Article:
Gay, F, Jackson, G, Rosiñol, L et al. (28 more authors) (2018) Maintenance Treatment and Survival in Patients With Myeloma: A Systematic Review and Network Meta-analysis. JAMA Oncology, 4 (10). pp. 1389-1397. ISSN 2374-2437

https://doi.org/10.1001/jamaoncol.2018.2961

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

Supplementary Appendix

Index

Additional Materials and Methods

Search Strategy

Search strategy for PubMed.gov

Full reference: National Center for Biotechnology Information (NCBI)[Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; [1988] – [cited 2017 Nov 23]. Available from: https://www.ncbi.nlm.nih.gov/
Search interface: http://www.ncbi.nlm.nih.gov/pubmed/
Database: "All Databases"
Dates of search: 25 May 2017 and 20 November 2017

Time segments and search filters:

Date of search	Search syntax	Results
05/25/2017	("multiple myeloma"[MeSH Terms] OR ("multiple"[All Fields] AND "myeloma"[All Fields]) OR "multiple myeloma"[All Fields] OR "myeloma"[All Fields]) AND ("maintenance"[MeSH Terms] OR "maintenance"[All Fields])	1208
11/20/2017	(myeloma[Title/Abstract] AND maintenance[Title/Abstract]) AND ("2017/05/25"[PDAT] : "3000"[PDAT])	41

After the search, we excluded results registered before December 31st 1999.

Search strategy for Cochrane Central Register of Controlled Trials

Full reference: National Center for Biotechnology Information (NCBI)[Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; [1988] – [cited 2017 Nov 23]. Available from: https://www.ncbi.nlm.nih.gov/
Search interface: http://www.ncbi.nlm.nih.gov/pubmed/
Dates of search: 25 May 2017 and 20 November 2017

Time segments and search filters:

Date of search	Search limits	Results
05/25/2017	/myeloma/ AND /maintenance/ keywords in Title, Abstract, Keywords in "Trials"	464
05/25/2017	/myeloma/ AND /maintenance/ keywords in Title, Abstract, Keywords in Cochrane Reviews, Other Reviews, Methods Studies, Technology Assessments, Economic Evaluations, Cochrane Groups.	9
11/20/2017	There are 42 results from 1090489 records for your search on "'myeloma" in Title, Abstract, Keywords and "maintenance" in Title, Abstract, Keywords , Publication Year from 2017 to 2017 in Trials'	42

After the search, we excluded results registered before December 31st 1999.

Additional sources considered

To ensure that no Randomized Controlled Trials (RCTs) were missing, we also considered additional sources: the websites Clinicaltrials.gov and Embase; the reference lists of the most recent meta-analyses and reviews on maintenance in newly diagnosed multiple myeloma (NDMM); and abstracts submitted to the most recent international hematology congresses (ASH 2016-2017, ASCO 2017, EHA 2017). These additional records were added manually to the PRISMA flowchart (main text – Figure 1).

ClinicalTrials.gov. Bethesda (US-MD): National Library of Medicine [cited 2017 Nov 23]. Available from: https://clinicaltrials.gov/.

Biomedical Research – Embase_Elsevier. Amsterdam (NL): Elsevier, c2017 [cited 2017 Nov 23]. Available from: www.elsevier.com/solutions/embase-biomedical-research.

American Society of Hematology [ASH], 59th Annual Meeting and Exposition (December 9-12, 2017). Oral and Poster Abstracts Database [cited 2017 Nov 23]. Published in Blood. 2016;128(22):92-5969. Available from: http://www.bloodjournal.org/content/128/22.

American Society of Hematology [ASH], 59th Annual Meeting and Exposition (December 9-12, 2017). Oral and Poster Abstracts Database [cited 2017 Nov 23]. Available from: https://ash.confex.com/ash/2017/webprogram/start.html. Published in Blood. 2017;130(Suppl 1):92-5599. Available from: http://www.bloodjournal.org/content/130/suppl_1.

American Society of Clinical Oncology, 2017 ASCO Annual Meeting. Oral and Poster Abstracts Database [cited 2017 Nov 21]. Available from: https://iplanner.asco.org/am2017/#/

European Hematology Association, 21st Congress of EHA (June 22-25, 2017). Oral and Poster Abstracts Database [cited 2017 Nov 23]. Available from: https://learningcenter.ehaweb.org/eha/#!*menu=6*browseby=3*sortby=2*ce_id=1181

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

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

Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol. 2015;15(1):58. doi:10.1186/s12874-015-0060-8

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.

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

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

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

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

Additional Statistical Methodology

Hazard Ratio Estimation – Mathematical formula for obtaining HR and SE

Where not available, the HR was estimated using the ratio between probabilities and the 95% CI was estimated using the p-value.[1]
In relation to the ISRCTN68454111 study, we estimated the HR between Thal vs no for the restricted analysis in the ASCT Setting (OS):

$$HR_{OS} = \frac{ln(\pi_{experimental,3})}{ln(\pi_{control,3})} = \frac{ln(0.75)}{ln(0.80)} = 1.289$$

The standard error (SE) was estimated using the 95% CI of HR:

$$SE = \frac{ln(HR_{up}) - ln(HR_{low})}{2\Phi(0.975)}$$

with Φ being the cumulative distribution function of the standard normal distribution.

Where the 95% CI was not available, we estimated the standard error (SE) using the p-value.
In relation to the MM-015 study, we estimated the SE between Len vs no for the primary analysis (PFS):

$$se_{PFS} = |ln(HR_{PFS})| / \frac{-0.717 + \sqrt{0.717^2 - 4 \cdot 0.416 \cdot ln(p_{value\,PFS})}}{2 \cdot 0.416} = 0.323$$

Additional methodologies for data collection and processing

Data collected for each study included publication date, cooperative group that conducted the study, year of initial patient enrollment and of last patient enrolled, number of patients randomized to each arm, pre-maintenance therapy (induction regimen, high-dose therapy and ASCT), maintenance therapy (treatment schedule and duration).

HRs and 95% CIs for PFS were available in published papers or were provided by authors in all but one trial, in which they could be estimated based on the probabilities of PFS and the p-value. For 2 trials, HRs and 95% CIs were available for PFS, but not for OS: in the MM-015, the landmark

analysis on OS was not performed; in the Myeloma XI, the OS analysis data were not yet available at the time of this NMA (Table 3S).

Every p-value <0.001 was considered as equal to 0.001. In case multiple sources reported on one study, the most updated published data were analyzed. When data for the main comparisons were not available or not estimable, the leading cooperative groups provided them.

Network consistency

This network meta-analysis does not involve direct or indirect pairwise comparisons. Consequently, we adopted a consistent model (main text, Figure 1).[2]

Frequentist approach

As the frequentist approach recently showed to be valid when prior distributions are little informative, we adopted also this approach using package "`netmeta`" to confirm the results of the NMA obtained with the Bayesian method.[3]

Additional Results

Study Selection

Overall, 1386 citations were retrieved from the database searches and 8 citations were manually included from other sources. After exclusion of 130 duplicates, 1264 abstracts were screened, 900 of which were excluded from further analysis. A total of 364 full-text articles where then screened, 302 of which were excluded. The main reason for exclusion was study design (n=197); in this category, we also included trials that evaluated maintenance with novel agents, but in which patients who received two different maintenance treatments also underwent different and non-comparable pre-maintenance therapies. The other main reasons were: study phase (n=53) and patient population (n=38); in the latter category, we also included trials evaluating maintenance with novel agents – thalidomide – in a population of patients not previously exposed to novel drugs.

Risk of Bias Assessment

Overall, the included trials presented minimal risk of bias (Table 2S). In the majority of studies, the greatest risks of bias were posed by absence of blinding of participants and study personnel (which is likely due to ethical considerations in the treatment of MM), and absence of blinding of outcome assessment. In the CALGB 100104, the fact that the placebo group included patients who were unblinded and crossed over to lenalidomide maintenance could be an additional bias. There were no incomplete outcomes reported nor selective reports, especially referring to the main comparisons (PFS and OS evaluation). Possible biases deriving from incomplete outcome data and selective reports could have been mainly related to the subgroup analyses. Indeed, the comparisons among different maintenance treatments in the subgroups of interest were not reported in all the trial results, or there was a different risk categorization. To solve this, the necessary data were provided by the different research groups. Another risk of bias is consequent to the lack of baseline data on a subset of patients, particularly data on chromosomal abnormalities, as well as on different cut-off used to define positivity. The main risk of bias is nevertheless related to the subgroup of patients with ISS Stage III disease and high-risk chromosomal abnormalities and it is due to the smaller sample size compared to patients with ISS Stage I/II disease and standard-risk chromosomal abnormalities. However, this reflects the distribution of these prognostic factors in the general population of patients with MM.

Summary of Network Geometry

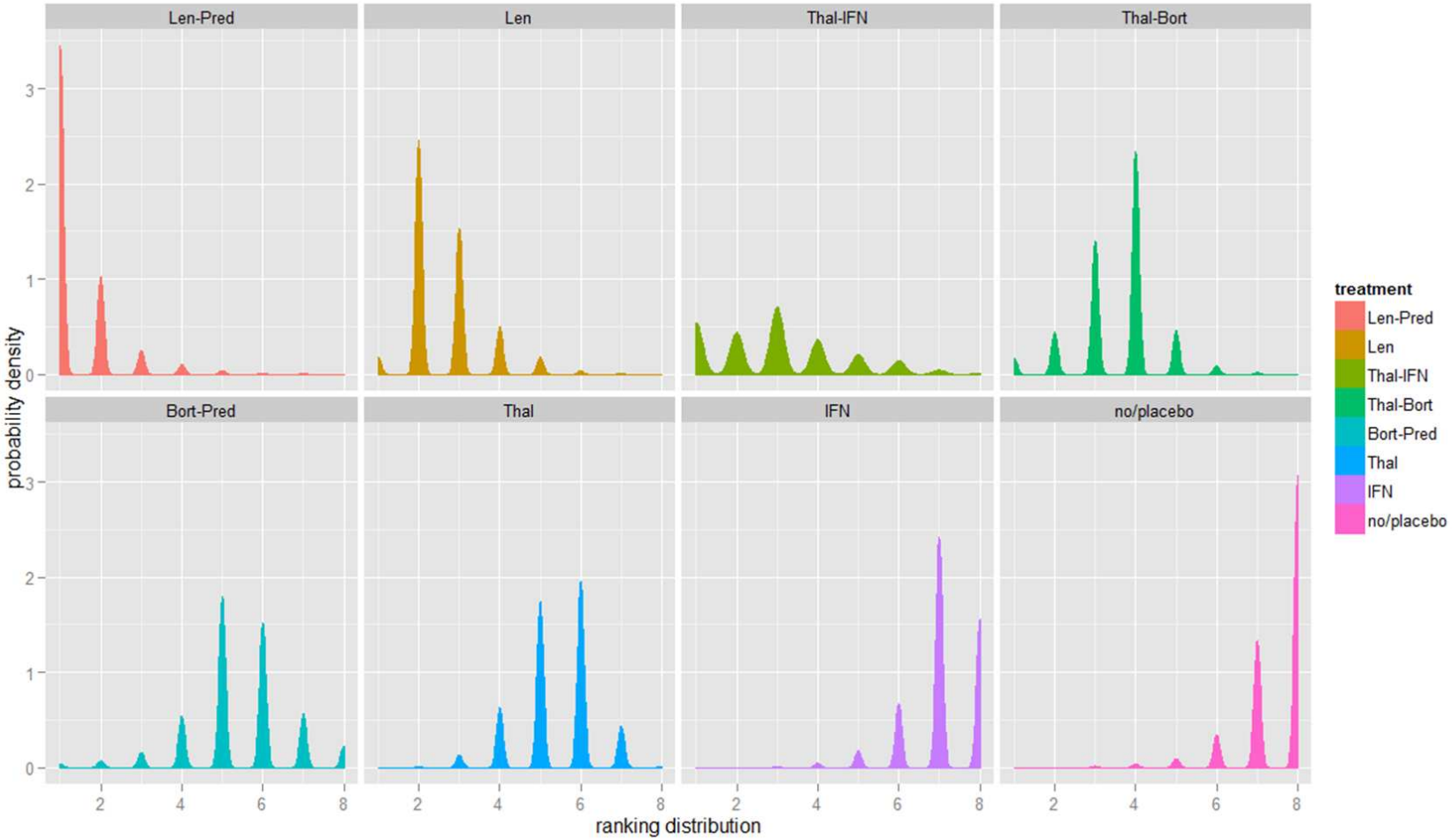
No maintenance/placebo was used as common comparator. The most frequently used comparison was lenalidomide alone vs no maintenance/placebo (5 trials); 2 studies compared lenalidomide-prednisone vs lenalidomide; one trial compared thalidomide vs no maintenance; one trial compared thalidomide-interferon vs interferon; and one trial compared thalidomide-bortezomib vs bortezomib prednisone. One trial provided a multi-arm comparison of three regimens: thalidomide-bortezomib vs thalidomide vs interferon (main text, Figure 1).

Frequentist Approach

The frequentist approach confirmed the results of the main analysis, of the restricted analysis in ASCT patients, of the subgroup analyses according to ISS Stage and chromosomal abnormalities and of the sensitivity analysis.

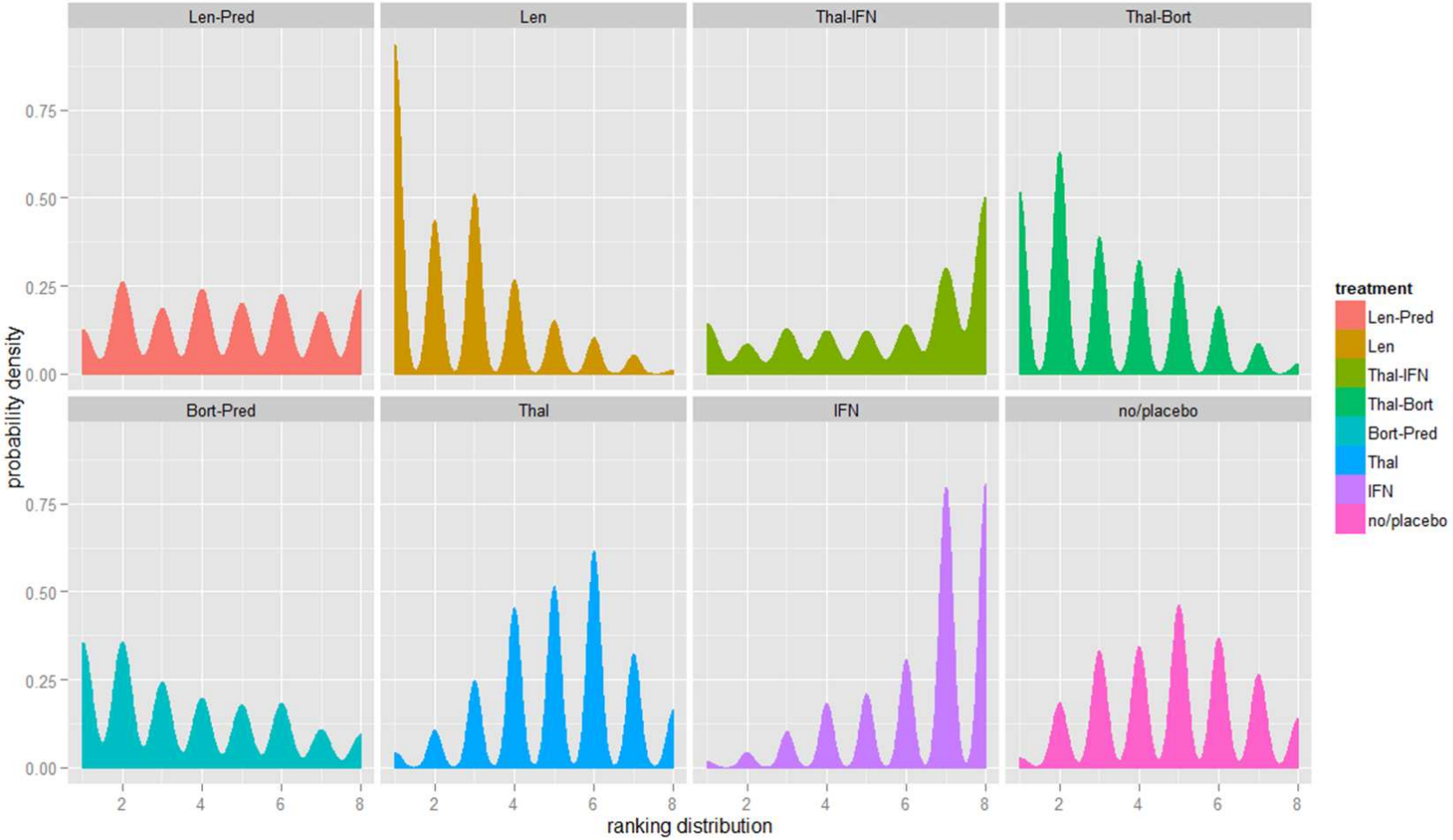
Supplementary Figures

Figure 1S. Primary Analysis Network
Panel A. Ranking distribution for PFS – density plot



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

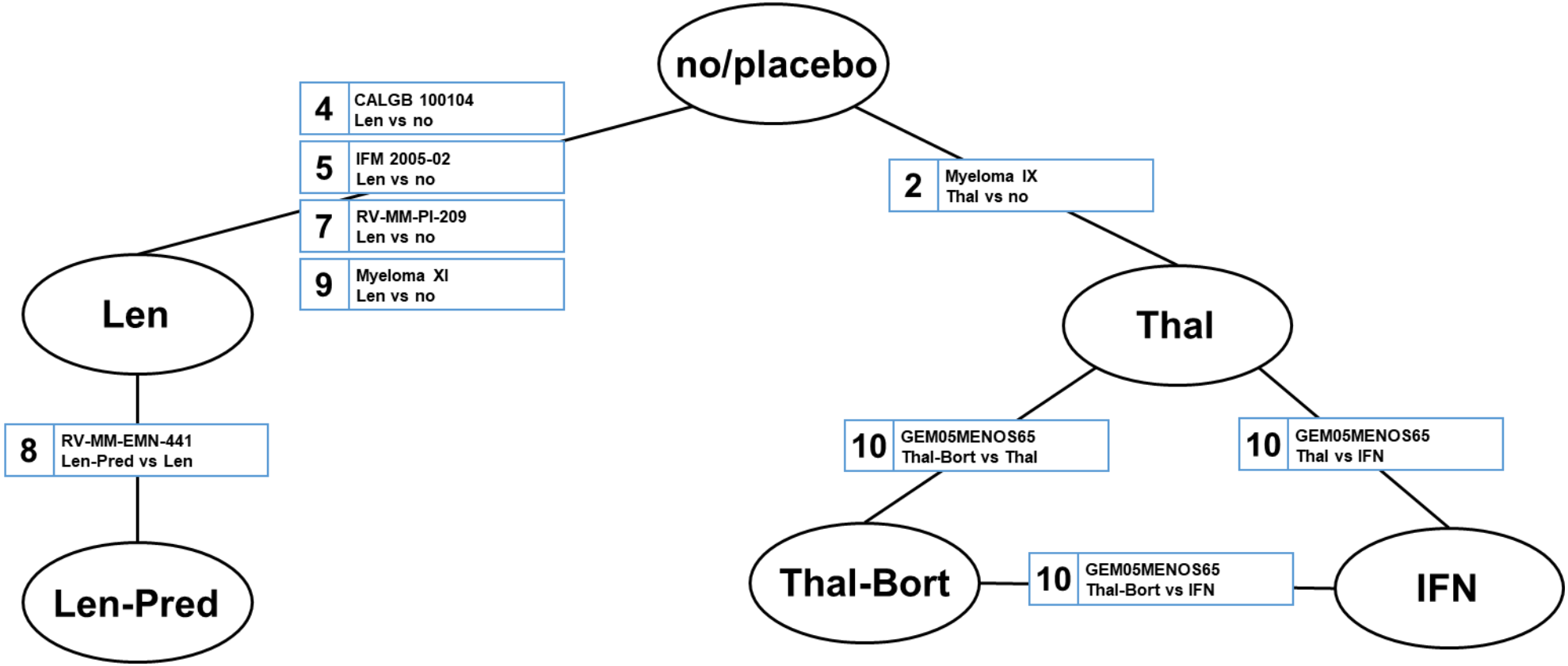
Panel B. Ranking distribution for OS – density plot



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

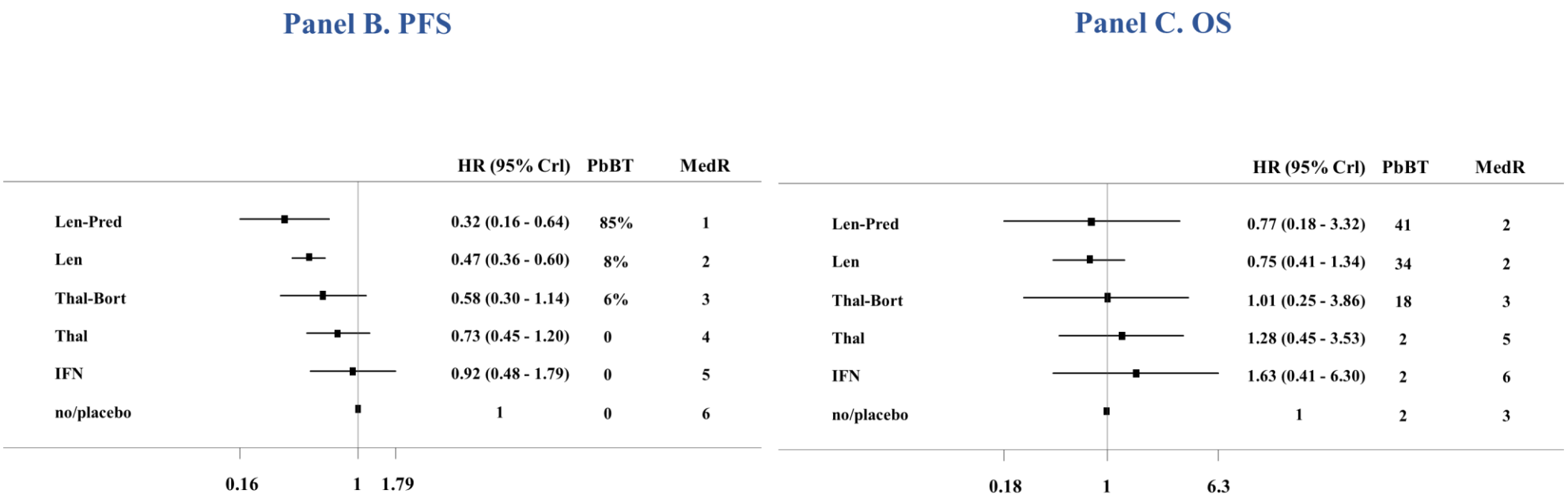
Figure 2S. Restricted Analysis in ASCT Setting

Panel A. Network of included trials



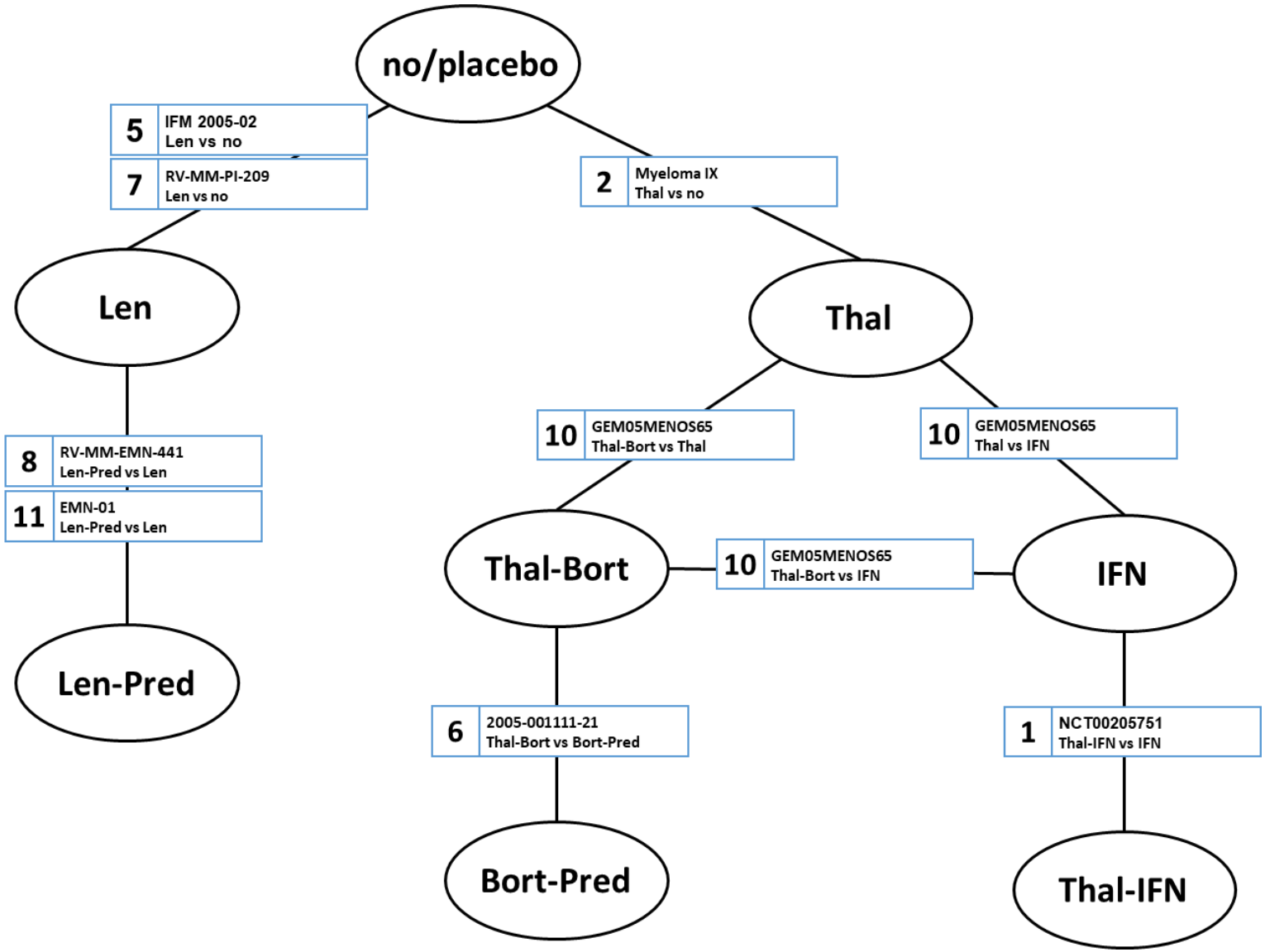
ASCT= Autologous stem cell transplantation; Thal = thalidomide; IFN = interferon; Len = lenalidomide; Bort = bortezomib; Pred = prednisone.

Panel B. Progression-free survival. **Panel C**. Overall Survival



ASCT= Autologous stem cell transplantation; 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.

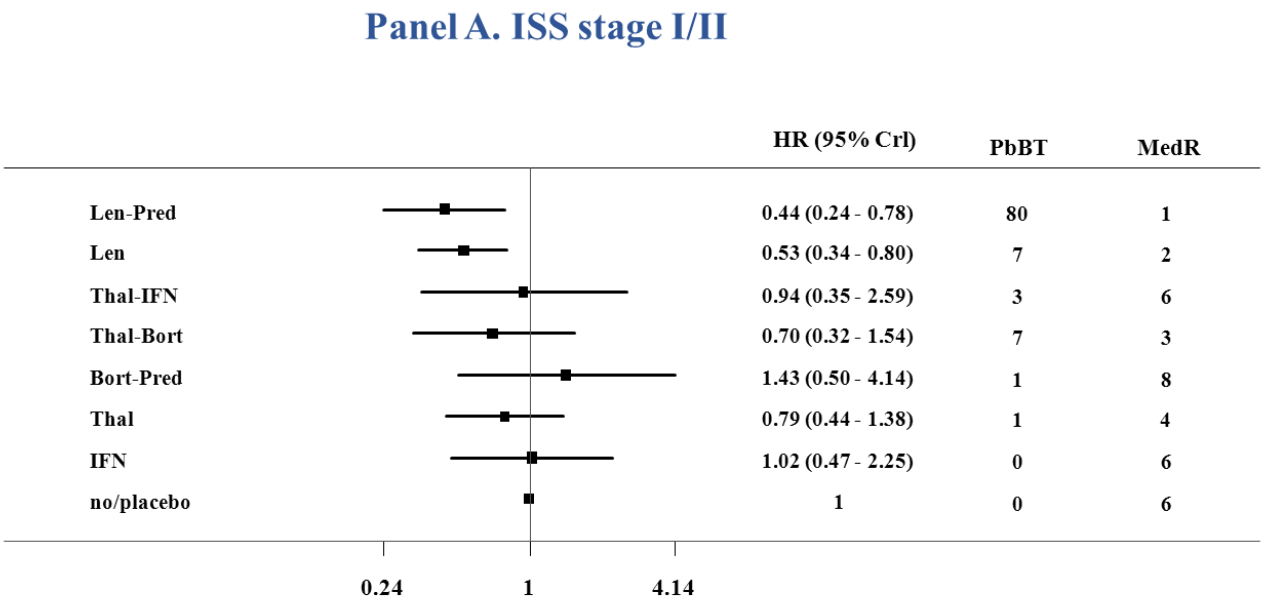
Figure 3S. Subgroup Analyses Network

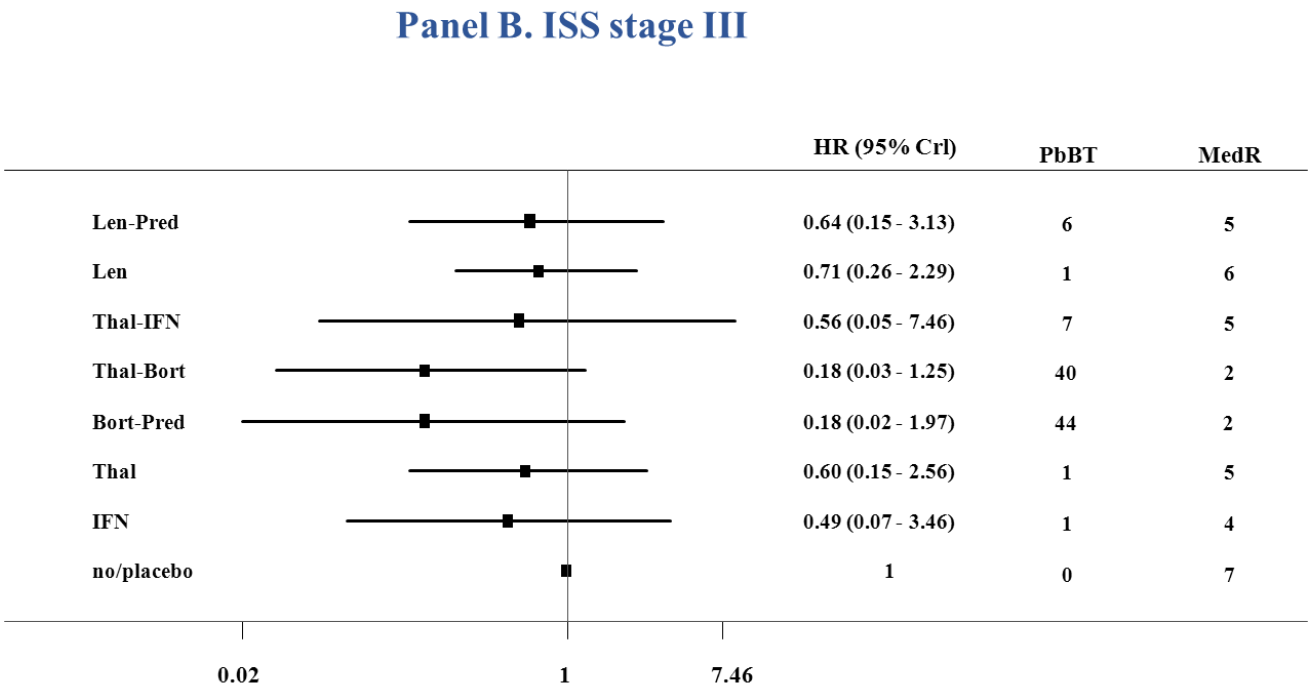


Thal = thalidomide; IFN = interferon; Len = lenalidomide; Bort = bortezomib; Pred = prednisone.

Figure 4S. Subgroup Analysis, Forest Plot of Network Meta-Analysis, PFS Results.

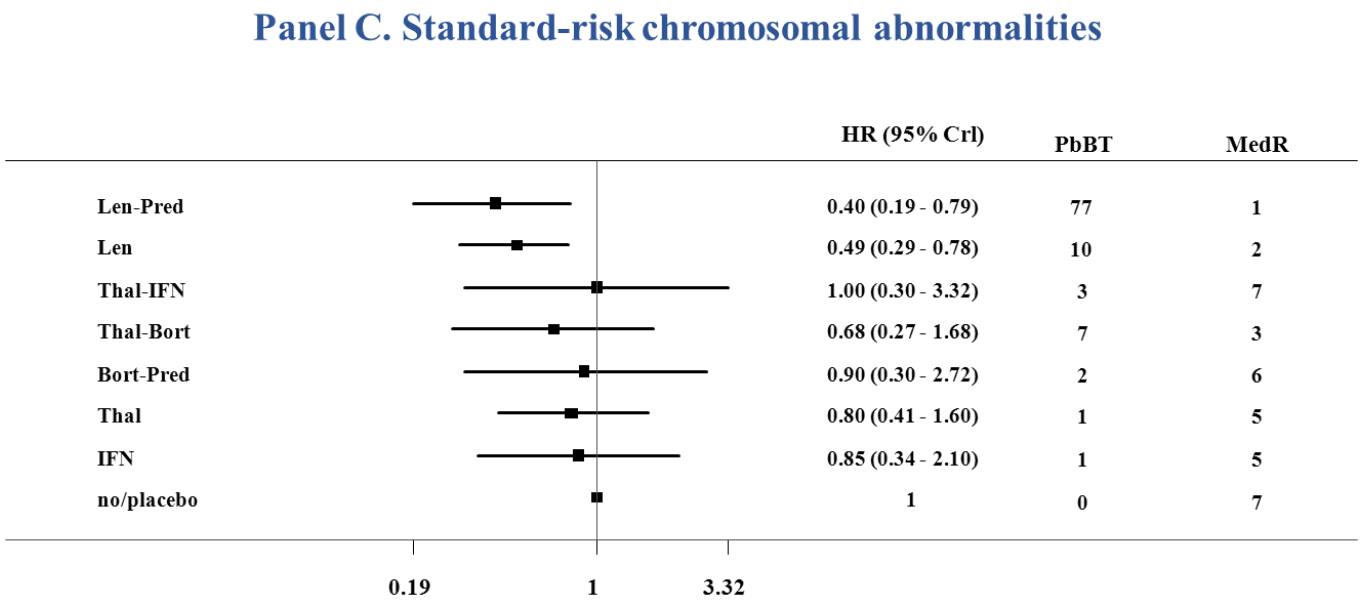
Panel A, ISS Stage I/II. **Panel B**, ISS Stage III.

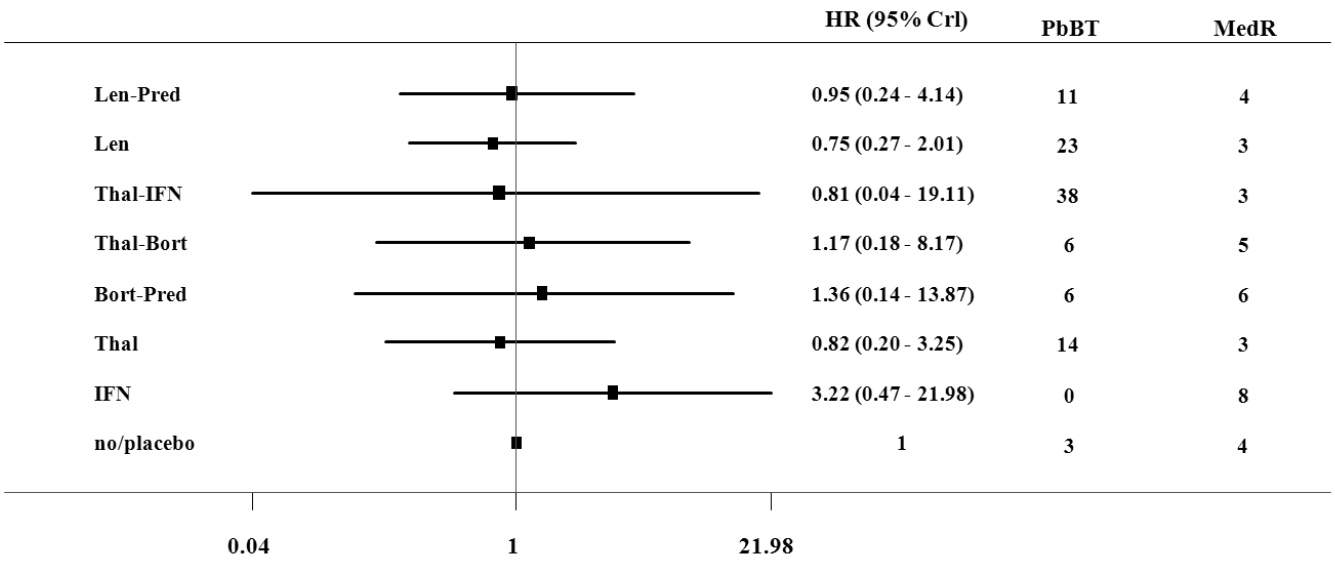




Thal = thalidomide; IFN = interferon; Len = lenalidomide; Bort = bortezomib; Pred = prednisone; PFS= progression-free survival; ISS= International Staging System; PbBT = probability of being the best treatment; MedR = median value of the ranking distribution for all the simulations.

Panel C, standard-risk chromosomal abnormalities. **Panel D**, high-risk chromosomal abnormalities.

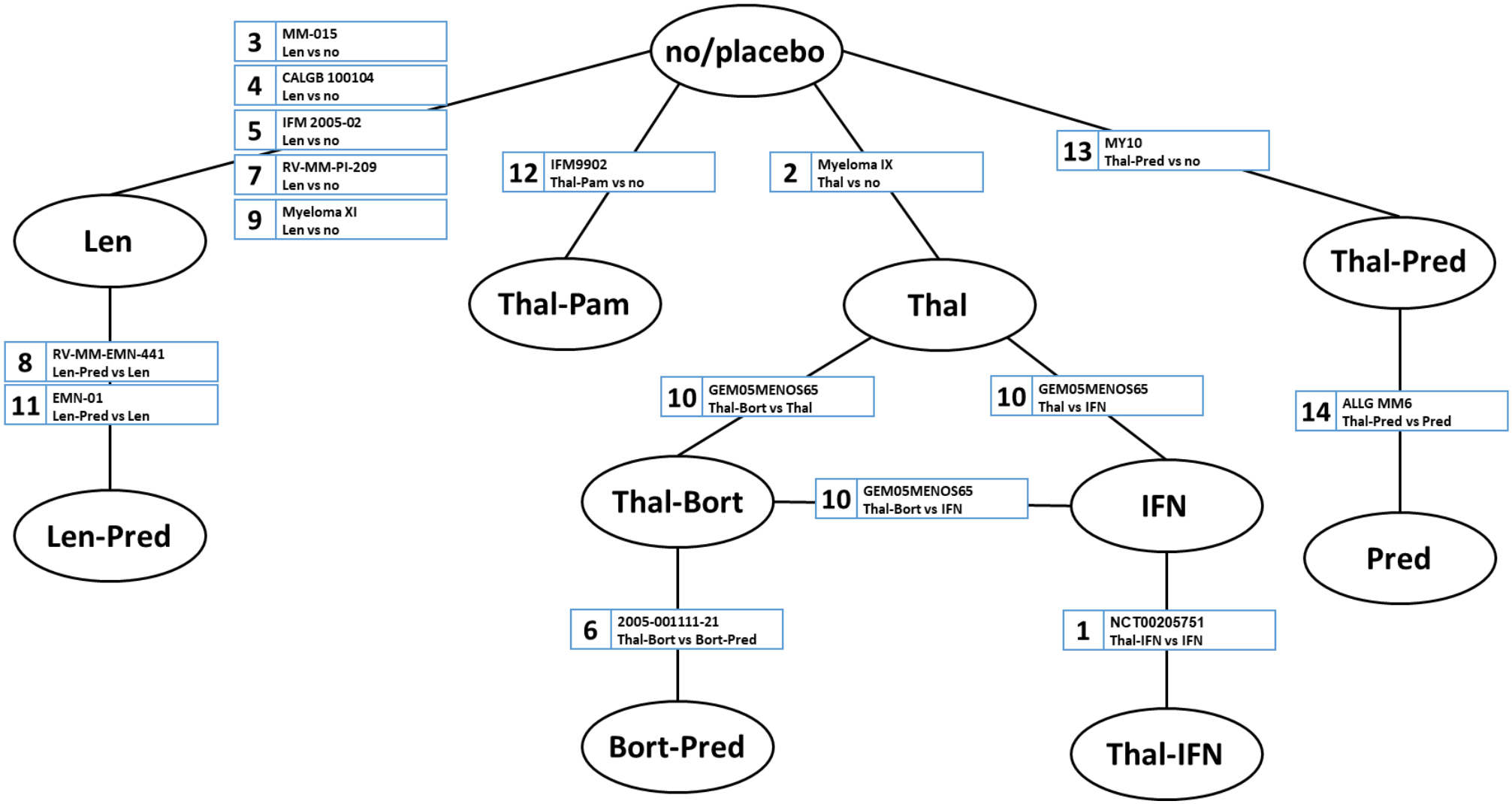




Thal = thalidomide; IFN = interferon; Len = lenalidomide; Bort = bortezomib; Pred = prednisone; PFS= progression-free survival; ISS= International Staging System; PbBT = probability of being the best treatment; MedR = median value of the ranking distribution for all the simulations.

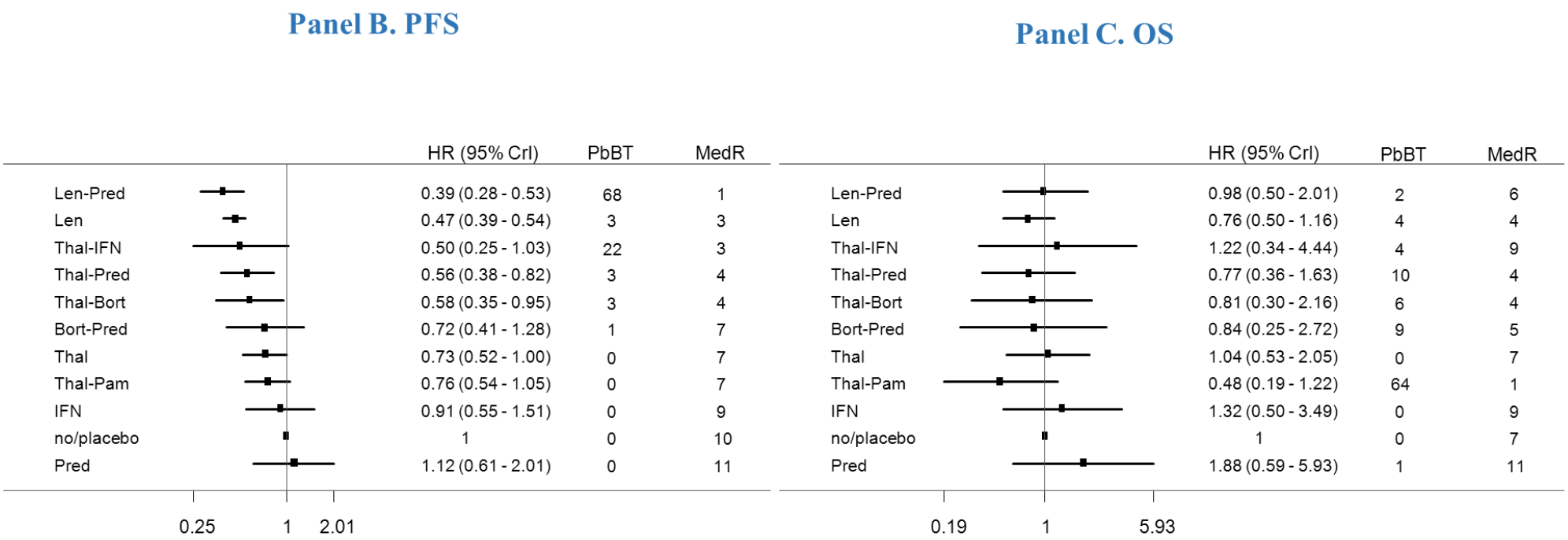
Figure 5S. Sensitivity Analysis

Panel A. Network of included trials



Thal = thalidomide; IFN = interferon; Len = lenalidomide; Bort = bortezomib; Pred = prednisone; Pam = pamidronate; PFS= progression-free survival; OS = overall survival.

Panel B. Progression-free survival. **Panel C.** Overall Survival



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

Supplementary Tables

Table 1S. Selected Trials – Trial characteristics

					Experimental Arm			Control Arm		
ID	**Trial**	**Enrollment Period**	**Median Follow-up (months)**	**Details on Pre-maintenance Therapy**	**Treatment**	**Treatment Schedule**	**Median Duration of Maintenance Therapy (months)**	**Treatment**	**Treatment Schedule**	**Median Duration of Maintenance Therapy (months)**
1	**NCT00205751**[4]	2001-2007	35	TD (50%) MP (50%)	Thal-IFN (N=64)	Thal 200 mg; INF 3 MU Twice a week	13.2	IFN (N=64)	3 MU thrice a week	8.3
2	**Myeloma IX**[5,6]	2003-2007	71°	MP/CTDa (50%); CTD/CVAD-MEL200-ASCT (50%)	Thal (N=408)	50 increased to 100 mg/day if tolerated	7	Observation (N=410)		
3	**MM-015**[7]	2007-2009	30°	MPR	Len (N=88)	10 mg/day 21 days every 28 days	n.a.	Observation (N=94)		
4	**CALGB 100104 (NCI-2009-00439)**[8–10]	2005-2009	91	V and/or T and/or R-based regimens (94%); no V/T/R (6%); Followed by MEL200-ASCT	Len (N=231)	10 mg/day	31	Placebo (N=229)		
5	**IFM 2005-02**[10,11]	2006-2008	98	VD (49%); VAD (45%); Other (6%) Followed by MEL200-ASCT	Len (N=307)	10 mg/day	25*	Placebo (N=307)		
6	**2005-001111-21**[12,13]	2006-2008	72°	VMP (50%) VTP (50%)	Thal-Bort (N=91)	Bort:1.3 mg/sqm on day 1,4,8,11, every 3 months; Thal 50 mg/day	Up to 36 (median n.a.)	Bort-Pred (N=87)	Bort:1.3 mg/sqm on days 1,4,8,11, every 3 months; Pred 50 mg every other day	Up to 36 (median n.a.)
7	**RV-MM-PI-209**[10,14]	2007-2009	63	RD-MPR (50%); RD-MEL200-ASCT (50%)	Len (N=126)	10 mg/day 21 days every 28 days	22.7	Observation (N=125)		
8	**RV-MM-EMN-441**[15]	2009-2011	42	RD-CRD (50%); RD-MEL200-ASCT (50%)	Len-Pred (N=117)	Len 10 mg 21 days every 28 days; Pred 50 mg every other day	29	Len (N=106)	10 mg 21 days every 28	25

					Experimental Arm			Control Arm		
ID	**Trial**	**Enrollment Period**	**Median Follow-up (months)**	**Details on Pre-maintenance Therapy**	**Treatment**	**Treatment Schedule**	**Median Duration of Maintenance Therapy (months)**	**Treatment**	**Treatment Schedule**	**Median Duration of Maintenance Therapy (months)**
9	**Myeloma XI**[16]	2010-2016	28°	CTD/CRD (50%) CTD/CRD-MEL200-ASCT (50%)	Len (N=857)	10 mg/day 21 days every 28 days	12 cycles	Observation (N=693)		
10	**GEM05MENOS65**[17]	2006-2009	59	VBMC/VBAP/B; VTD; TD	Thal-Bort (N=91)	Bort:1.3 mg/sqm day 1,4,8,11, every 3 months; Thal100 mg/day	Up to 36 (median 30)	Thal (N=88)	100 mg/day	Up to 36 (median 19,2)
								α2-IFN (N=92)	1.5-3 MU thrice a week	Up to 36 (median 19,2)
11	**EMN-01**[18,19]	2009-2012	64°	CPR/MPR/RD	Len-Pred (N=198)	Len 10 mg 21 days every 28 days; Pred 25 mg every other day	23	Len (N=204)	Len 10 mg 21 days every 28 days	20

°from enrollment; *mean value; TD = thalidomide-dexamethasone; MP = melphalan -prednisone; MEL200 = melphalan 200 mg/mq; ASCT = Autologous stem cell transplantation; CTDa = Cyclophosphamide-dexamethasone-thalidomide adjusted; CTD = Cyclophosphamide-dexamethasone-thalidomide; CVAD = cyclophosphamide-vincristine-doxorubicin-dexamethasone; MPR = melphalan-prednisone-lenalidomide; VMP = bortezomib-melphalan-prednisone; VTP = bortezomib-thalidomide-prednisone; RD = lenalidomide-dexamethasone; CRD = cyclophosphamide-lenalidomide-dexamethasone; VBMC/VBAP/B = vincristine, BCNU, melphalan, cyclophosphamide, prednisone/vincristine, BCNU, doxorubicin, dexamethasone/bortezomib; CPR = cyclophosphamide-prednisone-lenalidomide; Thal = thalidomide; IFN = interferon; Len = lenalidomide; Bort = bortezomib; Pred = prednisone; VD = bortezomib-dexamethasone; VAD = vincristine-doxorubicin-dexamethasone; V= bortezomib; T= thalidomide; R = lenalidomide; NA = not available.

Table 2S. Risk of bias assessment

Trial ID	Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
1	**NCT00205751**[4]	+	+	-	-	+	+
2	**Myeloma IX**[5,6]	+	+	-	-	+	+
3	**MM-015**[7]	+	+	+	+	+	+
4	**CALGB 100104**[8–10]	+	+	+	+	+	+
5	**IFM 2005-02**[10,11]	+	+	+	+	+	+
6	**2005-001111-21**[12,13]	+	+	-	-	+	+
7	**RV-MM-PI-209**[10,14]	-	+	-	-	+	+
8	**RV-MM-EMN-441**[15]	-	+	-	-	+	+
9	**Myeloma XI**[16]	+	+	-	-	+	+
10	**GEM05MENOS65**[17]	+	+	-	-	+	+
11	**EMN-01**[18,19]	+	+	-	-	+	+

+: low risk of bias; -: high-risk of bias.

Table 3S. Selected Trials – Trial results

			Arm		N° of patients		PFS				OS			
Study ID	**Trial**	**ASCT**	**Experimental**	**Control**	**Experimental**	**Control**	**HR**	**95% CI**	**P value**	**Median**	**HR**	**95% CI**	**P value**	**Median**
1	**NCT00205751**[4]	No	Thal-IFN	IFN	64	64	0.55	(0.36 - 0.86)	0,007	27 vs 13	0.93	(0.53 - 1.66)	0.81	53 vs 51
2	**Myeloma IX**[5,6]	Yes (50%)	Thal	Obs.	408	410	0.72	(0.62 - 0.85)	< 0.001	22 vs 15	1.04	(0.86 - 1.25)	0.70	60 vs 60
3	**MM-015**[7]	No	Len	Placebo	88	94	0.34	(0.18 - 0.64)*	< 0.001	26 vs 7	NA	NA	NA	NA
4	**CALGB 100104**[8–10]	Yes	Len	Placebo	231	229	0.38	(0.29 - 0.50)	< 0.001	39 vs 21	0.61	(0.46 - 0.80)	<0.001	113.8 vs 84.1
5	**IFM 2005-02**[10,11]	Yes	Len	Placebo	307	307	0.53	(0.47 - 0.68)	< 0.001	41 vs 43	0.91	(0.72 – 1.15)	0.44*	NR vs NR
6	**2005-001111-21**[12,13]	No	Thal-Bort	Bort-Pred	91	87	0.80	(0.71 - 0.85)	0.15	24 vs 30	0.97	(0.93 - 1.00)	0.15	40 vs 42
7	**RV-MM-PI-209**[10,14]	Yes (50%)	Len	Obs.	126	125	0.53	(0.36 - 0.57)	< 0.001	33 vs 16	0.81	(0.52 - 1.27)	0.36*	NR vs NR
8	**RV-MM-EMN-441**[15]	Yes (50%)	Len-Pred	Len	117	106	0.84	(0.59 - 1.20)	0,34	38 vs 29	1.53	(0.79 - 2.98)	0.21	NR vs NR
9	**Myeloma XI**[16]	Yes (50%)	Len	Obs.	857	693	0.46	(0.40 - 0.52)	< 0.001	37 vs 19	NA	NA	NA	NA
10	**GEM05MENOS65**[17]	Yes	Thal-Bort	Thal	91	88	0.79	(0.54 - 1.17)	0.25	50.6 vs 40.3	0.78	(0.41 - 1.48)	0.45	NR vs NR
		Yes	Thal	IFN	88	92	0.79	(0.55 - 1.16)	0.24	40.3 vs 32.5	0.79	(0.44 - 1.41)	0.43	NR vs NR
		Yes	Bort-Thal	IFN	91	92	0.63	(0.43 - 0.93)	0.02	50.6 vs 32.5	0.62	(0.33 - 1.14)	0.13	NR vs NR
11	**EMN-01**[18,19]	No	Len-Pred	Pred	198	204	0.82	(0.66 – 1.03)	0.08	22 vs 19	1.13	(0.86 – 1.63)	0.29	72 vs NR

*estimated based on published data, ASCT= Autologous stem cell transplantation; Obs., observation; Thal = thalidomide; IFN = interferon; Len = lenalidomide; Bort = bortezomib; Pred = prednisone; NA = not available; PFS= progression-free survival; OS = overall survival, NR = not reached. Data derived from the original publications and/or provided by the investigators when not available in the publication or in case of updated data.

Table 4S. Restricted analysis: ASCT trials. Trial results.

		Arm		Nº of pts		PFS		OS	
Study ID	**Trial**	**Experimental**	**Control**	**Experimental**	**Control**	**HR**	**95% CI**	**HR**	**95% CI**
2	**Myeloma IX**[5,6]	Thal	Observation	245	247	0.74	(0.60 - 0.90)	1.29	(0.83 – 1.99)*
4	**CALGB 100104**[8–10]	Len	Placebo	231	229	0.38	(0.29 - 0.50)	0.61	(0.46 - 0.80)
5	**IFM 2005-02**[10,11]	Len	Placebo	307	307	0.53	(0.47 - 0.68)	0.91	(0.72 – 1.15)
7	**RV-MM-PI-209**[10,14]	Len	Observation	67	68	0.50	(0.31 - 0.80)	0.72	(0.37 - 1.38)
8	**RV-MM-EMN-441**[15]	Len-Pred	Len	60	57	0.68	(0.41 – 1.13)	1.03	(0.37 – 2.84)
9	**Myeloma XI**[16]	Len	Observation	451	327	0.47	(0.39 - 0.57)	NA	NA
10	**GEM05MENOS65**[17]	Thal-Bort	Thal	91	88	0.79	(0.54 - 1.17)	0.78	(0.41-1.48)
		Thal	IFN	88	92	0.79	(0.55 - 1.16)	0.79	(0.44-1.41)
		Thal-Bort	IFN	91	92	0.63	(0.43 - 0.93)	0.62	(0.33-1.14)

*estimated based on published data, ASCT= Autologous stem cell transplantation; Thal = thalidomide; IFN = interferon; Len = lenalidomide; Bort = bortezomib; Pred = prednisone; NA = not available; PFS = progression-free survival; OS = overall survival. Data derived from the original publications and/or provided by the investigators when not available in the publication or in case of updated data.

Table 5S. Subgroup Analysis: prognostic factors. Trial results, HR and 95% CI for progression-free survival

		Arm		ISS Stage I/II		ISS Stage III		Standard-risk cytogenetic		High-risk cytogenetic	
Study ID	**Trial**	**Experimental**	**Control**	**No of pts (%)**	**HR (95% CI)**	**No of pts (%)**	**HR (95% CI)**	**No of pts (%)**	**HR (95% CI)**	**No of pts (%)**	**HR (95% CI)**
1	**NCT00205751**[4]	Thal-IFN	IFN	112 (88%)	0.92 (0.63-1.34)	12 (13%)	1.15 (0.41–3.18)	60 (91%)	1.17 (0.69 –1.96)	6 (9%)	0.25 (0.03- 2.37)
2	**Myeloma IX**[5,6]	Thal	Observation	476 (65%)	0.79 (0.64–0.96)	254 (35%)	0.60 (0.45–0.79)	370 (82%)	0.81 (0.65–1.02)	82 (18%)	0.81 (0.48-1.39)
5	**IFM 2005-02**[10,11]	Len	Placebo	482 (81%)	0.56 (0.45–0.68)	112 (19%)	0.52 (0.34–0.79)	427 (84%)	0.53 (0.42–0.66)	81 (16%)	0.68 (0.41-1.14)
6	**2005-001111-21**[12,13]	Thal-Bort	Bort-Pred	125 (70%)	0.49 (0.23–0.63)	53 (30%)	1.00 (0.94-1.11)	132 (82%)	0.75 (0.69–0.84)	28 (18%)	0.86 (0.83-0.91)
7	**RV-MM-PI-209**[10,14]	Len	Observation	216 (87%)	0.48 (0.34–0.88)	33 (13%)	1.24 (0.54-2.87)	104 69%	0.41 (0.25-0.67)	46 31%	0.83 (0.48-1.44)
8	**RV-MM-EMN-441**[15]	Len-Pred	Len	197 (88%)	0.83 (0.57–1.21)	26 (12%)	0.77 (0.29-2.05)	117 (74%)	0.82 (0.49-1.36)	41 (26%)	2.07 (0.97-4.42)
10	**GEM05MENOS65**[17]	Thal-Bort	Thal	226 84%	0.90 (0.58–1.38)	44 16%	0.29 (0.11–0.75)	195 (85%)	0.84 (0.54-1.31)	35 (15%)	1.43 (0.45-4.52)
		Thal	IFN		0.77 (0.50–1.17)		1.19 (0.50–2.83)		0.94 (0.60-1.45)		0.26 (0.08-0.77)
		Thal-Bort	IFN		0.69 (0.45–1.05)		0.38 (0.14–0.95)		0.79 (0.50-1.24)		0.36 (0.13-0.97)
11	**EMN-01**[18,19]	Len-Pred	Pred	310 (77%)	0.81 (0.62–1.05)	92 (23%)	0.97 (0.61–1.53)	252 (78%)	0.82 (0.62-1.09)	73 (22%)	0.92 (0.56-1.51)

ISS= International Staging System; Thal = thalidomide; IFN = interferon; Len = lenalidomide; Bort = bortezomib; Pred = prednisone. Data derived from the original publications and/or provided by the investigators when not available in the publication or in case of updated data. % were calculated on n° of patients whose data were available.

References

1. Altman DG, Bland JM. How to obtain the P value from a confidence interval. BMJ. 2011;343:d2304. doi:10.1136/BMJ.D2304
2. 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
3. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol. 2015;15(1):58. doi:10.1186/s12874-015-0060-8
4. 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
5. 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
6. 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
7. 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
8. 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
9. 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
10. 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
11. 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
12. 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
13. 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
14. 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
15. 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
16. 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.
17. 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
18. 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.
19. 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