Lenalidomide-based induction and maintenance in elderly newly diagnosed multiple myeloma patients: updated results of the EMN01 randomized trial

Sara Bringhen,[1] Mattia D'Agostino,[1] Laura Paris,[2] Stelvio Ballanti,[3] Norbert Pescosta,[4] Stefano Spada,[1] Sara Pezzatti,[5] Mariella Grasso,[6] Delia Rota-Scalabrini,[7] Luca De Rosa,[8] Vincenzo Pavone,[9] Giulia Gazzera,[1] Sara Aquino,[10] Marco Poggiu,[1] Armando Santoro,[11] Massimo Gentile,[12] Luca Baldini,[13] Maria Teresa Petrucci,[14] Patrizia Tosi,[15] Roberto Marasca,[16] Claudia Cellini,[17] Antonio Palumbo,[1]° Patrizia Falco,[18] Roman Hájek,[19,20] Mario Boccadoro[1] and Alessandra Larocca[1]

[1]Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy; [2]Hematology and Bone Marrow Transplant Unit, Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy; [3]Sezione di Ematologia e Immunologia Clinica, Ospedale Santa Maria della Misericordia, località Sant'Andrea delle Fratte, Perugia, Italy; [4]Reparto Ematologia e Centro TMO, Ospedale Centrale, Bolzano, Italy; [5]Divisione di Ematologia, Ospedale S. Gerardo, Monza, Italy; [6]Azienda Ospedaliera S. Croce-Carle, Cuneo, Italy; [7]Medical Oncology, Candiolo Cancer Institute FPO-IRCCS, Candiolo, Italy; [8]Hematology and Stem Cell Transplantation Unit, Az. Osp. S. Camillo-Forlanini, Rome, Italy; [9]UOC Ematologia e Trapianto, Az. Osp. C. Panico, Tricase (Lecce), Italy; [10]Ematologia e Centro Trapianti, IRCCS Ospedale Policlinico San Martino, Genova, Italy; [11]Istituto Clinico Humanitas, Humanitas University, Rozzano-Milano, Italy; [12]UOC Ematologia AO Cosenza, Cosenza, Italy; [13]UOC Ematologia, Università degli Studi di Milano, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Milano, Italy; [14]Hematology, Azienda Policlinico Umberto I, Roma, Italy; [15]UO Ematologia, Ospedale di Rimini, AUSL della Romagna, Rimini, Italy; [16]Hematology Unit, Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Modena, Italy; [17]U.O. Ematologia, Ospedale Santa Maria delle Croci, Ravenna, Italy. [18]SSD Ematologia, ASLTO4, Ospedali di Chivasso Cirié Ivrea, Italy; [19]Department of Hematooncology, University Hospital Ostrava, Ostrava, Czech Republic and [20]Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic

°AP is currently a GlaxoSmithKline AG employee.

 doi:10.3324/haematol.2019.226407

Received: May 20, 2019.

Accepted: September 26, 2019.

Pre-published: October 3, 2019.

Correspondence: *SARA BRINGHEN* - sarabringhen@yahoo.com

Lenalidomide-based induction and maintenance in elderly newly diagnosed multiple myeloma patients

Updated results of the EMN01 randomized trial

Supplementary appendix

Additional procedures: antithrombotic prophylaxis

Antithrombotic prophylaxis was mandatory: aspirin or low-molecular weight heparin or warfarin were permitted at physician's discretion.

Endpoints and assessments

The primary endpoint was progression-free survival (PFS); secondary endpoints included response rate, time to the first evidence of response, overall survival (OS), and incidence of grade ≥3 adverse events (AE).

Response and progression were assessed after each cycle during induction and then every 6 to 8 weeks until disease progression (PD). After PD was confirmed, patients were followed every 90 days to document subsequent treatment and survival status. All time to events were calculated from the time of random assignment to induction treatment arms for the analysis on induction treatment. All time to events in the analysis of maintenance treatment were calculated from the random assignment to maintenance treatment arms. PFS was calculated from the time of random assignments until the date of progression, relapse, death as a result of any cause, or the date the patient was last known to be in remission. Time to next treatment (TNT, post-hoc analysis) was calculated from the time of random assignments until the date the subsequent myeloma therapy was administered at progression or relapse, the date of death from any cause, or the date the patient was last known to be in remission. Progression-free survival 2 (PFS-2, post-hoc analysis) was calculated from the time of random assignments until the date of second progression or death for any cause or the date the patient was last known to be alive. PFS-2 was evaluated in order to detect possible negative effects of a maintenance-containing first-line treatment on the subsequent line of therapy.[1] OS was calculated from the time of random assignments until the date of death for any cause or the date the patient was last known to be alive. The response to treatment was defined by using International Uniform Response Criteria.[2] All AE were assessed at each visit and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (v3.0).[3]

Statistical analysis: supplementary information

For the comparisons between (i) doublet *vs.* triplet regimens, (ii) melphalan-prednisone-lenalidomide (MPR) *vs.* lenalidomide-dexamethasone (Rd) and (iii) MPR *vs.* cyclophosphamide-prednisone-lenalidomide (CPR), time-to-event data were analyzed with Cox proportional hazards models adjusted for International Staging System (ISS) stage, cytogenetic risk defined by fluorescence *in situ* hybridization (FISH), and age. Cox models for maintenance comparison between lenalidomide-prednisone (RP) and lenalidomide (R) were adjusted for induction treatment, ISS stage, cytogenetic risk defined by FISH, and age. A post-hoc analysis according to patient frailty was performed using interaction terms between treatment arm and International Myeloma Working Group (IMWG) frailty score (fit, intermediate-fit and frail patients).

Supplementary table S1. Geriatric score to define patients' frailty status

Parameter	Score
Age	
≤75 years	0
76-80 years	1
>80 years	2
ADL	
>4	0
≤4	1
IADL	
>5	0
≤5	1
CCI	
≤1	0
≥2	1
Patient status	**Additive total score**
Fit	0
Intermediate-fit	1
Frail	≥2

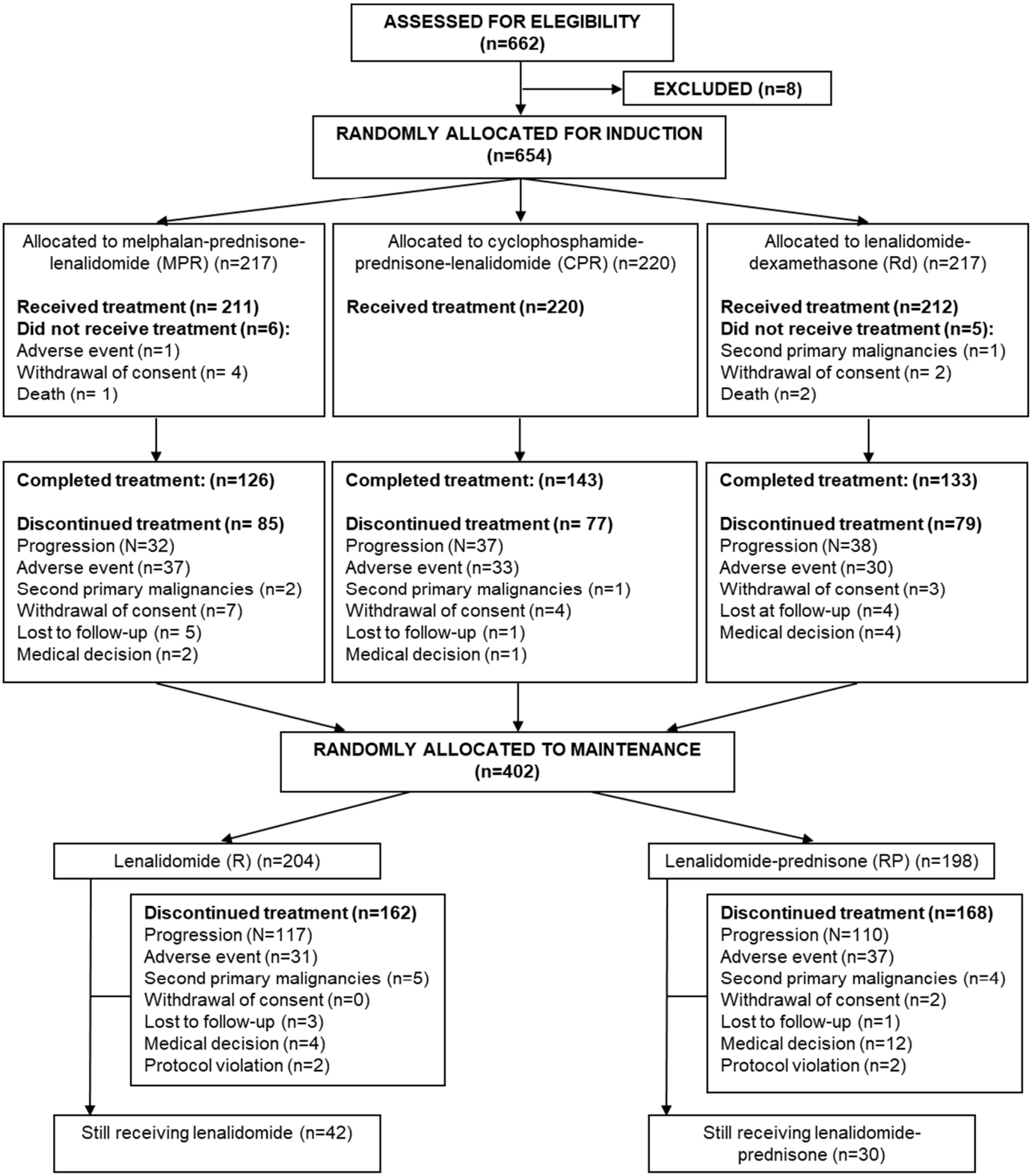
ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; CCI, Charlson Comorbidity Index.

Supplementary table S2. Grade ≥3 hematologic adverse events, non-hematologic adverse events, treatment discontinuation due to adverse events and toxic deaths in the induction and maintenance population according to patients' frailty status

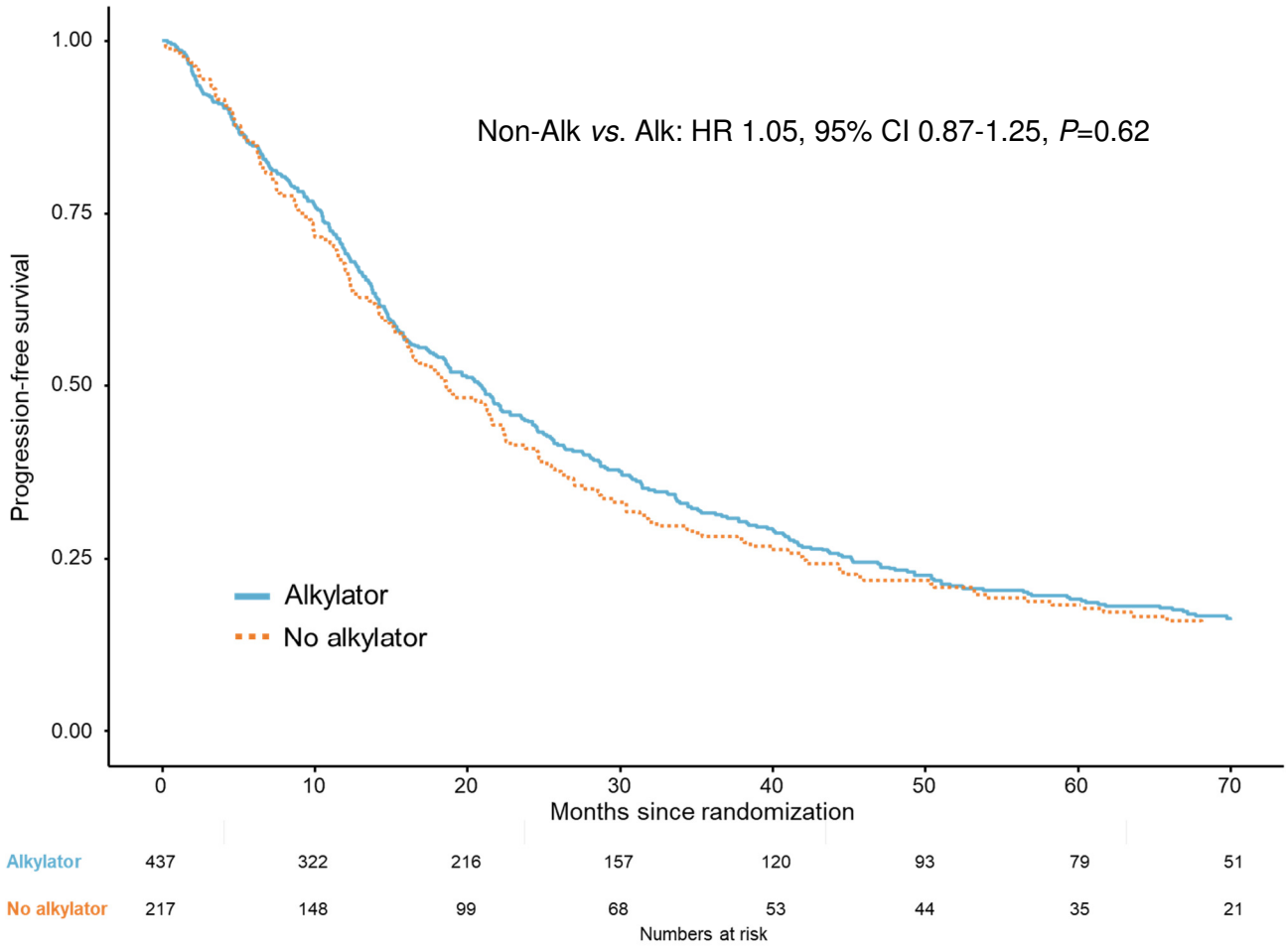
Trial population (n)	**Induction (n=643)**				**Maintenance (n=402)**			
Frailty Score class (n)	Fit (280)	Int (202)	Frail (161)	Chi-squared test	Fit (192)	Int (121)	Frail (89)	Chi-squared test
Hematologic AE G ≥3, n (%)	119 (43)	82 (41)	74 (46)	Int *vs.* Fit: NS Frail *vs.* Fit: NS	34 (18)	19 (16)	19 (21)	Int *vs.* Fit: NS Frail *vs.* Fit: NS
Non-hematologic AE G ≥3, n (%)	68 (24)	59 (29)	68 (42)	Int *vs.* Fit: NS Frail *vs.* Fit: p < 0.01	24 (13)	14 (12)	12 (13)	Int *vs.* Fit: NS Frail *vs.* Fit: NS
Discontinuation due to AE, n (%)	27 (10)	35 (17)	38 (24)	Int *vs.* Fit: p = 0.02 Frail *vs.* Fit: p < 0.01	30 (16)	25 (21)	22 (25)	Int *vs.* Fit: NS Frail *vs.* Fit: p=0.10
Death due to AE, n (%)	3 (1)	3 (1)	13 (8)	Int *vs.* Fit: NS Frail *vs.* Fit: p<0.01	4 (2)	3 (2)	6 (7)	Int *vs.* Fit: NS Frail *vs.* Fit: p = 0.10

AE, adverse events; G, grade; n, number; %, percentage; Int, intermediate-fit; NS, p>0.10.

Supplementary figure S1. Patient disposition



Supplementary figure S2. Progression-free survival according to alkylator-containing induction treatment (MPR + CPR, "Alk") *vs.* alkylator-free induction treatment (Rd, "Non-Alk")

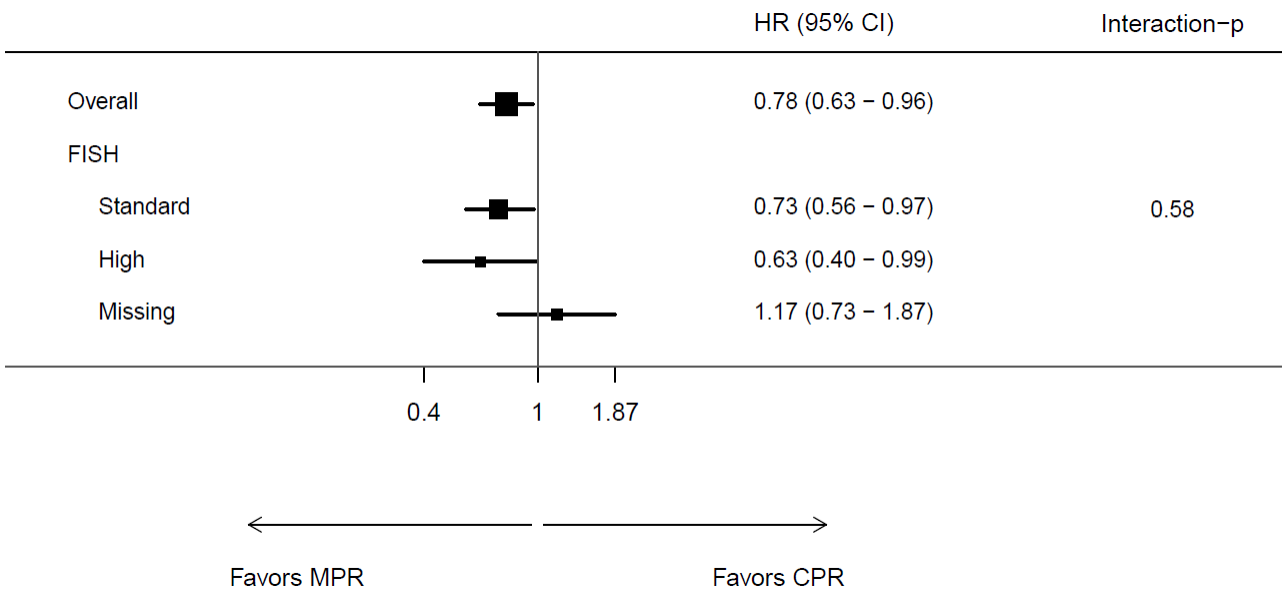


MPR, melphalan-prednisone-lenalidomide; CPR, cyclophosphamide-prednisone-lenalidomide; Rd, lenalidomide-dexamethasone; Alk, alkylator-containing induction treatment; Non-Alk, alkylator-free induction treatment; HR, hazard ratio; CI, confidence interval; *P*, p-value.

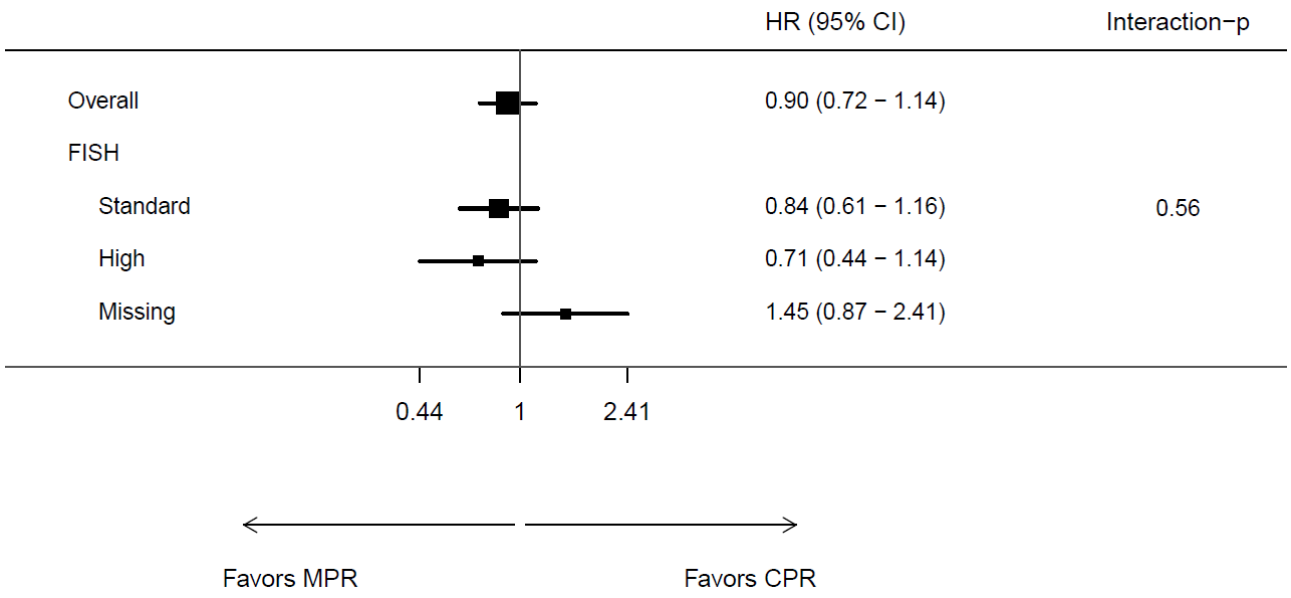
Supplementary figure S3. Induction treatment – Subgroup analysis according to cytogenetic risk

MPR vs. CPR (PFS, PFS-2 and OS); MPR vs. Rd (PFS, PFS-2 and OS).

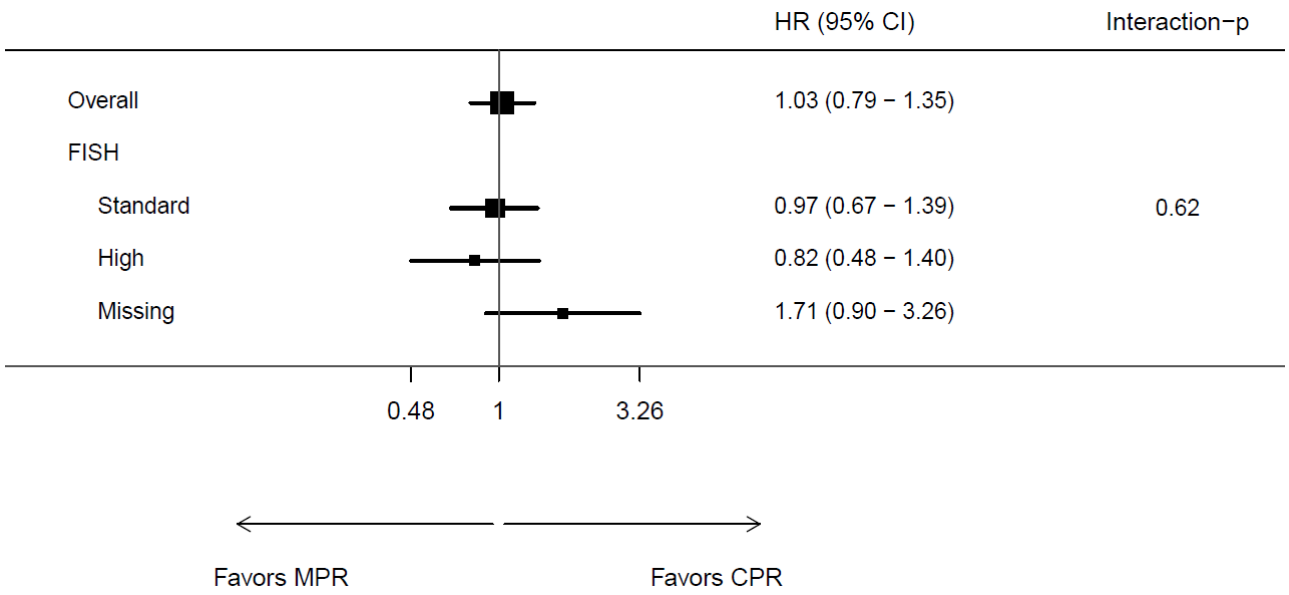
S3a. MPR *vs.* CPR - PFS



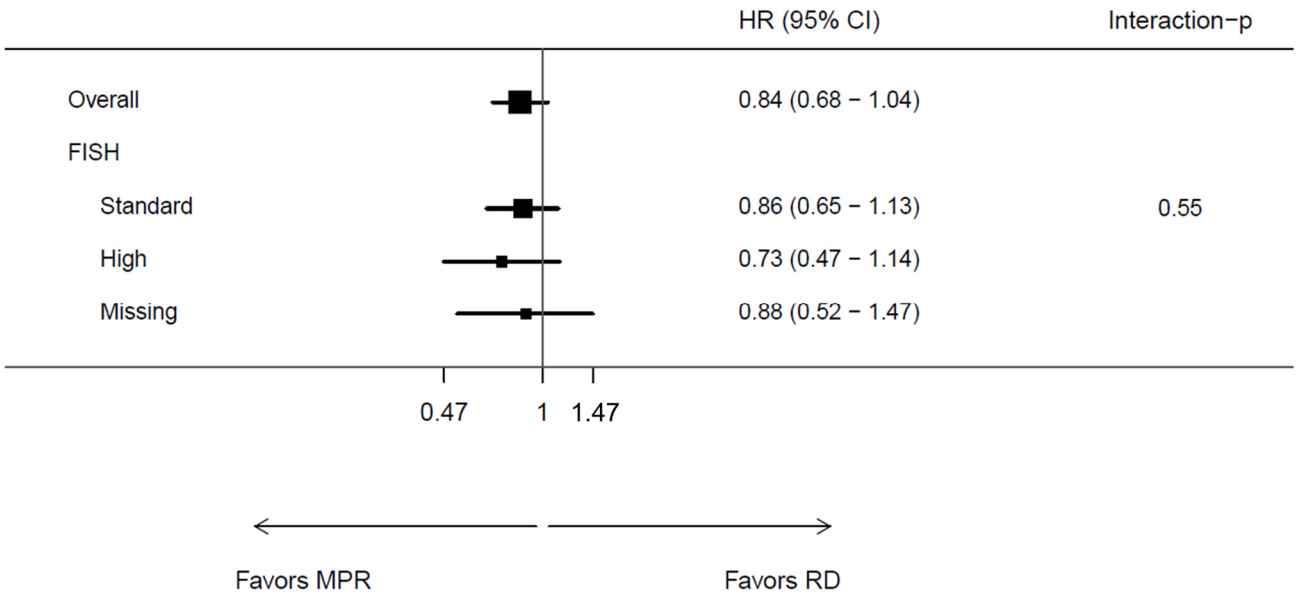
S3b. MPR *vs.* CPR - PFS-2



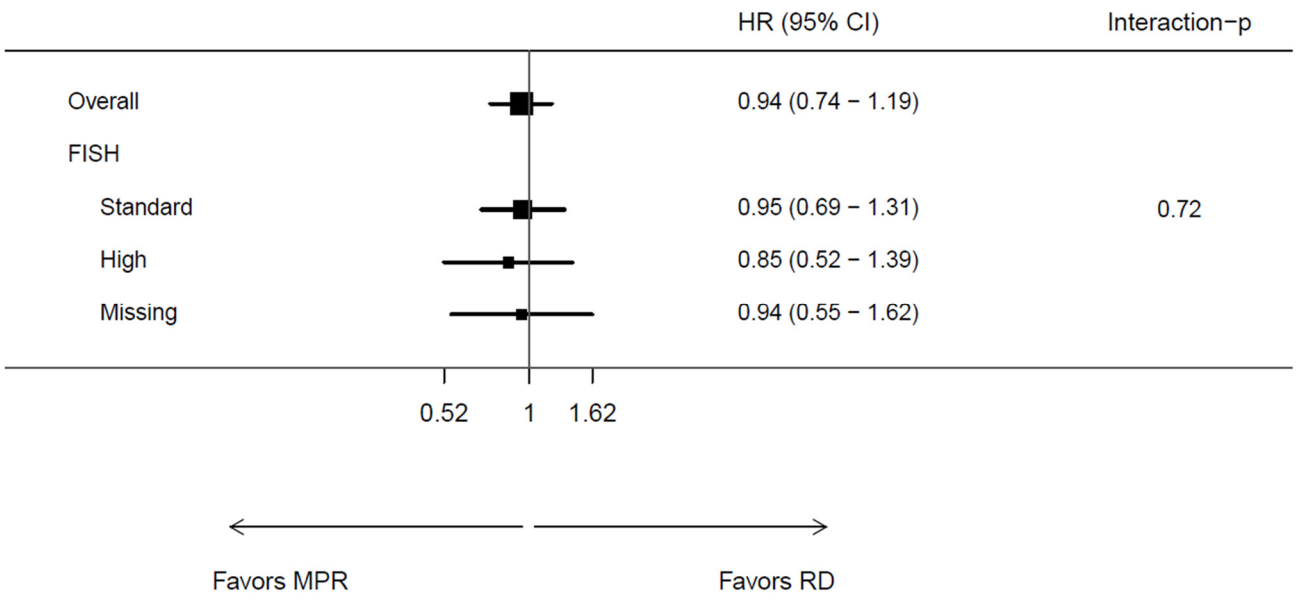
S3c. MPR *vs.* CPR - OS



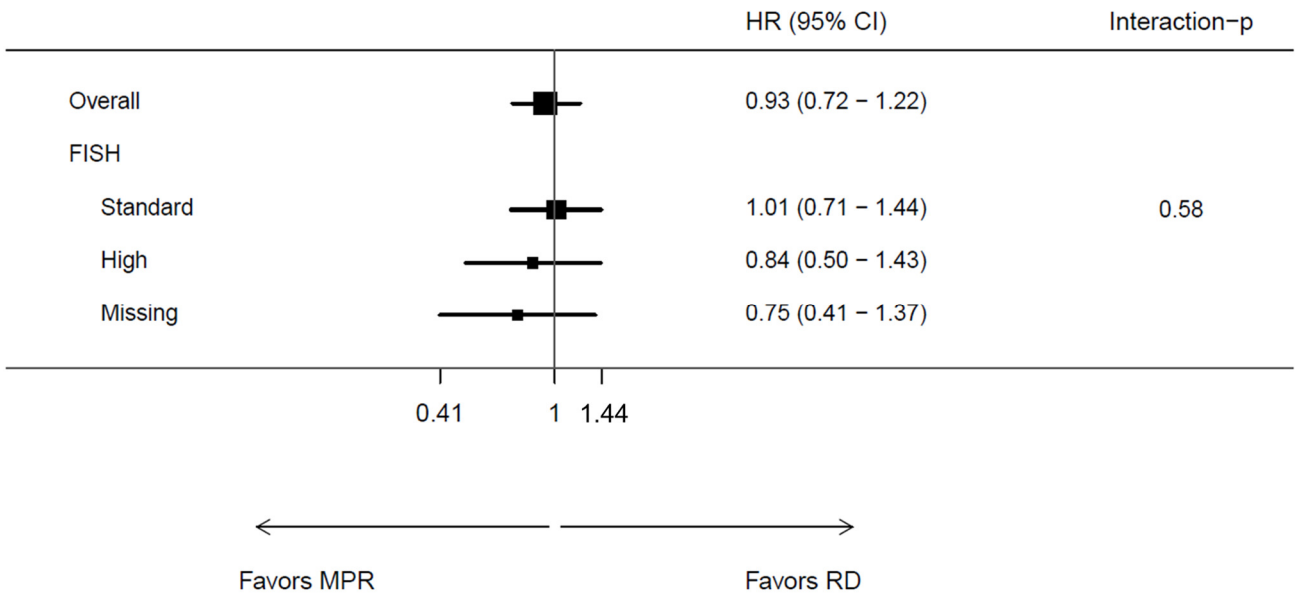
S3d. MPR *vs.* Rd - PFS



S3e. MPR *vs.* Rd - PFS-2



S3f. MPR *vs.* Rd - OS

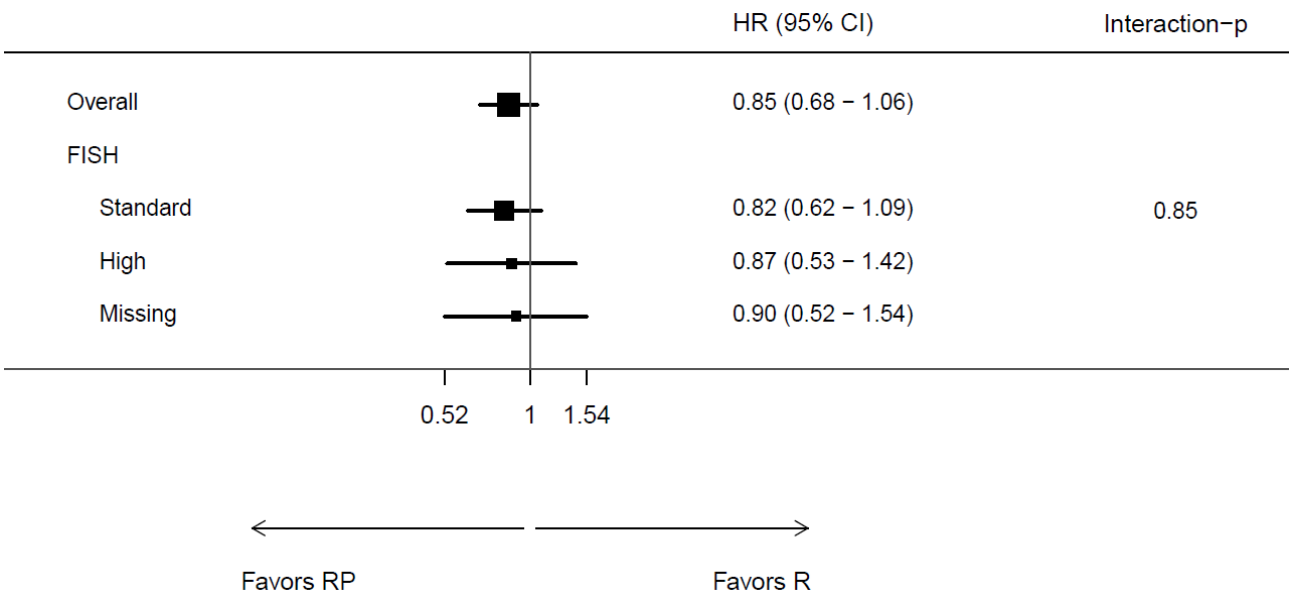


Abbreviations. MPR, melphalan-prednisone-lenalidomide; CPR, cyclophosphamide-prednisone-lenalidomide; Rd, lenalidomide-dexamethasone; PFS, progression-free survival; PFS-2, progression-free survival 2; OS, overall survival; FISH, fluorescence *in situ* hybridization; HR, hazard ratio; CI, confidence interval; Interaction-p, interaction p-value.

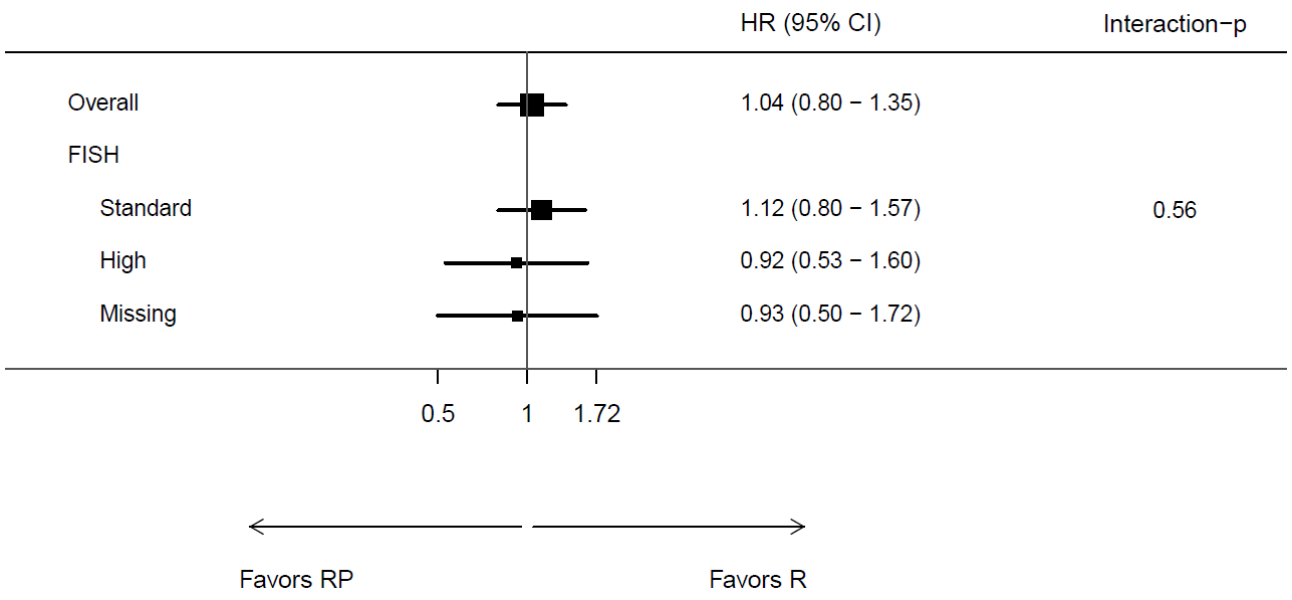
Supplementary figure S4. Maintenance treatment – Subgroup analysis according to cytogenetic risk

RP vs. R (PFS, PFS-2 and OS)

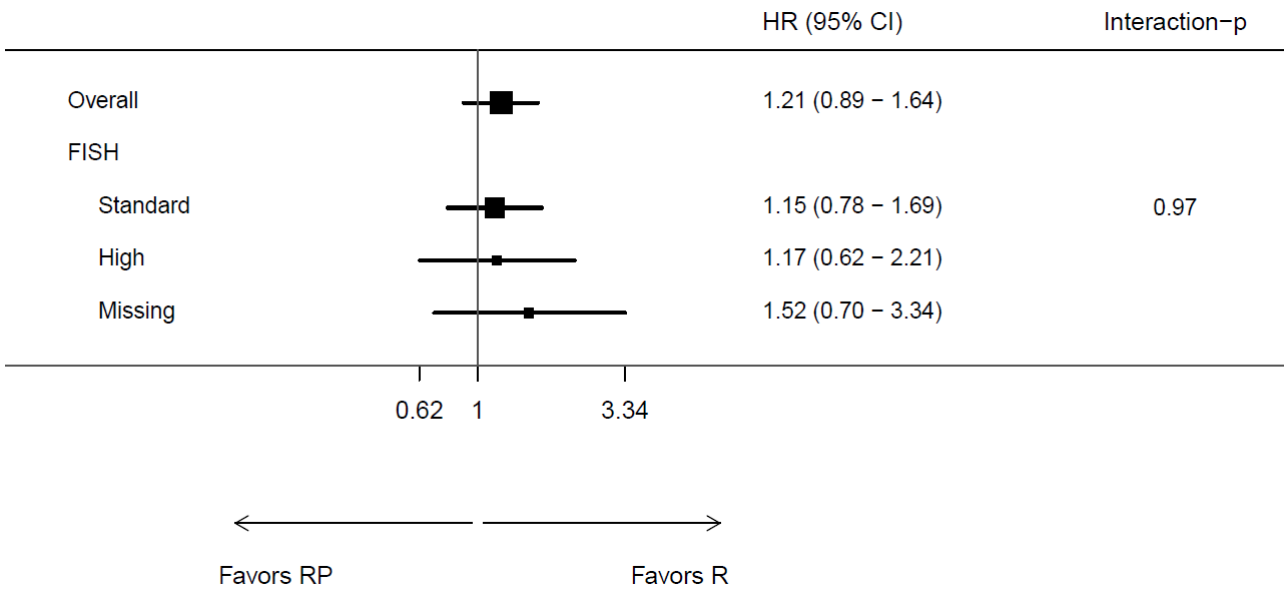
S4a. RP *vs.* R - PFS



S4b. RP *vs.* R - PFS-2



S4c. RP *vs.* R - OS



Abbreviations. RP, lenalidomide-prednisone; P, prednisone; PFS, progression-free survival; PFS-2, progression-free survival 2; OS, overall survival; FISH, fluorescence *in situ* hybridization; HR, hazard ratio; CI, confidence interval; Interaction-p, interaction p-value.

References

1. Palumbo A, Gay F, Cavallo F, et al. Continuous Therapy Versus Fixed Duration of Therapy in Patients With Newly Diagnosed Multiple Myeloma. J Clin Oncol 2015;33(30):3459–66.
2. Durie BGM, Harousseau J-L, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20(9):1467–1473.
3. National Cancer Institute [USA] - Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events (CTCAE) v3.0. 2006;August 9. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf (2006, accessed July 27, 2019).