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Upfront treatment for newly diagnosed transplant-ineligible multiple myeloma patients: A systematic review and network meta-analysis of 14,533 patients over 29 randomized clinical trials

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ABSTRACT

Choice of treatment for newly diagnosed transplant-ineligible multiple myeloma poses a difficult task due to an ever-increasing plethora of different regimens. Attempting to clarify this subject, we performed a systematic review and Bayesian network meta-analysis of 29 randomized clinical trials, enrolling 14,533 patients, and comparing 25 different treatment regimens regarding overall survival(OS), progression-free survival(PFS), complete response(CR), overall response rate(ORR) and toxicity. Head-to-head comparisons for all regimens and ranking of best treatments are reported. OS analysis showed superiority of lenalidomide(R) and bortezomib(V) containing regimens over thalidomide(T) protocols (e.g. Rd/CTD-HR:0.7;95%CrI:0.53-0.93, VMP/TD-HR:95%0.45;CrI:0.29-0.69). Concerning PFS, daratumumab(D) plus V (Dara-VMP) showed superior results over R (e.g. Dara-VMP/MPR-HR:0.52;95%CrI:0.34–0.77), V plus T (Dara-VMP/VTd-HR:0.56;95%CrI:0.37–0.65) and T (Dara-VMP/CTD-HR:0.34;95%CrI:0.23-0.49) containing regimens. Also, VRd and VMPT-VT performed well over other regimens. Dara-VMP showed superior response rates over R (ORR Dara-VMP/MPR-RR:6.27;95%CrI:2.18–18.95, CR Dara-VMP/MPR-RR:1.53;95%CrI:1.21-1.96) and T (ORR Dara-VMP/MPT-T-RR:4.05;95%CrI:1.19-13.26, CR Dara-VMP/MPT-T-RR:1.42;95%CrI:1.09-1.85; ORR Dara-VMP/CTD-RR:2.72;95%CrI:1.2–6.31, CR Dara-VMP/CTD-RR:1.2;95%CrI:1.05–1.36) including a higher rate of complete remission even when compared to VRd (RR:1.29;95%CrI:1.01–1.66). A higher rate of grade 3–4 adverse events was found for RD and CPR (thrombotic); VTd, VTP and VMPT-VT (neurological); RD and VAD (infectious); MPR-R and VAD (hematological); Vd and VTd (gastrointestinal); VAD, VMPCc and RD (cardiovascular). These results confirm obsolescence of classical regimens (such as VAD and MP) while pointing out benefits in efficacy resulting from incorporation of quadruplets and triplets combining new agents (Dara-VMP, VRd and VMPT-VT) and supports current rational of treatment until progression or prohibitive toxicity, especially when including lenalidomide. Based on this data, we would recommended incorporation of strategies combining novel agents (monoclonal antibodies, immunomodulatory imide drugs and proteasome inhibitors) in triplets or quadruplets and/or those comprising long term use of lenalidomide as standard frontline treatments. Moreover, this study settles daratumumab's place as an attractive alternative for upfront treatment.

1. Introduction

Multiple myeloma (MM) comprises almost 2% of all malignancies worldwide and has an incidence of 6.08 new cases per 100.000 persons every year. (Ludwig et al., 2010; Picot et al., 2011; Costa et al., 2017) More than half of these patients are older than 65 years, with a major incidence ranging from 75 to 79 years (Moreau et al., 2017; Rollig et al., 2015). Elderly patients have inherent biological frailties, frequently accompanied by several comorbidities, which preclude almost 70% of them from being eligible to transplant (Torimoto et al., 2015).

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Transplant-ineligible patients are warranted combined drug treatment regimens for an extended period of time, aiming at symptoms control and quality of life improvement (Moreau et al., 2015).

Within the last two decades, a plethora of new active drug classes have rapidly been added to MM therapeutic arsenal, like proteasome inhibitors (PIs), immunomodulatory imide drugs (IMiDs), histone deacetylase (HDAC) inhibitors, monoclonal antibodies (mAbs), along with corticosteroids and alkylating drugs. (Botta et al., 2017) The choice of one frontline regimen over another has been an increasingly challenging task due to the lack of comprehensive clinical trials comparing drug combinations and the inability of conventional meta-analysis design to thoroughly aggregate data. Indeed, network meta-analysis approach, a possible solution for this dilemma, has already been applied to this subgroup of patients (Buchberger et al., 2016; Liu et al., 2017; Satta et al., 2015; Weisel et al., 2016), but results are so far inconsistent, and the number of included trials remains discrepant.

Mixed treatment comparison (MTC) is a network meta-analysis approach that allows both direct and indirect comparisons to be accounted for in treatment effect estimation. It is also capable of performing ranking of treatment alternatives concerning their probability of being the best choice for each specific outcome. (Cooper et al., 2011; Hoaglin et al., 2011; Jansen et al., 2011) Ranking summarization of evidence can be very useful, although sometimes misleading, in judging comparative treatment effectiveness. In order to summarize current knowledge on frontline drug combination treatment regimens for transplant-ineligible MM patients we have conducted a comprehensive systematic review and mixed treatment comparison meta-analysis of all available therapeutic approaches, from inception to present time.

2. Methods

This study is a Bayesian mixed treatment comparison network meta-analysis, aggregating data from randomized clinical trials (RCT) evaluating frontline treatment for transplant-ineligible newly diagnosed multiple myeloma patients.

2.1. Information sources and search strategy

We have performed a comprehensive systematic review in order to identify all clinical trials comparing treatment approaches enrolling MM patients. Search strategy comprised terms defining MM and related disorders, available active drugs and a sensitive filter strategy for randomized clinical trials. (Haynes et al., 2005; Wilczynski et al., 2007a, 2007b) Included databases were MEDLINE, Embase, LILACS, SciELO, Cochrane CENTRAL and proceedings from major international meetings in hematology and oncology. We have also hand-searched references from all retrieved randomized clinical trials and prior systematic reviews (snowballing). Search strategy for databases screened is available in Appendix 1.

Duplicates were excluded before proceeding to study selection. All titles and abstracts retrieved were screened independently by teams of two researchers. Full-text articles also had its eligibility evaluated by two independent researchers. The last date of the search was May 1st, 2018. The review protocol has been registered in the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42018085108) and also approved by institutional ethics committee. We have followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for conducting this study and reporting our results. (Hutton et al., 2015; Shamseer et al., 2015)

2.2. Eligibility criteria

Selected patient population involved newly diagnosed transplant-ineligible MM patients. Definition of transplant-ineligibility relied on individual trial enrollment criteria and classification. Trials included could not enroll patients eventually undergoing transplantation (at the discretion of assistant physician), except for those where transplant was not included in the study design, and if patient was censored from survival analysis at that time point. Only randomized phase 2 and 3 clinical trials, with or without blinding were included in the systematic review. Abstracts or unpublished data were allowed to be included if they reported sufficient information for extraction. When methodology or study structure could not be completely evaluated from abstract-only reports, pending information was retrieved from clinical trial registries (e.g. ClinicalTrials.gov). No language or age restriction was applied.

Studies were excluded if there were no randomization procedure reported or if design was considered unclear. No prior treatment was allowed except for brief corticosteroid exposure. Refractory/Relapsed MM patients' studies were also excluded. Ancillary treatment approaches as bisphosphonates, kyphoplasty/vertebroplasty, radiation therapy, colony stimulating factors or erythropoietin were allowed if they were evenly distributed on trial arms, but trials comparing only bisphosphonate use were not considered for the purpose of this meta-analysis. Studies were also excluded if they did not report data on overall survival (OS) and/or progression free survival (PFS) hazard ratios (HR).

2.3. Study selection and data extraction

Eight reviewers participated in the screening and full-text evaluation. All abstracts screened and articles selected were reviewed and extraction proceeded by two of the eight reviewers, while a third reviewer would intervene if there was any discordance over data extracted. Data extracted was: title and reference details (first author, year of publication, study acronym, period of patient enrollment, site of the study), study population characteristics (age, sex, follow up, prognostic assessment), inclusion of therapy phase other than induction, ancillary treatments, number of enrolled patients, number of patients in each treatment arm, type of interventions and outcome data. For each trial, we evaluated hazard ratios (HRs) and 95% confidence intervals (CI) of overall survival (OS) and progression-free survival (PFS). Event-free survival and time to next treatment were also evaluated where PFS was unavailable. If CI was not reported, we extracted P-value of the effect measure to derive CI. Binary outcomes such as rate of complete response (CR) and overall response rate (ORR), as well as safety analysis (rate of grade 3 and/or 4 hematological, gastrointestinal, cardiovascular, neurological, infectious or thrombotic adverse events) were extracted as absolute frequency. Definition of CR and ORR relied in the criteria utilized within each study. Frequency of adverse events was considered to be the total number of patients experiencing any grade 3/4 events (1 or more episodes) during study period. If there were any data not clearly reported on manuscripts from reviewed articles or supplemental material, correspondent authors were contacted and asked to provide needed information. All data were extracted independently and registered on separate electronic spreadsheets, which were compiled and compared afterwards.

2.4. Quality assessment

Selected studies were assessed for quality and risk of bias considering recommendations from The Cochrane Collaboration (Higgins et al., 2011) group (including items such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete data outcome, selective reporting). We have also evaluated early trial interruption due to efficacy as a possible bias (Cannistra, 2004). This evaluation was also peer-reviewed and disparities were resolved by a third author. When information for bias assessment was not reported, corresponding author was contacted and asked to provide study details. If no contact could be established, evaluated item was ranked unclear.

2.5. Mixed treatment comparison meta-analysis

MTC (Lu and Ades, 2004) uses a Bayesian hierarquical framework to simultaneously compare multiple treatments via a common comparator. It is a generalized linear model for network meta-analysis. This approach combines direct and indirect evidence to summarize a comparison effect measure (point estimate and credible interval) whether a risk ratio (RR) or a HR. Contribution from this technique is that precision of estimates can be improved pending on completeness of meta-analysis network, also allowing inclusion of more than two arms trials and heterogeneous between-trials variability. Also, this method of meta-analysis is able to rank treatments against each other in order to quantify probability of being best ranked overall (for each specific outcome).

Goodness of fit of the models was evaluated by means of residual deviance and deviance information criteria (DIC). DIC value was used as a parameter to compare model adjustment between random and fixed models. Eventually, MTC analyses were performed considering a fixed effect model, due to the fact that the absolute majority of comparisons derived from one trial each. Similarity assumption (based on the premise that the true treatment effect comparing any two interventions would be similar across all trials (Donegan et al., 2010)) was evaluated by judging and comparing baseline characteristics, methodological quality and outcome measurement from each individual study. Homogeneity assumption among trials comparing similar treatments was tested through I^2 statistic. Consistency assumption was assessed through posterior plots and the Bayesian P-values produced by the node-splitting method described by Dias et al. (2010). Significance level was set to 0.05/k (k = number of comparisons) to adjust for multiple comparisons.

Outcomes reported are relative effects of treatments as HR for OS and PFS, and RR for binary outcomes (CR, ORR and adverse events) along with corresponding 95% credible intervals (Bayesian equivalent for confidence intervals). For ranking probabilities evaluation, we chose to use the surface under the cumulative ranking (SUCRA) curve (Mavridis et al., 2014; Chaimani et al., 2013; Salanti et al., 2011), which provides a numerical summary of the rank distribution of each treatment schedule on the different endpoints. The larger the SUCRA curve value (up to 1), the higher the probability of being the first ranked intervention. Pairwise meta-analysis and MTC was carried out with R software by using *meta* and *gemtc* packages.

3. Results

3.1. Study selection

The PRISMA flowchart illustrating study selection process is shown in Fig. 1. We have opted to include a comprehensive time period of each database indexing, from inception to present time. A total of 17,360 references were retrieved from databases and peer-reviewed after exclusion of duplicates, including both full articles and meeting abstracts. From these studies, eventually 58 reports published from 1990 to 2018, concerning 29 RCT, were sorted out for inclusion in quantitative network meta-analysis. (Hjorth et al., 1990; Oken et al., 1997; Palumbo et al., 2004; Takenaka et al., 2004; Ludwig et al., 2005; Facon et al., 2006; Palumbo et al., 2006; Facon et al., 2007; Shustik et al., 2007; Palumbo et al., 2008; Rajkumar et al., 2008; San Miguel et al., 2008; Dimopoulos et al., 2009; Hulin et al., 2009; Ludwig et al., 2009; Mateos et al., 2009; Palumbo et al., 2009; Mateos et al., 2010a, 2010b; Palumbo et al., 2010; Rajkumar et al., 2010; Wijermans et al., 2010; Morgan et al., 2011; Palumbo et al., 2011; Sacchi et al., 2011; Spicka et al., 2011; Palumbo et al., 2012; Facon et al., 2013; Magarotto et al., 2013; Niesvizky et al., 2013; Palumbo et al., 2013; San Miguel et al., 2013; Benboubker et al., 2014; Facon et al., 2014; Mateos et al., 2014; Palumbo et al., 2014; Stewart et al., 2014; Zweegman et al., 2014; Bahlis et al., 2015a, 2015b; Dimopoulos et al., 2015; Facon et al., 2015a, 2015b; Facon et al., 2015c; Hulin et al., 2015a, 2015b; Lu et al., 2015; Niesvizky et al., 2015; Stewart et al., 2015; Durie et al., 2016; Hulin et al., 2016; Hungria et al., 2016; Magarotto et al., 2016; Zweegman et al., 2016) These RCT enrolled a total of 14,533 patients, with a balanced distribution over gender, and comprised mainly an older population (69% of selected studies had a median sample age over 70 years), distributed in study sites throughout Europe, Asia, North America and South America. Median follow-up ranged from 18 to 82.8 months and prognostic information from patients was considered reasonably homogeneous. The majority of studies (65.5%) reported bisphosphonate use allowance. Overall, studies were considered similar with respect to population, trial design, general methodology and outcome measurement.

Only three trials (Rajkumar et al., 2008; Sacchi et al., 2011; Mateos et al., 2018) did not report overall survival (OS) hazard ratio (HR), other two trials (Hjorth et al., 1990; Rajkumar et al., 2010) did not report progression-free survival (PFS) HR. Overall Response Rate (ORR) data was available for all studies except for one (Pawlyn et al., 2018, 2017), while complete response (CR) data was missing in three (Hjorth et al., 1990; Shustik et al., 2007; Pawlyn et al., 2018, 2017) of them. Among adverse events, data was not available in four trials (Hjorth et al., 1990; Palumbo et al., 2004; Facon et al., 2006; Wijermans et al., 2010) for hematological, six trials (Hjorth et al., 1990; Facon et al., 2006; Shustik et al., 2007; Palumbo et al., 2011, 2012; Stewart et al., 2014, 2015; Pawlyn et al., 2018, 2017) for neurological, three trials (Hulin et al., 2009; Stewart et al., 2014, 2015; Pawlyn et al., 2018, 2017) for infectious, six trials (Oken et al., 1997; Takenaka et al., 2004; Ludwig et al., 2005; Shustik et al., 2007; Mateos et al., 2018; Pawlyn et al., 2017) for thrombotic, thirteen trials (Oken et al., 1997; Facon et al., 2006; Shustik et al., 2007; San Miguel et al., 2008; Hulin et al., 2009; Mateos et al., 2009, 2010b; Wijermans et al., 2010; Morgan et al., 2011; Sacchi et al., 2011; Spicka et al., 2011; Niesvizky et al., 2013; San Miguel et al., 2013; Stewart et al., 2014; Niesvizky et al., 2015; Stewart et al., 2015; Hungria et al., 2016; Mateos et al., 2018; Pawlyn et al., 2017), for cardiovascular, and seven trials (Hjorth et al., 1990; Shustik et al., 2007; Rajkumar et al., 2008, 2010; Facon et al., 2013; Magarotto et al., 2013; Palumbo et al., 2013; Benboubker et al., 2014; Facon et al., 2014; Bahlis et al., 2015a, 2015b; Dimopoulos et al., 2015; Facon et al., 2015a, 2015b; Facon et al., 2015c; Hulin et al., 2015a, 2015b; Lu et al., 2015; Hulin et al., 2016; Magarotto et al., 2016; Pawlyn et al., 2018, 2017), for gastrointestinal events. Characteristics of the 29 included RCT are available in Table 1.

3.2. Quality assessment

Risk of bias was evaluated as recommended by the Cochrane Collaboration (Higgins et al., 2011), aiming at 7 different study attributes: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and early interruption of the trial. Overall, studies were of low to moderate risk of bias, although non-blinding of participants and personnel was a major drawback for most of them. Still, underreporting on randomization and concealment method compromised the evaluation of some studies. Details on quality assessment are illustrated in Table 2.

3.3. Treatment group allocation and network assembling

A total of 63 therapeutic arms over 29 RCT were reviewed and categorized in 25 regimen structures. Those treatment groups were allocated based on main constituents of each protocol, where slightly different doses and drug variants were allowed. Main protocols included were: Dara-VMP (daratumumab, bortezomib, melphalan and prednisone); VRd (lenalidomide, bortezomib and dexamethasone); VMPT-VT (bortezomib, melphalan, prednisone and thalidomide followed by bortezomib and thalidomide maintenance); VMP (bortezomib, melphalan and prednisone); VTP (bortezomib, thalidomide and

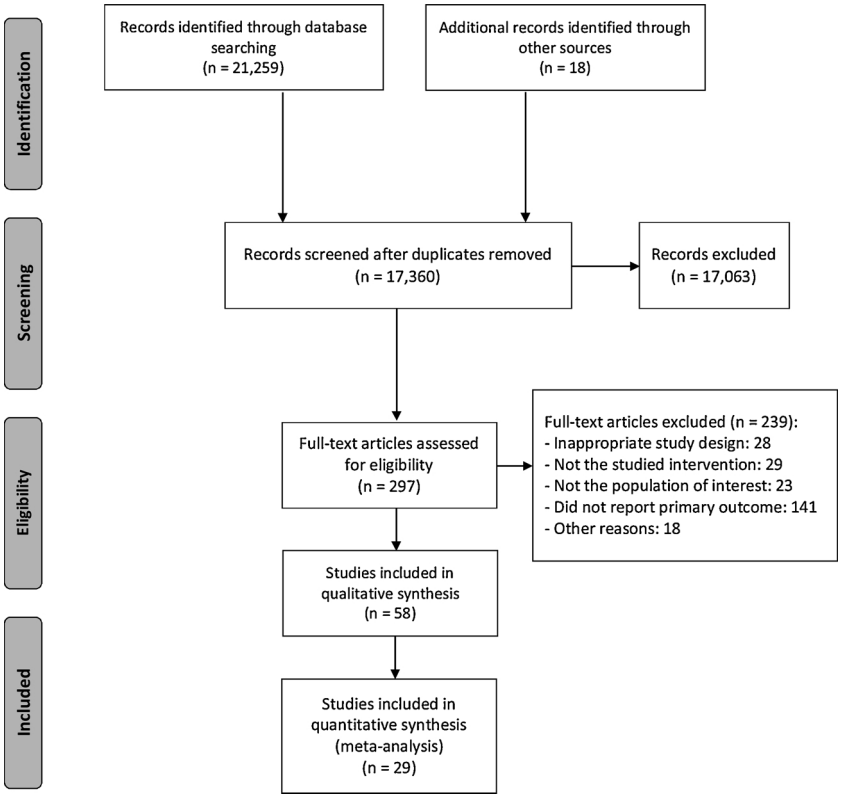

Fig. 1. PRISMA Flowchart for study selection and review.

prednisone); Vd (bortezomib and dexamethasone); VTd (bortezomib, thalidomide and dexamethasone); MPR-R (melphalan, prednisone and lenalidomide plus lenalidomide maintenance); MPR (melphalan, prednisone and lenalidomide); MPT-T (melphalan, prednisone and thalidomide plus thalidomide maintenance); MPT (melphalan, prednisone and thalidomide); CPR (cyclophosphamide, prednisone and lenalidomide); Rdc (lenalidomide and dexamethasone continuously); Rd (lenalidomide and dexamethasone for limited planned period); RD (lenalidomide and high dose dexamethasone); CRD (cyclophosphamide, lenalidomide and dexamethasone); CTd (cyclophosphamide, thalidomide and dexamethasone); TD (thalidomide and dexamethasone); MD (melphalan and dexamethasone); VMPC (vincristine, melphalan, prednisone and cyclophosphamide); VMPCc (vincristine, melphalan, prednisone and cyclophosphamide continuously); MP (melphalan and prednisone); VAD (vincristine, doxorrubicina and dexamethasone); NU-based (Nitrosourea-based regimens: carmustine or ranimustine) and Dex (dexamethasone monotherapy). Details on each included study therapeutic protocols are available in Table 3. Network plot for the outcomes analyzed is shown in Fig. 2 (detailed information on network plots for individual outcomes is given as supplementary material – Appendix 2).

3.4. Survival analysis

Comparison among treatment options concerning OS and PFS, with HR and 95% credible interval (CrI), are shown in Fig. 3. Overall, concerning OS, lenalidomide (R) containing regimens fared better than other combinations, except for RD and CRD. Among bortezomib (V) and thalidomide (T) containing regimens, the combination of the two drugs (VMPT-VT) resulted in superior results than both agents separately, although VTP and VTd combinations did not perform similarly. Regimens lacking the incorporation of novel agents (R, T or V) definitely performed worse among all. Noticeably, RD and TD, high dose dexamethasone containing regimens, showed poorer results in OS, corroborating current knowledge upon high dose dexamethasone toxicity over this subgroup of patients.

While considering PFS, Dex resulted in the worst profile, being significantly inferior to all other treatments compared. MP also demonstrated poor results in face of novel agents. Regimens comprising maintenance phases, whether R or T (VRd, MPR-R, VMPT-VT and MPT-T) fared better than treatments with limited treatment period. R containing combinations showed consistently better results, along with daratumumab combined with bortezomib. This last regimen proved itself superior even when compared to R containing regimens, being statistically superior to protocols considered highly effective in MM such as MPR, Rdc, Rd, VMP and VTd.

There were three pairwise comparisons with more than one study for survival outcomes (MPT/MP, VAD/MP and MPR-R/MPT-T). Moderate to high heterogeneity was found when evaluating I^2 statistic for some comparisons regarding OS (MPT/MP 61.9%, VAD/MP 84.7% and MPR-R/MPT-T 59.7%) and PFS (VAD/MP 88.5% and MPR-R/MPT-T 74.7%). No significant inconsistency was found between direct and indirect evidence for these outcomes.

3.5. Complete remission and overall response rate

Results for simultaneous comparisons among included treatments, concerning response outcomes, presenting risk ratios (RR) and 95% CrI, are shown in Fig. 4. Results on CR analysis were more impressive with triplets and quadruplets, and Dara-VMP showed the best performance overall, leading to CR rates superior to regimens such as MPR, Rdc, VMP and MPT-T. Combinations of bortezomib and thalidomide (VMPT-VT and VTP) showed superiority when compared to several R containing regimens. Dex and MP regimens fared undoubtedly worse than other treatments. Of note, CPR also performed unsatisfactorily when compared to T, V and other R containing regimens.

ORR analysis presented an overall significant inferiority of non-T/B/L containing protocols (namely, Dex, NU-based, VMCPc, VMCP, MP,

Table 1
Characteristics of the studies included in meta-analysis.

Main Author	Acronym	Number of Publications	Publication Year	Enrollment Period	Region	Total Study Population	Median Age	Male Sex	Median Follow Up	Prognostic Information	Follow Up Includes Maintenance Phase	Patients were allowed to undergo BMT	High Risk Cytogenetic Profile	Bisphosphonate Use	Study Intervention
Durie	SWOG S0777	1	2016	04/2008-02/2012	USA	471	43% > 65 years	275/471 (58.4%)	55 months	ISS III - 157/471 (33%)	No	Yes, at discretion of the attending physician. Patients were censored.	Not reported	Not reported	VRd and Rdc
Facon	IFM 95-01	1	2006	06/1995-09/1998	France and Belgium	488	70 years	249/488 (51%)	82.8 months	ISS III - 293/488 (60%)	No	No	Not reported	Yes - Pamidronate	MP and Dex
Facon	IFM 99-06	1	2007	05/2000-08/2005	France, Belgium and Switzerland	447	183/447 (41%) > 70 years	238/447 (53.2%)	51.5 months	ISS III - 127/410 (31%)	No	Yes, patients underwent attenuated dose melphalan conditioning.	t(11:14) 37/223 (17%) and t(4:14) 24/222 (11%)	Yes - Clodronate	MPT, MP and VAD
Hjorth		1	1990	10/1983-12/1986	Sweden	162	69 years	94/162 (58%)	45 months	Durie-Salmon III (A or B) - 108/162 (66.7%)	Yes	No	Not reported	Not reported	MP and VMCP
Hulin	IFM 01/01	1	2009	04/2002-12/2006	France and Belgium	229	78.5 years	104/229 (45.4%)	47.5 months	ISS III - 65/202 (32%)	Yes	No	Not reported	Yes - Clodronate	MPT and MP
Hulin, Facon, Benboubker, Dimopoulos	FIRST Trial (MM-020/IFM07-01)	13	2013-2016	08/2008-03/2011	18 countries (not discriminated)	1623	73 years	854/1623 (52.6%)	45.5 months (2016)*	ISS III - 659/1623 (40.6%)	No	No	142/762 (18.6%)	Yes (Allowed, but not defined by protocol)	Rdc, Rd and MPT
Hungria		1	2016	07/2006-04/2013	Brazil and Argentina	82	72.2 years	36/82 (43.9%)	37.5 months	ISS III - 32/82 (39%)	Yes	No	Not reported	Yes (Allowed, but not defined by protocol)	MPT and CTD
Ludwig		1	2005	05/1994-12/2001	Austria, Germany, Switzerland, Belgium, Hungary, Slovakia, Greece and the Czech Republic	292	67 years	141/292 (48%)	49 months	Durie-Salmon III (A or B) - 197/292 (67%)	Yes	No	Not reported	Not reported	VMCPc and VMCP
Ludwig		1	2009	08/2001-10/2007	Austria, Czech Republic, Slovakia, Hungary and Croatia	289	72 years	144/288 (50%)	28.1 months	ISS III - 193/288 (67%)	Yes	No	Not reported	Yes - Zoledronate	TD and MP
Magarotto, Palumbo		3	2013-2016	08/2009-09/2012	Italy and Czech Republic	654	74 years	322/662 (48.6%)	39 months (2016)*	ISS III - 179/662 (27%)	No	No	133/525 (25.3%)	Not reported	CPR, MPR and Rd
Mateos	GEM2005	2	2010-2014	03/2006-10/2008	Spain	260	73 years	130/260 (50%)	72 months (2014)*	ISS III - 87/260 (33.4%)	Yes	No	27/260 (10.4%)	Yes (Allowed, but not defined by protocol)	VTP and VMP
	VISTA Trial	6	2008-2013	12/2004-09/2006		682	71 years				No	No	20/163 (12.2%)		VMP and MP

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Table 1 (*continued*)

Main Author	Acronym	Number of Publications	Publication Year	Enrollment Period	Region	Total Study Population	Median Age	Male Sex	Median Follow Up	Prognostic Information	Follow Up Includes Maintenance Phase	Patients were allowed to undergo BMT	High Risk Cytogenetic Profile	Bisphosphonate Use	Study Intervention
Mateos, Dimopoulos, San Miguel					22 countries (not discriminated)			341/682 (50%)	60.1 months (2013)*	ISS III - VMP 35% e MP 34%				Yes (Allowed, but not defined by protocol)	
Mateos	ALCYONE Trial	1	2017	02/2015-07/2016	25 countries (North and South America, Europe and Asia)	706	71 years	327/706 (46.3%)	16.5 months	ISS III – 271/706 (38.4%)	No	No	98/616 (15.9%)	Not reported	VMP and Dara-VMP
Morgan	MRC Myeloma IX	1	2011	2003-2007	UK	849	73 years	473/849 (55.7%)	44 months	ISS III - 333/849 (39.2%)	Yes	No	186/849 (21.9%)	Yes - Randomization to Zoledronate or Clodronate until progression	CTD and MP
Niesvizky	UPFRONT	2	2013-2015	06/2007-03/2010	USA	502	74.5 years	261/502 (51.9%)	42.7 months (2015)*	ISS III - 157/502 (31.3%)	Yes	No	Not reported	Yes (Allowed, but not defined by protocol)	VTd, VMP and Vd
Oken		1	1997	08/1979-07/1983	USA	465	64 years	112/425 (24.1%)	29 months	Durie-Salmon III (A or B) - MP 58/230 (25.2%) e VBMCP 58/235 (24.7%)	Yes	No	Not reported	Not reported	MP and Nitrosourea (NU) -Based Regimen
Palumbo	M97G Trial	1	2004	10/1997-12/2000	Italy	194	65 years	105/194 (54.1%)	39 months	Durie-Salmon III (A or B) - 58/95 (61%) e 62/99 (62.6%)	No	Yes, patients underwent attenuated dose melphalan conditioning.	Not reported	Not reported	VAD and MP
Palumbo		2	2006-2008	01/2002-05/2005	Italy	331	72 years	Not reported	38.4 months (2008)*	Durie-Salmon III (A or B) - 206/331 (62.2%)	Yes	No	Not reported	Not reported	MPT and MP
Palumbo		3	2009-2014	05/2006-01/2009	Italy	511	71 years	252/511 (49.3%)	54 months (2014)*	ISS III - 104/407 (25.5%)	Yes	No	180/376 (47.9%)	Yes - Pamidronate or Clodronate allowed	VMPT-VT and VMP
Palumbo	MM-015	2	2011-2012	02/2007-09/2008	European countries, Australia and Israel	459	72 years	228/459 (49.7%)	30 months (2012)*	ISS III - 226/459 (49.2%)	Yes	No	31/184 (16.8%)	Yes (Allowed, but not defined by protocol)	MPR-R, MPR and MP
Pawlyn	Myeloma XI Trial	2	2016-2017	2010 – 2019	UK	1852	74 years	Not reported	Not reported	Not reported	Yes	No	Not reported	Not reported	CRD and CTD
Rajkumar		1	2008	03/2003-04/2005	USA	470	64.4 years	238/470 (50.6%)	18 months	Durie-Salmon III (A or B) - 157/235 (66.8%) e	No	Yes, at discretion of the attending physician. Patients were censored.	Not reported	Yes (Allowed, but not defined by protocol)	TD and Dex

(*continued on next page*)

Table 1 (*continued*)

Main Author	Acronym	Number of Publications	Publication Year	Enrollment Period	Region	Total Study Population	Median Age	Male Sex	Median Follow Up	Prognostic Information	Follow Up Includes Maintenance Phase	Patients were allowed to undergo BMT	High Risk Cytogenetic Profile	Bisphosphonate Use	Study Intervention
Rajkumar	ECOG-ACRIN E4A03	1	2010	11/2004-04/2006	USA	445	66 years	253/457 (55.4%)	35.8 months	145/235 (61.7%) ISS III - 107/445 (24%)	No	Yes, at discretion of the attending physician. Patients were censored.	Not reported	Yes - Pamidronate or Zoledronate allowed	Rdc and RD
Sacchi		1	2011	01/2005-12/2008	Italy	118	79 years	55/118 (46.6%)	30 months	ISS III - 30/118 (25.4%)	Yes	No	Not reported	Yes (Allowed, but not defined by protocol)	MPT and MP
Shustik		1	2007	06/1995-07/2003	Canada	466	70.9 years	188/466 (40%)	62.4 months	Durie-Salmon III (A or B) - 331/466 (71%)	Yes	No	Not reported	Yes (Allowed, but not defined by protocol)	MD and MP
Stewart	E1A06	2	2014-2015	02/2008-11/2011	USA	306	76.6 years	167/306 (54.6%)	40.7 months (2015)*	ISS III - 95/306 (31%)	Yes	No	Not reported	Yes (Allowed, but not defined by protocol)	MPT-T and MPR-R
Takenaka		1	2004	07/1993-08/1998	Japan	210	63 years	106/210 (5%)	43 months	Durie-Salmon III (A or B) - 123/210 (58%)	No	No	Not reported	Not reported	NU-Based Regimen And VMCP
Wijermans	HOVON49	1	2010	09/2002-07/2007	Belgium, Netherlands, Norway, Sweden, Denmark	333	73 years	186/333 (55.8%)	39 months	ISS III - 61/225 (27.1%)	Yes	No	33/182 (18.1%)	Yes - Pamidronate or Clodronate allowed	MPT and MP
Zweegman	HOVON87/NMSG18	2	2014-2016	03/2009-10/2012	Belgium, Netherlands, Norway, Sweden, Denmark	637	73 years	346/637 (54.3%)	36 months (2016)*	ISS III - 165/637 (25.9%)	Yes	No	7.50%	Yes (Allowed, but not defined by protocol)	MPT-T and MPR-R

*For multiple publication RCT we have considered the longer follow up report for each outcome (date of publication between parentheses).

Table 2
Quality assessment of included studies.

Author	Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Early Interruption
Durie	2016	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk	No
Facon	2006	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk	No
Facon	2007	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	No
Hjorth	1990	Unclear	Unclear	High Risk	Unclear	High Risk	High Risk	No
Hulin	2009	Unclear	Unclear	Low Risk	Unclear	Low Risk	Low Risk	Yes
Hulin	2013-2016	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Low Risk	No
Hungria	2016	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	No
Ludwig	2005	Low Risk	Low Risk	Unclear	Unclear	Low Risk	Low Risk	No
Ludwig	2009	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk	No
Magarotto	2013-2016	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	No
Mateos	2010-2014	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk	No
Mateos	2008-2013	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Low Risk	No
Mateos	2017	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk	No
Morgan	2011	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk	No
Niesvizky	2013-2015	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk	No
Oken	1997	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	No
Palumbo	2004	Low Risk	Low Risk	High Risk	Unclear	Unclear	Unclear	No
Palumbo	2006-2008	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Low Risk	No
Palumbo	2009-2014	Unclear	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	No
Palumbo	2011-2012	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	No
Pawlyn	2016-2017	Low Risk	Unclear	High Risk	Unclear	Unclear	Unclear	No
Rajkumar	2008	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	No
Rajkumar	2010	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Low Risk	Yes
Sacchi	2011	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	No
Shustik	2007	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk	No
Stewart	2014-2015	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	No
Takenaka	2004	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk	No
Wijermans	2010	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	No
Zweegman	2014-2016	Unclear	Unclear	High Risk	Unclear	Unclear	Unclear	No

MD and VAD), TD and MPT in comparison to other regimens. Also, some B-containing regimens showed better results than R containing treatments (Vd, VTd, VMP and VMPT-VT when compared to MPR and CPR, and also to Rdc and Rd versus VMPT-VT). Moreover, Dara-VMP showed higher ORR than R containing regimens, including VRd.

Pairwise comparisons with more than one reporting trial for response outcomes were the same as in survival outcomes. No relevant heterogeneity was found when evaluating I^2 statistic for CR (0%–34%) and PFS (0%–39%) for those studies. No significant inconsistency was found between direct and indirect evidence for these outcomes.

3.6. Safety/toxicity

We have assessed six different categories of adverse events (thromboembolic, neurological, infectious, hematological, gastrointestinal and cardiovascular). RR and 95% CrI for all simultaneous head-to-head comparisons for each adverse event evaluated are listed as supplementary material (Appendix 3). Overall rates of adverse events reported were considered low across studies (overall mean below 15%), except for hematological adverse events (34.9%).

Concerning hematological adverse events, R containing protocols were associated with more events than V containing regimens (MPR and MPR-R against VTd and Vd) and T containing protocols (MPR and MPR-R against TD). Also, regimens containing melphalan showed higher rates of toxicity than their counterparts (VMPT-VT, VMP and MPT against VTd, Vd and TD). VAD also showed relevant hematological toxicity when compared to T (CTD and TD) and V (Vd and VTD) containing regimens. Dex, as expected, resulted in inferior toxicity compared to other treatments.

For cardiovascular events, a trend towards a higher toxicity was observed with RD and VAD regimens. Underreporting of this outcome compromised further conclusions due to lack of information from more than 40% of the included studies. Gastrointestinal events were particularly frequent with V containing regimens, with or without T (Vd, VTd, VMP and VMPT-VT). Infectious events were seen especially with R containing regimens, mainly with RD. VAD also showed an unfavorable performance compared to other treatments. Thrombotic events were shown to be associated with R and T regimens, especially RD, along with T containing regimens (TD, MPT and CTD) and T and V combined (VTd and VTP).

There were two pairwise comparisons with more than one study for hematological events (MPT/MP and MPR-R/MPT-T); and other two for infectious, gastrointestinal, thrombotic and cardiovascular events (MPT/MP and VAD/MP). Only one pairwise comparison had more than one study concerning neurological events. Moderate to high heterogeneity was found in some of such comparisons when evaluating I^2 statistic, such as in hematological (MPT/MP 61%% and MPR-R/MPT-T 92.8%), gastrointestinal (MPT/MP 61%) and cardiovascular (VAD/MP 77%) events. Only low to moderate heterogeneity was found with thrombotic (0%–49%), neurological (15%) and infectious events (0%–31%). Also, no significant inconsistency was found between direct and indirect evidence for these outcomes.

3.7. Ranking of treatment regimens

Aside from computing effect measures comparing treatments, MTC meta-analysis can also rank treatments on their probability of being best among all alternatives analyzed. The surface under the cumulative ranking (SUCRA) curve value, an estimate of the probability of being the best regimen, was calculated for each treatment under all outcomes evaluated. The compiled results of rankings for each outcome are shown in Fig. 5.

OS outcome was leaded by VRd, followed by VMPT-VT, MPR-R, Rdc and CPR. Except for VMPT-VT, all regimens contained R. Also, only one regimen (CPR) did not contain at least two novel agent classes (proteasome inhibitors and immunomodulatory drugs). PFS showed a similar pattern, with MPR-R ranking best, but notably alongside Dara-VMP, followed by MPT-T, VRd, VMPT-VT and Rdc. Of note, regimens with continuous treatment structures (MPR-R, MPT-T, VRd and Rdc) were found on both set of best treatments group, concerning OS and

Table 3
Details on treatments from included studies (drugs and doses).

Study	Treatment Details
Durie, 2016	Rd - Lenalidomide 25 mg D1-D21 + Dexamethasone 40 mg D1, D8, D15, D22 every 28 days x 6 cycles + Maintenance with same regimen until progression VRd - Bortezomib 1.3 mg/m2 D1, D4, D8, D11 + Lenalidomide 25 mg D1-D14 + Dexamethasone 20 mg D1, D2, D4, D5, D8, D9, D11, D12 every 21 days x 8 cycles + Maintenance with Rd (as above)
Facon, 2006	Dex - Dexamethasone 40 mg/day D1-D4, D9-D12 and D17-D20 (2 cycles) and after D1-D4 only + Dex-IFN - IFN A2B 3 MU 3x/week + Dexamethasone dose from Dex MP - Melphalan 0.25 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 every 6 weeks + M-Dex - Melphalan dose from MP and Dexamethasone dose from Dex
Facon, 2007	MP - Melphalan 0.25 mg/kg + Prednisone 2 mg/kg MPT - Melphalan 0.25 mg/kg + Prednisone 2 mg/kg + Thalidomide up to 400 mg/day VAD - Dexamethasone 40 mg/day D1-D4 + Doxorubicin 50 mg/m2 D1 + Vincristine 1 mg D1 (2 cycles) + 2 reduced conditioning auto-transplant (Melphalan 100 mg/m2) 2 months apart
Hjorth, 1990	MP - Melphalan 0.25 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 cycle every 6 weeks VMCP - Vincristine 1 mg D1 + Melphalan 5 mg/m2 D1-D4 + Cyclophosphamide 100 mg/m2 D1-D4 + Prednisone 60 mg/m2 D1-D3 alternating every 3 weeks with VBAP - Vincristine 1 mg D1 + BCNU 30 mg/m2 D1 + Doxorubicin 30 mg/m2 D1 + Prednisone 60 mg/m2 D1-D4
Hulin, 2009	MP - Melphalan 0.2 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 every 6 weeks MPT - Melphalan 0.2 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 + Thalidomide 100 mg/day every 6 weeks
Hulin, 2016	Rdc - Lenalidomide 25 mg/day D1-D21 + Dexamethasone 40 mg D1, D8, D15 and D22 every 28 days continuously Rd - Lenalidomide 25 mg/day D1-D21 + Dexamethasone 40 mg D1, D8, D15 and D22 every 28 days x 18 cycles MPT - Melphalan 0.25 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 + Thalidomide 200 mg/day every 6 weeks x 12 cycles
Hungria, 2016	CTD - Cyclophosphamide 50 mg/d + Dexamethasone 40 mg D1-D4 and D15-D18 (for 2 cycles and only D1-D4 thereafter) + Thalidomide 100-200 mg/day MPT - Melphalan 4 mg/m2 + Prednisone 40 mg/m2 D1-D7 every 4 weeks + Thalidomide 100-200 mg/day
Ludwig, 2005	VMCP - Vincristine 2 mg D1 + Melphalan 15 mg/m2 D1 + Cyclophosphamide 450 mg/m2 D1 + Prednisolone 40 mg D1-D7 and 25 mg 3x/sem D8-D14 every 4 weeks VMCPc - Vincristine 2 mg D1 + Melphalan 15 mg/m2 D1 + Cyclophosphamide 450 mg/m2 D1 + Prednisolone 40 mg D1-D7 and 25 mg 3x/week D8-D28 every 4 weeks
Ludwig, 2009	MP - Melphalan 0.25 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 every 4-6 weeks TD - Thalidomide 50-400 mg/day + Dexamethasone 40 mg D1-D4 and D15-D18 (even cycles) and D1-D4 (odd cycles)
Magarotto/Palumbo, 2016	CPR - Lenalidomide 25 mg/day D1-D21 + Cyclophosphamide 50 mg D1-D21 + Prednisone 25 mg alternate days x 9 cycles + Maintenance with Lenalidomide 10 mg D1-D21 with or without Prednisone until progression/toxicity Rd - Lenalidomide 25 mg/day D1-D21 + Dexamethasone 40 mg D1, D8, D15 and D22 every 28 days x 9 cycles + Maintenance with Lenalidomide 10 mg D1-D21 with or without Prednisone until progression/toxicity MPR - Melphalan 0.18 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 + Lenalidomide 10 mg D1-D21 × 9 cycles + Maintenance with Lenalidomide 10 mg D1-D21 with or without Prednisone until progression/toxicity
Mateos, 2010	VMP - Melphalan 9 mg/m2 D1-D4 + Prednisone 60 mg/m2 D1-D4 + Bortezomib 1.3 mg/m2 (D1, D4, D8, D11, D22, D25, D29, D32 first 4 cycles and D1, D8, D22, D29 C5-C9) every 6 weeks until progression/toxicity VTP - Thalidomide 100 mg/day + Prednisone 60 mg/m2 D1-D4 + Bortezomib 1.3 mg/m2 (D1, D4, D8, D11, D22, D25, D29, D32 in C1 and D1, D8, D15 and D22 thereafter) every 6 weeks until progression/toxicity
Mateos, 2017	Dara-VMP - Daratumumab 16 mg/kg (+ Dexamethasone 20 mg) weekly at cycle 1, thrice weekly in cycles 2-9 and every 4 weeks afterwards (until progression/toxicity) + Melphalan 9 mg/m2 D1-D4 + Prednisone 60 mg/m2 D2-D4 + Bortezomib 1,3 mg/m2 (D1, D4, D8, D11, D22, D25, D29, D32 in cycle 1 and D1, D8, D22, D29 from cycle 2 to 9) every 6 weeks. VMP - Melphalan 9 mg/m2 D1-D4 + Prednisone 60 mg/m2 D2-D4 + Bortezomib 1,3 mg/m2 (D1, D4, D8, D11, D22, D25, D29, D32 in cycle 1 and D1, D8, D22, D29 from cycle 2 to 9) every 6 weeks.
Morgan, 2011	CTD - Cyclophosphamide 500 mg/weekl + Thalidomide 200 mg + Dexamethasone 20 mg D1-D4 and D15-D18 every 28 days MP - Melphalan 7 mg/m2 D1-D4 + Prednisone 40 mg/m2 D1-D4 every 4 weeks
Niesvizky, 2013	Vd - Bortezomib 1.3 mg/m2 D1, D4, D8, D11 + Dexamethasone 20 mg D1, D2, D4, D5 D8, D9, D11, D12 (4 cycles) and D1, D2, D4, D5 (5-8 cycles) x 8 cycles VMP - Bortezomib 1.3 mg/m2 D1, D4, D8, D11 + Melphalan 9 mg/m2 and Prednisone 60 mg/m2 D1-D4 × 8 cycles VTd - Bortezomib 1.3 mg/m2 D1, D4, D8, D11 + Dexamethasone 20 mg D1, D2, D4, D5 D8, D9, D11, D12 (4 cycles) and D1, D2, D4, D5 (5-8 cycles) + Thalidomide 100 mg x 8 cycles
Oken, 1997	MP - Melphalan 8 mg/m2 D1-D4 + Prednisone 60 mg/m2 D1-D4 every 4 weeks NU-Based Regimen - Melphalan 8 mg/m2/day D1-D4 + Carmustine (BCNU) 20 mg/m2 D1 + Cyclophosphamide 400 mg/m2 D1 + Vincristine 1.2 mg/m2 D1 + Prednisone 40 mg/m2/day D1-D7 (and 20 mg/m2 D8-D14 first 3 cycles) every 35 days
Palumbo, 2004	MP - Melphalan 6 mg/m2 + Prednisone 60 mg/m2 D1-D7 every 4 weeks VAD - Dexamethasone 40 mg/day D1-D4 + Doxorubicin 50 mg/m2 D1 + Vincristine 1 mg D1 (2 cycles) + 1 reduced conditioning auto-transplant (Melphalan 100 mg/m2)
Palumbo, 2008	MP - Melphalan 4 mg/m2 + Prednisone 40 mg/m2 D1-D7 every 4 weeks MPT - Melphalan 4 mg/m2 + Prednisone 40 mg/m2 D1-D7 + Thalidomide 100 mg/day every 4 weeks
Palumbo, 2012	MP - Melphalan 0.18 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 MPR - Melphalan 0.18 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 + Lenalidomide 10 mg D1-D21 MPR-R - Melphalan 0.18 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 + Lenalidomide 10 mg D1-D21 + Maintenance with Lenalidomide 10 mg D1-D19
Palumbo, 2014	VMP - Melphalan 9 mg/m2 D1-D4 + Prednisone 60 mg/m2 D1-D4 + Bortezomib 1.3 mg/m2 (D1, D4, D8, D11, D22, D25, D29, D32 first 4 cycles and D1, D8, D22, D29 C5-C9) every 6 weeks VMPT-VT - Melphalan 9 mg/m2 D1-D4 + Prednisone 60 mg/m2 D1-D4 + Bortezomib 1.3 mg/m2 (D1, D4, D8, D11, D22, D25, D29, D32 first 4 cycles and D1, D8, D22, D29 C5-C9) + Thalidomide 50 mg/day every 6 weeks + Maintenance with Bortezomib 1.3 mg/m2 every 2 weeks + Thalidomide 50 mg/day
Pawlyn, 2017	CRD - Cyclophosphamide 500 mg D1 and D21 + Lenalidomide 25 mg D1-D21 + Dexamtehasone 40 mg D1-D4 and D12-D15 (every 28 days). CTD - Cyclophosphamide 500 mg D1, D8, D15 + Thalidomide 200 mg/day + Dexamtehasone 40 mg D1-D4 and D12-D15 (every 21 days).
Rajkumar, 2008	Dex - Dexamethasone 40 mg/day D1-D4, D9-D12 and D17-D20 every 4 weeks TD - Thalidomide 200 mg/day contínuo + Dexamethasone 40 mg/day D1-D4, D9-D12 and D17-D20 every 4 weeks
Rajkumar, 2010	RD - Lenalidomide 25 mg/day D1-D21 + Dexamethasone 40 mg D1-D4, D9-D12 and D17-D20 every 28 days Rdc - Lenalidomide 25 mg/day D1-D21 + Dexamethasone 40 mg D1, D8, D15 and D22 every 28 days

(*continued on next page*)

Table 3 (*continued*)

Study	Treatment Details
Sacchi, 2011	MP - Melphalan 0.25 mg/kg D1-D4 + Prednisone 60 mg/m2 D1-D4 every 28 days MPT - Melphalan 0.25 mg/kg D1-D4 + Prednisone 60 mg/m2 D1-D4 + Thalidomide 100 mg/day every 28 days
San Miguel, 2013	MP - Melphalan 9 mg/m2 D1-D4 + Prednisone 60 mg/m2 D1-D4 every 6 weeks fo 9 cycles VMP - Melphalan 9 mg/m2 D1-D4 + Prednisone 60 mg/m2 D1-D4 + Bortezomib 1.3 mg/m2 (D1, D4, D8, D11, D22, D25, D29, D32 first 4 cycles and D1, D8, D22, D29 C5-C9) every 6 weeks for 9 cycles
Shustik, 2007	MD - Melphalan 9 mg/m2 D1-D4 + Dexamethasone 40 mg/day for 4 days every 14 days MP - Melphalan 9 mg/m2 D1-D4 + Prednisone 100 mg D1-D4 every 4 weeks
Stewart, 2015	MPR-R - Melphalan 0.18 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 + Lenalidomide 10 mg D1-D21 + Maintenance with Lenalidomide 10 mg D1-D20 MPT-T - Melphalan 0.18 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 + Thalidomide 200 mg D1-D28 every 28 days + Maintenance with Thalidomide 100 mg/day
Takenaka, 2004	mCOP/MP (included under VMCP protocol) - Cyclophosphamide 350 mg/m2 D1 and D8 + Vincristine 1 mg/m2 D1 and D8 + Prednisolona 40 mg/m2 D1-D3, D8-D10 and D22-D24 + Melphalan 3 mg/m2 D22-D24 every 6 weeks NU-Based Regimen - Ranimustine (MCNU) 50 mg/m2 D1 + Cyclophosphamide 350 mg/m2 D1 and D22 + Vincristine 1 mg/m2 D1 and D22 + Prednisolone 60 mg/m2 D1-D3 and D22-D24 + Melphalan 3 mg/m2 D1-D3 and D22-D24 every 6 weeks
Wijermans, 2010	MP - Melphalan 0.25 mg/kg + Prednisone 1 mg/kg MPT - Melphalan 0.25 mg/kg + Prednisone 1 mg/kg + Thalidomide 200 mg/day
Zweegman, 2016	MPR-R - Melphalan 0.18 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 + Lenalidomide 10 mg D1-D21 + Maintenance with Lenalidomide 10 mg D1-D21 MPT-T - Melphalan 0.18 mg/kg D1-D4 + Prednisone 2 mg/kg D1-D4 + Thalidomide 200 mg D1-D28 every 28 days + Maintenance with 100 mg/day

PFS.

Response outcomes were both (CR and ORR) leaded by Dara-VMP, closely followed by V containing regimens (with and without immunomodulatory drugs). Concerning CR, following daratumumab, observed protocols were VMPT-VT, VTP, VMP, Vd and VRd. ORR results presented an equivalent pattern to CR, with VMPT-VT, Vd, VTd, RD and VTP following daratumumab.

Lowest ranked treatments for thrombotic events were RD, CPR, Rdc, VTP and Vd. Neurological events were found in higher rates with V with or without T containing regimens (VTd, VTP, VMPT-VT, Vd and

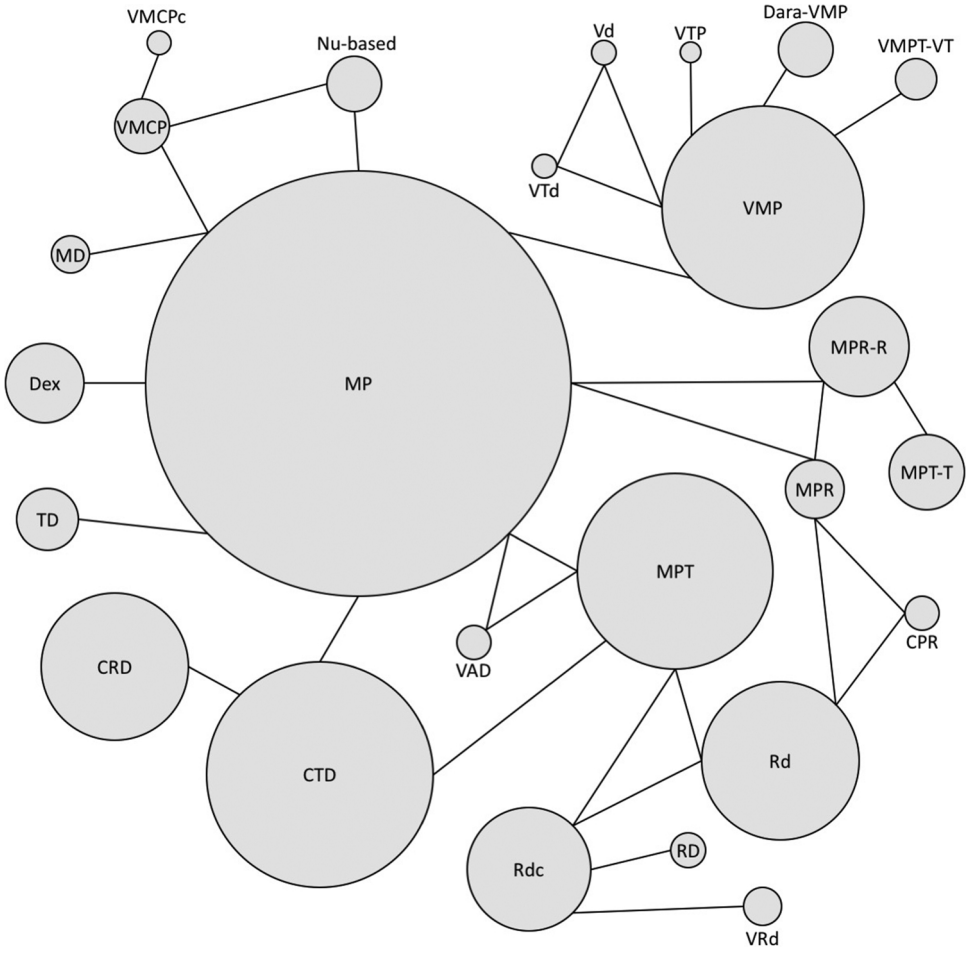

Fig. 2. Network plot.*.
*Depicted network plot refers to the Hematological AE outcome. Network plots for each of the different outcomes assessed is available as supplementary material (Appendix 2.)

Dara-VMP	0.91 (0.58-1.42)	1.02 (0.61-1.66)	0.52 (0.34-0.77)	0.66 (0.45-0.97)	0.45 (0.31-0.66)	0.45 (0.30-0.66)	0.37 (0.25-0.55)		0.86 (0.61-1.21)	0.5 (0.38-0.65)	0.97 (0.57-1.63)	0.56 (0.37-0.85)	0.46 (0.31-0.68)	0.46 (0.32-0.66)	0.41 (0.27-0.63)	0.34 (0.23-0.49)	0.27 (0.18-0.41)	0.37 (0.25-0.54)	0.31 (0.21-0.46)	0.27 (0.20-0.38)	–	–	–	0.16 (0.11-0.23)
–	VRd	1.12 (0.69-1.78)	0.56 (0.40-0.8)	0.72 (0.58-0.91)	0.5 (0.38-0.66)	0.49 (0.36-0.66)	0.40 (0.28-0.59)	–	0.94 (0.62-1.42)	0.54 (0.38-0.78)	1.06 (0.64-1.75)	0.62 (0.38-0.99)	0.51 (0.32-0.80)	0.51 (0.38-0.67)	0.45 (0.28-0.73)	0.37 (0.27-0.52)	0.30 (0.20-0.44)	0.41 (0.29-0.58)	0.34 (0.24-0.49)	0.30 (0.22-0.41)	–	–	–	0.18 (0.12-0.25)
–	0.92 (0.5-1.7)	MPR-R	0.51 (0.34-0.74)	0.65 (0.43-0.98)	0.44 (0.30-0.66)	0.44 (0.29-0.66)	0.36 (0.23-0.56)	–	0.84 (0.52-1.35)	0.49 (0.32-0.75)	0.95 (0.81-1.09)	0.55 (0.33-0.93)	0.45 (0.27-0.76)	0.45 (0.31-0.67)	0.40 (0.24-0.69)	0.33 (0.22-0.50)	0.27 (0.17-0.42)	0.36 (0.24-0.56)	0.30 (0.20-0.47)	0.27 (0.18-0.39)	–	–	–	0.16 (0.10-0.24)
–	0.73 (0.46-1.1)	0.79 (0.53-1.2)	MPR	1.28 (1-1.63)	0.87 (0.71-1.08)	0.86 (0.69-1.07)	0.71 (0.52-0.98)	–	1.66 (1.14-2.38)	0.96 (0.71-1.29)	1.85 (1.25-2.77)	1.08 (0.71-1.66)	0.90 (0.59-1.35)	0.89 (0.71-1.12)	0.8 (0.51-1.23)	0.66 (0.50-0.86)	0.53 (0.38-0.73)	0.72 (0.54-0.97)	0.60 (0.44-0.82)	0.53 (0.42-0.67)	–	–	–	0.31 (0.23-0.42)
–	0.82 (0.58-1.2)	0.89 (0.51-1.6)	1.1 (0.76-1.7)	Rdc	0.68 (0.58-0.8)	0.68 (0.56-0.81)	0.55 (0.42-0.74)	–	1.29 (0.92-1.81)	0.75 (0.57-0.98)	1.44 (0.94-2.27)	0.85 (0.56-1.28)	0.69 (0.47-1.03)	0.69 (0.60-0.81)	0.62 (0.41-0.94)	0.51 (0.40-0.65)	0.41 (0.30-0.55)	0.56 (0.43-0.72)	0.47 (0.35-0.62)	0.41 (0.34-0.50)	–	–	–	0.24 (0.19-0.31)
–	0.74 (0.55-1.0)	0.8 (0.48-1.4)	1.02 (0.72-1.4)	0.9 (0.75-1.1)	Rd	0.99 (0.88-1.11)	0.81 (0.62-1.07)	–	1.88 (1.35-2.63)	1.09 (0.84-1.40)	2.12 (1.38-3.22)	1.25 (0.83-1.85)	1.02 (0.69-1.49)	1.02 (0.89-1.16)	0.90 (0.60-1.36)	0.75 (0.59-0.94)	0.60 (0.45-0.80)	0.81 (0.64-1.05)	0.68 (0.53-0.90)	0.60 (0.51-0.72)	–	–	–	0.36 (0.28-0.45)
–	0.79 (0.56-1.1)	0.86 (0.51-1.5)	1.11 (0.77-1.5)	0.97 (0.75-1.3)	1.1 (0.9-1.3)	CPR	0.82 (0.61-1.11)	–	1.92 (1.35-2.70)	1.11 (0.84-1.44)	2.12 (1.40-3.33)	1.25 (0.82-1.88)	1.03 (0.69-1.53)	1.03 (0.86-1.21)	0.92 (0.60-1.40)	0.75 (0.59-0.98)	0.61 (0.45-0.82)	0.83 (0.63-1.08)	0.69 (0.52-0.92)	0.61 (0.50-0.75)	–	–	–	0.36 (0.28-0.47)
–	0.48 (0.31-0.74)	0.58 (0.31-1.07)	0.73 (0.46-1.17)	0.65 (0.48-0.89)	0.72 (0.53-0.99)	0.68 (0.47-0.97)	CRD	–	2.32 (1.61-3.33)	1.33 (1.01-1.78)	2.63 (1.63-4.16)	1.51 (1-2.32)	1.25 (0.83-1.88)	1.25 (0.98-1.58)	1.11 (0.72-1.72)	0.91 (0.79-1.07)	0.74 (0.54-1.01)	1.01 (0.75-1.33)	0.84 (0.63-1.13)	0.74 (0.59-0.92)				0.44 (0.33-0.57)
–	0.33 (0.17-0.63)	0.36 (0.16-0.78)	0.45 (0.23-0.89)	0.4 (0.23-0.7)	0.44 (0.25-0.8)	0.42 (0.23-0.77)	0.60 (0.32-1.14)	RD	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
–	0.93 (0.56-1.6)	1.01 (0.51-1.96)	1.3 (0.74-2.2)	1.1 (0.74-1.7)	1.3 (0.82-1.9)	1.18 (0.77-1.85)	1.72 (1.13-2.63)	2.8 (1.4-5.7)	VMPT-VT	0.58 (0.47-0.71)	1.12 (0.68-1.85)	0.65 (0.45-0.95)	0.54 (0.38-0.77)	0.54 (0.39-0.73)	0.48 (0.33-0.70)	0.39 (0.28-0.54)	0.32 (0.22-0.46)	0.43 (0.31-0.60)	0.36 (0.26-0.51)	0.32 (0.24-0.42)	–	–	–	0.19 (0.13-0.26)
–	0.65 (0.42-0.99)	0.71 (0.38-1.3)	0.89 (0.56-1.4)	0.79 (0.58-1.1)	0.88 (0.65-1.2)	0.83 (0.59-1.16)	1.20 (0.90-1.61)	2.0 (1.1-3.7)	0.7 (0.53-0.93)	VMP	1.92 (1.23-3.03)	1.13 (0.83-1.53)	0.93 (0.70-1.25)	0.93 (0.74-1.16)	0.83 (0.60-1.14)	0.68 (0.54-0.87)	0.55 (0.41-0.74)	0.75 (0.57-0.98)	0.63 (0.48-0.83)	0.55 (0.46-0.67)	–	–	–	0.33 (0.25-0.42)
–	0.84 (0.44-1.6)	0.91 (0.75-1.1)	1.2 (0.74-1.8)	1.03 (0.57-1.9)	1.1 (0.65-2.0)	1.06 (0.59-1.89)	1.56 (0.81-2.94)	2.6 (1.1-5.8)	0.91 (0.45-1.8)	1.3 (0.68-2.5)	MPT-T	0.58 (0.34-1.01)	0.48 (0.28-0.81)	0.48 (0.31-0.72)	0.42 (0.24-0.74)	0.35 (0.22-0.54)	0.28 (0.17-0.45)	0.38 (0.24-0.60)	0.32 (0.20-0.51)	0.28 (0.19-0.43)	–	–	–	0.17 (0.10-0.26)
–	0.6 (0.34-1.03)	0.65 (0.32-1.3)	0.82 (0.46-1.5)	0.73 (0.46-1.2)	0.81 (0.51-1.3)	0.77 (0.45-1.23)	1.11 (0.70-1.75)	1.8 (0.88-3.8)	0.64 (0.41-1.01)	0.92 (0.65-1.3)	0.71 (0.34-1.5)	VTd	0.81 (0.60-1.11)	0.81 (0.56-1.20)	0.73 (0.46-1.13)	0.60 (0.40-0.89)	0.48 (0.31-0.74)	0.66 (0.44-0.99)	0.55 (0.37-0.84)	0.49 (0.34-0.70)	–	–	–	0.29 (0.19-0.43)
–	0.58 (0.34-1.0)	0.63 (0.31-1.3)	0.8 (0.45-1.4)	0.71 (0.45-1.1)	0.78 (0.5-1.2)	0.71 (0.45-1.19)	1.07 (0.68-1.69)	1.8 (0.86-3.7)	0.63 (0.4-0.98)	0.89 (0.64-1.3)	0.69 (0.33-1.4)	0.97 (0.69-1.4)	Vd	1 (0.69-1.42)	0.89 (0.58-1.36)	0.73 (0.50-1.06)	0.59 (0.39-0.88)	0.80 (0.54-1.19)	0.67 (0.45-1.01)	0.59 (0.42-0.84)	–	–	–	0.35 (0.24-0.51)
–	0.62 (0.43-0.87)	0.67 (0.38-1.2)	0.84 (0.57-1.2)	0.75 (0.62-0.9)	0.83 (0.69-0.99)	0.78 (0.6-1.0)	1.13 (0.89-1.44)	1.9 (1.04-3.4)	0.66 (0.45-0.96)	0.95 (0.74-1.2)	0.73 (0.4-1.3)	1.03 (0.67-1.6)	1.1 (0.69-1.6)	MPT	0.89 (0.60-1.31)	0.73 (0.60-0.89)	0.59 (0.45-0.76)	0.80 (0.65-1)	0.68 (0.53-0.85)	0.59 (0.52-0.67)	–	–	–	0.35 (0.28-0.43)
–	0.44 (0.26-0.74)	0.47 (0.24-0.93)	0.6 (0.34-1.04)	0.53 (0.34-0.82)	0.59 (0.38-0.91)	0.56 (0.34-0.91)	0.80 (0.52-1.23)	1.3 (0.66-2.7)	0.47 (0.31-0.72)	0.67 (0.49-0.91)	0.52 (0.25-1.1)	0.73 (0.46-1.2)	0.75 (0.47-1.2)	0.71 (0.48-1.1)	VTP	0.82 (0.55-1.21)	0.66 (0.43-1.02)	0.90 (0.59-1.36)	0.75 (0.5-1.14)	0.66 (0.46-0.96)	–	–	–	0.39 (0.26-0.59)
–	0.52 (0.34-0.78)	0.56 (0.31-1.02)	0.71 (0.46-1.1)	0.63 (0.47-0.84)	0.7 (0.53-0.93)	0.67 (0.48-0.91)	0.96 (0.86-1.07)	1.6 (0.84-2.9)	0.56 (0.38-0.83)	0.8 (0.61-1.04)	0.62 (0.33-1.2)	0.87 (0.56-1.3)	0.89 (0.58-1.4)	0.84 (0.68-1.05)	1.2 (0.78-1.8)	CTD	0.80 (0.61-1.05)	1.09 (0.85-1.38)	0.91 (0.71-1.19)	0.81 (0.69-0.94)	–	–	–	0.48 (0.38-0.60)
–	0.29 (0.17-0.5)	0.32 (0.16-0.63)	0.4 (0.23-0.7)	0.36 (0.23-0.55)	0.39 (0.25-0.61)	0.37 (0.23-0.59)	0.54 (0.35-0.83)	0.89 (0.44-1.8)	0.31 (0.19-0.52)	0.45 (0.29-0.69)	0.35 (0.17-0.71)	0.49 (0.28-0.85)	0.5 (0.29-0.87)	0.47 (0.32-0.71)	0.67 (0.39-1.1)	0.56 (0.37-0.86)	TD	1.35 (1.01-1.81)	1.14 (0.84-1.53)	1.01 (0.80-1.25)	–	–	–	0.59 (0.48-0.73)
–	0.59 (0.38-0.91)	0.64 (0.35-1.2)	0.81 (0.51-1.3)	0.72 (0.52-0.99)	0.8 (0.58-1.1)	0.77 (0.53-1.08)	1.09 (0.79-1.51)	1.8 (0.95-3.4)	0.64 (0.41-0.98)	0.91 (0.66-1.2)	0.7 (0.37-1.3)	0.99 (0.62-1.6)	1.01 (0.64-1.6)	0.96 (0.74-1.2)	1.4 (0.87-2.1)	1.1 (0.84-1.5)	2.04 (1.3-3.2)	VAD	0.84 (0.64-1.11)	0.74 (0.61-0.89)	–	–	–	0.43 (0.34-0.56)
–	0.5 (0.32-0.76)	0.54 (0.29-0.99)	0.67 (0.44-1.08)	0.63 (0.46-0.83)	0.67 (0.5-0.91)	0.63 (0.44-0.91)	0.92 (0.68-1.23)	1.52 (0.83-2.86)	0.53 (0.36-0.83)	0.77 (0.59-1.02)	0.59 (0.31-1.12)	0.83 (0.53-1.32)	0.83 (0.56-1.33)	0.83 (0.63-1.03)	1.14 (0.77-1.72)	0.96 (0.73-1.3)	1.70 (1.11-2.63)	0.83 (0.63-1.16)	MD	0.87 (0.72-1.07)	–	–	–	0.52 (0.40-0.67)
–	0.45 (0.31-0.66)	0.49 (0.28-0.87)	0.62 (0.41-0.94)	0.55 (0.44-0.69)	0.61 (0.49-0.76)	0.56 (0.43-0.77)	0.84 (0.68-1.04)	1.4 (0.75-2.5)	0.49 (0.34-0.69)	0.7 (0.57-0.85)	0.54 (0.29-0.99)	0.76 (0.51-1.1)	0.78 (0.52-1.2)	0.74 (0.64-0.84)	1.04 (0.72-1.5)	0.87 (0.73-1.1)	1.5 (1.1-2.3)	0.77 (0.6-0.98)	0.91 (0.74-1.1)	MP	–	–	–	0.59 (0.50-0.69)
–	0.5 (0.32-0.78)	0.55 (0.29-1.02)	0.69 (0.43-1.1)	0.61 (0.44-0.85)	0.68 (0.49-0.94)	0.63 (0.44-0.92)	0.93 (0.68-1.28)	1.5 (0.8-2.9)	0.54 (0.35-0.83)	0.77 (0.56-1.1)	0.6 (0.31-1.2)	0.84 (0.53-1.3)	0.86 (0.54-1.4)	0.82 (0.62-1.1)	1.2 (0.74-1.8)	0.97 (0.72-1.3)	1.7 (1.1-2.7)	0.85 (0.6-1.2)	1.0 (0.74-1.4)	1.1 (0.88-1.4)	VMCP	–	–	–
–	0.43 (0.25-0.74)	0.47 (0.23-0.94)	0.59 (0.34-1.05)	0.61 (0.44-0.85)	0.59 (0.37-0.92)	0.55 (0.33-0.89)	0.80 (0.51-1.26)	1.3 (0.64-2.7)	0.47 (0.27-0.79)	0.67 (0.43-1.04)	0.52 (0.25-1.1)	0.73 (0.41-1.3)	0.75 (0.43-1.3)	0.7 (0.47-1.1)	0.99 (0.58-1.7)	0.84 (0.54-1.3)	1.5 (0.86-2.6)	0.73 (0.46-1.2)	0.87 (0.56-1.4)	0.96 (0.65-1.4)	0.86 (0.63-1.2)	VMCPc	–	–
–	0.52 (0.33-0.8)	0.56 (0.3-1.04)	0.71 (0.44-1.1)	0.63 (0.46-0.88)	0.7 (0.5-0.97)	0.65 (0.45-0.95)	0.96 (0.69-1.33)	1.6 (0.83-3.03)	0.56 (0.37-0.85)	0.8 (0.58-1.1)	0.62 (0.32-1.2)	0.87 (0.54-1.4)	0.89 (0.56-1.4)	0.84 (0.64-1.1)	1.2 (0.77-1.8)	1.0 (0.74-1.4)	1.8 (1.1-2.8)	0.88 (0.62-1.2)	1.0 (0.76-1.4)	1.1 (0.91-1.5)	1.03 (0.97-1.1)	1.2 (0.87-1.6)	NU-based	–
–	0.39 (0.26-0.59)	0.42 (0.23-0.78)	0.54 (0.34-0.84)	0.48 (0.35-0.64)	0.53 (0.39-0.71)	0.49 (0.35-0.69)	0.72 (0.54-0.96)	1.2 (0.63-2.2)	0.42 (0.28-0.63)	0.6 (0.45-0.79)	0.46 (0.25-0.88)	0.65 (0.42-1.02)	0.67 (0.43-1.04)	0.63 (0.5-0.8)	0.89 (0.59-1.4)	0.75 (0.58-0.99)	1.3 (0.87-2.04)	0.66 (0.49-0.9)	0.59 (0.78-1.04)	0.86 (0.71-1.05)	0.78 (0.57-1.1)	0.9 (0.58-1.4)	0.75 (0.55-1.02)	Dex

Fig. 3. OS and PFS HR with 95% CrI for network meta-analysis comparisons over treatments.

VMP in this order). Infectious events presented the most unfavorable results with VAD (the only anthracycline containing regimen among those included), but also frequent among the worst ranked treatments concerning this adverse events were those regimens containing R (RD, Rdc, MPR, VRd and Rd) and daratumumab (Dara-VMP). Hematological events were mostly seen with VAD and melphalan containing regimens combined with T or R. (MPR, MPR-R, MPT and VMPT-VT). The worst profile in gastrointestinal events were seen mainly with combinations of V, T and melphalan containing regimens (Vd, VTd, MD, VMP and VMPT-VT, in this order). Finally, cardiovascular events were more prone to result from older regimens (VAD, VMPC and VMPCc) but also with RD. The regimen with the least attractive safety profile overall was RD.

Dara- VMP	1.29 (1.01-1.66)	1.40 (1.09-1.81)	1.53 (1.21-1.96)	1.35 (1.09-1.69)	1.40 (1.13-1.75)	1.51 (1.19-1.96)	1.14 (0.90-1.47)	1.06 (0.83-1.38)	1.16 (0.90-1.49)	1.42 (1.09-1.85)	1.11 (0.83-1.51)	1.09 (0.83-1.49)	1.61 (1.31-2.0)	1.14 (0.83-1.51)	1.20 (1.05-1.36)	2 (1.53-2.56)	1.63 (1.23-2.17)	1.96 (1.51-2.56)	2.32 (1.92-2.85)	2.63 (2.12-3.22)	2.56 (1.92-3.33)	1.92 (1.51-2.43)	2.94 (2.32-3.84)
1.91 (0.77-4.88)	VRd	1.08 (0.90-1.33)	1.19 (1.01-1.40)	1.05 (0.90-1.20)	1.08 (0.96-1.23)	1.17 (0.99-1.38)	0.90 (0.71-1.06)	0.83 (0.62-1.04)	0.90 (0.71-1.12)	1.09 (0.90-1.35)	0.83 (0.62-1.13)	0.83 (0.62-1.12)	1.25 (1.08-1.42)	0.90 (0.66-1.14)	0.90 (0.76-1.14)	1.53 (1.21-1.92)	1.26 (0.98-1.61)	1.51 (1.20-1.92)	1.81 (1.53-2.12)	2.04 (1.58-2.70)	2 (1.44-2.77)	1.49 (1.20-1.81)	2.32 (1.81-2.85)
3.05 (0.93-9.44)	1.58 (0.49-4.94)	MPR-R	1.09 (0.96-1.25)	1 (0.83-1.13)	1 (0.83-1.16)	1.07 (0.90-1.28)	0.83 (0.66-0.99)	0.76 (0.58-0.95)	0.83 (0.66-1.03)	1.01 (0.90-1.07)	0.76 (0.58-1.04)	0.76 (0.58-1.03)	1.14 (0.97-1.33)	0.83 (0.62-1.05)	0.83 (0.71-1.05)	1.40 (1.12-1.75)	1.14 (0.90-1.47)	1.40 (1.09-1.78)	1.66 (1.42-1.96)	1.88 (1.44-2.43)	1.81 (1.31-2.5)	1.36 (1.09-1.66)	2.12 (1.66-2.63)
6.27 (2.18-18.95)	3.28 (1.19-9.32)	2.07 (0.93-4.86)	MPR	0.90 (0.76-1)	0.90 (0.83-1.02)	1 (0.83-1.12)	0.76 (0.62-0.90)	0.66 (0.55-0.83)	0.76 (0.62-0.90)	0.90 (0.76-1.06)	0.71 (0.55-0.90)	0.71 (0.55-0.90)	1.04 (0.90-1.17)	0.76 (0.58-0.90)	0.76 (0.66-0.90)	1.28 (1.04-1.58)	1.05 (0.83-1.33)	1.28 (1.03-1.58)	1.51 (1.33-1.75)	1.72 (1.35-2.17)	1.66 (1.21-2.27)	1.25 (1.03-1.49)	1.92 (1.56-2.38)
3.07 (1.51-6.61)	1.61 (0.91-2.96)	1.01 (0.38-2.89)	0.49 (0.2-1.19)	Rdc	1.03 (0.97-1.09)	1.12 (0.98-1.28)	0.83 (0.76-0.90)	0.76 (0.62-0.96)	0.83 (0.71-1.04)	1.04 (0.90-1.25)	0.83 (0.62-1.05)	0.83 (0.62-1.05)	1.19 (1.11-1.28)	0.83 (0.66-1.06)	0.90 (0.76-1.05)	1.44 (1.20-1.78)	1.19 (0.97-1.49)	1.44 (1.17-1.78)	1.72 (1.53-1.92)	1.96 (1.56-2.5)	1.88 (1.40-2.56)	1.40 (1.19-1.66)	2.17 (1.78-2.70)
3.28 (1.6-7.02)	1.72 (1.02-3)	1.09 (0.41-3.06)	0.52 (0.22-1.24)	1.07 (0.84-1.35)	Rd	1.07 (0.96-1.21)	0.83 (0.71-0.90)	0.76 (0.62-0.90)	0.83 (0.66-1)	1.01 (0.83-1.20)	0.76 (0.58-1.02)	0.76 (0.58-1.01)	1.14 (1.07-1.23)	0.83 (0.66-1.03)	0.83 (0.71-1.01)	1.40 (1.16-1.69)	1.16 (0.90-1.44)	1.40 (1.13-1.72)	1.66 (1.49-1.85)	1.88 (1.49-2.38)	1.81 (1.35-2.43)	1.36 (1.14-1.61)	2.12 (1.75-2.56)
16.43 (3.54-137.94)	8.53 (1.92-67.28)	5.38 (1.09-46.11)	2.59 (0.6-19.96)	5.23 (1.3-39.36)	4.89 (1.24-36.02)	CPR	0.76 (0.62-0.90)	0.71 (0.55-0.90)	0.76 (0.62-0.90)	0.90 (0.76-1.12)	0.71 (0.55-0.96)	0.71 (0.55-0.96)	1.06 (0.90-1.20)	0.76 (0.58-0.97)	0.76 (0.66-0.97)	1.29 (1.04-1.61)	1.07 (0.83-1.36)	1.29 (1.03-1.63)	1.53 (1.33-1.78)	1.75 (1.35-2.27)	1.69 (1.23-2.32)	1.26 (1.03-1.53)	1.96 (1.56-2.43)
2.53 (0.79-8.05)	1.33 (0.46-3.82)	0.83 (0.22-3.21)	0.4 (0.11-1.42)	0.82 (0.33-1.97)	0.77 (0.3-1.9)	0.15 (0.02-0.81)	RD	0.90 (0.71-1.17)	1.02 (0.83-1.28)	1.25 (1.01-1.53)	1 (0.71-1.28)	1 (0.71-1.28)	1.40 (1.23-1.61)	1 (0.76-1.29)	1.05 (0.83-1.29)	1.72 (1.38-2.17)	1.42 (1.11-1.81)	1.72 (1.35-2.17)	2.04 (1.75-2.43)	2.32 (1.78-3.03)	2.27 (1.63-3.12)	1.66 (1.36-2.08)	2.63 (2.08-3.33)
1.11 (0.78-1.56)	0.58 (0.23-1.46)	0.37 (0.11-1.19)	0.18 (0.06-0.51)	0.36 (0.16-0.75)	0.34 (0.15-0.7)	0.07 (0.01-0.32)	0.44 (0.14-1.39)	VMPT-VT	1.09 (1.01-1.19)	1.35 (1.05-1.72)	1.04 (0.83-1.25)	1.03 (0.83-1.25)	1.51 (1.25-1.85)	1.08 (0.90-1.25)	1.13 (0.90-1.42)	1.85 (1.47-2.38)	1.53 (1.17-2)	1.85 (1.44-2.38)	2.22 (1.85-2.63)	2.5 (1.92-3.33)	2.43 (1.75-3.33)	1.81 (1.44-2.27)	2.77 (2.22-3.57)
1.73 (1.4-2.16)	0.91 (0.37-2.19)	0.57 (0.19-1.82)	0.28 (0.09-0.77)	0.56 (0.27-1.11)	0.53 (0.25-1.05)	0.11 (0.01-0.49)	0.69 (0.22-2.14)	1.56 (1.2-2.06)	VMP	1.21 (0.97-1.56)	1 (0.83-1.12)	0.90 (0.76-1.12)	1.38 (1.14-1.69)	1 (0.90-1.11)	1.03 (0.83-1.28)	1.69 (1.35-2.12)	1.40 (1.08-1.81)	1.69 (1.33-2.17)	2.04 (1.72-2.38)	2.27 (1.75-2.94)	2.22 (1.61-3.03)	1.63 (1.35-2.04)	2.56 (2.04-3.22)
4.05 (1.19-13.26)	2.11 (0.62-6.96)	1.34 (0.91-1.96)	0.64 (0.26-1.55)	1.31 (0.43-3.78)	1.23 (0.41-3.51)	0.25 (0.03-1.28)	1.6 (0.39-6.52)	3.66 (1.06-12.34)	2.34 (0.7-7.54)	MPT-T	0.76 (0.58-1.04)	0.76 (0.58-1.03)	1.13 (0.95-1.35)	0.83 (0.62-1.05)	0.83 (0.66-1.05)	1.38 (1.09-1.75)	1.14 (0.90-1.47)	1.38 (1.08-1.78)	1.63 (1.38-1.96)	1.85 (1.42-2.43)	1.81 (1.29-2.5)	1.35 (1.08-1.66)	2.08 (1.63-2.63)
2.11 (0.62-7.55)	1.1 (0.24-5.13)	0.7 (0.13-3.82)	0.34 (0.07-1.7)	0.68 (0.17-2.9)	0.64 (0.16-2.74)	0.13 (0.01-0.94)	0.84 (0.16-4.55)	1.9 (0.55-6.93)	1.22 (0.37-4.3)	0.52 (0.09-3)	VTd	1 (0.83-1.16)	1.44 (1.13-1.88)	1.04 (0.83-1.28)	1.08 (0.83-1.42)	1.78 (1.35-2.38)	1.47 (1.08-2)	1.78 (1.33-2.38)	2.12 (1.69-2.70)	2.38 (1.75-3.33)	2.32 (1.61-3.33)	1.72 (1.33-2.27)	2.70 (2-3.57)
1.76 (0.53-5.74)	0.92 (0.21-3.82)	0.58 (0.11-3)	0.28 (0.06-1.3)	0.56 (0.14-2.21)	0.53 (0.14-2.06)	0.1 (0.01-0.73)	0.69 (0.14-3.54)	1.59 (0.48-5.25)	1.02 (0.31-3.25)	0.43 (0.08-2.32)	0.83 (0.24-2.79)	Vd	1.47 (1.13-1.88)	1.04 (0.83-1.28)	1.09 (0.83-1.44)	1.81 (1.35-2.38)	1.49 (1.08-2.04)	1.78 (1.33-2.43)	2.12 (1.69-2.70)	2.43 (1.78-3.33)	2.32 (1.63-3.33)	1.75 (1.33-2.27)	2.70 (2.04-3.57)
5.17 (2.68-10.72)	2.72 (1.51-5.07)	1.71 (0.66-4.83)	0.83 (0.35-2.01)	1.69 (1.29-2.23)	1.58 (1.21-2.09)	0.32 (0.04-1.29)	2.06 (0.82-5.29)	4.67 (2.39-9.85)	2.99 (1.61-6.01)	1.28 (0.46-3.89)	2.48 (0.6-9.9)	2.99 (0.79-11.37)	MPT	0.71 (0.55-0.90)	0.76 (0.62-0.90)	1.23 (1.02-1.47)	1.01 (0.83-1.25)	1.21 (1-1.49)	1.44 (1.33-1.61)	1.63 (1.31-2.08)	1.58 (1.19-2.12)	1.19 (1.01-1.38)	1.85 (1.53-2.22)
1.22 (0.73-1.99)	0.64 (0.23-1.72)	0.4 (0.12-1.39)	0.19 (0.06-0.61)	0.4 (0.17-0.89)	0.37 (0.16-0.84)	0.07 (0.01-0.36)	0.48 (0.14-1.62)	1.1 (0.65-1.83)	0.7 (0.45-1.08)	0.3 (0.08-1.09)	0.58 (0.15-2.05)	0.69 (0.2-2.44)	0.23 (0.1-0.5)	VTP	1.05 (0.83-1.35)	1.72 (1.33-2.22)	1.42 (1.06-1.88)	1.72 (1.31-2.27)	2.04 (1.66-2.5)	2.32 (1.75-3.12)	2.22 (1.58-3.12)	1.66 (1.31-2.12)	2.56 (2-3.33)
2.72 (1.2-6.31)	1.43 (0.6-3.38)	0.9 (0.31-2.84)	0.43 (0.15-1.22)	0.89 (0.44-1.71)	0.83 (0.41-1.61)	0.17 (0.02-0.77)	1.08 (0.35-3.25)	2.46 (1.07-5.78)	1.58 (0.71-3.54)	0.67 (0.21-2.27)	1.29 (0.29-5.62)	1.56 (0.38-6.28)	0.53 (0.27-0.96)	2.25 (0.91-5.65)	CTD	1.63 (1.33-2.04)	1.35 (1.06-1.72)	1.63 (1.31-2.04)	1.96 (1.69-2.27)	2.22 (1.72-2.85)	2.12 (1.56-2.94)	1.58 (1.31-1.92)	2.5 (2-3.03)
12.65 (3.49-49.38)	6.62 (1.72-26.15)	4.2 (0.94-19.4)	2 (0.48-8.66)	4.08 (1.18-14.65)	3.82 (1.1-13.63)	0.77 (0.08-4.99)	5 (1.11-23.54)	11.44 (3.06-43.99)	7.3 (2.03-27.95)	3.12 (0.68-15.3)	6 (1.02-35.33)	7.25 (1.26-41.41)	2.42 (0.73-8.32)	10.39 (2.7-42.59)	4.65 (1.29-17.51)	TD	0.83 (0.62-1.06)	1 (0.76-1.26)	1.19 (1.01-1.38)	1.35 (1.04-1.75)	1.29 (0.90-1.78)	1 (0.76-1.19)	1.49 (1.29-1.75)
3.33 (1.51-7.67)	1.75 (0.76-3.99)	1.1 (0.37-3.51)	0.53 (0.19-1.46)	1.08 (0.58-2.02)	1.01 (0.54-1.88)	0.18 (0.018-0.97)	1.32 (0.46-3.87)	3 (1.34-7.07)	1.92 (0.9-4.33)	0.82 (0.26-2.74)	1.59 (0.36-6.79)	1.91 (0.47-7.78)	0.64 (0.36-1.12)	2.74 (1.14-6.89)	1.22 (0.57-2.66)	0.26 (0.07-0.96)	VAD	1.20 (0.90-1.58)	1.44 (1.17-1.75)	1.63 (1.21-2.17)	1.58 (1.12-2.22)	1.17 (0.90-1.49)	1.81 (1.40-2.38)
	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	MD	1.19 (1-1.42)	0.76 (0.55-0.97)	1.35 (1.03-1.75)	1 (0.76-1.20)	1.51 (1.19-1.92)
13.6 (7.74-26.18)	7.16 (3.67-14.5)	4.49 (1.77-12.81)	2.18 (0.9-5.41)	4.44 (2.93-6.89)	4.15 (2.75-6.45)	0.85 (0.11-3.47)	5.44 (2.07-14.72)	12.29 (6.88-24.24)	7.84 (4.68-14.66)	3.36 (1.23-10.19)	6.53 (1.67-24.95)	7.83 (2.15-28.78)	2.63 (1.9-3.71)	11.24 (5.68-23.91)	5 (2.92-9.08)	1.08 (0.34-3.5)	4.1 (2.43-7.13)	–	MP	1.12 (0.90-1.38)	1.09 (0.83-1.44)	0.83 (0.71-0.90)	1.26 (1.07-1.49)
	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	VMCP	1 (0.83-1.16)	0.71 (0.58-0.90)	1.12 (0.83-1.44)
	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	VMCPc	0.76 (0.55-0.98)	1.16 (0.83-1.58)
	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	NU-based	1.56 (1.26-1.92)
29.81 (8.14-119.03)	15.41 (4.07-64.43)	9.79 (2.21-48.42)	4.72 (1.11-21.48)	9.57 (2.83-36.56)	8.98 (2.66-33.7)	1.81 (0.18-12.37)	11.72 (2.6-59.33)	26.83 (7.34-109.26)	17.19 (4.78-67.99)	7.32 (1.56-37.3)	14.12 (2.4-86.29)	17.07 (3-103.19)	5.66 (1.72-20.91)	24.41 (6.34-103.5)	10.85 (3.01-43.28)	2.33 (1.1-5.46)	8.91 (2.46-34.07)	–	2.15 (0.69-7.51)	–	–	–	Dex

Fig. 4. CR and ORR RR with 95% CrI for network meta-analysis comparisons over treatments.

4. Discussion

Treatment for transplant-ineligible MM patients has evolved enormously during the last two decades, resulting in a proliferation of new drugs and protocols. Although this impressively productive pipeline is undoubtedly welcomed by oncologists and hematologists worldwide, the rapid pace in which new technologies are incorporated into practice prevent adequate judgement on what would be the best choice among all alternatives. In this context, the present study aims at defining a new horizon of efficacy stratification for the treatment of MM.

Previous meta-analysis using this same statistical framework were already published. Liu et al. (2017) reported a network meta-analysis (NMA) concerning first-line treatment for transplant-ineligible patients. However, only 19 studies were eventually included in this study, evaluating a total of 7235 patients distributed over 17 different treatments. As the number of included studies were lower than the amount we have evaluated, this report could not assemble a complete network for PFS and therefore had to analyze two separate subnetworks. This study also did not aim at evaluating safety/toxicity outcomes, and therefore could not attain a final balanced ranking including this information. This study did not add information to the report from Weisel et al. (2016) that has performed a NMA comprising a similar context of patients, including 18 RCT and managed to extract HR from Kaplan-Meier curves through a graphical approach. Again, as the number of selected studies were lower, this study had to deal with two separate networks (preventing simultaneous comparisons of all treatments), and no safety/toxicity analysis was pursued. Recently, Blommestein et al. (2019) also published a NMA on first-line regimens for transplant-ineligible MM, but the only reported outcome in the study was PFS and search strategy covered a narrower time period (from 1999 to March, 2016), retrieving only 21 trials and incorporating 24 treatments. Other published meta-analyses found for this specific population had a conventional framework (and therefore were restricted to pairwise comparisons) or are already obsolete.

In our study, we have managed to comprehensively and systematically review current and past medical literature and select all of the already attempted treatment strategies for transplant-ineligible MM patients. As a result, more than 20 different regimens, epitomes of the history of MM management, could be weighed against each other and their use reinforced, challenged or even discouraged. Such an information would only be possible through a mixed treatment comparison meta-analysis structure. Also, this is one of the first network meta-analysis to include daratumumab as one of the analyzed drugs, establishing its place on therapeutic arsenal for frontline treatment of transplant-ineligible patients.

OS and PFS outcomes were unanimous in highlight the importance of R as part of the first line treatment of transplant-ineligible patients. Although V and T were also reasonable options, one seeking for longer survival endpoints should clearly incorporate R maintenance in its management. Daratumumab also has shown a very significant effect on PFS. Accordingly, usage of triplets, containing both R + V, T + V or Daratumumab + V, would also be strongly recommended. Response outcomes underscored the deep effect of V and daratumumab on lowering tumor burden. Safety analysis corroborated current knowledge upon toxicity profile, such as gastrointestinal events in V, thrombotic events in T and R and neurologic events in V and T containing regimens. It also ratified the abandonment of high dose dexamethasone for this set of patients. Considering the balance between efficacy and toxicity, and based on our results, we would recommend against regimens with low to moderate efficacy profile while posing high levels of toxicity such as those with high dose dexamethasone (e.g. RD an TD) and classical regimens (e.g. VAD, MP and CTD). On the other hand, data clearly favor regimens combining two classes of novel agents such as Dara-VMP, VRd and VMPT-VT, however neurological and infectious AE should be monitored with VMPT-VT and Dara-VMP, respectively.

Finally, we have observed that overall best ranked treatments presented the most toxic profiles among regimens, and on the other hand, “safest” treatments (e.g. Dex) showed poor results when concerning survival and response outcomes. This adds to the understanding that effective control comes at the inherent cost of toxicity, and that one seeking for longer survival times will inevitably have some compromise in quality of life. Balance among these parameters for each individual patient is the oncologist/hematologist conundrum.

Regimen	OS	PFS	CR	ORR	Thrombotic AE	Neurological AE	Infectious AE	Hematological AE	Gastrointestinal AE	Cardiovascular AE
Dara-VMP		0.885	0.948	0.941		0.352	0.212	0.388		
VMPT-VT	0.888	0.832	0.908	0.913	0.515	0.095	0.303	0.191	0.303	
VRd	0.960	0.847	0.725	0.663	0.476	0.809	0.516	0.526		0.304
MPR-R	0.867	0.886	0.542	0.541	0.844		0.636	0.057	0.557	0.693
VMP	0.632	0.539	0.737	0.775	0.797	0.209	0.514	0.405	0.217	
VTd	0.526	0.617	0.644	0.842	0.332	0.090	0.621	0.910	0.121	
Rdc	0.827	0.715	0.512	0.595	0.283	0.818	0.305	0.479		0.397
VTP	0.214	0.403	0.872	0.795	0.296	0.094	0.973	0.771	0.561	
MPR	0.699	0.541	0.250	0.399	0.403	0.927	0.340	0.069	0.717	0.766
Rd	0.734	0.445	0.468	0.532	0.453	0.959	0.549	0.570		0.668
MPT-T	0.783	0.876	0.402	0.522	0.727		0.465	0.304	0.350	0.537
MPT	0.568	0.510	0.278	0.349	0.488	0.611	0.761	0.150	0.721	0.581
Vd	0.496	0.478	0.716	0.853	0.311	0.141	0.274	0.927	0.029	
CTD	0.363	0.297	0.566	0.749	0.342	0.493	0.341	0.685	0.577	
CPR	0.798	0.416	0.098	0.425	0.181	0.907	0.634	0.408		0.668
NU-based	0.390			0.233		0.314	0.728	0.250	0.808	
CRD	0.425	0.369						0.302		
VAD	0.520	0.357	0.472	0.360	0.740	0.731	0.014	0.000	0.469	0.190
RD	0.094		0.598	0.818	0.077	0.768	0.077	0.778		0.067
VMCP	0.333			0.055		0.306	0.664	0.710	0.485	0.231
MD	0.325	0.226		0.217			0.330	0.629	0.186	
VMCPc	0.210			0.079		0.240	0.672	0.643	0.678	0.075
TD	0.029	0.126	0.138	0.214	0.502	0.434	0.428	0.927	0.656	0.735
MP	0.209	0.129	0.104	0.122	0.821	0.579	0.754	0.439	0.919	0.786
Dex	0.111	0.006	0.023	0.009	0.913	0.625	0.887	0.981	0.648	0.802

Fig. 5. Ranking of treatments included in network meta-analysis for each outcome.

However, limitations to this study should be also discussed. We assembled a very sensitive search strategy and as a result a great number of references were evaluated. Eventually, more than 250 articles were selected for full text review, but regrettably more than half of these studies were withdrawn due to the lack of HR reporting. HR as an effect measure was only incorporated in MM clinical trials after the 1980s, gradually gaining popularity on the 1990s. Thus, a significant amount of evidence was not included in this meta-analysis because of lack of appropriate information. Still, much of this research comprised older therapeutic options, implying minor impact on reported results. We did not apply graphical extraction techniques (Tierney et al., 2007) due to possible inaccuracy of resulting estimates. Another important aspect is that HR extracted from Cox regression model analyses are susceptible to bias and imprecision as a result of non-compliance with specific model assumptions, a limitation that has been unequivocally demonstrated previously (Batson et al., 2016).

Furthermore, allocation of treatments in therapeutic groups, as we did, is susceptible to doubts regarding equivalence owing to intrinsic specific differences among some of the protocols included arbitrarily in the same group of comparison, although we have based our similarity assumption on known main drugs of each regimen. Thus, variation in treatment effect due to arbitrary allocation should not be disregarded. Instability of effect measures for some outcomes is possibly a result of this shortcoming. Meta-analysis is no more than a heuristic approach to solve a complex problem, and as so, one should consider that heterogeneity and complexity of patients, treatments and study designs could all influence to some point its results.

Similarity assumption over population characteristics, study design and endpoint measurements was considered adequate, but significant heterogeneity was present for some outcomes, and this should also be accounted for while examining the present results. No significant inconsistency was found in examining direct and indirect evidence. For some reports, lack of available data and difficulties in contacting authors had also impacted negatively in completeness of information.

The present systematic review, as far as we are concerned, have compiled the greatest number of studies in a network meta-analysis yet. It was our objective to include older regimens together with novel agents to definitely establish their obsolescence in face of newer protocols. Novel agents, such as Daratumumab, R and V should be essential part of MM current treatment, assembled in triplets or quadruplets and possibly incorporating R in maintenance phase until progression or toxicity. The role of second generation proteasome inhibitors and immunomodulatory drugs within this framework should settled on further prospective studies in newly diagnosed MM patients.

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Ethics committee approval

Not applicable.

Declaration of Competing Interest

Authors have no conflict of interest to disclose.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2019.07.001.

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