OR aflucoson*:ab,ti OR anaflogistico:ab,ti OR arcodexan*:ab,ti OR azium:ab,ti OR calonat:ab,ti OR cebedex:ab,ti OR colofoam:ab,ti OR cortidron*:ab,ti OR cortisumman:ab,ti OR dacortin*:ab,ti OR dalalone:ab,ti OR decacortin:ab,ti OR decadeltoson*:ab,ti OR decadion:ab,ti OR decadr*n*:ab,ti OR decaesadril:ab,ti OR decamethasone:ab,ti OR decasone:ab,ti OR decaspray:ab,ti OR decasterolone:ab,ti OR decilone:ab,ti OR decofluor:ab,ti OR dectancyl:ab,ti OR dekacort:ab,ti OR delladec:ab,ti OR deltafluoren:ab,ti OR deltafluorene:ab,ti OR dergramin:ab,ti OR deronil:ab,ti OR desacort:ab,ti OR desacortone:ab,ti OR desadrene:ab,ti OR desalark:ab,ti OR desameton*:ab,ti OR 'dexa cortisyl':ab,ti OR 'dexa dabrosan':ab,ti OR 'dexa korti':ab,ti OR 'dexa scherosan':ab,ti OR 'dexa scherozon':ab,ti OR 'dexa scherozone':ab,ti OR dexachel:ab,ti OR dexacort*:ab,ti OR dexadabroson:ab,ti OR dexadecadrol:ab,ti OR dexadrol:ab,ti OR dexagen:ab,ti OR dexahelvacort:ab,ti OR dexakorti:ab,ti OR dexalocal:ab,ti OR dexamecortin:ab,ti OR dexameson*:ab,ti OR dexametason*:ab,ti OR dexameth:ab,ti OR dexametha*on*:ab,ti OR dexamethonium:ab,ti OR dexan:ab,ti OR dexane:ab,ti OR dexapot:ab,ti OR dexaschero*on*:ab,ti OR dexason*:ab,ti OR dexinoral:ab,ti OR dexionil:ab,ti OR dexone:ab,ti OR dextelan:ab,ti OR dezone:ab,ti OR doxamethasone:ab,ti OR esacortene:ab,ti OR exadion*:ab,ti OR firmalone:ab,ti OR fluormone:ab,ti OR fluorocort:ab,ti OR fluorodelta:ab,ti OR fortecortin:ab,ti OR gammacorten*:ab,ti OR grosodexon*:ab,ti OR hexadecad*ol:ab,ti OR hexadiol:ab,ti OR hexadrol:ab,ti OR isnacort:ab,ti OR isoptodex:ab,ti OR isoptomaxidex:ab,ti OR 'lokalison f':ab,ti OR luxazone:ab,ti OR marvidione:ab,ti OR maxidex:ab,ti OR mediamethasone:ab,ti OR megacortin:ab,ti OR mephameson*:ab,ti OR metasolon*:ab,ti OR methazonion*:ab,ti OR millicorten:ab,ti OR millicortenol:ab,ti OR 'mk 125':ab,ti OR mk125:ab,ti OR nisomethasona:ab,ti OR novocort:ab,ti OR 'nsc 34521':ab,ti OR nsc34521:ab,ti OR opticorten:ab,ti OR opticortinol:ab,ti OR oradex*n*:ab,ti OR orgadrone:ab,ti OR policort:ab,ti OR posurdex:ab,ti OR prodexona:ab,ti OR prodexone:ab,ti OR sanamethasone:ab,ti OR spoloven:ab,ti OR triamcimetil:ab,ti OR visumethazone:ab,ti
60	'melphalan'/de
61	melph*lan:ab,ti OR alkeran:ab,ti OR 'cb 3025':ab,ti OR cb3025:ab,ti OR 'levo sarcolysin':ab,ti OR levofalan:ab,ti OR melfalan:ab,ti OR melphalon:ab,ti OR 'nsc 8806':ab,ti OR nsc8806:ab,ti OR 'phenylalanine 2037':ab,ti OR 'phenylalanine mustard':ab,ti
62	'vincristine'/de
63	vincristine:ab,ti OR vincristin:ab,ti OR 'l 37231':ab,ti OR l37231:ab,ti OR 'vin cristine':ab,ti OR vincrisul:ab,ti
64	'cyclophosphamide'/de
65	cyclophosphamide:ab,ti OR 'b 518':ab,ti OR b518:ab,ti OR carloxan:ab,ti OR clafen:ab,ti OR cycloblastin*:ab,ti OR 'cyclofos amide':ab,ti OR cyclofosfamid*:ab,ti OR cyclophosphamid*:ab,ti OR cyclophosphan*:ab,ti OR cyclostin:ab,ti OR cycloxan:ab,ti OR cyphos:ab,ti OR cytophosphan*:ab,ti OR cytoxan:ab,ti OR 'endocyclo phosphate':ab,ti OR end*xan*:ab,ti OR genoxal:ab,ti OR 'mitoxan neosan':ab,ti OR neosar:ab,ti OR noristan:ab,ti OR 'nsc 26271':ab,ti OR 'nsc 2671':ab,ti OR procytox:ab,ti OR procytoxide:ab,ti OR se*doxan:ab,ti
66	'doxorubicin'/de
67	doxorubicin:ab,ti OR adriablastin:ab,ti OR adriablastin*:ab,ti AND adriacin:ab,ti OR adriamicin*:ab,ti OR adriblastin*:ab,ti OR caelyx:ab,ti OR doxil:ab,ti OR doxorubicine:ab,ti OR 'fi 106':ab,ti OR fi106:ab,ti OR lipodox:ab,ti OR myocet:ab,ti OR 'nsc 123127':ab,ti OR nsc123127:ab,ti OR rastocin:ab,ti OR resmycin:ab,ti OR 'rp 25253':ab,ti OR rp25253:ab,ti OR rubex:ab,ti OR sarcodoxome:ab,ti OR 'tlc d 99':ab,ti
68	'carmustine'/de
69	carmustine:ab,ti OR bcnu:ab,ti OR bicnu:ab,ti OR carmubis:ab,ti OR carmubris:ab,ti OR carmustin:ab,ti OR gliadel:ab,ti OR nitrumon:ab,ti OR 'nsc 409962':ab,ti
70	'prednisone'/de
71	prednisone:ab,ti OR ancortone:ab,ti OR biocortone:ab,ti OR colisone:ab,ti OR cortidelt:ab,ti OR 'de cortisyl':ab,ti OR decortancyl:ab,ti OR de*ortin*:ab,ti OR dehydrocortisone:ab,ti OR delitisone:ab,ti OR deltacort*n*:ab,ti OR deltacortisone:ab,ti OR deltasone:ab,ti OR deltra:ab,ti OR 'di-adreson':ab,ti OR diadreson:ab,ti OR en*orton*:ab,ti OR hostacortin:ab,ti OR insone:ab,ti OR meprison:ab,ti OR metacortandracin:ab,ti OR meticorten:ab,ti OR meticortine:ab,ti OR 'nsc 10023':ab,ti OR nsc10023:ab,ti OR orasone*:ab,ti OR paracort:ab,ti OR precort:ab,ti OR precortal:ab,ti OR prednisone*:ab,ti OR pronizone:ab,ti OR rectodelt:ab,ti OR ultracorten:ab,ti OR urtilone:ab,ti
72	'prednisolone'/de
73	prednisolone:ab,ti OR antisolon*:ab,ti OR aprednislon*:ab,ti OR benisolon*:ab,ti OR berisolon*:ab,ti OR caberdelta:ab,ti OR 'co hydeltra':ab,ti OR codelcortone:ab,ti OR cortadelton*:ab,ti OR cortelinter:ab,ti OR cortisolone:ab,ti OR dacortin:ab,ti OR decortril:ab,ti OR dehydrocortex:ab,ti OR dehydrocortisol*:ab,ti OR dehydrohydrocortison*:ab,ti OR delcortol:ab,ti OR deltacortef:ab,ti OR deltacortenolo:ab,ti OR deltacortil:ab,ti OR deltacortoil:ab,ti OR deltaderm:ab,ti OR deltaglycortril:ab,ti OR deltahycortol:ab,ti OR deltahydrocortison*:ab,ti OR deltaophticor:ab,ti OR deltasolone:ab,ti OR deltastab:ab,ti OR deltidrosol:ab,ti OR deltisilone:ab,ti OR deltisolon*:ab,ti

#	Search term
	OR deltolasson*:ab,ti OR deltoson*:ab,ti OR dicortol:ab,ti OR domucortone:ab,ti OR encort*lon*:ab,ti OR glistelone:ab,ti OR hostacortin:ab,ti OR hydeltra:ab,ti OR hydeltrone:ab,ti OR hydrelta:ab,ti OR hydrocortancyl:ab,ti OR hydrocortidelt:ab,ti OR hydrodeltalone:ab,ti OR hydrodeltisone:ab,ti OR hydroretrocortin*:ab,ti OR inflanefran:ab,ti OR insolone:ab,ti OR keteocort:ab,ti OR leocortol:ab,ti OR mediasolone:ab,ti OR meprisolon*:ab,ti OR metacortalon*:ab,ti OR metacortandralon*:ab,ti OR metacortelone:ab,ti OR meticortelone:ab,ti OR metiderm:ab,ti OR morlone:ab,ti OR mydrapred:ab,ti OR nisolon:ab,ti OR nisolone:ab,ti OR 'nsc 9120':ab,ti OR nsc9120:ab,ti OR panafcortolone:ab,ti OR panafort:ab,ti OR paracortol:ab,ti OR phlogex:ab,ti OR precortalon:ab,ti OR precortancyl:ab,ti OR precortisyl:ab,ti OR predartrin*:ab,ti OR prednedome:ab,ti OR prednelan:ab,ti OR prednicoelin:ab,ti OR prednicort:ab,ti OR prednicortelone:ab,ti OR prednifor:ab,ti OR predniment:ab,ti OR predniretard:ab,ti OR prednis:ab,ti OR prednivet:ab,ti OR prednorsolon*:ab,ti OR predonine:ab,ti OR predorgasolon*:ab,ti OR prelone:ab,ti OR prenolone:ab,ti OR prezolon:ab,ti OR scherisolon:ab,ti OR serilone:ab,ti OR solone:ab,ti OR solupren*:ab,ti OR spiricort:ab,ti OR spolotane:ab,ti OR sterolone:ab,ti OR supercorti*ol:ab,ti OR taracortelone:ab,ti OR wysolone:ab,ti
74	‘pomalidomide’/de
75	pomalidomide:ab,ti OR imnovid:ab,ti OR pomalyst:ab,ti OR 'cc-4047':ab,ti OR 'cc 4047':ab,ti OR cc4047:ab,ti
76	‘panobinostat’/de
77	panobinostat:ab,ti OR farydak:ab,ti OR ‘lbh-589’:ab,ti OR ‘lbh589’:ab,ti OR ‘lbh 589’:ab,ti
78	‘carfilzomib’/de
79	carfilzomib:ab,ti OR kyprolis:ab,ti OR ‘pr-171’:ab,ti OR ‘pr171’:ab,ti OR ‘pr 171’:ab,ti
80	‘daratumumab’/de
81	daratumumab:ab,ti OR darzalex:ab,ti
82	`ixazomib’/de
83	ixazomib:ab,ti OR ninlaro:ab,ti OR mln9708:ab,ti OR ‘mln 9708’:ab,ti OR ‘mln-9708’:ab,ti
84	‘elotuzumab’/de
85	elotuzumab:ab,ti OR empliciti:ab,ti OR HuLuc63:ab,ti OR BMS-901608:ab,ti
86	#50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85
87	#44 AND #49 AND #86
88	#44 AND #49 AND #86 AND [1-1-2013]/sd NOT [31-12-2015]/sd

1.2 Cochrane

Database name Cochrane
Search interface http://www.thecochranelibrary.com/view/0/index.html
Date of search 5 March 2016
Time segment 2010 to 2016
Search filter Controlled clinical trials

Table Cochrane search strategy

#	Search term
1	MeSH descriptor: [Multiple Myeloma] explode all trees
2	myeloma*
3	proteasome inhibitor
4	bortezomib
5	(velcade OR ps341 OR "ps-341" OR (ps NEAR/1 341))
6	lenalidomide
7	revimid OR revlimid OR "cc 5013" OR cc5013 OR "cdc 501" OR "cdc 5013" OR cdc501 OR cdc5013 OR "enmd 0997" OR enmd0997 OR "imid 3" OR imid3
8	thalidomide
9	thalidomid OR thalimodide OR thalomid OR contergan OR distaval OR isomin OR "k-17" OR kedavon OR kevadon OR neurosedin OR neurosedyne OR "nsc 66847" OR sedalis OR "shin naito" OR softenon OR synovir OR talimol OR talizer OR telagan OR telargan
10	bendamustine
11	"cimet 3393" OR cytostasan OR cytostasane OR "imet 3393" OR ribomustin OR treanda
12	MeSH descriptor: [Dexamethasone] this term only
13	MeSH descriptor: [Thalidomide] this term only
14	MeSH descriptor: [Melphalan] this term only
15	MeSH descriptor: [Vincristine] this term only
16	MeSH descriptor: [Cyclophosphamide] this term only
17	MeSH descriptor: [Doxorubicin] this term only
18	MeSH descriptor: [Carmustine] this term only
19	MeSH descriptor: [Prednisone] this term only
20	MeSH descriptor: [Prednisolone] this term only
21	('aeroseb dex' OR aflucoson* OR anaflogistico OR arcodexan* OR azium OR calonat OR cebedex OR colofoam OR cortidron* OR cortisumman OR dacortin* OR dalalone OR decacortin OR decadeltoson* OR decadion OR decadr*n* OR decaesadril OR decamethasone OR decasone OR decaspray OR decasterolone OR decilone OR decofluor OR dectancyl OR dekacort OR delladec OR deltafluoren OR deltafluorene OR dergramin OR deronil OR desacort OR desacortone OR desadrene OR desalark OR desameton* OR 'dexa cortisyl' OR 'dexa dabrosan' OR 'dexa korti' OR 'dexa scherosan' OR 'dexa scherozon' OR 'dexa scherozone' OR dexachel OR dexacort* OR dexadabroson OR dexadecadrol OR dexadrol OR dexagen OR dexahelvacort OR dexakorti OR dexalocal OR dexamecortin OR dexameson* OR dexametason* OR dexameth OR dexametha*on* OR dexamethonium OR dexan OR dexane OR dexapot OR dexaschero*on* OR dexason* OR dexinoral OR dexionil OR dexone OR dextelan OR dezone OR doxamethasone OR esacortene OR exadion* OR firmalone OR fluormone OR fluorocort OR fluorodelta OR fortecortin OR gammacorten* OR grosodexon* OR hexadecad*ol OR hexadiol OR hexadrol OR isnacort OR isoptodex OR isoptomaxidex OR 'lokalison f' OR luxazone OR marvidione OR maxidex OR mediamethasone OR megacortin OR mephameson* OR metasolon* OR methazonion* OR millicorten OR millicortenol OR 'mk 125' OR mk125 OR nisomethasona OR novocort OR 'nsc 34521' OR nsc34521 OR opticorten OR opticortinol OR oradex*n* OR

#	Search term
	orgadrone OR policort OR posurdex OR prodexona OR prodexone OR sanamethasone OR spoloven OR triamcimetil OR visumethazone):ti,ab,kw
22	(melph*lan OR alkeran OR 'cb 3025' OR cb3025 OR 'levo sarcolysin' OR levofalan OR melfalan OR melphalon OR 'nsc 8806' OR nsc8806 OR 'phenylalanine 2037' OR 'phenylalanine mustard'):ti,ab,kw
23	(vincristine OR vincristin OR 'l 37231' OR l37231 OR 'vin cristine' OR vincrisul):ti,ab,kw
24	(cyclophosphamide OR 'b 518' OR b518 OR carloxan OR clafen OR cycloblastin* OR 'cyclofos amide' OR cyclofosfamid* OR cyclophosphamid* OR cyclophosphan* OR cyclostin OR cycloxan OR cyphos OR cytophosphan* OR cytoxan OR 'endocyclo phosphate' OR end*xan* OR genoxal OR 'mitoxan neosan' OR neosar OR noristan OR 'nsc 26271' OR 'nsc 2671' OR procytox OR procytoxide OR se*doxan):ti,ab,kw
25	(doxorubicin OR adriablastin OR adriablastin* AND adriacin OR adriamicin* OR adriblastin* OR caelyx OR doxil OR doxorubicine OR 'fi 106' OR fi106 OR lipodox OR myocet OR 'nsc 123127' OR nsc123127 OR rastocin OR resmycin OR 'rp 25253' OR rp25253 OR rubex OR sarcodoxome OR 'tlc d 99'):ti,ab,kw
26	(carmustine OR bcnu OR bicnu OR carmubis OR carmubris OR carmustin OR gliadel OR nitrumon OR 'nsc 409962'):ti,ab,kw
27	(prednisone OR ancortone OR biocortone OR colisone OR cortidelt OR 'de cortisyl' OR decortancyl OR de*ortin* OR dehydrocortisone OR delitisone OR deltacort*n* OR deltacortisone OR deltasone OR deltra OR 'di-adreson' OR diadreson OR en*orton* OR hostacortin OR insone OR meprison OR metacortandracin OR meticorten OR meticortine OR 'nsc 10023' OR nsc10023 OR orasone* OR paracort OR precort OR precortal OR prednisone* OR pronizone OR rectodelt OR ultracorten OR urtilone):ti,ab,kw
28	(prednisolone OR antisolon* OR aprednislon* OR benisolon* OR berisolon* OR caberdelta OR 'co hydeltra' OR codelcortone OR cortadelton* OR cortelinter OR cortisolone OR dacortin OR decortril OR dehydrocortex OR dehydrocortisol* OR dehydrohydrocortison* OR delcortol OR deltacortef OR deltacortenolo OR deltacortil OR deltacortoil OR deltaderm OR deltaglycortril OR deltahycortol OR deltahydrocortison* OR deltaophticor OR deltasolone OR deltastab OR deltidrosol OR deltisilone OR deltisolon* OR deltolasson* OR deltoson* OR dicortol OR domucortone OR encort*lon* OR glistelone OR hostacortin OR hydeltra OR hydeltrone OR hydrelta OR hydrocortancyl OR hydrocortidelt OR hydrodeltalone OR hydrodeltisone OR hydroretrocortin* OR inflanefran OR insolone OR keteocort OR leocortol OR mediasolone OR meprisolon* OR metacortalon* OR metacortandralon* OR metacortelone OR meticortelone OR metiderm OR morlone OR mydrapred OR nisolon OR nisolone OR 'nsc 9120' OR nsc9120 OR panafcortolone OR panafort OR paracortol OR phlogex OR precortalon OR precortancyl OR precortisyl OR predartrin* OR prednedome OR prednelan OR prednicoelin OR prednicort OR prednicortelone OR prednifor OR predniment OR predniretard OR prednis OR prednivet OR prednorsolon* OR predonine OR predorgasolon* OR prelone OR prenolone OR prezolon OR scherisolon OR serilone OR solone OR solupren* OR spiricort OR spolotane OR sterolone OR supercorti*ol OR taracortelone OR wysolone):ti,ab,kw
29	pomalidomide
30	(imnovid OR pomalyst OR “cc-4047” OR “cc 4047” OR cc4047):ti,ab,kw
31	panobinostat
32	(farydak OR “lbh-589” OR “lbh589” OR “lbh 589”):ti,ab,kw
33	carfilzomib
34	(kyprolis OR “pr-171” OR “pr171” OR “pr 171”):ti,ab,kw
35	daratumumab
36	(darzalex):ti,ab,kw
37	ixazomib
38	(ninlaro OR mln9708 OR “mln 9708” OR “mln-9708” OR (proteasome NEXT/1 inhibit*)):ti,ab,kw
39	elotuzumab
40	(empliciti OR HuLuc63 OR BMS-901608):ti,ab,kw
41	(#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40)
42	(#1 OR #2)
31	(#41 AND #42)

#	Search term
32	(#41 AND #42), Publication Year from 2013 to 2015 in Trials

1.3 MEDLINE® In-Process

Database name MEDLINE® In-Process
Search interface http://www.ncbi.nlm.nih.gov/pubmed/
Date of search 5 March 2016
Time segment None
Search filter Limited to In-Process citations

Table MEDLINE® In-Process search

#	Search term
1	Search myeloma*
2	Search Bortezomib
3	Search Lenalidomide
4	Search Thalidomide
5	Search Bendamustine
6	Search Dexamethasone
7	Search Melphalan
8	Search Vincristine
9	Search Cyclophosphamide
10	Search Doxorubicin
11	Search Carmustine
12	Search Prednisone
13	Search Prednisolone
14	Search velcade
15	Search proteasome inhibitor
16	Search revlimid
17	Search treanda
18	Search cytoxan
19	Search endoxan
20	Search neosar
21	Search adriamycin
22	Search caelyx
23	Search doxil
24	Search gliadel
25	Search ancortone
26	Search encortone
27	Search pomalidomide
28	Search imnovid

#	Search term
29	Search pomalyst
30	Search panobinostat
31	Search farydak
32	Search carfilzomib
33	Search kyprolis
34	Search daratumumab
35	Search darzalex
36	Search ixazomib
37	Search ninlaro
38	Search elotuzumab
39	Search empliciti
40	Search ((((((((((((((((((((((((((((((((((((#2) OR #3) OR #4) OR #5) OR #6) OR #7) OR #8) OR #9) OR #10) OR #11) OR #12) OR #13) OR #14) OR #15) OR #16) OR #17) OR #18) OR #19) OR #20) OR #21) OR #22) OR #23) OR #24) OR #25) OR #26) OR #27) OR #28) OR #29) OR #30) OR #31) OR #32) OR #33) OR #34) OR #35) OR #36) OR #37) OR #38) OR #39
41	Search (#1) AND #40
42	Search #41 AND inprocess[sb]

1.4 Trials in progress

Database name Clinicaltrials.gov
Search interface http://www.clinicaltrial.gov
Date of search 21 June 2016
Time segment None
Search filter Limited to randomised, interventional studies in multiple myeloma

Table Search strategy for trials in progress

#	Search term
1	Search term: random* Limited to condition: multiple myeloma Limited to study type: interventional studies

Appendix 2 Inclusion and exclusion criteria

Inclusion criteria

Population:

Age: adults aged ≥18 years
Gender: any
Race: any
Stage of disease: any
Line of therapy:
- Any (for chemotherapy setting)
- First-line (for transplant setting)

Type of therapy
- Any (for chemotherapy setting)
- Pre-transplant induction therapy (for transplant setting)
- Post-transplant consolidation or maintenance therapy (for transplant setting)

Interventions:

Pre-specified novel treatments options
- Bortezomib
- Lenalidomide
- Thalidomide
- Bendamustine

Comparators:

Pre-specified novel treatments options
- Bortezomib
- Lenalidomide
- Thalidomide
- Bendamustine

Pre-specified conventional treatments options
- Dexamethasone
- Melphalan
- Vincristine
- Cyclophosphamide
- Doxorubicin
- Liposomal doxorubicin
- Carmustine
- Prednisone
- Prednisolone
- Placebo/no treatment

Publication timeframe:
- 1999 onwards for database searches
- Last 4 years for conference searching

Exclusion criteria

Study design:
- RCTs with any blinding status
- Non-randomised controlled clinical trials
- Uncontrolled clinical trials (single arm studies)
- Observational studies

Language restrictions:
- English only

Phase I studies
Pharmacokinetic studies

No subgroup analysis for MM
Conference abstracts published prior to 2008
Conference abstracts (other than those searched for this review) published after 2008 (retrieved from the literature database)
Transplant setting
    Preparative regimen
    Conditioning regimen
    Mobilisation regimen

Appendix 3.1 PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6 (appendix 1)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6 (appendix 2)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Appendix 3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Appendix 3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9 (Figure 1)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9 (Table 1)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9 (Table 1)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-11 (Figure 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix 3

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-12 (Appendix 5, 6, 7, 8)
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	8

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Appendix 3.2 Risk of bias assessment using the Cochrane Collaboration's tool

Author	Year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessors: efficacy (detection bias)	Blinding of outcome assessors: safety (detection bias)	Incomplete outcome data: efficacy (attrition bias)	Incomplete outcome data: safety (attrition bias)	Selective reporting (reporting bias)	Other bias
Facon	2006	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Unclear	Unclear	High risk
Facon	2007	Low risk	Unclear	High risk	Low risk	Low risk	High risk	High risk	Unclear	High risk
Morgan	2013	Low risk	Unclear	High risk	Low risk	Low risk	Unclear	Unclear	Unclear	Low risk

Rajkumar	2008	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear	Unclear	Low risk
Ludwig	2009	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Unclear	Unclear	Unclear
Palumbo	2008	Low risk	Low risk	High risk	Low risk	Low risk	High risk	High risk	Unclear	High risk
Hulin	2009	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Waage	2010	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear	Unclear	Low risk
Beksac	2010	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Unclear	Unclear	Low risk
Wijermans	2010	Low risk	Unclear	High risk	Low risk	Low risk	Unclear	Unclear	Unclear	High risk
Sacchi	2011	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Unclear	Unclear	Low risk
Hungria	2016	Low risk	Unclear	High risk	Low risk	Low risk	Low risk	Low risk	Unclear	High risk
San Miguel	2008	Low risk	Unclear	High risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Mateos	2014	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Niesvizky	2015	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Palumbo	2014	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Zonder	2011	Low risk	Unclear	High risk	Low risk	Low risk	Low risk	Unclear	Unclear	High risk
Benboubkher	2014	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Zweegman	2016	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Unclear	Unclear	Low risk
Stewart	2015	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Magarotto	2016	Low risk	Unclear	High risk	Low risk	Low risk	Unclear	Unclear	Unclear	Low risk
Palumbo	2012	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Durie	2017	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Unclear	Unclear	High risk
Mateos	2018	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk

Appendix 4 R script Netmeta

```
#############################################################################################################

#############################################################################################################
# Network meta-analysis of newly diagnosed  not transplant eligble multiple myeloma treatments
# using R-package netmeta
# accompanying publication titled "Efficacy of first-line treatments for multiple myeloma patients not eligible for
# stem cell transplantation - A Network Meta-analysis"
# by Blommestein & Van Beurden-Tan et al. (2018)
#############################################################################################################
        #############
#install.packages("netmeta")

# set working directory
setwd("C:/R netmeta")

#############################################################################################################
# The Multiple Myeloma data.
#############################################################################################################

# Data abstracted from phase III randomized controlled trials found in systematic literature review
# with time period 01 January 1999 to 01 March 2016

# Data is entered as contrast-level data to be used in the 'netmeta' package.

# We stored this data into a data.frame called 'myeloma_data'.

# myeloma_data had the columns:
# TE (holding relative treatment effect estimates for pairs of treatments within studies, ie. log hazard ratio),
# seTE (holding standard errors for the treatment effect estimates TE),
# treat1.long (holding treatment names for the first of a pair of treatments),
# treat2.long (holding treatment names for the second of a pair of treatments),
# treat1 (holding abbreviated treatment names for the first of a pair of treatments),
# treat2 (holding abbreviated treatment names for the second of a pair of treatments),
# studlabel (holding study labels)

# Load the data:
myeloma_data = read.csv("data/TNEMM_NMA_data.csv") # Read data file; must be in curr. work. dir.

###### Load required R packages ##########################################################################

# netmeta (version 0.9-7, built under R version 3.3.3)
library("netmeta")

###### Prepare data for package ##########################################################################

# Note: Data (myeloma_data) is imported as contrast-level.
# Data is ready as loaded in.

###### Choose and run model ##############################################################################

net1 <- netmeta(TE, seTE, treat1, treat2, studlab, data=myeloma_data, sm="HR",
```

```
        details.chkmultiarm=TRUE, comb.random=TRUE, reference.group="D",
        tol.multiarm = 0.05)

###### Draw network ##############################################################################
netgraph(net1)
netgraph(net1, dim="3d")

###### Assess the degree of heterogeneity and inconsistency ######################################

# Heterogeneity and inconsistency statistics.
net1$Q
net1$df
net1$pval.Q
net1$Q.heterogeneity
net1$Q.inconsistency
net1$I2

# A graphical tool for locating inconsistency in network meta-analyses.
netheat(net1, random=TRUE)

###### Report relative effect estimates ##########################################################
# To produce summary of netmeta model
summary(net1,ref="D",digits=2)

# Rank treatments
net1.rank<-netrank(net1, small.values = "good")

# Forest plot
forest.netmeta(net1, reference.group = "D", sortvar = -net1.rank$Pscore.random, digits.Pscore = 2,
        leftcols="studlab", leftlabs="Treatment", rightcols=c("effect", "ci", "Pscore"),
        rightlabs="P-Score", just.addcols="right" , xlab="HR progression-free survival", label.right="          Favors `D`",
        label.left="Favors other treatment          ", xlim=c(0.05,20))

forest.netmeta(net1, reference.group = "MPT/MPT-T", sortvar = -net1.rank$Pscore.random, digits.Pscore = 2,
        leftcols="studlab", leftlabs="Treatment", rightcols=c("effect", "ci", "Pscore"),
        rightlabs="P-Score", just.addcols="right" , xlab="HR progression-free survival", label.right="          Favors
        `MPT/MPT-T`",
        label.left="Favors other treatment          ", xlim=c(0.1,10))


# Split direct and indirect evidence in network meta-analysis
options(max.print=1000000)
netsplit(net1)
##################################################################################################
# SCENARIO ANALYSES
#
# #1: differentiate between MPT and MPT-T (thal maintenance split) [MPT-T: GIMEMA, HOVON49, TMSG, NMSG,
        HOVON87, E1A06]
# #2: Weisel replication (VISTA, IFM 01/01, IFM 99/66, Sacchi and FIRST)
# #3: Fixed effect model
##################################################################################################

###### SA1: Different grouping for Thal maintenance (MPT-T and MPT)
```

```
# Load the data:
mmData1 = read.csv("data/TNEMM_NMA_data-ThalMaintSA.csv")

# Model
net1.ThalSA <- netmeta(TE, seTE, treat1, treat2, studlab, data=mmData1, sm="HR",
                details.chkmultiarm=TRUE, comb.random=TRUE, reference.group="D",
                tol.multiarm = 0.05)

# Rank treatments
net1.ThalSA.rank<-netrank(net1.ThalSA, small.values = "good")

# Forest plot
forest.netmeta(net1.ThalSA, reference.group = "D", sortvar = -net1.ThalSA.rank$Pscore.random, digits.Pscore = 2,
          leftcols="studlab", leftlabs="Treatment", rightcols=c("effect", "ci", "Pscore"),
          rightlabs="P-Score", just.addcols="right" , xlab="HR progression-free survival", label.right="               Favors D",
          label.left="Favors other treatment           ", xlim=c(0.05,20))

###### SA2: Weisel replication (VISTA, IFM 01/01, IFM 99/66, Sacchi and FIRST)

# Load the data:
mmData2 = read.csv("data/TNEMM_NMA_data-Weisel.csv")

# Fixed effect model
net1.Weis <- netmeta(TE, seTE, treat1, treat2, studlab, data=mmData2, sm="HR",
                details.chkmultiarm=TRUE, comb.random=TRUE, reference.group="Rd")

# Rank treatments
net1.Weis.rank<-netrank(net1.Weis, small.values = "good")

# Forest plot
forest(net1.Weis, ref="Rd", sortvar = -net1.Weis.rank$Pscore.random , digits.Pscore = 2,
     leftcols="studlab", leftlabs="Treatment", rightcols=c("effect", "ci", "Pscore"),
     rightlabs="P-Score", just.addcols="right" , xlab="HR progression-free survival", label.right="            Favors RD",
     label.left="Favors other treatment           ", xlim=c(0.2,5) )

###### SA3: Fixed effect model
net1.FE <- netmeta(TE, seTE, treat1, treat2, studlab, data=myeloma_data, sm="HR",
                details.chkmultiarm=TRUE, comb.random=FALSE, reference.group="D",
                tol.multiarm = 0.05)

net1.FE.rank<-netrank(net1.FE, small.values = "good")

forest(net1.FE, ref="D", sortvar = -net1.FE.rank$Pscore.random, digits.Pscore = 2,
     leftcols="studlab", leftlabs="Treatment", rightcols=c("effect", "ci", "Pscore"),
     rightlabs="P-Score", just.addcols="right" , xlab="HR progression-free survival", label.right="               Favors D",
     label.left="Favors other treatment           ", xlim=c(0.05,20) )
##############################################################################

##### END NETMETA R SCRIPT

##############################################################################
```

##

DATA

#

#1: main analysis

#2: scenario analysis #1 Different grouping for Thal maintenance (MPT-T and MPT)

#3: scenario analysis #2 Replicating Weisel's NMA

#4: scenario analysis #4 Fixed effect model

##

#1: data for main analysis [[file name: TNEMM_NMA_data.csv]]

TE	seTE	treat1	treat2	studlab
-0.70694	0.132986	TD	D	Rajkumar2008
0.26266	0.160183	TD	MP	Ludwig2009
-0.47235	0.133484	MPT/MPT-T	MP	Palumbo2008
-0.48749	0.147472	MPT/MPT-T	MP	IFM-01/01
-0.11723	0.122169	MPT/MPT-T	MP	NMSG
-0.35525	0.261358	MPT/MPT-T	MP	TMSG
-0.23902	0.12195	MPT/MPT-T	MP	HOVON49
-0.40103	0.289061	MPT/MPT-T	MP	Sacchi2011
-0.22754	0.136104	VMP	VTP	GEM2005
-0.21647	0.078876	CTD(a)	MP	MRC-MIX
-0.58344	0.176245	VMP	MP	VISTA
-0.54876	0.10524	VMPT-VT	VMP	GIMEMA0305
-0.58867	0.180076	Rd	D	S0232
-0.14464	0.093809	MPR-R	MPT/MPT-T	HOVON87
-0.33927	0.117128	VRd	Rd	S0777
-0.18005	0.135835	MPT/MPT-T	MPR-R	E1A06
-0.69918	0.136942	DaraVMP	VMP	ALCYONE
-0.67856	0.13421	MPT/MPT-T	MP	IFM-99/06
-0.11964	0.313441	MPT/MPT-T	CTD	Hungria2016
0.108844	0.144491	VD	VMP	UPFRONT
-0.2169	0.12426	MPR-R	Rd	EMN01
-0.70552	0.168967	MPR-R	MPR	MM-015
0.328408	0.084639	MPT/MPT-T	Rd	FIRST
-0.28476	0.098832	MP	D	Facon2006
-0.14518	0.122699	M100	MP	IFM-99/06
0.101185	0.375549	TD	CTD	Hungria2016
-0.11245	0.154629	VTD	VMP	UPFRONT
0.004314	0.0588	CPR	Rd	EMN01
0.173842	0.11798	MP	MPR	MM-015
0.354638	0.079689	Rd18	Rd	FIRST

-0.41903	0.107257	MD	D	Facon2006
-0.53472	0.146053	MPT/MPT-T	M100	IFM-99/06
-0.31326	0.395568	MPT/MPT-T	TD	Hungria2016
0.11289	0.152666	VD	VTD	UPFRONT
-0.22676	0.123291	MPR-R	CPR	EMN01
-0.91864	0.156192	MPR-R	MP	MM-015
-0.03289	0.07624	MPT/MPT-T	Rd18	FIRST
0.139955	0.106084	MP	MD	Facon2006
-0.08317	0.094656	DI	D	Facon2006
0.231945	0.099595	DI	MP	Facon2006
0.370823	0.10788	DI	MD	Facon2006

#2: data for scenario analysis #1 with thalidomide maintenance split [[file name: TNEMM_NMA_data-ThalMaintSA.csv]]

TE	seTE	treat1	treat2	studlab
-0.70694	0.132986	TD	D	Rajkumar2008
0.26266	0.160183	TD	MP	Ludwig2009
-0.47235	0.133484	MPT-T	MP	Palumbo2008
-0.48749	0.147472	MPT	MP	IFM-01/01
-0.11723	0.122169	MPT-T	MP	NMSG
-0.35525	0.261358	MPT-T	MP	TMSG
-0.23902	0.12195	MPT-T	MP	HOVON49
-0.40103	0.289061	MPT	MP	Sacchi2011
-0.22754	0.136104	VMP	VTP	GEM2005
-0.21647	0.078876	CTD(a)	MP	MRC-MIX
-0.58344	0.176245	VMP	MP	VISTA
-0.54876	0.10524	VMPT-VT	VMP	GIMEMA0305
-0.58867	0.180076	Rd	D	S0232
-0.14464	0.093809	MPR-R	MPT-T	HOVON87
-0.33927	0.117128	VRd	Rd	S0777
-0.18005	0.135835	MPT-T	MPR-R	E1A06
-0.69918	0.136942	DaraVMP	VMP	ALCYONE
-0.67856	0.13421	MPT	MP	IFM-99/06
-0.11964	0.313441	MPT	CTD	Hungria2016
0.108844	0.144491	VD	VMP	UPFRONT
-0.2169	0.12426	MPR-R	Rd	EMN01
-0.70552	0.168967	MPR-R	MPR	MM-015
0.328408	0.084639	MPT	Rd	FIRST
-0.28476	0.098832	MP	D	Facon2006
-0.14518	0.122699	M100	MP	IFM-99/06
0.101185	0.375549	TD	CTD	Hungria2016
-0.11245	0.154629	VTD	VMP	UPFRONT
0.004314	0.0588	CPR	Rd	EMN01
0.173842	0.11798	MP	MPR	MM-015

0.354638	0.079689	Rd18	Rd	FIRST
-0.41903	0.107257	MD	D	Facon2006
-0.53472	0.146053	MPT	M100	IFM-99/06
-0.31326	0.395568	MPT	TD	Hungria2016
0.11289	0.152666	VD	VTD	UPFRONT
-0.22676	0.123291	MPR-R	CPR	EMN01
-0.91864	0.156192	MPR-R	MP	MM-015
-0.03289	0.07624	MPT	Rd18	FIRST
0.139955	0.106084	MP	MD	Facon2006
-0.08317	0.094656	DI	D	Facon2006
0.231945	0.099595	DI	MP	Facon2006
0.370823	0.10788	DI	MD	Facon2006

#3: data for scenario analysis #2 Replicating Weisel's NMA [[file name: TNEMM_NMA_data-Weisel.csv]]

TE	seTE	treat1	treat2	studlab
-0.48749	0.147472	MPT	MP	IFM-01/01
-0.40103	0.289061	MPT	MP	Sacchi2011
-0.58344	0.176245	VMP	MP	VISTA
-0.67856	0.13421	MPT	MP	IFM-99/06
0.328408	0.084639	MPT	Rd	FIRST

#4: data for scenario analysis #3 Fixed effect model See #1 [[file name: TNEMM_NMA_data.csv]]

Appendix 5 HR based on direct and indirect evidence

Comparison	Number of studies providing direct evidence	Direct evidence proportion	Estimated treatment effect (HR) in network meta-analysis	Estimated treatment effect (HR) derived from direct evidence	Estimated treatment effect (HR) derived from indirect evidence	Ratio of direct versus indirect	z-value of test for disagreement	p-value of test for disagreement
CPR:CTD	0	0	0.8332	.	0.8332	.	.	.
CPR:CTD(a)	0	0	0.8152	.	0.8152	.	.	.
CPR:D	0	0	0.4577	.	0.4577	.	.	.
CPR:DaraVMP	0	0	2.3674	.	2.3674	.	.	.
CPR:DI	0	0	0.5067	.	0.5067	.	.	.
CPR:M100	0	0	0.6693	.	0.6693	.	.	.
CPR:MD	0	0	0.7282	.	0.7282	.	.	.
CPR:MP	0	0	0.6565	.	0.6565	.	.	.
CPR:MPR	0	0	0.6935	.	0.6935	.	.	.
CPR:MPR-R	1	0.82	1.1777	1.2545	0.8818	1.4226	0.58	0.5629
CPR:MPT	0	0	0.9823	.	0.9823	.	.	.
CPR:Rd	1	0.89	1.0498	1.0043	1.5196	0.6609	-0.58	0.5629
CPR:Rd18	0	0	0.8376	.	0.8376	.	.	.
CPR:TD	0	0	0.7034	.	0.7034	.	.	.
CPR:VD	0	0	1.0922	.	1.0922	.	.	.
CPR:VMP	0	0	1.1766	.	1.1766	.	.	.
CPR:VMPT-VT	0	0	2.0368	.	2.0368	.	.	.
CPR:VRd	0	0	1.4738	.	1.4738	.	.	.
CPR:VTD	0	0	1.2684	.	1.2684	.	.	.
CPR:VTP	0	0	0.9371	.	0.9371	.	.	.
CTD(a):CTD	0	0	1.0222	.	1.0222	.	.	.
D:CTD	0	0	1.8204	.	1.8204	.	.	.
DaraVMP:CTD	0	0	0.352	.	0.352	.	.	.
DI:CTD	0	0	1.6445	.	1.6445	.	.	.
M100:CTD	0	0	1.245	.	1.245	.	.	.
MD:CTD	0	0	1.1442	.	1.1442	.	.	.
MP:CTD	0	0	1.2692	.	1.2692	.	.	.
MPR:CTD	0	0	1.2015	.	1.2015	.	.	.
MPR-R:CTD	0	0	0.7075	.	0.7075	.	.	.
MPT:CTD	1	0.83	0.8483	0.8872	0.686	1.2933	0.28	0.781
Rd:CTD	0	0	0.7937	.	0.7937	.	.	.
Rd18:CTD	0	0	0.9948	.	0.9948	.	.	.
TD:CTD	1	0.69	1.1846	1.1065	1.3757	0.8043	-0.28	0.781

Comparison	Number of studies providing direct evidence	Direct evidence proportion	Estimated treatment effect (HR) in network meta-analysis	Estimated treatment effect (HR) derived from direct evidence	Estimated treatment effect (HR) derived from indirect evidence	Ratio of direct versus indirect	z-value of test for disagreement	p-value of test for disagreement
VD:CTD	0	0	0.7629	.	0.7629	.	.	.
VMP:CTD	0	0	0.7082	.	0.7082	.	.	.
VMPT-VT:CTD	0	0	0.4091	.	0.4091	.	.	.
VRd:CTD	0	0	0.5654	.	0.5654	.	.	.
VTD:CTD	0	0	0.6569	.	0.6569	.	.	.
VTP:CTD	0	0	0.8891	.	0.8891	.	.	.
D:CTD(a)	0	0	1.7809	.	1.7809	.	.	.
DaraVMP:CTD(a)	0	0	0.3443	.	0.3443	.	.	.
DI:CTD(a)	0	0	1.6088	.	1.6088	.	.	.
M100:CTD(a)	0	0	1.218	.	1.218	.	.	.
MD:CTD(a)	0	0	1.1194	.	1.1194	.	.	.
MP:CTD(a)	1	1	1.2417	1.2417	.	.	.	.
MPR:CTD(a)	0	0	1.1754	.	1.1754	.	.	.
MPR-R:CTD(a)	0	0	0.6922	.	0.6922	.	.	.
MPT:CTD(a)	0	0	0.8298	.	0.8298	.	.	.
Rd:CTD(a)	0	0	0.7765	.	0.7765	.	.	.
Rd18:CTD(a)	0	0	0.9732	.	0.9732	.	.	.
TD:CTD(a)	0	0	1.1589	.	1.1589	.	.	.
VD:CTD(a)	0	0	0.7464	.	0.7464	.	.	.
VMP:CTD(a)	0	0	0.6928	.	0.6928	.	.	.
VMPT-VT:CTD(a)	0	0	0.4002	.	0.4002	.	.	.
VRd:CTD(a)	0	0	0.5531	.	0.5531	.	.	.
VTD:CTD(a)	0	0	0.6427	.	0.6427	.	.	.
VTP:CTD(a)	0	0	0.8699	.	0.8699	.	.	.
DaraVMP:D	0	0	0.1933	.	0.1933	.	.	.
DI:D	1	0.88	0.9034	0.9202	0.7885	1.167	0.22	0.8278
M100:D	0	0	0.6839	.	0.6839	.	.	.
MD:D	1	0.88	0.6285	0.6577	0.4499	1.4618	0.52	0.6007
MP:D	1	0.51	0.6972	0.7522	0.6437	1.1686	0.44	0.66
MPR:D	0	0	0.66	.	0.66	.	.	.
MPR-R:D	0	0	0.3887	.	0.3887	.	.	.
MPT:D	0	0	0.466	.	0.466	.	.	.
Rd:D	1	0.5	0.436	0.5551	0.3437	1.6151	1.18	0.2398

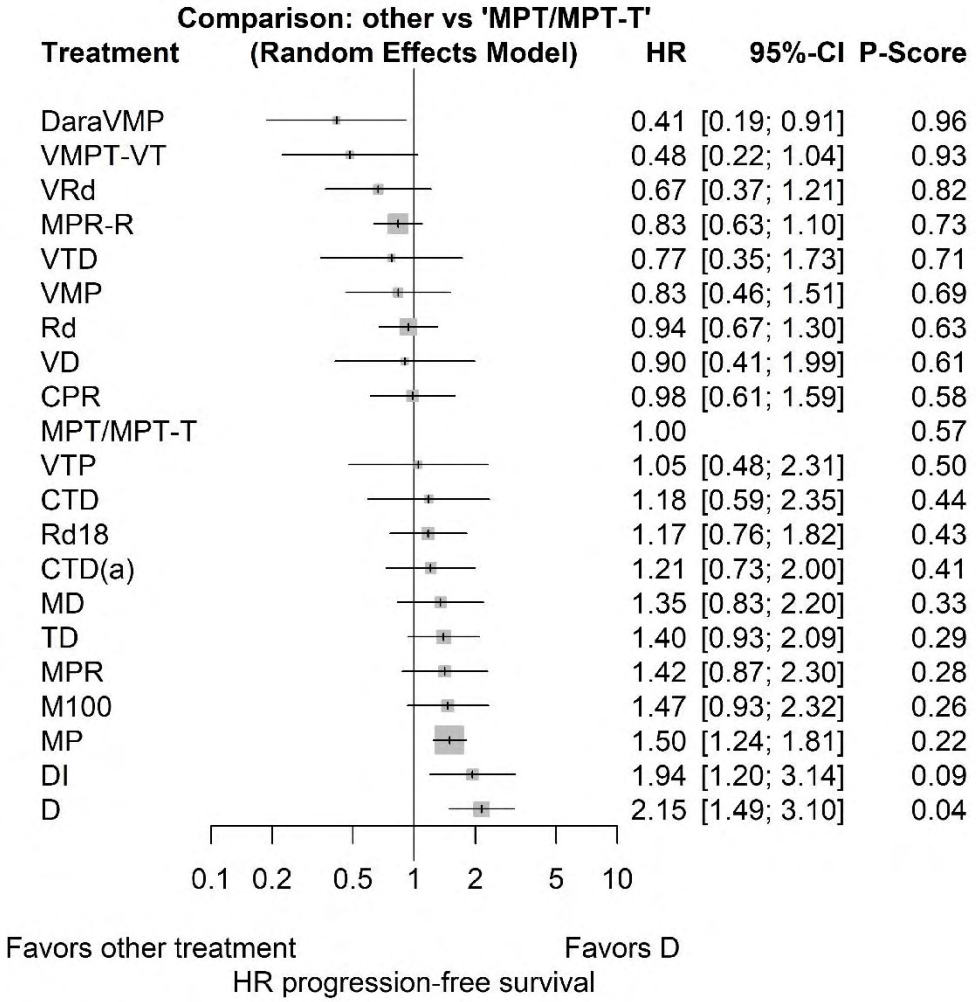
Comparison	Number of studies providing direct evidence	Direct evidence proportion	Estimated treatment effect (HR) in network meta-analysis	Estimated treatment effect (HR) derived from direct evidence	Estimated treatment effect (HR) derived from indirect evidence	Ratio of direct versus indirect	z-value of test for disagreement	p-value of test for disagreement
Rd18:D	0	0	0.5465	.	0.5465	.	.	.
TD:D	1	0.58	0.6508	0.4932	0.9593	0.5141	-1.64	0.102
VD:D	0	0	0.4191	.	0.4191	.	.	.
VMP:D	0	0	0.389	.	0.389	.	.	.
VMPT-VT:D	0	0	0.2247	.	0.2247	.	.	.
VRd:D	0	0	0.3106	.	0.3106	.	.	.
VTD:D	0	0	0.3609	.	0.3609	.	.	.
VTP:D	0	0	0.4884	.	0.4884	.	.	.
DI:DaraVMP	0	0	4.6722	.	4.6722	.	.	.
M100:DaraVMP	0	0	3.5373	.	3.5373	.	.	.
MD:DaraVMP	0	0	3.2508	.	3.2508	.	.	.
MP:DaraVMP	0	0	3.6061	.	3.6061	.	.	.
MPR:DaraVMP	0	0	3.4136	.	3.4136	.	.	.
MPR-R:DaraVMP	0	0	2.0101	.	2.0101	.	.	.
MPT:DaraVMP	0	0	2.41	.	2.41	.	.	.
Rd:DaraVMP	0	0	2.2551	.	2.2551	.	.	.
Rd18:DaraVMP	0	0	2.8264	.	2.8264	.	.	.
TD:DaraVMP	0	0	3.3658	.	3.3658	.	.	.
VD:DaraVMP	0	0	2.1676	.	2.1676	.	.	.
VMP:DaraVMP	1	1	2.0121	2.0121	.	.	.	.
VMPT-VT:DaraVMP	0	0	1.1623	.	1.1623	.	.	.
VRd:DaraVMP	0	0	1.6063	.	1.6063	.	.	.
VTD:DaraVMP	0	0	1.8665	.	1.8665	.	.	.
VTP:DaraVMP	0	0	2.5262	.	2.5262	.	.	.
M100:DI	0	0	0.7571	.	0.7571	.	.	.
MD:DI	1	1	0.6958	0.6902	.	.	.	.
MP:DI	1	0.87	0.7718	0.793	0.6389	1.2411	0.31	0.7573
MPR:DI	0	0	0.7306	.	0.7306	.	.	.
MPR-R:DI	0	0	0.4302	.	0.4302	.	.	.
MPT:DI	0	0	0.5158	.	0.5158	.	.	.
Rd:DI	0	0	0.4827	.	0.4827	.	.	.
Rd18:DI	0	0	0.6049	.	0.6049	.	.	.
TD:DI	0	0	0.7204	.	0.7204	.	.	.
VD:DI	0	0	0.4639	.	0.4639	.	.	.
VMP:DI	0	0	0.4307	.	0.4307	.	.	.
VMPT-VT:DI	0	0	0.2488	.	0.2488	.	.	.

Comparison	Number of studies providing direct evidence	Direct evidence proportion	Estimated treatment effect (HR) in network meta-analysis	Estimated treatment effect (HR) derived from direct evidence	Estimated treatment effect (HR) derived from indirect evidence	Ratio of direct versus indirect	z-value of test for disagreement	p-value of test for disagreement
VRd:DI	0	0	0.3438	.	0.3438	.	.	.
VTD:DI	0	0	0.3995	.	0.3995	.	.	.
VTP:DI	0	0	0.5407	.	0.5407	.	.	.
M100:MD	0	0	1.0881	.	1.0881	.	.	.
M100:MP	1	0.81	0.9809	0.8649	1.6979	0.5094	-1.13	0.258
M100:MPR	0	0	1.0362	.	1.0362	.	.	.
M100:MPR-R	0	0	1.7597	.	1.7597	.	.	.
M100:MPT	1	0.75	1.4678	1.707	0.9222	1.8511	1.13	0.258
M100:Rd	0	0	1.5686	.	1.5686	.	.	.
M100:Rd18	0	0	1.2515	.	1.2515	.	.	.
M100:TD	0	0	1.051	.	1.051	.	.	.
M100:VD	0	0	1.6319	.	1.6319	.	.	.
M100:VMP	0	0	1.758	.	1.758	.	.	.
M100:VMPT-VT	0	0	3.0433	.	3.0433	.	.	.
M100:VRd	0	0	2.2022	.	2.2022	.	.	.
M100:VTD	0	0	1.8952	.	1.8952	.	.	.
M100:VTP	0	0	1.4002	.	1.4002	.	.	.
MP:MD	1	0.88	1.1093	1.1502	0.8458	1.3599	0.42	0.6731
MPR:MD	0	0	1.0501	.	1.0501	.	.	.
MPR-R:MD	0	0	0.6183	.	0.6183	.	.	.
MPT:MD	0	0	0.7414	.	0.7414	.	.	.
Rd:MD	0	0	0.6937	.	0.6937	.	.	.
Rd18:MD	0	0	0.8694	.	0.8694	.	.	.
TD:MD	0	0	1.0353	.	1.0353	.	.	.
VD:MD	0	0	0.6668	.	0.6668	.	.	.
VMP:MD	0	0	0.619	.	0.619	.	.	.
VMPT-VT:MD	0	0	0.3575	.	0.3575	.	.	.
VRd:MD	0	0	0.4941	.	0.4941	.	.	.
VTD:MD	0	0	0.5741	.	0.5741	.	.	.
VTP:MD	0	0	0.7771	.	0.7771	.	.	.
MP:MPR	1	0.87	1.0564	1.1899	0.4788	2.4852	1.29	0.1976
MP:MPR-R	1	0.31	1.7939	2.5059	1.546	1.6208	1.46	0.1443
MP:MPT	7	0.83	1.4963	1.4783	1.5895	0.93	-0.28	0.7806
MP:Rd	0	0	1.5991	.	1.5991	.	.	.
MP:Rd18	0	0	1.2759	.	1.2759	.	.	.
MP:TD	1	0.49	1.0714	0.769	1.4766	0.5208	-1.68	0.0937
MP:VD	0	0	1.6636	.	1.6636	.	.	.
MP:VMP	1	1	1.7922	1.7922	.	.	.	.

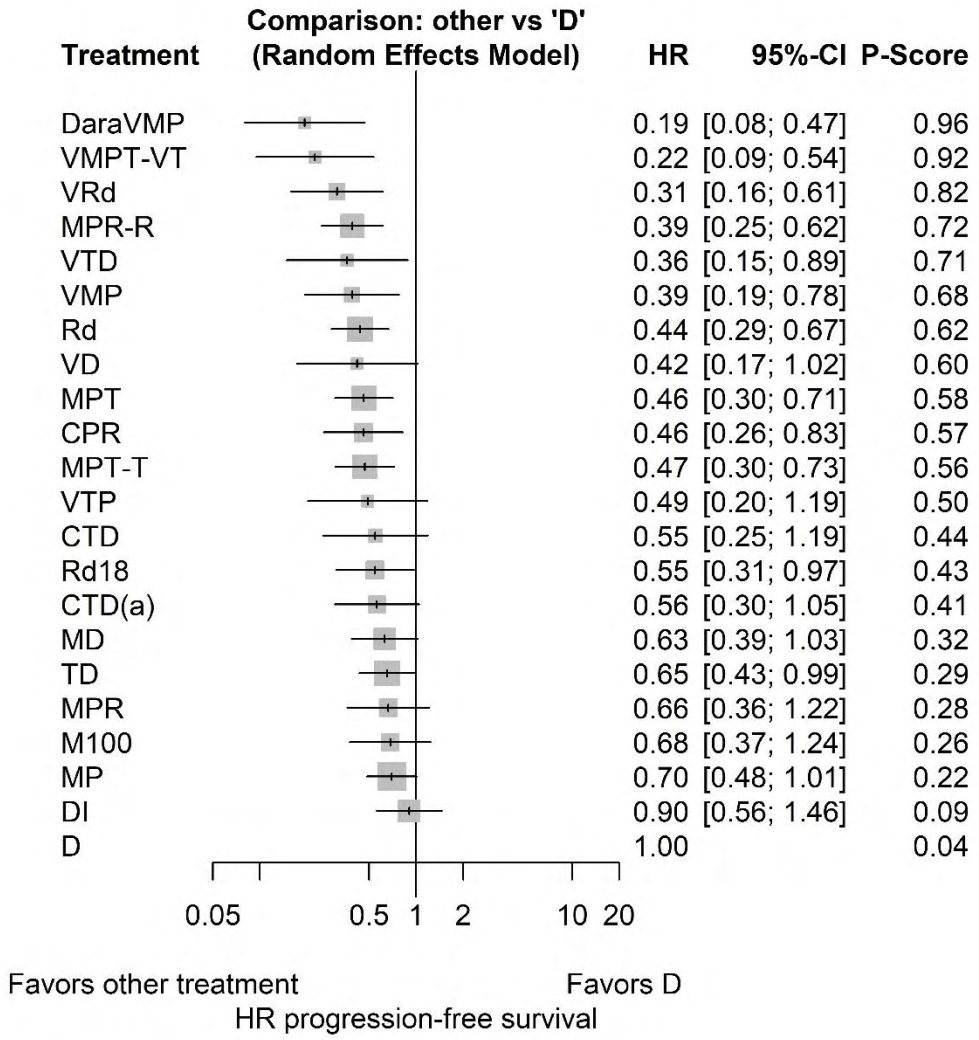
Comparison	Number of studies providing direct evidence	Direct evidence proportion	Estimated treatment effect (HR) in network meta-analysis	Estimated treatment effect (HR) derived from direct evidence	Estimated treatment effect (HR) derived from indirect evidence	Ratio of direct versus indirect	z-value of test for disagreement	p-value of test for disagreement
MP:VMPT-VT	0	0	3.1025	.	3.1025	.	.	.
MP:VRd	0	0	2.245	.	2.245	.	.	.
MP:VTD	0	0	1.932	.	1.932	.	.	.
MP:VTP	0	0	1.4275	.	1.4275	.	.	.
MPR:MPR-R	1	0.77	1.6982	2.0249	0.9531	2.1245	1.29	0.1976
MPR:MPT	0	0	1.4164	.	1.4164	.	.	.
MPR:Rd	0	0	1.5137	.	1.5137	.	.	.
MPR:Rd18	0	0	1.2077	.	1.2077	.	.	.
MPR:TD	0	0	1.0142	.	1.0142	.	.	.
MPR:VD	0	0	1.5748	.	1.5748	.	.	.
MPR:VMP	0	0	1.6965	.	1.6965	.	.	.
MPR:VMPT-VT	0	0	2.9368	.	2.9368	.	.	.
MPR:VRd	0	0	2.1251	.	2.1251	.	.	.
MPR:VTD	0	0	1.8289	.	1.8289	.	.	.
MPR:VTP	0	0	1.3513	.	1.3513	.	.	.
MPR-R:MPT	2	0.6	0.8341	1.0057	0.627	1.6039	1.65	0.0981
MPR-R:Rd	1	0.48	0.8914	0.805	0.9806	0.821	-0.55	0.5832
MPR-R:Rd18	0	0	0.7112	.	0.7112	.	.	.
MPR-R:TD	0	0	0.5972	.	0.5972	.	.	.
MPR-R:VD	0	0	0.9273	.	0.9273	.	.	.
MPR-R:VMP	0	0	0.999	.	0.999	.	.	.
MPR-R:VMPT-VT	0	0	1.7294	.	1.7294	.	.	.
MPR-R:VRd	0	0	1.2514	.	1.2514	.	.	.
MPR-R:VTD	0	0	1.077	.	1.077	.	.	.
MPR-R:VTP	0	0	0.7957	.	0.7957	.	.	.
MPT:Rd	1	0.48	1.0687	1.3888	0.8351	1.6629	1.51	0.1313
MPT:Rd18	1	0.87	0.8527	0.9676	0.3641	2.6575	1.47	0.1414
MPT:TD	1	0.2	0.716	0.7311	0.7123	1.0264	0.05	0.9594
MPT:VD	0	0	1.1118	.	1.1118	.	.	.
MPT:VMP	0	0	1.1978	.	1.1978	.	.	.
MPT:VMPT-VT	0	0	2.0734	.	2.0734	.	.	.
MPT:VRd	0	0	1.5004	.	1.5004	.	.	.
MPT:VTD	0	0	1.2912	.	1.2912	.	.	.
MPT:VTP	0	0	0.954	.	0.954	.	.	.

Comparison	Number of studies providing direct evidence	Direct evidence proportion	Estimated treatment effect (HR) in network meta-analysis	Estimated treatment effect (HR) derived from direct evidence	Estimated treatment effect (HR) derived from indirect evidence	Ratio of direct versus indirect	z-value of test for disagreement	p-value of test for disagreement
Rd:Rd18	1	0.87	0.7979	0.7014	1.8477	0.3796	-1.47	0.1414
Rd:TD	0	0	0.67	.	0.67	.	.	.
Rd:VD	0	0	1.0404	.	1.0404	.	.	.
Rd:VMP	0	0	1.1208	.	1.1208	.	.	.
Rd:VMPT-VT	0	0	1.9401	.	1.9401	.	.	.
Rd:VRd	1	1	1.4039	1.4039	.	.	.	.
Rd:VTD	0	0	1.2082	.	1.2082	.	.	.
Rd:VTP	0	0	0.8927	.	0.8927	.	.	.
Rd18:TD	0	0	0.8398	.	0.8398	.	.	.
Rd18:VD	0	0	1.3039	.	1.3039	.	.	.
Rd18:VMP	0	0	1.4047	.	1.4047	.	.	.
Rd18:VMPT-VT	0	0	2.4317	.	2.4317	.	.	.
Rd18:VRd	0	0	1.7596	.	1.7596	.	.	.
Rd18:VTD	0	0	1.5143	.	1.5143	.	.	.
Rd18:VTP	0	0	1.1188	.	1.1188	.	.	.
VD:TD	0	0	0.644	.	0.644	.	.	.
VMP:TD	0	0	0.5978	.	0.5978	.	.	.
VMPT-VT:TD	0	0	0.3453	.	0.3453	.	.	.
VRd:TD	0	0	0.4772	.	0.4772	.	.	.
VTD:TD	0	0	0.5545	.	0.5545	.	.	.
VTP:TD	0	0	0.7506	.	0.7506	.	.	.
VMP:VD	1	1	0.9283	0.8969	.	.	.	.
VMPT-VT:VD	0	0	0.5362	.	0.5362	.	.	.
VRd:VD	0	0	0.741	.	0.741	.	.	.
VTD:VD	1	1	0.8611	0.8932	.	.	.	.
VTP:VD	0	0	1.1654	.	1.1654	.	.	.
VMP:VMPT-VT	1	1	1.7311	1.7311	.	.	.	.
VMP:VRd	0	0	1.2526	.	1.2526	.	.	.
VMP:VTD	1	1	1.078	1.119	.	.	.	.
VMP:VTP	1	1	0.7965	0.7965	.	.	.	.
VMPT-VT:VRd	0	0	0.7236	.	0.7236	.	.	.
VMPT-VT:VTD	0	0	0.6227	.	0.6227	.	.	.
VMPT-VT:VTP	0	0	0.4601	.	0.4601	.	.	.
VRd:VTD	0	0	0.8606	.	0.8606	.	.	.
VRd:VTP	0	0	0.6358	.	0.6358	.	.	.
VTP:VTD	0	0	1.3535	.	1.3535	.	.	.

Appendix 6 Figure Results comparison versus MPT



Appendix 7 Figure Results scenario analysis separating MPT and MPT-T comparison versus D

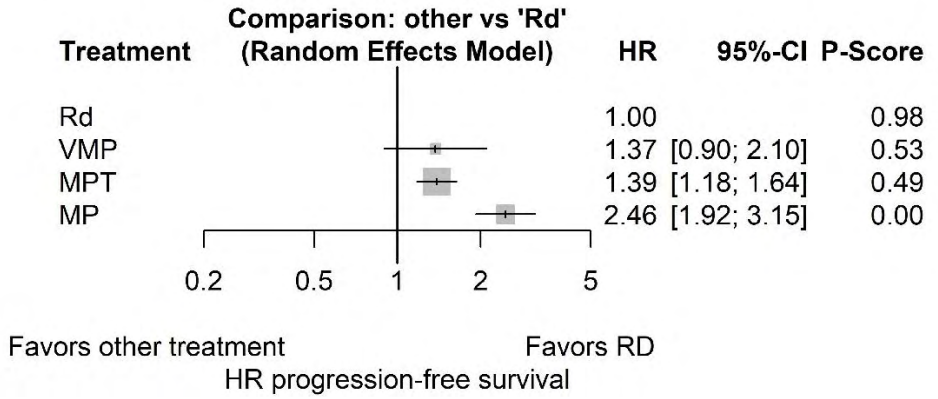


Appendix 8 Results scenario analysis 2

Table Results scenario 2

	HR obtained by Weisel et al.		HR scenario analysis 2	
	HR	95% CrI	HR	95% CI
Rd v MP	0.39	[0.31-0.50]	0.41	[0.32-0.52]
Rd v MPT	0.69	[0.59-0.80]	0.72	[0.61-0.85]
Rd v VMP	0.7	[0.49-0.99]	0.73	[0.48-1.11]

Figure Forestplot scenario 2



Appendix 9 Figure Results scenario fixed effect model