Triplet vs doublet lenalidomide-containing regimens for the treatment of elderly patients with newly diagnosed multiple myeloma

UNIVERSITÀ DEGLI STUDI DI TORINO

Triplet vs Doublet lenalidomide-containing regimens for the treatment of Elderly Patients with Newly Diagnosed Multiple Myeloma.

Valeria Magarotto,[1] Sara Bringhen,[1] Massimo Offidani,[2] Giulia Benevolo,[3] Francesca Patriarca,[4] Roberto Mina,[1] Antonietta Pia Falcone,[5] Lorenzo De Paoli,[6] Giuseppe Pietrantuono,[7] Silvia Gentili,[2] Caterina Musolino,[8] Nicola Giuliani,[9,10] Annalisa Bernardini,[1] Concetta Conticello,[11] Stefano Pulini,[12] Giovannino Ciccone,[13] Vladimír Maisnar,[14] Marina Ruggeri,[1] Renato Zambello,[15] Tommasina Guglielmelli,[16] Antonio Ledda,[17] Anna Marina Liberati,[18] Vittorio Montefusco,[19] Roman Hajek,[20] Mario Boccadoro,[1] Antonio Palumbo.[1]

1 Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy; 2 Clinica di Ematologia, AUO Ospedali Riuniti di Ancona, Ancona, Italy; 3 S.C. Ematologia, Dipartimento di Ematologia ed Oncologia, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, San Giovanni Battista, Torino, Italy; 4 Azienda Ospedaliera-Universitaria di Udine, DISM università di Udine, Italy; 5 IRCCS Casa Sollievo della Sofferenza, Unità di Ematologia, San Giovanni Rotondo, Italy; 6 Division of Hematology, Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont and Maggiore Hospital, Novara, Italy; 7 UO Ematologia e Trapianto Cellule Staminali Emopoietiche, IRCCS, Centro di Riferimento Oncologico della Basilicata, Rionero in Vulture, Italy; 8 U.O.C. ematologia azienda ospedaliera universitaria " G.Martino" Messina, Italy; 9 U.O. Di Ematologia e CTMO, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy; 10 Myeloma Unit, Dipartimento di Medicina Clinica e Sperimentale, Università degli Studi di Parma, Parma, Italy; 11 Divisione di Ematologia, Azienda Policlinico-OVE, Università di Catania, Catania, Italy; 12 Dipartimento di Ematologia, Medicina Trasfusionale e Biotecnologie, U.O. Ematologia Clinica. Ospedale Civile "Spirito Santo", Pescara, Italy; 13 Unit of Clinical Epidemiology, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino and CPO Piemonte, Italy; 14 4th Dept. of Medicine – Hematology, Charles University Hospital Hradec Kralove, Hradec Kralove, Czech Republic; 15 Padua School of Medicine, Department of Medicine, Hematology and Clinical Immunology, Padua, Italy; 16 Divisione di Medicina Interna ed Ematologia, AUO San Luigi Gonzaga, Orbassano, Italy; 17 Emat/CTMO Ospedale "R. Binaghi" Cagliari, Cagliari, Italy; 18 AO S.Maria di Terni, SC Oncoematologia, Terni, Italy; 19 Division of hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; 20 Department of Haematooncology, University Hospital Ostrava and University of Ostrava, Czech Republic.

Correspondence to:

Dr Antonio Palumbo, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Via Genova, 3 - 10126 Torino, Italy; Email: appalumbo@yahoo.com Tel: +39 011 633 4260/4301; Fax: +39 011 633 4187

Running head:

Triplet vs doublet lenalidomide-based regimens in elderly MM

Abstract

Lenalidomide-dexamethasone improved outcome in newly diagnosed elderly multiple myeloma (MM) patients. We randomized 662 patients ≥65 years or transplant-ineligible to receive induction with melphalan-prednisone-lenalidomide (MPR) or cyclophosphamide-prednisone-lenalidomide (CPR) or lenalidomide plus low-dose dexamethasone (Rd). The primary endpoint was progression-free survival (PFS) in triplet (MPR+CPR) vs doublet (Rd) lenalidomide-containing regimens. After a median follow-up of 39 months, the median PFS was 22 months for the triplet combinations and 21 months for the doublet (p=0.284). The median overall survival (OS) was not reached in both groups, and the 4-year OS was 67% for the triplet and 58% for the doublet (p=0.709). By considering the three treatment arms separately, no difference in outcome was detected between MPR, CPR and Rd. The most common grade ≥3 toxicity was neutropenia: 64% in MPR, 29% in CPR and 25% in Rd patients (p<0.0001). Grade ≥3 non-hematologic toxicities were similar among groups and were mainly infections (6.5-11%), constitutional (3.5-9.5%) and cardiac (4.5-6%), with no difference between the arms. In conclusion, in the overall population, the alkylator-containing triplets MPR and CPR were not superior to the alkylator-free doublet Rd, which was associated with lower toxicity.

This study was registered at www.clinicaltrials.gov #NCT01093196.

Keypoint

- Triplet lenalidomide-based regimens did not induce any advantage over doublet lenalidomide-based regimen in elderly myeloma patients

Introduction

Multiple myeloma (MM) is the second most frequent hematologic cancer, with a median age at diagnosis of around 70 years.[1] MM is still an incurable disease, but novel agents, such as the proteasome inhibitor bortezomib and immunomodulatory drugs thalidomide and lenalidomide have considerably improved progression-free survival (PFS) and overall survival (OS) of patients.[2-6] In Europe, melphalan-prednisone-thalidomide (MPT) and melphalan-prednisone-bortezomib (VMP) are considered the standards of care for MM patients over 65 years of age or not eligible for autologous stem cell transplantation.[2,3,7-13] Recently, two large phase III trials have shown the superiority of lenalidomide-containing regimens over the standard treatments approved for the treatment elderly patients with newly diagnosed MM.[14,15] The MM-015 trial showed that the combination melphalan-prednisone-lenalidomide (MPR) followed by maintenance with lenalidomide (MPR-R) significantly prolonged PFS (31 months) in comparison with melphalan-prednisone (13 months, $p<0.001$) or MPR without maintenance (14 months, $p<0.001$). The major benefit was observed in patients 65 to 75 years of age ($p=0.001$ for treatment-by-age interaction).[14] The FIRST trial showed that lenalidomide plus low-dose dexamethasone (Rd) given until disease progression was associated with a significant improvement in PFS (25.5 months) when compared with melphalan-prednisone-thalidomide (21.2 months) or Rd for a fixed period of 18 months (20.7 months) (HR for the risk of progression or death was 0.72 for continuous Rd vs MPT and 0.70 for continuous Rd vs 18 months of Rd; $p<0.001$ for both comparisons).The advantage of Rd given continuously or for a fixed period was evident both in patients older or younger than 75 years of age.[15]

To date, a formal comparison between a triplet alkylator-containing regimen vs a doublet alkylator-free regimen, both including lenalidomide, has not been performed yet. In this phase III trial, we compared a triplet lenalidomide-containing regimen (MPR or CPR) with a doublet lenalidomide-containing regimen (Rd), in order to evaluate which was the best drug to combine with lenalidomide (alkylating agents or steroids). The primary end-point was PFS with the triplet versus the doublet lenalidomide-containing regimens.

Patients and Methods

Study Patients

Patients with newly diagnosed MM ineligible for high-dose therapy plus stem-cell transplantation because of age (≥ 65 years) or coexisting comorbidities could be enrolled. Inclusion criteria were measurable disease and Karnofsky performance status ≥ 60%. Patients agreed to use contraception and women of childbearing age had a pregnancy test before enrollment. Exclusion criteria included renal impairment (creatinine level ≥30 ml/min), uncontrolled or severe cardiovascular disease and other malignancies within the past 3 years. The study was approved by the institutional review board at each of the participating centers. All patients gave written informed consent before entering the study, which was performed in accordance with the Declaration of Helsinki.

Study Design and Intervention

This is a multicenter randomized (1:1:1) phase III clinical trial that involved 58 centers in Italy and 9 centers in Czech Republic. The primary endpoint was PFS; secondary endpoints included response rate, time to the first evidence of response, OS, and incidence of any grade 3 or higher adverse events. Per protocol, patients were stratified by age (≤ 75 years vs > 75 years). Based on the recent International Myeloma Working Group geriatric score that stratifies patients according to their frailty status (fit, intermediate-fitness, and frail),[16] a post-hoc analysis not prespecified in the original protocol including age (≤ 80 vs > 80 years), comorbidities (according to Charlson score) and cognitive/physical status (according to the Activities of Daily Living and the Instrumental Activities of Daily Living scores) was conducted. The definitions of fit, intermediate-fitness, and frail patients based on age, Charlson score, the Activities of Daily Living and the Instrumental Activities of Daily Living scores are summarized in the Supplementary Appendix.

Patients enrolled were randomly allocated to receive induction treatment with nine 28-day cycles of MPR (n=217) or CPR (n=220) or Rd (n=217). Upfront dose reductions of dexamethasone, melphalan and cyclophosphamide were performed according to patients age. MPR patients received lenalidomide 10 mg/day for 21 days; oral melphalan 0.18 mg/Kg for 4 days in patients 65-75 years old and 0.13 mg/Kg in those >75 years; prednisone 1.5 mg/Kg for 4 days. CPR patients received lenalidomide 10 mg/day for 21 days; oral cyclophosphamide 50 mg every other day for 28 days in patients 65-75 years old and 50 mg every other day for 21 days in those >75 years; prednisone 25 mg every other day. Rd patients received lenalidomide 25 mg/day for 21 days; dexamethasone 40 mg on days 1,8,15,22 in patients 65-75 years old and 20 mg in those >75 years. After induction, patients were randomized to receive maintenance treatment with lenalidomide alone at 10 mg on

days 1-21 every 28 days, or in combination with prednisone at 25 mg every other day continuously. After the inclusion of the first 120 patients, the protocol was amended to increment the dose of lenalidomide and cyclophosphamide in patients 65-75 years old in the CPR group, due to negligible toxicities in comparison with the two other treatment arms. CPR induction schedule was changed to lenalidomide 25 mg/day for 21 days and oral cyclophosphamide 50 mg/day for 21 days. All new patients randomized to CPR arm received the new schema after the approval of the amendment. Treatment was withheld on withdrawal of the patient's consent, disease progression or the occurrence of any grade 4 hematologic adverse events or grade 3-4 non-hematologic adverse event; less serious toxicities were managed through established dose-modification guidelines. Antithrombotic prophylaxis was mandatory: aspirin or low-molecular weight heparin or warfarin were permitted at physician's discretion.

Assessments of Endpoint

The primary endpoint was PFS in patients treated with triplet in comparison with those who received a doublet combination. PFS was calculated from the time of induction randomization until the date of progression, relapse, death from any cause, or the date the patient was last known to be in remission. OS in triplet vs doublet was a secondary end-point and was calculated from the time of induction randomization until the date of death from any cause or the date the patient was last known to be alive. Efficacy and safety assessments were performed every 4 weeks until relapse, or until evidence of disease progression, or when clinically indicated. Evaluation of the response to the treatments was performed according to the International Response Criteria for Multiple Myeloma.[17] Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Statistical analysis

The study was designed as a 2x2 factorial trial, with two main comparisons of PFS: between induction regimens (triplet vs doublet); and between maintenance treatments (lenalidomide-prednisone vs lenalidomide alone). The design of the study was to show superiority of a three-drug regimen over a two-drug regimen. A sample size of 640 patients (430 in MPR+CPR group vs 210 in Rd group) was determined to provide a power of 80% to detect a hazard ratio (HR) of PFS ≤ 0.75 comparing patients receiving MPR+CPR with those receiving Rd, by using a log-rank test with a two-sided alpha of 0.05. An interim analysis of safety was planned when approximately 85 patients

had received at least one treatment. Patients were analyzed on an intention-to-treat basis for all time-to-event endpoints. Times of observation were censored on November 1, 2014. Response rates and safety were analyzed in patients who received at least one dose of study drugs. Response rates and the incidence of any adverse event were compared with the χ^2 test or Fisher's exact test when appropriate. Survival data were analyzed with the Kaplan-Meier method, and treatment groups were compared with the log-rank test. Time to event was expressed as median with interquartile range (IQR). The Cox proportional hazard model was used to estimate HR values and the 95% confidence interval (CI) for the intention-to-treat population.

Results

Between August 2009 and September 2012, a total of 662 patients were enrolled. Eight patients were excluded from randomization for screening failure (Figure 1). Six hundred fifty-four patients were randomly assigned to receive induction with MPR (n=217) or CPR (n=220) or Rd (n=217). Baseline demographics and patients characteristics were well balanced among the three groups (Table 1). Median age was 74 years in the MPR arm, 73 years in the CPR arm, 74 years in the Rd arm. About 25% of patients were classified as frail. At the time of analysis, all patients had completed the assigned induction treatment and 402 patients were randomly allocated to maintenance treatment. The median duration of treatment was 18 months (range 1-62 months).

Efficacy

After a median follow-up of 39 months, the median PFS was 22 months with the triplet combinations and 21 months with the doublet (HR 0.906, CI 0.739-1.111; p=0.344; Figure 2A). The median OS was not reached; the 4-year OS was 67% with triplet regimens and 58% with doublet (HR 0.945, CI 0.700-1.274; p=0.709; Figure 2B). By comparing the three arms separately, the median PFS was 24 months in the MPR, 20 months in the CPR and 21 months in the Rd groups (Figure 3A). The 4-year OS was 65% with MPR, 68% with CPR and 58% with Rd (Figure 3B). After nine induction cycles, the overall response rate (at least partial response, PR) was similar in the three groups: 71% with MPR, 68% with CPR and 74% with Rd (Table 2).

A post-hoc analysis according to patient frailty was performed (Supplementary Appendix). By the primary comparison, in fit patients, the median PFS was 23 months with the triplet regimens and 22 months with the doublet regimen, and the respective 4-year OS was 77% and 57%. In intermediate-fitness patients, the median PFS was 22 months with the triplets and 20 months with the doublet,

and the 4-year OS was 67% and 72% in the two groups respectively. In frail patients, the median PFS was 18 months with the triplet regimens and 22 months with the doublet regimen, and the 4-year OS was 44% and 50%.

By comparing the three arms separately, in fit patients, the median PFS was 30 months in MPR, 22 months in CPR and 22 months in Rd patients (MPR vs Rd: HR= 0.671, CI 0.461-0.976, p=0.037; Figure 4A). The 4-year OS was 77% in both MPR and CPR groups and 57% in the Rd group. In intermediate-fitness patients, the median PFS was 19 months in MPR, 23 months in CPR and 20 months in Rd patients. The 4-year OS was 61% in the MPR arm and 72% both in the CPR and Rd arms. In frail patients, the median PFS was 23 in MPR, 14 in CPR and 22 months in Rd patients. The 4-year OS was 43% with MPR, 45% with CPR and 50% with Rd.

Safety

During the induction treatment, the most frequent grade ≥3 toxicities were hematologic. At least one grade ≥3 hematologic adverse event was reported in 68% of MPR, 32% of CPR and in 29% of Rd patients (p<0.0001; Table 3). Neutropenic fever occurred in 5 (3%) MPR, 4 CPR (2%) and 2 (1%) Rd patients. Per protocol, granulocyte colony-stimulating factor (G-CSF) was administered in case of febrile neutropenia and grade 3-4 neutropenia. In this study, 57% of MPR, 23% of CPR and 20% of Rd patients (p<0.0001) received G-CSF, reducing the duration of neutropenia and the risk of infections. The rate of at least one grade ≥3 non-hematologic adverse event did not exceed 31% in all the three arms. The most frequent grade ≥3 non-hematologic toxicities were infections (11% with MPR, 6.5% with CPR and 9% with Rd) constitutional events (9.5% with MPR, 3.5% with CPR and 5% with Rd) and cardiac toxicities (4.5% with MPR, 6% with CPR and 6% with Rd), and no significant differences were detected among the three arms (Table 3). A very low incidence of thromboembolic events were recorded: 3% in the MPR, 5% in the CPR and 2% in the Rd arms. Among the 643 evaluable patients, 203 (32%) patients received low molecular weight heparin, 300 (47%) aspirin, 87 (14%) both, 16 (2%) warfarin and 37 (5%) did not receive any prophylaxis. Grade ≥3 peripheral neuropathy was not significant in each arm. Thirteen cases of second primary malignancies (SPM) were recorded: 7 (3%) in the MPR, 3 (1%) in the CPR and 3 (1%) in the Rd groups. Of these, 5 SPM occurred during induction: 3 (1.5%) in the MPR and 2 (1%) in the CPR arms. All SPM were solid, but one case of acute lymphoblastic leukemia in the CPR group. Median time to SPM occurrence was 15 months (range 5-36 months). The rate of discontinuation due to

adverse events was similar in the three arms: 37/211 (18%) in the MPR, 33/220 (15%) in the CPR and 30/212 (14%) in the Rd groups. Lenalidomide was reduced in 45 (21%) MPR, 40 (18%) CPR and 34 (16%) Rd patients, without significant differences among the three arms. During the induction phase, 27 deaths not related to the progression of disease occurred: 8 (4%) in the MPR, 9 (5%) in the CPR and 10 (4%) in the Rd arms. Nineteen of them were related to the treatment: 5 in the MPR (1 sudden death, 3 infections and 1 stroke), 8 in the CPR groups (1 pulmonary embolism, 5 cardiologic toxicities, 1 stroke, 1 infection) and 6 in the Rd (1 sudden death, 1 decline of general condition, 1 stroke and 3 cardiologic toxicities).

In a post-hoc analysis, the incidence of at least one hematologic adverse event in fit patients was 75% for MPR, 34% for CPR patients and 29% in those who received Rd (p=0.0001 for both MPR vs Rd and MPR vs CPR). The rate of non-hematologic adverse events was: 25% in MPR, 22% in CPR and 27% in Rd patients. The rate of discontinuation due to adverse events was 13% in patients treated with MPR, 8% in patients who received CPR and 10% in those who received Rd. Three fit patients died due to treatment-related toxicity (one per arm). In intermediate-fitness patients, the incidence of hematologic toxicity was 61% in MPR, 33% in CPR and 25% in Rd (MPR vs Rd and MPR vs CPR p=0.0001). At least one non-hematologic adverse event occurred in 29% of MPR, 32% of CPR and 26% of Rd patients. An increased rate of discontinuation due to toxicities was detected independently of treatment randomization: 20% with MPR, 13% with CPR and 18% with Rd. Two intermediate-fitness patients in the MPR and 2 in the Rd groups died due to treatment-related toxicities. In frail patients the incidence of at least one hematologic adverse event was 75% with MPR, 28% with CPR and 3% with Rd (p=0.0001 for both MPR vs Rd and MPR vs CPR). The incidence of non-hematologic toxicities was 47% in MPR, 42% in CPR and 38% in Rd patients. Frail patients had the highest rate of discontinuation due to adverse events and this was more evident in the alkylator-containing regimens: 23% with MPR, 30% with CPR and 18% with Rd. A higher number of frail patients died due to toxicity: 2 in the MPR (2 infections) and 7 in the CPR (5 cardiologic events, 1 infection, 1 stroke) and 3 in the Rd (3 cardiologic events) groups.

Discussion

This is the first randomized phase III trial that compared two alkylator-containing triplet regimens (MPR and CPR) with an alkylator-free doublet regimen (Rd) in patients with multiple myeloma who were ineligible for stem cell transplantation. After a median follow-up of 39 months no PFS

difference was noticed between triplet and doublet regimens, thus the hypothesis of the trial has not been confirmed. By analyzing the 3 arms separately, we found that the addition of an alkylating agent did not lead to any advantage in terms of response and outcome.

In our study, the median PFS with Rd was slightly shorter than the one reported in the FIRST study (25.5 months with continuous Rd and 20.7 months with Rd for 18 months).[15] In addition, our response rate was comparable to one reported in the FIRST trial, where the ORR with Rd was 73%-75%. However, we reported a complete response rate of 3% with Rd, which is lower than the 15% of the FIRST trial. Of note, the median duration of continuous Rd in that trial was 18.4 months, while in our study Rd was administered only for 9 months as induction treatment followed by maintenance including lenalidomide at lower dose. Maintenance therapy might have had an impact on PFS but the current follow-up does not allow to draw definitive conclusions. A future analysis with a longer follow-up is planned to better evaluate the impact of maintenance therapy. The more intense regimens of the FIRST study induced an increase in the extra-hematologic toxicity. This suggests that continuous treatment with Rd can be a valuable option to prolong PFS and to achieve a deeper response, and reducing the dose during maintenance can be a valuable strategy to improve tolerability.

In our trial, the major safety concern was the higher hematologic toxicity reported with MPR compared with both Rd and CPR ($p<0.0001$). Non-hematologic adverse events were comparable in the three arms, with an incidence not higher than 10%. In the FIRST study, a higher incidence of infections (29% in continuous Rd, 22% in Rd 18-months and 17% in MPT) and cardiac events (12% in continuous Rd, 7% in Rd 18 months and 9% in MPT) was reported.[15] This difference could be due to the longer administration of dexamethasone in the FIRST trial as compared with our study. A more intensive induction treatment with Rd administered for a limited duration (9 months), followed by a less intensive, continuous treatment with lenalidomide alone appears a sensible and effective choice.

In our trial, the incidence of SPM (2%) was not higher than the rates reported in other studies with lenalidomide-containing regimens. Of note, the incidence was higher with the alkylator-containing regimens, with 3 cases of SPM reported in the Rd group versus 10 cases in the MPR and CPR groups. This is in line with a previous meta-analysis that demonstrated an increased risk of SPM with lenalidomide in combination with melphalan.[18]

Cyclophosphamide showed to be less toxic and associated with a lower risk of SPM than melphalan, and thus may be considered an alternative.[18,19] Nevertheless, we found no particular advantage in terms of efficacy with CPR over the two-drug regimen Rd. Despite the amendment, a too low dose of cyclophosphamide might have been adopted in our study. Because of this limitation, no definitive conclusions can be drawn regarding CPR. To date, in the elderly setting, one phase 2 trial has evaluated cyclophosphamide 300 mg/m^2 in combination with carfilzomib and dexamethasone with positive results.[20] This may provide the rationale for testing this dose also in lenalidomide-containing regimens.

Determining treatment doses only based on age could be a limit. Therefore, we conducted a post-hoc analysis and classified patients as fit, intermediate-fitness and frail.[16] With all the limitations of a post-hoc analysis, we found a PFS advantage with MPR as compared with Rd (HR 0.671, p=0.037) and CPR in fit patients. Intermediate-fitness and frail patients did not benefit from the addition of an alkylating agent. Hematologic toxicities were similar in fit, intermediate-fitness and frail patients within each treatment arm. MPR was confirmed to be the combination with the highest incidence of hematologic adverse events, independently of the patients' frailty status. On the other hand, frailty influenced the risk of non-hematologic toxicities, discontinuation and treatment-related deaths. In MPR frail patients, infection was the only cause of death, thus reflecting the marked immune depression with this combination; in Rd and CPR frail patients, cardiovascular toxicity was the major cause of death, and this is in line with the toxicity profile of the two combinations. Nevertheless, caution is necessary when interpreting these data, as the frailty analysis was not prespecified, thus no definitive conclusions can be drawn. Future studies including frailty evaluation may validate our results. In the real life, a simple geriatric evaluation in the outpatient setting can be performed and may be a valuable tool to guide clinicians in the treatment decision process.

In conclusion, this trial showed that in real-life elderly myeloma patients, the alkylator-containing triplet regimens MPR or CPR were not superior to the alkylator-free doublet Rd. This is in line with the registrational FIRST study, where Rd has been demonstrated to be effective for all elderly patients.[15]

In the era of novel effective drugs, new attractive therapeutic options are now available and Rd should be optimized through the addition of novel agents. Recently the addition of carfilzomib to Rd showed to be effective in the relapsed setting,[21] and results of a phase 1-2 trial demonstrated that

this combination is well tolerated and effective also in newly diagnosed patients.[22] Also monoclonal antibodies, such as elotuzumab, showed to be effective in combination with Rd in the relapsed setting, and further investigation in the newly diagnosed setting is needed.[23] In the next future, trials will confirm the role of novel agents in this setting, and these agents may increase the treatment armamentarium against myeloma.

Authorship: VMagarotto, SB, GC, MB, and AP designed the study, and supervised its conduct and the data analysis. VMagarotto, SB, MO, GB, FP, RB, APF, LDP, GP, SG, CM, NG, AB, CC, SP, VMaisnar, MR, RZ, TG, AL, AML, VMontefusco, RH recruited patients in the source studies and provided relevant data. VMagarotto collected and assembled the data. GC performed the statistical analysis. VMagarotto, SB and AP analysed and interpreted the data. VMagarotto and AP drafted the initial manuscript. All authors were given unrestricted access to the data, critically reviewed the manuscript drafts, approved the final version, and made the decision to submit it for publication.

Conflicts of interest: SB has received honoraria from Celgene; MO has received honoraria from Celgene; FP has served on the advisory board for Mundipharma, Bristol, Janssen, MSD, and received honorariafrom MSD, Janssen, Celgene; SG has received honoraria from Celgene; NG has received research support from Celgene and Janssen; VMaisnar has received consultancy fess from Celgene and Janssen, and honoraria from Amgen; RZ has served on the advisory board for Celgene and Jannsen Cilag; TG has received research support from Celgene; RH has received consultancy fess from Celgene and Janssen, and honoraria from Amgen; MB has received research support, consultancy fees from and served on the scientific advisory board of Celgene; AP has received consultancy fees and honoraria from Celgene.

Acknowledgements: We thank all the patients who participated in the study, the nurses Silvia Boscolo and Concetta Calicchio, the data managers Antonella Fiorillo, Elena Tigano, and the editorial assistant Giorgio Schirripa.

References

1. Howlader N, Noone AM, Krapcho M, et al, eds. SEER cancer statistics review, 1975-2010. Bethesda, MD: National Cancer Institute, based on November 2012 SEER data submission, posted to the SEER website, 2013. http://seer.cancer.gov/csr/1975_2010/ Accessed May 10, 2015.

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

3. Mateos MV1, Richardson PG, Schlag R, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. *J Clin Oncol.* 2010;28(13): 2259-2266.

4. Palumbo A, Bringhen S, Rossi D, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. *J Clin Oncol*. 2010; 28(34): 5101-5109.

5. Palumbo A, Bringhen S, Larocca A, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: updated follow-up and improved survival. *J Clin Oncol.* 2014;32(7): 634-640.

6. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet Oncol*. 2010;11(1):29-37.

7. Palumbo A, Bringhen S, Caravita T, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. *Lancet.* 2006;367(9513):825-831.

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

9. Facon T, Mary JY, Hulin C, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet.* 2007;370(9594):1209-1218.

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

11. Wijermans P, Schaafsma M, Termorshuizen F, et al. Phase III Study of the Value of Thalidomide Added to Melphalan Plus Prednisone in Elderly Patients With Newly Diagnosed Multiple Myeloma: The HOVON 49 Study. *J Clin Oncol.* 2010;28(19):3160-3166.

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

13. Beksac M, Haznedar R, Firatli-Tuglular T, et al. Addition of thalidomide to oral melphalan/prednisone in patients with multiple myeloma not eligible for transplantation: results of a randomized trial from the Turkish Myeloma Study Group. *Eur J Haematol.* 2010;86(1):16-22.

14. 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.

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

16. Palumbo A, Bringhen S, Mateos MV, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. *Blood*. 2015;125(13):2068-2074.

17. Durie BGM, Harousseau J-L, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia.* 2006;20(9):1467–1473.

18. 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.

19. Bringhen S, Petrucci MT, Larocca A, et al. Carfilzomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed multiple myeloma: a multicenter, phase 2 study. *Blood.* 2014;124(1):63-69.

20. Bringhen S, Petrucci MT, Larocca A, et al. Carfilzomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed multiple myeloma: a multicenter, phase 2 study. *Blood*. 2014 ;124(1):63-9.

21. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2015;372(2):142-52.

22. Jakubowiak AJ, Dytfeld D, Griffith KA, et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. *Blood*. 2012;120(9):1801-9.

23. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. *N Engl J Med*. 2015;373(7):621-31.

Table 1. Demographics and baseline characteristics of the patients

Patients characteristics	Melphalan-Prednisone-Lenalidomide (n=218)	Cyclophosphamide-Prednisone-Lenalidomide (n=222)	Lenalidomide-dexamethasone (n= 222)
Age (years)	**63-91**	**63-87**	**50-89**
Median	74	73	74
> 75 years (%)	86 (39%)	80 (36%)	83 (37%)
Sex (male)	**108 (50%)**	**106 (48%)**	**108 (49%)**
Karnofsky score	60-100	60-100	60-100
Median	80	90	90
< 80 (%)	52 (24%)	44 (20%)	44 (20%)
Fitness			
Fit	89 (41%)	98 (44%)	98 (45%)
Intermediate-fitness	79 (36%)	70 (32%)	57 (26%)
Frail	49 (23%)	54 (24%)	65 (28%)
Data missing	1 (1%)	0	2 (1%)
Clearance creatinine (ml/min)	30-168	30-152	30-150
Median (ml/min)	70	67	65
International staging system score			
I	61 (28%)	59 (27%)	62 (28%)
II	97 (45%)	103 (46%)	99 (45%)
III	59 (27%)	60 (27%)	60 (27%)
Missing data	1 (0.5%)	0	1 (0.5%)
Cytogenetic abnormalities at FISH			
Data available	163 (75%)	177 (80%)	185 (83%)
Data missing	55 (25%)	45 (20%)	37 (17%)
High risk*	38 (17%)	48 (22%)	47 (25%)

* At least one among deletion17p (del17) or translocation (4;14) [t(4;14)] or translocation (14;16) [t(14;16)]

Table 2 Response rates

Response	Melphalan Prednisone Lenalidomide (n=211)	Cyclophosphamide Prednisone Lenalidomide (n=220)	Lenalidomide dexamethasone (n= 212)
Overall response rate	**150 (71%)**	**150 (68%)**	**157 (74%)**
Complete Response	7 (3%)	1 (0.5%)	6 (3%)
Very Good Partial Response	48 (23%)	44 (20%)	65 (31%)
Partial Response	95 (45%)	105 (48%)	86 (41%)
Stable Disease	51 (24%)	62 (28%)	49 (23%)
Not Evaluable*	8 (4%)	3 (1%)	5 (2%)
Progressive disease	2 (1%)	5 (2%)	1 (0.5%)
Median time to response (months)	2	2	1.8

* Patients not evaluable for not completing first induction cycle: Rd (1 sudden death; 1 death not specified; 1 hearth failure; medical decision; 1 lost at follow-up); MPR: (4 adverse events [2 Fever of unknown origin, 1 not specified, 1 diarrhea and renal failure]; 2 lost at follow-up ; 1 death for pneumonia and 1 sudden death); CPR (1 withdrawal of consent; 1 death for sepsis; 1 death for atrial fibrillation).

Table 3 Grade ≥ 3 adverse events during induction treatment

Grade ≥ 3 Adverse Event	Melphan- Prednisone-Lenalidomide (n= 211)	Cyclophosphamide Prednisone Lenalidomide (n=220)	Lenalidomide-Dexamethasone (n=212)
HEMATOLOGIC			
At least one event	143 (68%)	71 (32%)	61 (29%)
Anemia	32 (15%)	14 (6%)	9 (4%)
Neutropenia*	136 (64%)	63 (29%)	52 (25%)
Thrombocytopenia	37 (18%)	19 (9%)	15 (7%)
NON-HEMATOLOGIC			
At least one event	**66 (31%)**	**66 (30%)**	**63 (30%)**
Cardiologic	**9 (4.5%)**	**11 (6%)**	**13 (6%)**
Arrithmia	2 (1%)	2(1%)	3 (1.5%)
Acute Myocardial infarction	1 (0.5%)	4(2%)	4 (2%)
Heart failure	2(1%)	3(1.5%)	4 (2%)
Other	4(2%)	2(1%)	2 (1%)
Vascular	**7 (3.5%)**	**12 (5%)**	**7 (3%)**
Deep Vein Thrombosis/Thromboembolism	6 (3%)	10 (5%)	5 (2%)
Stroke	1 (0.5%)	2 (1%)	2 (1%)
Constitutional	**19 (9.5%)**	**7 (3.5%)**	**11 (5%)**
Fever	10 (5%)	2 (1%)	3 (1.5%)
Fatigue	6 (3%)	4(2%)	5(2%)
Other	3 (1.5%)	1(0.5%)	3(1.5%)
Dermatologic	**9 (5%)**	**17 (8%)**	**11 (5%)**
Infection	**23 (11%)**	**16 (6.5%)**	**20 (9%)**
Pneumonia	2 (1%)	6(2.5%)	4(2%)
Bronchitis	1 (0.5%)	0	3 (1.5%)
Sepsis	2 (1%)	2 (1%)	2 (1%)
Enteritis	0	2 (1%)	2 (1%)
Febrile neutropenia	8 (4%)	4 (2%)	3 (1.5%)
Viral reactivation	6 (2%)	0	1 (0.5%)
Other/not specified	4 (1%)	2 (1%)	5 (1%)
Peripheral Neurolopathy	**6 (3%)**	**6 (3%)**	**5 (2%)**
Second Primary Malignancies	**3 (1.5%)**	**2 (1%)**	**0**
Hematologic	0	1 (0.5%)	0
Solid	3 (1.5%)	1 (0.5%)	0
Discontinuation due to adverse events	**37 (18%)**	**33 (15%)**	**30 (14%)**

*G-CSF administration: Rd 43 (20%); MPR 120 (57%); CPR 51 (23%)

Figure legend

Figure 1. Patient disposition

Figure 2. Kaplan Mayer estimates of progression-free survival (PFS) and overall survival (OS) in the doublet non alkylating agent-containing vs triplet alkylating agent-containing regimens vs after a median follow-up of 39 months. Panel A shows PFS; the median PFS was 21 months in the non-alkylating agent-containing doublet vs 22 months in the alkylating agent-containing triplet regimens. Panel B shows OS; the 4-year OS was 58% in the non-alkylating agent-containing doublet vs 67% in the alkylating agent-containing triplet regimens.

Figure 3. Kaplan Mayer estimates of PFS and OS according to treatment arm. Panel A shows PFS; the median PFS was 21 months with Rd, 24 months with MPR, and 20 months with CPR. Panel B shows OS; the 4-year OS was 58% with Rd, 65%with MPR, and 68% with CPR.

Figure 1

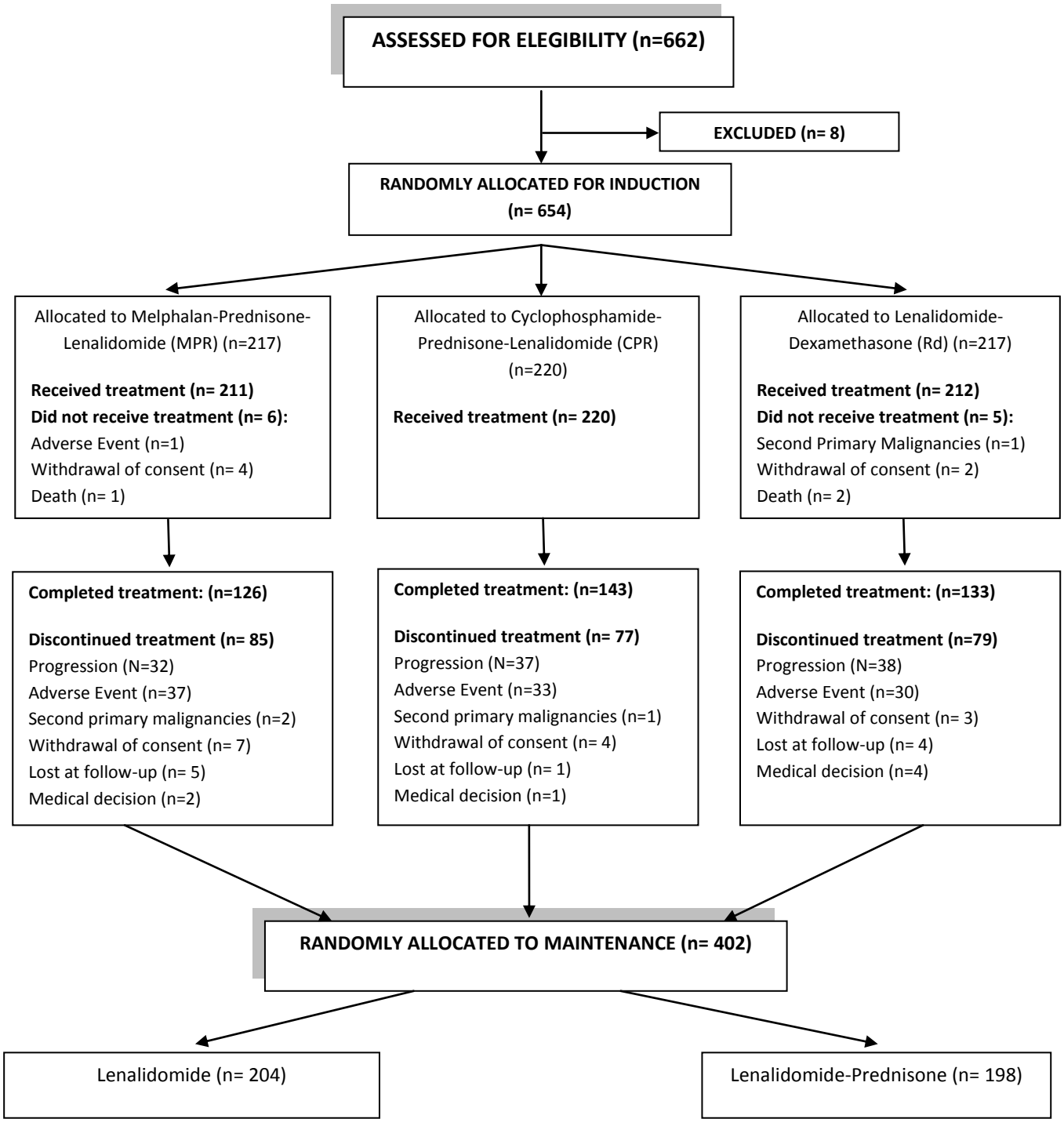
ASSESSED FOR ELEGIBILITY (n=662)
EXCLUDED (n= 8)
RANDOMLY ALLOCATED FOR INDUCTION (n= 654)
Allocated to Melphalan-Prednisone-Lenalidomide (MPR) (n=217)
Received treatment (n= 211)
Did not receive treatment (n= 6):
Adverse Event (n=1)
Withdrawal of consent (n= 4)
Death (n= 1)
Allocated to Cyclophosphamide-Prednisone-Lenalidomide (CPR) (n=220)
Received treatment (n= 220)
Allocated to Lenalidomide-Dexamethasone (Rd) (n=217)
Received treatment (n= 212)
Did not receive treatment (n= 5):
Second Primary Malignancies (n=1)
Withdrawal of consent (n= 2)
Death (n= 2)
Completed treatment: (n=126)
Discontinued treatment (n= 85)
Progression (N=32)
Adverse Event (n=37)
Second primary malignancies (n=2)
Withdrawal of consent (n= 7)
Lost at follow-up (n= 5)
Medical decision (n=2)
Completed treatment: (n=143)
Discontinued treatment (n= 77)
Progression (N=37)
Adverse Event (n=33)
Second primary malignancies (n=1)
Withdrawal of consent (n= 4)
Lost at follow-up (n= 1)
Medical decision (n=1)
Completed treatment: (n=133)
Discontinued treatment (n=79)
Progression (N=38)
Adverse Event (n=30)
Withdrawal of consent (n= 3)
Lost at follow-up (n= 4)
Medical decision (n=4)
RANDOMLY ALLOCATED TO MAINTENANCE (n= 402)
Lenalidomide (n= 204)
Lenalidomide-Prednisone (n= 198)

Figure 2A

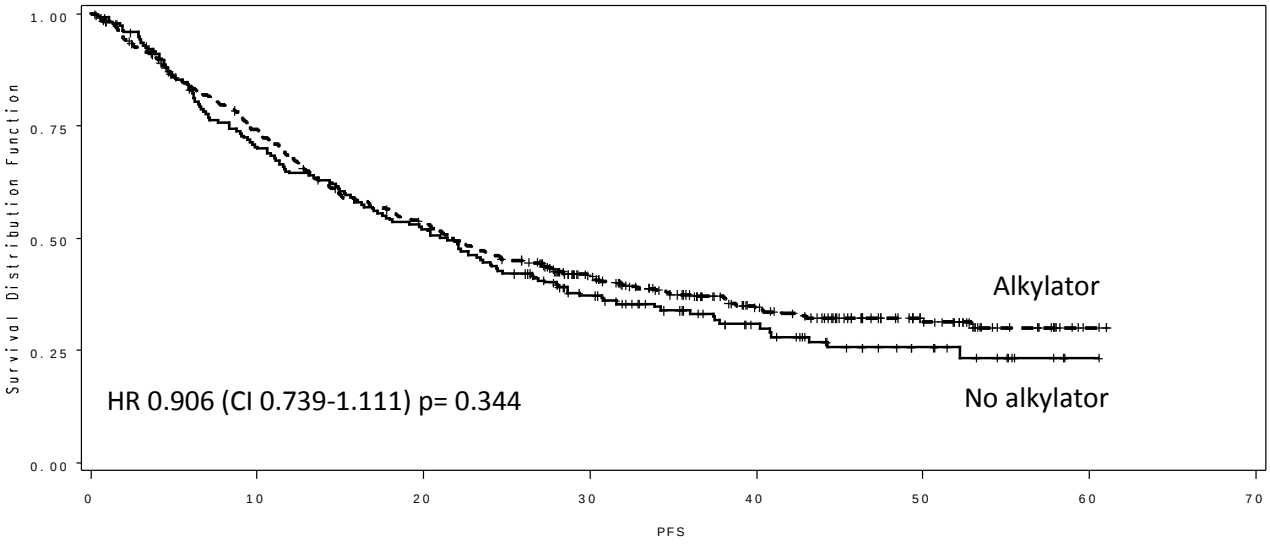

Figure 2B

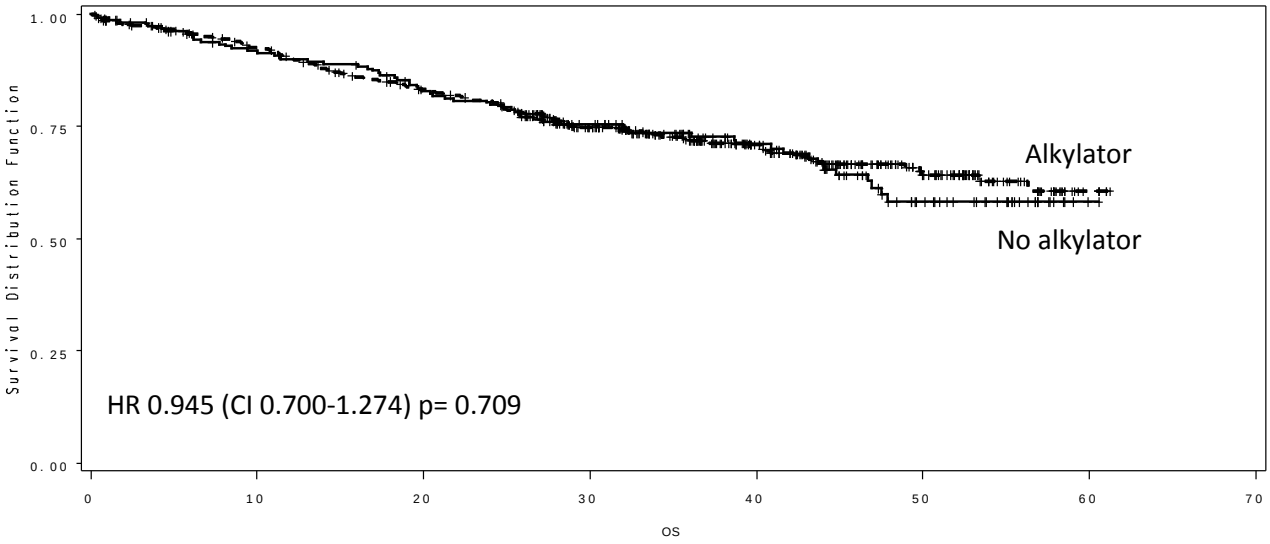

Figure 3A

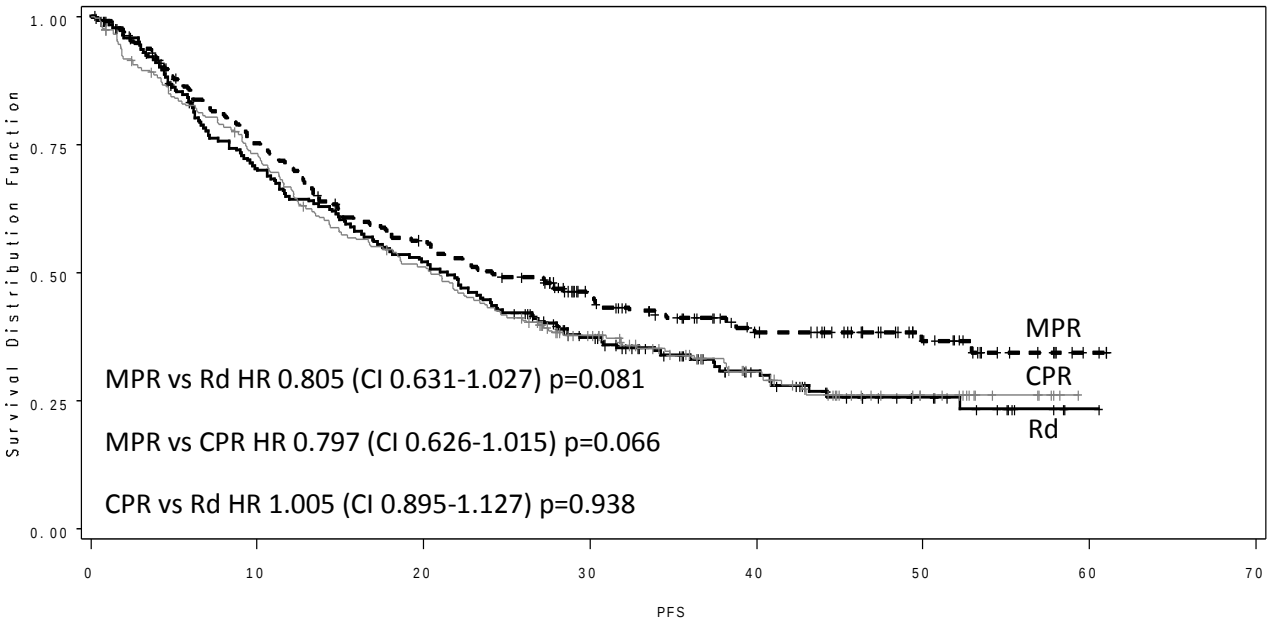

Figure 3B