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SYSTEMATIC LITERATURE REVIEW AND NETWORK META-ANALYSIS ON MAINTENANCE TREATMENT IN MYELOMA: A MULTI-GROUP REPORT

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ABSTRACT

Importance. Several trials demonstrated the impact of novel agent-based maintenance in newly diagnosed multiple myeloma (NDMM), but there is no current evidence demonstrating the superiority of one regimen over the other, due to the lack of direct/indirect comparisons.

Objective. Our objective was to analyse and compare the effectiveness of different maintenance regimens in NDMM.

Data Sources. We performed two independent searches in PubMed.gov and Cochrane, and then we identified all the records registered after 1999 and on or before November 20, 2017.

Study Selection. By blinded review, we identified prospective phase III randomized trials evaluating novel agent-based maintenance in NDMM patients; the included studies compared at least two maintenance approaches; comparators included placebo and 'no maintenance'. From 364 screened records, 11 studies were included.

Data Extraction and Synthesis. We followed (independent extraction) the guidelines provided by the PRISMA Report and the EQUATOR Network. The evidence was synthesized using a network meta-analysis (NMA). To allow comparison of all treatments, 'no maintenance' was selected as common comparator and the effect of placebo was assumed to be the same as no treatment. The best option was identified by a Bayesian consistency model based on HR, 95% Credible Index (CrI), probability of being the best treatment (PbBT), and median ranking distribution (MedR).

Main Outcomes and Measures. Outcomes of interest were progression-free survival (PFS) and overall survival (OS).

Results. Eleven trials and 8 treatments were included. By PFS analysis, lenalidomide-based regimens (lenalidomide-prednisone, lenalidomide alone) were identified as the most effective options (HR 0.39 and 0.47; MedR 1 and 2; overall PbBT 74%). Four treatments (thalidomide-interferon, thalidomide-bortezomib, bortezomib-prednisone, thalidomide alone) showed a HR in favor of maintenance. By OS analysis, lenalidomide alone was identified as the best option (HR 0.76; MedR 2; PbBT 38%), followed by bortezomib-thalidomide and bortezomib-prednisone. Similar features were noticed in the restricted network including transplant trials, in the sensitivity analysis, and in most of the prognostic subgroups.

Conclusions and Relevance. Based on PFS and OS results of this NMA, lenalidomide maintenance can be considered the best treatment option, by synthesizing the available evidence of novel agent-based maintenance in the last 20 years.

KEY POINTS

Question. What is the current best maintenance approach in myeloma?

Findings. This NMA included 11 trials and 8 treatments. Six maintenance treatments prolonged PFS vs no maintenance: lenalidomide-based regimens were identified as the most effective options. On OS analysis, lenalidomide alone was identified as the best option. Similar features were noticed in the restricted network including transplant trials, in the sensitivity analysis, and in most of the prognostic subgroups.

Conclusions and Relevance. By synthesizing the available evidence of novel agent-based maintenance in the last 20 years, lenalidomide maintenance can be currently considered the best treatment option.

INTRODUCTION

The "continuous therapy" (CT) approach has been evaluated extensively in newly diagnosed multiple myeloma (NDMM), across age groups and treatment strategies upfront, in several trials with different designs. It generally consists of multi-agent chemotherapy for a fixed time, followed by a less intensive but prolonged maintenance treatment. Some trials showed the benefit of thalidomide continuous therapy in terms of progression-free survival (PFS), with inconsistent results for overall survival (OS).[1–10] The efficacy of continuous thalidomide is compromised by its poor tolerability, with peripheral neuropathy mainly limiting the long-term use. In a trial randomizing patients to bortezomib-based induction, ASCT and bortezomib maintenance vs vincristine-doxorubicin-dexamethasone induction, ASCT and thalidomide maintenance, bortezomib-based therapy prolonged PFS, with a better safety profile.[11,12] Bortezomib-thalidomide maintenance has also been evaluated both in the non-transplant and transplant settings.[13–17] A meta-analysis showed improved PFS as well as OS with lenalidomide maintenance vs no maintenance/placebo in the post-transplant setting.[18] Recent data from the Myeloma XI trial confirmed these findings.[19,20]

Despite the well-recognized importance of maintenance, there is no evidence demonstrating the overall superiority of one regimen over the others, due to the lack of direct or indirect comparisons. Furthermore, there are several well-known factors that may affect outcome, such as baseline prognostic features (International Staging System [ISS] Stage[21] and chromosomal abnormalities[22]). Direct comparisons in specific patient subsets are lacking as well.

We performed a systematic literature review to identify the randomized trials in NDMM evaluating maintenance treatments using novel agents and then a network meta-analysis (NMA) to synthesize the efficacy (PFS, OS) of each regimen over the others. To do this, we collected and, whenever necessary, re-analysed the data of each study included in the network. Our main goal was to compare the efficacy of each treatment vs no maintenance/placebo overall and in specific patient subgroups.

MATERIAL AND METHODS

Systematic literature review and studies selection

This meta-analysis adheres to the guidelines provided by the PRISMA report and the EQUATOR Network.[23,24] We performed 2 independent searches (FG/UP) in the databases PubMed.gov and Cochrane Central Register of Controlled Trials (RCTs) using the search terms myeloma and maintenance. We excluded records registered before December 31, 1999, since our aim was to focus on novel agents only. The entire search had a cut-off date of November 20, 2017 and was restricted to articles in English. To ensure that no RCTs were missing, we also considered additional sources (Appendix), which were added manually to the PRISMA Flowchart (Figure 1).

Eligibility criteria were defined in terms of population, interventions, comparisons, outcomes, and study design (PICOS) criteria.[23] The study population of interest comprised NDMM patients; the studies included are prospective randomized phase III trials that compared at least two maintenance approaches; maintenance treatments should include one or more novel agents (thalidomide, lenalidomide, bortezomib) in at least one arm; comparators included placebo and no maintenance. To specifically evaluate the impact of maintenance, we excluded trials in which patients who received two different maintenance treatments underwent different and non-comparable pre-maintenance therapies (no stratification according to induction at the time of maintenance randomization), since in such trials the final outcomes could be related to the combined effect of both induction and maintenance. To analyze the impact of maintenance in the context of a current treatment approach, we excluded maintenance trials that enrolled only patients who did not receive novel agents during induction, since this is no longer a standard approach. Nevertheless, these trials were subsequently included in a sensitivity analysis. Outcomes of interest included PFS and OS.

After removing duplicates by blinded review, titles and abstracts of the citations were screened for inclusion using Excel 2013 (Microsoft Corporation, Redmond, US-WA) and then full-text articles were examined to assess suitability.

The Cochrane Collaboration's tool for assessing risk of bias in randomized trials was used.[20] Risks of bias were assessed independently by 2 reviewers (FG/SS); when data were not reported in the main publications, we asked authors of the different papers to provide them (Appendix).

Data extraction

Data were independently extracted from all eligible RCTs that reported hazard ratios (HRs) and confidence intervals (CIs) for PFS and/or OS, or provided data to estimate HRs and CIs in case the study did not report these parameters. Where not available, the HR was estimated using the ratio between probabilities and the 95% CI was estimated using the p-value (Appendix).[25]

HRs and p-values for PFS and OS were collected for the main comparison (all patients included in the main analysis). We performed a restricted analysis of PFS and OS in patients previously treated with ASCT; in this analysis, for trials enrolling both patients who had received ASCT and not, only 95% CI and HR of the subgroup of ASCT patients were included.

Subgroup analyses according to prognostic features were performed. For these analyses, we included only studies with available data on both ISS Stage and cytogenetic risk. HRs and p-values for PFS were collected for the subsequent subsets: ISS Stage I/II, ISS Stage III; high-risk chromosomal abnormalities detected by FISH (del(17p) and/or t(14;14) and/or t(14;16)), standard-risk (absence of del(17p), t(14;14), t(14;16)). For these subgroup analyses we focused on PFS only, due to the small number of patients in each subgroup, which could be a limitation, even more relevant in the OS analysis, given the lower number of events. Whenever data were either unavailable in the full-text articles, or non-comparable due to different risk categorization, these were provided by the cooperative groups.

Network meta-analysis

The NMA was conducted using the natural log transformations of HRs, and their 95% CIs to estimate standard errors (SEs).

To include all trials within one framework we had to choose a common comparator, and we chose "no maintenance/placebo". We assumed that placebo treatment was equivalent to "no maintenance" and that there were no differences in efficacy due to dosages or schemes (for thalidomide, lenalidomide, lenalidomide-prednisone and bortezomib-thalidomide). We used the R-Project software (v3.1.1, R Foundation for Statistical Computing, 1993-2017) and the "`gemtc`" and "`R2WinBUGS`" packages to perform the analysis with WinBugs (version 14, The BUGS Project, 1997-2017). Since no loop nor design inconsistencies were present, the NMA was conducted following the Bayesian consistency framework.[26]

The simulation was performed using the Markov Chain Monte Carlo (MCMC) technique with three different chains, and each of them produced 500,000 interactions with 300,000 burn-in samples and 15 thinning rates. The output of Bayesian NMA is a posterior distribution of relative effect size, and we obtained the HR as a mean value, and 95% Credible Interval (95% CrI) as the 2.5th and 97.5th percentiles. Subsequent to perform all the simulations, we calculated the percentage of simulations in which every single treatment ranked first, in order to determine its probability of being the best treatment (PbBT). For each treatment, we estimated the median value of the ranking distribution for all the simulations (MedR). This allowed us to consider not only when a treatment ranked first, but also any other ranking it could obtain. The best option was identified on the basis of MedR, HR with 95% CrI and PbBT.

RESULTS

Study selection

Sixty-two publications were included, corresponding to 11 trials (Figure 1; Appendix).

All trials started enrollment after 2001, 4 trials enrolled only patients ineligible for ASCT, 4 trials included both patients eligible and not for ASCT, and 3 trials enrolled only patients eligible for ASCT. Eight maintenance options were evaluated: no maintenance/placebo, interferon (INF), thalidomide alone (Thal), thalidomide-bortezomib (Thal-Bort), thalidomide-interferon (Thal-INF), lenalidomide alone (Len), lenalidomide-prednisone (Len-Pred) and bortezomib-prednisone (Bort-Pred). Table 1S summarizes the main characteristics of the included trials and each maintenance treatment schedule.[13,16–19,27–37] Overall, the included trials presented minimal risk of bias (Appendix).

Primary analysis: PFS and OS with different maintenance strategies

The primary analysis network was composed of all the selected trials (5073 patients) (Figure 2). On PFS analysis, lenalidomide-based regimens had the most favorable HR (Len-Pred HR 0.39; Len HR 0.47); they ranked, on median, first and second in all the simulations; overall, they resulted the most effective options in 74% of the simulations. Four treatments (Thal-INF, Thal-Bort, Bort-Pred, Thal) showed a HR in favor of maintenance (HR from 0.50 to 0.73); only one (INF) did not show any benefit. On OS analysis, Len was identified as the best option, based again on HR, MedR and PbBT, followed by Thal-Bort and Bort-Pred. No benefit was suggested with the other regimens (Figure 3; Figure 1S).

Restricted Analysis: PFS and OS in ASCT setting

Seven trials (Myeloma IX, CALGB-100104, IFM-2005-02, RV-MM-PI-209, RV-MM-EMN-441, Myeloma XI, GEM05MENOS65) were included (2917 patients), (Figure 2S; Table 4S).

Results were similar to those of the primary analysis network. Regarding PFS, lenalidomide-based maintenance regimens were identified as the best options; Thal-Bort and Thal showed a HR in favor of maintenance (HR from 0.58 to 0.73), and no benefit was noticed with INF. On OS analysis,

Len-based regimens were the best option; no benefit with any other regimen was noticed (Figure 2S - Panels B-C).

Subgroup analyses: prognostic features

Eight trials (NCT00205751, Myeloma IX, IFM-2005-02, 2005-001111-21, RV-MM-PI-209, RV-MM-EMN-441, GEM05MENOS65, EMN-01) were included in the subgroup analysis (Figure 3S; Table 5S). Two trials were excluded (CALGB 100104, MM-015) since no data on cytogenetic abnormalities were available; one trial (Myeloma XI) was not included since the publication of the main paper is still underway.

The subgroup analysis in good prognosis patients (ISS Stage I/II disease [n=2144] and standard-risk chromosomal abnormalities [n=1657]) confirmed lenalidomide-based maintenance as the best option in this subsets, on the basis of HR, MedR and PbBT. Subgroup analysis on poor prognosis patients, although limited by a lower sample size, suggested a major benefit of bortezomib-based maintenance in patients with ISS Stage III disease [n=626] but failed to detect the advantage of any regimen over no maintenance/placebo in patients with high-risk chromosomal abnormalities [n=392] (Figure 4S).

Sensitivity analyses

A sensitivity analysis was conducted on a slightly broader network of 14 trials (6516 patients), (Figure 5S). This analysis added to the primary analysis three trials (IFM9902, MY10 and ALLG MM6) and three maintenance options (thalidomide-pamidronate, thalidomide-prednisone and prednisone)[8–10] in a population of patients not previously exposed to novel agents. The analysis for PFS confirmed lenalidomide-based therapies as the best option. In terms of OS, the trend was again similar to the one of the main analysis, except for the OS advantage with thalidomide-pamidronate.

DISCUSSION

Maintenance treatment is defined as any therapy administered after the completion of the induction period in patients either responsive or non-progressive, with the goal of prolonging survival.[38,39] The optimal maintenance therapy should be a convenient treatment, with a good compliance and tolerability. In the last 20 years, several trials have evaluated maintenance with either one or more of these drugs. Most of trials showed the benefit of long-term novel-agent-based treatment in both young, ASCT-eligible patients and elderly patients. Nevertheless, direct comparisons of such regimens are lacking, and it is hard to draw conclusions.

The primary objective of this meta-analysis was to synthetize all the available evidence on maintenance with thalidomide, bortezomib and lenalidomide in NDMM (ASCT and non-ASCT settings) and to contribute identifying the best maintenance approach. We used HRs as effect measure for survival and included all the treatments evaluated during the last 20 years into a single network, including the most recently published studies. To enable the comparison, we had to arbitrarily choose a common comparator, and we opted for no maintenance/placebo.

Lenalidomide showed to be the best maintenance option. In terms of PFS, lenalidomide and lenalidomide-prednisone were the most effective treatments. In terms of OS, lenalidomide alone was the best option. This is not surprising: firstly, five randomized trials showed a significant PFS advantage with lenalidomide alone vs no maintenance/placebo;[19,30–32,40,41] secondly, a recent meta-analysis demonstrated a significant OS advantage of lenalidomide alone vs no maintenance/placebo in the post-ASCT setting;[18] and thirdly, two trials showed a moderate PFS benefit adding prednisone to lenalidomide vs lenalidomide alone, but no OS advantage.[35,37,36]

Thal-INF, Thal alone, Thal-Bort and Bort-Pred showed a HR for PFS in favour of maintenance but no OS benefit. Differently from lenalidomide alone, all these regimens were evaluated in a single trial each; their estimated lower effectiveness was therefore based on single-trial results, which could be a limitation.

Long-term use of lenalidomide undoubtedly has advantages, due to the lack of neuropathy, which is the main factor limiting the long-term use of both thalidomide and bortezomib. The main toxicities associated with lenalidomide maintenance include neutropenia, thrombocytopenia, cutaneous rash and, in the long term, diarrhoea.

INF alone showed no PFS or OS benefit in comparison with no maintenance/placebo. These results are in contrast to some previous studies[42,43,44] conducted in the pre-novel agent era, and could be partly related to a stronger effect of INF in patients not previously exposed to novel drugs.

Results of our main analysis were confirmed in the post-ASCT setting, supporting the recent approval of the drug by FDA and EMA in this setting.

Yet, it remains to be defined as to whether all patients require maintenance or not or, most importantly, if the choice of the agent/s should be dictated by disease characteristics. The benefit of lenalidomide in high-risk patients is still a matter of debate, based on conflicting results of published studies, and on the potentially higher effectiveness of bortezomib in this setting. Sub-analyses of several trials[30,32,34,35,45] suggested the suboptimal efficacy of Lenalidomide alone in high-risk patients, but recent results of the Myeloma XI trial did show a benefit also in high-risk disease;[19] yet, patients who received lenalidomide maintenance in the Myeloma XI trial were previously treated with IMiDs and were sensitive to the drug. Various studies showed the efficacy of bortezomib in high-risk patients;[11,12,14,15,46] nevertheless, this was associated more often with a bortezomib-based induction and consolidation/maintenance rather than with maintenance itself. Updated results of the HOVON65/GMMGHD4 trial suggested that the negative effect of del17 was abrogated by bortezomib-based induction and maintenance, while there was only a trend for improved OS in patients with t(4;14) and 1q gain.[12] A recent retrospective comparison of bortezomib vs lenalidomide therapy in elderly patients suggested an advantage of bortezomib upfront in patients with either del17, t(4;14) or t(14;16).[47] Again, head-to-head comparisons in specific subgroups are lacking. This NMA is the first one trying to evaluate which is the drug of choice as maintenance in patients with different prognostic features. Good prognosis patients (ISS I/II and standard-risk chromosomal abnormalities)

highly benefit from maintenance, and Lenalidomide-based therapy showed to be the best option in this subset. Subgroup analyses in high-risk patients are limited by the lower number of patients. Despite these low numbers, Bortezomib-based maintenance seems to be more beneficial for ISS III patients. No specific advantage of any maintenance over the other was noticed in patients with high-risk chromosomal abnormalities. It remains uncertain as to whether this is related to the small sample size, the different cut-off used to define positivity or the extremely poor prognosis of these patients. Considering the poor prognosis related to these chromosomal abnormalities, the conflicting results on the efficacy of lenalidomide alone, the absence of clear advantage of one agent over the other and the retrospective nature of this analysis, we cannot conclude that lenalidomide alone is sufficient for high-risk patients and a better choice would probably be to combine lenalidomide with proteasome inhibitors, instead of using only one agent.[48]

To perform this NMA and include all trials within the same network, we made two assumptions. The first one is that the effect of placebo was the same as no maintenance. Trials using placebo as control vs observation have the advantage to reduce bias in reporting quality of life and in grading adverse events (such as anxiety, fatigue, pain), where knowing or not to be on therapy may partially affect the subjective evaluation. Nevertheless, the main aims of our analysis were PFS and OS; events like progression and death are not influenced by the use of placebo or simple observation, therefore we believe that the assumption of placebo = no maintenance can be acceptable for this type of analysis. Of note, only 3 trials included in our NMA used placebo, and they all evaluated lenalidomide maintenance; the estimation of the effect of lenalidomide maintenance is based on 5 trials and this further minimizes the risk of bias. The second assumption is that different thalidomide doses (50-200 mg), lenalidomide schedules (28 days continuously or 21 /28 days), and prednisone doses (50-25 mg) had an equivalent effect. Although this latter assumption might be a limitation, there are data suggesting similar survival in patients randomized to different thalidomide doses;[49] likewise, slightly different schedules of lenalidomide maintenance induced similar median PFS;[31,32,34,45] in the EMN441 trial, 50 mg of prednisone was not well tolerated in the long-term, and median time to dose

reductions (25 mg) was six months; thereafter prednisone could be administered for a longer time, thus making similar the dose administered in the two trials.[35]

We excluded from this NMA trials that evaluated continuous therapy upfront but administered two different maintenance treatments after different and non-comparable pre-maintenance therapies since in such trials the final outcome is probably related to the combined effect of both induction and maintenance, rather than maintenance itself. The impact of some of these continuous approaches has been evaluated in two NMAs, which reported a PFS and OS advantage of lenalidomide-dexamethasone (Rd) over the other therapies, including MPT and VMP (fixed duration) in elderly patients.[50,51] More recently, Bort-Rd for 8 cycles, followed by continuous Rd showed better PFS and OS vs continuous Rd alone, in patients without an immediate intent to ASCT.[52] In the transplant setting, randomized trials showed the efficacy of long-term thalidomide[7,53] (but mainly compared with a treatment not including any novel agent) and the superiority of Bort-based pre-transplant induction followed by bortezomib maintenance over vincristine-doxorubicin-dexamethasone pre-transplant induction followed by thalidomide maintenance.[11,12]

To analyze the impact of maintenance in the context of current treatment approaches, we excluded from our primary analysis three trials[8–10] that evaluated thalidomide maintenance post-ASCT in patients who did not receive novel agents-based induction. Since this could be a limitation, these trials were subsequently included in a sensitivity analysis, whose PFS results were similar to the main one; an unexpected OS advantage was noticed with thalidomide-pamidronate. This could at least in part be related to the estimation required to calculate the HR, and/or to a stronger effect of thalidomide in patients not previously treated with novel drugs. An advantage in favor of thalidomide-based maintenance was not evident in the other trials.

We did not report on adverse events, drug discontinuations and quality of life, because our main objectives were PFS and OS. In addition, since we used "no treatment" as common comparator, adverse events, discontinuations and quality of life were not available and the comparison across trials could not be possible. These are indeed key factors: the oral administration and the good

tolerability, with no worsening in quality of life,[54] support the use of lenalidomide for the majority of patients in the context of the current available drugs. An increase in second primary malignancies with prolonged lenalidomide therapy has been reported,[31,32,45,55] but the survival benefit overcame the risk in all the trials. The optimal dose (10 vs 15 mg) and schedule (21/28 days or continuously) are still open issues. Main grade 3-4 non-hematologic toxicities were similar in patients treated with different doses and schedules in the trials evaluating lenalidomide maintenance post-ASCT, but both grade 3-4 neutropenia and thrombocytopenia were lower in patients treated with 10 mg 21/28 days if compared to 10 mg escalated to 15 and administered continuously.[31,32,34,45] The optimal duration is still to be determined. Some trials evaluated maintenance until progression, others for up to 2-3 years, but no randomized trial addressed so far the benefit of treatment until progression vs 2-3 years. Because of toxicity, thalidomide could be often administered only for a few months and bortezomib administration was planned for a maximum of 2-3 years. Although lenalidomide therapy was planned in the majority of the studies as treatment until progression, the mean duration of treatment was around 30 months.[18] Duration of therapy is therefore strictly related to tolerability and most of the trials showed that the effective duration of maintenance is limited to 2 to 3 years. Another unanswered question is the benefit of upfront continuous lenalidomide vs lenalidomide-containing triplets at first relapse, since there are no data available on the effectiveness of the currently approved lenalidomide-containing triplets in patient refractory to lenalidomide.

Despite the assumptions and limitations of this NMA, our results support the use of lenalidomide maintenance in the majority of patients. Still, better treatment options are required in patients with aggressive disease, who may benefit from combinations of proteasome inhibitors and immunomodulatory agents. There are ongoing trials evaluating maintenance with second-generation proteasome inhibitors alone or plus immunomodulatory agents and with monoclonal antibodies. These well-tolerated drugs, which could have a potential efficacy in standard but also in high-risk disease, could become available in the maintenance setting in the next future, and increase the treatment options for MM patients.

References

1. Palumbo A, Bringhen S, Caravita T, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet. 2006;367(9513):825-831. doi:10.1016/S0140-6736(06)68338-4
2. 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. doi:10.1182/blood-2009-08-237974
3. 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 (London, England). 2007;370(9594):1209-1218. doi:10.1016/S0140-6736(07)61537-2
4. 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. doi:10.1111/j.1600-0609.2010.01524.x
5. 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. doi:10.1200/JCO.2009.26.1610
6. 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. doi:10.1200/JCO.2008.21.0948
7. Barlogie B, Pineda-Roman M, van Rhee F, et al. Thalidomide arm of Total Therapy 2 improves complete remission duration and survival in myeloma patients with metaphase cytogenetic abnormalities. Blood. 2008;112(8):3115-3121. doi:10.1182/blood-2008-03-145235
8. Spencer A, Prince HM, Roberts AW, et al. Consolidation Therapy With Low-Dose Thalidomide and Prednisolone Prolongs the Survival of Multiple Myeloma Patients Undergoing a Single Autologous Stem-Cell Transplantation Procedure. J Clin Oncol. 2009;27(11):1788-1793. doi:10.1200/JCO.2008.18.8573
9. Stewart AK, Trudel S, Bahlis NJ, et al. A randomized phase 3 trial of thalidomide and prednisone as maintenance therapy after ASCT in patients with MM with a quality-of-life assessment: the National Cancer Institute of Canada Clinicals Trials Group Myeloma 10 Trial. Blood. 2013;121(9):1517-1523. doi:10.1182/blood-2012-09-451872
10. Attal M, Harousseau J-L, Leyvraz S, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood. 2006;108(10):3289-3294. doi:10.1182/blood-2006-05-022962
11. Sonneveld P, Schmidt-Wolf IGH, van der Holt B, et al. Bortezomib Induction and Maintenance Treatment in Patients With Newly Diagnosed Multiple Myeloma: Results of the Randomized Phase III HOVON-65/ GMMG-HD4 Trial. J Clin Oncol. 2012;30(24):2946-2955. doi:10.1200/JCO.2011.39.6820
12. Goldschmidt H, Lokhorst HM, Mai EK, et al. Bortezomib before and after high-dose therapy in myeloma: long-term results from the phase III HOVON-65/GMMG-HD4 trial. Leukemia. August 2017:Epub ahead of print. doi:10.1038/leu.2017.211
13. Rosiñol L, Oriol A, Teruel AI, et al. Bortezomib and thalidomide maintenance after stem cell transplantation for multiple myeloma: a PETHEMA/GEM trial. Leukemia. 2017;31(9):1922-1927. doi:10.1038/leu.2017.35
14. 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. doi:10.1200/JCO.2013.52.0023
15. Palumbo A, Bringhen S, Rossi D, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. J Clin Oncol. 2010;28(34):5101-5109. doi:10.1200/JCO.2010.29.8216
16. Mateos M-V, Oriol A, Martínez-López 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 myelom. Lancet Oncol. 2010;11(10):934-941. doi:10.1016/S1470-2045(10)70187-X
17. Mateos M-V, Oriol A, Martinez-Lopez J, et al. GEM2005 trial update comparing VMP/VTP as induction in elderly multiple myeloma patients: do we still need alkylators? Blood. 2014;124(12):1887-1893. doi:10.1182/blood-2014-05-573733
18. McCarthy PL, Holstein SA, Petrucci MT, et al. Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis. J Clin Oncol. 2017;35(29):3279-3289. doi:10.1200/JCO.2017.72.6679
19. Jackson G, Davies FE, Pawlyn C, et al. Lenalidomide Maintenance Significantly Improves Outcomes Compared to Observation Irrespective of Cytogenetic Risk: Results of the Myeloma XI Trial. Blood. 2017;130(Suppl_1):Abstract #436 [ASH 2017 59th Meeting]. http://www.bloodjournal.org/content/130/Suppl_1/436.
20. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. doi:10.1136/BMJ.D5928
21. Greipp PR, San Miguel J, Durie BGM, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23(15):3412-3420. doi:10.1200/JCO.2005.04.242
22. Munshi NC, Anderson KC, Bergsagel PL, et al. Consensus recommendations for risk stratification in multiple myeloma: report of the International Myeloma Workshop Consensus Panel 2. Blood. 2011;117(18):4696-4700. doi:10.1182/blood-2010-10-300970
23. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. Ann Intern Med. 2015;162(11):777. doi:10.7326/M14-2385
24. Systematic reviews/Meta-analyses/HTA | Study Designs | The EQUATOR Network. UK EQUATOR Centre, Centre for Statistics in Medicine, NDORMS, University of Oxford. https://www.equator-network.org/?post_type=eq_guidelines&eq_guidelines_study_design=systematic-reviews-and-meta-analyses&eq_guidelines_clinical_specialty=0&eq_guidelines_report_section=0&s=. Accessed February 23, 2018.
25. Altman DG, Bland JM. How to obtain the P value from a confidence interval. BMJ. 2011;343:d2304. doi:10.1136/BMJ.D2304
26. Higgins JPT, 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. doi:10.1002/jrsm.1044
27. Ludwig H, Adam Z, Tóthová E, et al. Thalidomide maintenance treatment increases progression-free but not overall survival in elderly patients with myeloma. Haematologica. 2010;95(9):1548-1554. doi:10.3324/haematol.2009.020586
28. Morgan GJ, Gregory WM, Davies FE, et al. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. Blood. 2012;119(1):7-15. doi:10.1182/blood-2011-06-357038
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. doi:10.1158/1078-0432.CCR-12-3211
30. Palumbo A, Hajek R, Delforge M, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med. 2012;366(19):1759-1769. doi:10.1056/NEJMoa1112704
31. Holstein SA, Jung S-H, Richardson PG, et al. Updated analysis of CALGB (Alliance) 100104 assessing lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma: a randomised, double-blind, phase 3 trial. Lancet Haematol. 2017;4(9):e431-e442. doi:10.1016/S2352-3026(17)30140-0
32. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after Stem-Cell Transplantation for Multiple Myeloma. N Engl J Med. 2012;366(19):1770-1781. doi:10.1056/NEJMoa1114083
33. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide Maintenance after Stem-Cell Transplantation for Multiple Myeloma. N Engl J Med. 2012;366(19):1782-1791. doi:10.1056/NEJMoa1114138
34. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med. 2014;371(10):895-905. doi:10.1056/NEJMoa1402888
35. Gay F, Oliva S, Petrucci MT, et al. Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: a randomised, multicentre, phase 3 trial. Lancet Oncol. 2015;16(16):1617-1629. doi:10.1016/S1470-2045(15)00389-7
36. Bringhen S, Offidani M, Musto P, et al. Long Term Outcome of Lenalidomide-Dexamethasone (Rd) Vs Melphalan-Lenalidomide-Prednisone (MPR) Vs Cyclophosphamide-Prednisone-Lenalidomide (CPR) As Induction Followed By Lenalidomide-Prednisone (RP) Vs Lenalidomide (R) As Maintenance in a Community-Based. Blood. 2017;130(Suppl_1):Abstract #901 [ASH 2017 59th Meeting]. http://www.bloodjournal.org/content/130/Suppl_1/901.
37. Magarotto V, Bringhen S, Offidani M, et al. Triplet vs doublet lenalidomide-containing regimens for the treatment of elderly patients with newly diagnosed multiple myeloma. Blood. 2016;127(9):1102-1108. doi:10.1182/blood-2015-08-662627
38. Ludwig H, Durie BGM, McCarthy P, et al. IMWG consensus on maintenance therapy in multiple myeloma. Blood. 2012;119(13):3003-3015. doi:10.1182/blood-2011-11-374249
39. Reece DE. Posttransplantation Maintenance Therapy and Optimal Frontline Therapy in Myeloma. Hematology. 2011;2011(1):197-204. doi:10.1182/asheducation-2011.1.197
40. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. N Engl J Med. 2017;376(14):1311-1320. doi:10.1056/NEJMoa1611750
41. Jackson GH, Davies FE, Pawlyn C, et al. Lenalidomide Is a Highly Effective Maintenance Therapy in Myeloma Patients of All Ages; Results of the Phase III Myeloma XI Study. Blood. 2016;128(22):Abstract #1143. http://www.bloodjournal.org/content/128/22/1143?sso-checked=true.
42. Mandelli F, Avvisati G, Amadori S, et al. Maintenance Treatment with Recombinant Interferon Alfa-2b in Patients with Multiple Myeloma Responding to Conventional Induction Chemotherapy. N Engl J Med. 1990;322(20):1430-1434. doi:10.1056/NEJM199005173222005
43. Cunningham D, Powles R, Malpas J, et al. A randomized trial of maintenance interferon following high-dose chemotherapy in multiple myeloma: long-term follow-up results. Br J Haematol. 1998;102(2):495-502. http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2141.1998.00795.x/full.
44. Fritz E, Ludwig H. Interferon-alpha treatment in multiple myeloma: meta-analysis of 30 randomised trials among 3948 patients. Ann Oncol Off J Eur Soc Med Oncol. 2000;11(11):1427-1436. https://academic.oup.com/annonc/article/11/11/1427/163178.

45. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide Maintenance after Stem-Cell Transplantation for Multiple Myeloma. N Engl J Med. 2012;366(19):1782-1791. doi:10.1056/NEJMoa1114138
46. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3. Lancet. 2010;376(9758):2075-2085. http://linkinghub.elsevier.com/retrieve/pii/S0140673610614249.
47. Larocca A, Offidani M, Musto P, Patriarca F, De Paoli L, Corradini P. 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):Abstract #744 [ASH 2017 59th Meeting]. http://www.bloodjournal.org/content/130/Suppl_1/744?sso-checked=true.
48. Nooka AK, Kaufman JL, Muppidi S, et al. Consolidation and maintenance therapy with lenalidomide, bortezomib and dexamethasone (RVD) in high-risk myeloma patients. Leukemia. 2014;28(3):690-693. doi:10.1038/leu.2013.335
49. Yakoub-Agha I, Hulin C, Doyen C, et al. A Multicenter Prospective Randomized Study Testing Non-Inferiority of Thalidomide 100 mg/day as Compared with 400 mg/day in Patients with Refractory/Relapsed Multiple Myeloma: First Results of the Final Analysis of the IFM 01-02 Study. Blood. 2005;106(11):Abstract #364. http://www.bloodjournal.org/content/106/11/364.
50. 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. doi:10.1080/10428194.2016.1177772
51. Liu X, Chen J, He YA, et al. Comparing efficacy and survivals of initial treatments for elderly patients with newly diagnosed multiple myeloma: a network meta-analysis of randomized controlled trials. Onco Targets Ther. 2017;10:121-128. doi:10.2147/OTT.S123680
52. Durie BGM, 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 (London, England). 2017;389(10068):519-527. doi:10.1016/S0140-6736(16)31594-X
53. Lokhorst HM, Schmidt-Wolf I, Sonneveld P, et al. Thalidomide in induction treatment increases the very good partial response rate before and after high-dose therapy in previously untreated multiple myeloma. Haematologica. 2008;93(1):124-127. doi:10.3324/haematol.11644
54. Abonour R, Durie BGM, Jagannath S, et al. Health-Related Quality of Life of Patients with Newly Diagnosed Multiple Myeloma Receiving Any or Lenalidomide Maintenance after Autologous Stem Cell Transplant in the Connect ® MM Disease Registry. Blood. 2016;128(22):Abstract #537. http://www.bloodjournal.org/content/128/22/537?sso-checked=true.
55. Palumbo A, Bringhen S, Kumar SK, et al. Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data. Lancet Oncol. 2014;15(3):333-342. doi:10.1016/S1470-2045(13)70609-0

Main figures: titles and legends

Figure 1. PRISMA Flowchart

Figure 2. Primary analysis Network

Figure Legend. Thal = thalidomide; IFN = interferon; Len = lenalidomide; Bort = bortezomib; Pred = prednisone.

Figure 3. Primary analysis: Forest Plot of Network Meta-Analysis Results.

Panel A shows PFS results; Panel B shows OS results.

Figure Legend. Thal = thalidomide; IFN = interferon; Len = lenalidomide; Bort = bortezomib; Pred = prednisone; PFS= progression-free survival; OS = overall survival; PbBT = probability of being the best treatment; MedR = median value of the ranking distribution for all the simulations.