Published Ahead of Print on February 27, 2020, as doi:10.3324/haematol.2019.243428.

haematologica
Journal of The Ferrata Storti Foundation

Carfilzomib, cyclophosphamide and dexamethasone for newly diagnosed, high-risk myeloma patients not eligible for transplant: a pooled analysis of two studies

by Roberto Mina, Francesca Bonello, Maria Teresa Petrucci, Anna Marina Liberati, Concetta Conticello, Stelvio Ballanti, Pellegrino Musto, Attilio Olivieri, Giulia Benevolo, Andrea Capra, Milena Gilestro, Piero Galieni, Michele Cavo, Agostina Siniscalchi, Antonio Palumbo, Vittorio Montefusco, Gianluca Gaidano, Paola Omedé, Mario Boccadoro, and Sara Bringhen

Haematologica 2020 [Epub ahead of print]

Citation: Roberto Mina, Francesca Bonello, Maria Teresa Petrucci, Anna Marina Liberati, Concetta Conticello, Stelvio Ballanti, Pellegrino Musto, Attilio Olivieri, Giulia Benevolo, Andrea Capra, Milena Gilestro, Piero Galieni, Michele Cavo, Agostina Siniscalchi, Antonio Palumbo, Vittorio Montefusco, Gianluca Gaidano, Paola Omedé, Mario Boccadoro, and Sara Bringhen. Carfilzomib, cyclophosphamide and dexamethasone for newly diagnosed, high-risk myeloma patients not eligible for transplant: a pooled analysis of two studies.
Haematologica. 2020; 105:xxx
doi:10.3324/haematol.2019.243428

Carfilzomib, cyclophosphamide and dexamethasone for newly diagnosed, high-risk myeloma patients not eligible for transplant: a pooled analysis of two studies

Roberto Mina[1], Francesca Bonello[1], Maria Teresa Petrucci[2], Anna Marina Liberati[3], Concetta Conticello[4], Stelvio Ballanti[5], Pellegrino Musto[6], Attilio Olivieri[7], Giulia Benevolo[8], Andrea Capra[1], Milena Gilestro[1], Piero Galieni[9], Michele Cavo[10], Agostina Siniscalchi[11], Antonio Palumbo[1*], Vittorio Montefusco[12], Gianluca Gaidano[13], Paola Omedé[1], Mario Boccadoro[1], Sara Bringhen[1]

Affiliations

1. Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy;
2. Division of Hematology, Department of Cellular Biotechnologies and Hematology, Sapienza University of Rome, Italy;
3. Università degli Studi di Perugia, Struttura Complessa Universitaria Oncoematologia - Azienda Ospedaliera Santa Maria di Terni, Italy;
4. Division of Hematology, AOU Policlinico-OVE, University of Catania, Catania, Italy;
5. Reparto di Ematologia con TMO, Ospedale Santa Maria della Misericordia, Perugia, Italy;
6. Regional Department of Haematology and Unit of Haematology and Stem Cell Transplantation, IRCCS-CROB, Referral Cancer Center of Basilicata, Rionero in Vulture (Pz), Italy;
7. Clinica di Ematologia, Università Politecnica delle Marche, Ancona, Italy
8. Hematology, Città della Salute e della Scienza, Turin, Italy;
9. Division of Hematology, Ospedale "C. e G. Mazzoni", ASUR Marche-AV5, Ascoli Piceno, Italy;
10. "Seràgnoli" Institute of Hematology, Bologna University School of Medicine, Bologna, Italy;
11. UOC Ematologia, Ospedale S. Eugenio, ASLRM2, Rome, Italy;
12. Hematology Department, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy;
13. Division of Hematology, Department of Translational Medicine, Università del Piemonte Orientale, Novara, Italy;

*Currently employed at GlaxoSmithKline AG.

Correspondence to:
Dr. Sara Bringhen, MD, PhD, Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, via Genova 3 - 10126 Torino, Italy. E-mail: sarabringhen@yahoo.com Tel: +39 011 633 4260/4301; Fax: +39 011 633 4187.
ORCID ID: 0000-0003-4539-6363

Abstract word count = 235
Text word count = 2526
Number of tables/figures = 4
Number of references = 31

Running title: KCyd in high-risk NDMM

Abstract

Despite remarkable advances in the treatment of multiple myeloma in the last decades, the prognosis of patients harboring high-risk cytogenetic abnormalities remains dismal as compared to that of standard-risk patients. Proteasome inhibitors demonstrated to partially ameliorate the prognosis of high-risk patients. We pooled together data from two phase I/II trials on transplant-ineligible patients with multiple myeloma receiving upfront carfilzomib cyclophosphamide and dexamethasone followed by carfilzomib maintenance. The aim of this analysis was to compare treatment outcomes in patients with standard- versus high-risk cytogenetic abnormalities detected by fluorescence in situ hybridization (FISH) analysis. High risk was defined by the presence of at least one chromosomal abnormality, including t(4;14), del17p and t(14;16). Overall, 94 patients were included in the analysis: 57 (61%) in the standard-risk and 37 (39%) in the high-risk group. Median follow-up was 38 months. In standard- vs. high-risk patients, we observed similar progression-free survival (3-year PFS: 52% vs. 43%, respectively; p=0.50), overall survival (3-year OS: 78% vs. 73%; p=0.38), and overall response rate (88% vs 95%; p=0.47), with no statistical differences between the two groups. No difference in terms of progression-free survival was observed between patients with or without del17p.

Carfilzomib, used both as induction and maintenance agent for transplant-ineligible newly diagnosed multiple myeloma patients, mitigated the poor prognosis carried by high-risk cytogenetics and resulted into similar progression-free survival and overall survival, as compared to standard-risk patients.

ClinicalTrials.gov IDs: NCT01857115 (IST-CAR-561) and NCT01346787 (IST-CAR-506).

Keywords: multiple myeloma, high-risk cytogenetic abnormalities, FISH, carfilzomib, cyclophosphamide, dexamethasone, elderly patients, once-weekly schedule, twice-weekly schedule, newly diagnosed, transplant-ineligible, induction, maintenance, pooled analysis

Article summary

The aim of our analysis was to pool together data from two phase I/II (IST-CAR-561) and phase II (IST-CAR-506) studies in order to compare the efficacy of carfilzomib-based regimens for the treatment of newly diagnosed, transplant ineligible multiple myeloma patients with standard- vs. high-risk cytogenetics.

Our analysis suggested that a carfilzomib-based treatment is effective as upfront treatment for high-risk, transplant-ineligible multiple myeloma patients. In standard- vs. high-risk patients, we observed similar progression-free survival (3-year PFS: 52% vs. 43%, respectively; p=0.50), overall survival (3-year OS: 78% vs. 73%; p=0.38), and overall response rate (88% vs. 95%; p=0.47), with no statistical differences between the two groups. Moreover, no difference in terms of progression-free survival was observed between patients with or without del17p.

INTRODUCTION

Multiple myeloma (MM) is a plasma cell dyscrasia with a heterogeneous prognosis ranging from few years to more than a decade, according to both disease-related factors (such as albumin and B2M levels, cytogenetic abnormalities [CA] or presence of extramedullary disease) and patient-related factors (age, comorbidities, frailty status).[1–3] To date, one of the most powerful prognostic markers in MM is the presence of either primary (translocations) or secondary (deletions or amplifications) recurrent CAs detected by fluorescent in situ hybridization (FISH). Deletions of chromosome 17p and TP53 have been reported in 5-20% of MM patients according to the cut-off adopted by laboratories and have been clearly associated to a dismal prognosis.[4] Another adverse CA is t(4;14), which is carried by 12 to 15% of MM patients and leads to the deregulation of fibroblast growth factor receptor 3 (FGFR3) and multiple myeloma SET domain (MMSET).[5,6] Eventually, the occurrence of t(14;16) has been associated to worse progression-free survival (PFS) and overall survival (OS) in a study published by the Mayo clinic,[7] although some doubts have been cast by another study by the Intergroupe francophone du myélome (IFM)[8] and conflicting results have been thereafter reported even in patients treated in the novel agent era. The presence of at least one of these 3 abnormalities identifies a subgroup of patients at high risk of relapse and death.[9]

MM is mainly a disease of the elderly, with a median age at diagnosis of 69 years.[10] Older patients are usually considered not eligible for high-dose chemotherapy and autologous stem-cell transplantation; in this population, the initial therapeutic approach includes either a triplet proteasome inhibitor (PI)-based regimen (bortezomib-melphalan-prednisone, VMP), a two-drug regimen containing an immunomodulatory agent (IMiD; lenalidomide-dexamethasone, Rd), or a combination of both a PI and an IMiD (bortezomib-lenalidomide-dexamethasone, VRD).[11] In the VISTA study that led to the approval of the VMP combination, the median PFS was 19.8 months in high-risk (HiR) patients by FISH and 23 months in standard-risk (SR) ones (HR:1.29).[12,13] In the FIRST study, among patients receiving continuous Rd, the median PFS was 8.4 months in HiR patients vs 31.1 in SR patients.[14,15]

Carfilzomib is a 2nd generation PI currently approved for relapsed and/or refractory (RR)MM patients. In the phase III ENDEAVOR trial comparing carfilzomib-dexamethasone (Kd) to bortezomib-dexamethasone (Vd) the PFS and OS advantage of Kd observed in the overall population was also retained in HiR patients (median PFS in HiR patients treated with Kd vs Vd: 8.8 vs 6.0 months, p=0.007).[16] Similarly, in the phase III ASPIRE trial, the triplet carfilzomib-lenalidomide-dexamethasone (KRd) proved to be superior to Rd also in patients with HiR CA (median PFS in HiR patients treated with KRd vs Rd: 23.1 vs 13.9 months, p=0.08).[17] Taken together, these results suggest that carfilzomib-based regimens might at least partially overcome the negative impact of HiR cytogenetics in MM patients.

We previously published the results of two phase I/II trials showing that the combination carfilzomib-cyclophosphamide-dexamethasone (KCyd), followed by carfilzomib maintenance, was effective and well tolerated in newly diagnosed (ND)MM elderly patients.[18,19] Here we report the results of a pooled analysis of patient data from the two trials aiming at evaluating the efficacy of a carfilzomib-based therapy in SC and HiR patients.

METHODS

Study design and treatment

We pooled together data from two phase I/II (IST-CAR-561; NCT01857115) and phase II (IST-CAR-506; NCT01346787) studies. Both trials enrolled NDMM patients older than 65 years of age or younger but not eligible for autologous stem-cell transplantation (ASCT). Ethics committees or institutional review boards at the study sites approved both studies, which were done in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Details of study procedures have been previously published.[18–20] Briefly, in both trials treatment consisted of 9 28-day cycles of KCyD followed by maintenance with single-agent carfilzomib until disease progression or intolerance. Carfilzomib was administered once weekly (70 mg/m^2) in the IST-CAR-561 study and twice weekly (36 mg/m^2) in the IST-CAR-506 one. The same doses and schedules of cyclophosphamide (300 mg on days 1,8 and 15, orally) and dexamethasone (40 mg on days 1,8,15 and 22) were used in both studies.

Endpoints

The aim of our analysis was to compare treatment efficacy, in terms of response to therapy, PFS, PFS-2 and OS in patients with SR vs HiR cytogenetics receiving carfilzomib-based regimens.

Cytogenetic risk was centrally assessed by FISH analysis and t(4;14), t(11;14), t(14;16), del13 and del17p were evaluated in both studies. A 15% cut-off point was used for detection of translocations and a 10% cut-off point for deletions. FISH analysis was performed on CD138+

purified plasma cells. According to the Revised International Staging System (R-ISS) criteria proposed by the International Myeloma Working Group (IMWG) in 2015, high cytogenetic risk was defined by the presence of at least one CA among del17p, t(4;14) or t(14;16).[21] Patients' fitness was defined according to the IMWG frailty score[2] and patients were classified as either fit, intermediate fit or unfit.

Statistical analysis

Data from the two trials were pooled together and analyzed. Comparisons between different patient groups were performed using Fisher's exact test. PFS was calculated from the date of enrollment to the date of progression or death or the date the patient was last known to be in remission. PFS-2 was calculated from the date of enrollment to the date of second relapse/progression or death or the date the patient was last known to be in remission. OS was calculated from the date of enrollment to the date of death or the date the patient was last known to be alive.

Time-to-event data were analyzed using the Kaplan-Meier method; survival curves were compared with the log-rank test. The Cox proportional hazards model was used to estimate the hazard ratio (HR) values and the 95% confidence intervals (CIs). All reported p-values were two-sided at the conventional 5% significance level. In order to account for potential confounders, the comparison SR versus HiR was adjusted for age, International Staging System (ISS), IMWG frailty score and trial (once- vs twice-weekly carfilzomib).

Data were analyzed using R software (Version 3.5.1).

RESULTS

Among the 121 patients that were enrolled in the two trials (63 patients from IST-CAR-561 and 58 patients from IST-CAR-506), complete cytogenetic data were available for 94 patients: 57 patients (61%) in the SR and 37 (39%) in the HiR group according to FISH analysis; among the HiR ones, t(4;14) was present in 12 patients (13%), t(14;16) in 4 patients (4%) and del17p in 22 (23%) patients. The median percentage of plasma cells with t(4;14) was 80% (range, 15-99), with t(14;16) was 85% and with del17p was 34% (10-95).

Baseline characteristics were well balanced between SR and HiR patients and are summarized in **Table 1**. Median age at enrollment was 72 years (range 60-86) for the entire population; no significant differences in terms of age, sex, ISS stage and frailty status were observed between the two groups.

Median follow-up was 38 months for the entire cohort. Ninety-two of 94 patients started the induction phase (1 withdrew consent and 1 was lost to follow-up before commencing therapy): 56/57 in the SR and 36/37 in the HiR group. Seventy patients (74%) started the maintenance phase: 42 (74%) in the SR and 28 (76%) in the HR group (p=1.00). The median duration of treatment was 16.9 months in SR patients and 14.6 months in HiR patients.

Responses to therapy are shown in **Table 2**. No significant differences in terms of overall response rate (ORR) were observed between SR and HiR patients both after the induction phase (86% and 92% respectively, p=0.52) and overall (induction and maintenance phases; 88% and 95% respectively, p=0.47). Also, the rate of complete response (CR) after the induction phase (19% vs 22%, p=0.80) and the maintenance phase (23% vs 24%, p=1) was similar in SR vs HiR patients.

Median PFS was similar between SR (not reached [NR]) and HiR (27.8 months) patients (HR 0.81, 95% CI 0.44-1.48, p=0.50); at 3-years 52% and 43% of patients were alive and free from progression in the two groups, respectively. Median PFS-2 was NR and 44.1 months respectively (HR 0.67, 95% CI 0.32-1.39, p=0.28). No significant differences were observed in median OS in SR and HiR patients respectively (median OS: NR vs NR, HR 0.72, 95% CI 0.34-1.52, p=0.38), with 78% of patients in the SR and 73% in the HiR group being alive at 3 years from diagnosis. (**Figure 1A-C**).

No significant differences in terms of median PFS, PFS-2 and OS were observed among patients with or without del17p (**Figure 2**; PFS: 35 vs 35.7 months, HR 0.92, 95% CI 0.47-1.82, p=0.82; PFS-2: 44.1 months vs NR, HR 1.20, 95% CI 0.55-2.64, p=0.65 ; OS: 47.5 months vs NR, HR 1.17, 95% CI 0.52-2.62, p=0.70). When adopting a higher cut-off for del17p positivity (>20%), no significant PFS difference was noted between del17p-negative and -positive patients (median, 35.7 vs 35 months).

DISCUSSION

The aim of our analysis was to evaluate whether a carfilzomib-based upfront treatment could abrogate the negative impact of HiR cytogenetics and ameliorate the prognosis of transplant-ineligible MM patients carrying HiR CAs.

Our results showed similar ORR and CR/stringent CR rates between SR and HiR patients according to the cytogenetic profile, as well as no significant differences in terms of PFS, PFS-2 and OS between the two groups. Furthermore, KCyd seemed to mitigate the poor prognosis conferred by del17p in terms of PFS, PFS-2 and OS.

In Europe, Rd and VMP are currently the first-line regimens of choice for the treatment of older NDMM patients. To date, however, no prospective data on the comparison of VMP and Rd have been published, and the results of the first prospective, phase IV trial comparing these two standards of care are awaited (NCT03829371). However, we have recently published a pooled analysis of two phase III studies in which patients were treated either with VMP or Rd plus lenalidomide maintenance (Rd-R), showing a PFS (HR: 0.54) and OS (HR: 0.73) advantage in HiR patients receiving bortezomib upfront.[22] These results were in line with those generated in another phase III study in the transplant setting, in which bortezomib partially improved the poor prognosis of HiR patients carrying t(4;14) and/or del17p.[23]

In the ASPIRE trial, the addition of carfilzomib to Rd (KRd) improved the median PFS of approximatively 10 months compared to Rd in patients with HiR cytogenetics, although median PFS in HiR patients treated with KRd (23 months) remained approximatively 6 months shorter than in SR patients (29 months).[17] In the ENDEAVOR trial, the doublet Kd proved to be superior to Vd in HiR patients (HR for PFS: 0.64, 95% CI 0.45-0.92, p=0.007), although median PFS was inferior in HiR vs SR patients receiving Kd (8.8 months vs NR, respectively).[16] In HiR RRMM patients, ixazomib in combination with Rd also proved to be effective as compared to Rd (HR 0.54, 95% CI 0.32-0.91, p=0.021), with similar median PFS in HiR and SR patients treated with this triplet (21.4 and 20.6 months, respectively).[24] The efficacy of newer PIs in HiR patients may be even more pronounced in the upfront setting, in which the probability of HiR patients treated with KRd of achieving at least a very good partial response (≥VGPR) or a CR was similar to that of SR patients.[25] In the phase II FORTE study, similar at least VGPR rates (79% vs. 86%) and minimal residual disease negativity (62% vs. 49%) were obtained with 8 cycles of KRd irrespective of ASCT in both SR and HiR disease according to the R-ISS.[26] These results confirmed the efficacy in HiR patients that we observed with carfilzomib in the non-transplant setting.

The IMWG recommends the inclusion of a PI in the upfront treatment of HiR NDMM patients.[21] Our results are in line with the evidence that PIs, especially the 2nd generation ones such as carfilzomib, can at least partially abrogate the adverse impact of high risk CAs and ameliorate the prognosis of HiR patients.

As we mentioned above, current approved treatment options in transplant-ineligible NDMM patients include Rd, VMP with or without daratumumab and VRD, with Dara-Rd coming soon. Despite the pitfalls of cross-trial comparisons, the median PFS and OS observed in HiR patients receiving carfilzomib-based therapy in our analysis compare favorably with those observed in HiR patients receiving Rd in the FIRST trial[15] (PFS: 8.4 months; OS: 29.3 months) and VMP in the VISTA study[12] (median PFS: 19.8 months), with results similar to those observed in HiR patients treated with Dara-Rd in the phase III MAIA study.[27] Daratumumab, combined to either VMP or Rd, will represent the new standard of care in the upfront treatment of transplant-ineligible patients. The median PFS of patients treated with Dara-VMP was 36.4 months in the recently updated ALCYONE study and NR at 30 months in the MAIA study with Dara-Rd.[28,29] Despite these impressive results, the PFS benefit seemed striking in SR patients (HR 0.39 for Dara-VMP and 0.49 for Dara-Rd), while it was less evident in HiR patients (HR 0.78 for Dara-VMP and 0.85 for Dara-Rd). In the era of anti-CD38-based first-line regimens, HiR genetic lesions are still an unfavorable prognostic factor and HiR patients continue to represent an unmet medical need.

Our analysis has some limitations. First of all, the small number of patients analyzed does not allow to draw definite conclusions on this topic, but prompts further evaluation of carfilzomib as induction therapy in transplant-ineligible patients. We used a 10% cut-off to define the positivity or negativity for del17p, even though the median percentage of plasma cells with del17p was sensibly higher (34%, range 17-80). The exact cut-off to be used to define del17p positivity is a matter of controversy: while the Mayo Clinic group showed no correlation between PFS and OS and the mutational burden in del17p patients, a recent study published by Thakurta et al. showed a positive correlation between a high cancer clonal fraction and survival outcomes.[30,31] Remarkably, our results remained consistent when a higher cut-off for del17p positivity was adopted (>20%, as in the ENDEAVOR trial). At the very time when the two trials included in our analysis were being designed, the impact of other HiR genetic features, such as bi-allelic inactivation, was still unknown, and therefore it could not be addressed in our work.

The prolonged use of carfilzomib in our study may have had a beneficial role in HiR patients. The available evidence suggests that continuous therapy could be superior to fixed duration therapy and could particularly benefit HiR patients. However, continuous therapy is not sufficient to overcome the poor prognosis of adverse CA. For instance, in the FIRST study, the median PFS of HiR patients treated with continuous Rd was only 9 months.[14,15] In our analysis, the median duration of therapy was similar between SR and HiR patients (16.9 vs 14.6 months), meaning that both groups of patients benefited from prolonged treatment.

In conclusion, the results of our pooled analysis suggest that a carfilzomib-based treatment is effective as upfront treatment for HiR, transplant-ineligible MM patients. Carfilzomib may contribute to fill the gap between SR and HiR patients, thus improving the poor prognosis of the latter. Our results provide the basis for a further investigation of carfilzomib as upfront therapy for the treatment of HiR MM patients.

Role of the funding source
The IST-CAR-561 (NCT01857115) study was sponsored by Stichting Hemato-Oncologie voor Volwassenen Nederland (HOVON, the Netherlands), in collaboration with Fondazione Neoplasie Sangue ONLUS (Italy). The IST-CAR-506 (NCT01346787) study was sponsored by the HOVON Foundation and co-sponsored by Fondazione Neoplasie Sangue ONLUS. Both trials were supported by funding from AMGEN (Onyx Pharmaceuticals), which had no role in study design, data collection, data analysis, data interpretation, writing of the report or publication of this article. The corresponding author had full access to all the data in the two studies and had final responsibility for the decision to prepare and submit this manuscript for publication, together with the other authors.
We thank the patients who participated in these studies and their families; the study co-investigators, nurses, and coordinators at each of the clinical sites.

Acknowledgements
We thank all the patients who participated in the study, the nurses Rosalia Capobianco and Giacomo Castorina and the data managers Debora Caldarazzo and Federica Leotta.

Contributors
Substantial contributions to the conception or design: RM, FB, PO, MB, and SB.
Acquisition, analysis, or interpretation of data: all authors.
First draft: RM, FB, AC, MG, PO, and SB.
Statistical analysis: AC.
Supervision: MB and SB.
Critical revision for important intellectual content: all authors.
Final approval of the version to be published: all authors.
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

Conflicts of Interest
RM has received honoraria from Amgen, Celgene, Takeda and Janssen and served on the advisory boards for Janssen.
MTP has received honoraria from Celgene, Janssen-Cilag, BMS, Takeda, and Amgen; has served on the advisory boards for Celgene, Janssen-Cilag, BMS, Takeda, and Amgen.
AML has received honoraria from Janssen, Celgene, Bristol-Myers Squibb, Servier; has received clinical trial support from Novartis, AbbVie, Roche, Amgen, Celgene; has served on the advisory boards of AbbVie, Amgen, Takeda, Servier; and has undertaken consultancy for Incyte.

StB has received honoraria for attending meetings from Janssen and Celgene.
PM has received personal fees from Amgen, Novartis, BMS, Celgene, Janssen and Takeda.
GB has served on the advisory boards for Novartis, Celgene, and Amgen.
MC has received grants from Janssen and Celgene; has received personal fees from Janssen, Celgene, Amgen, BMS and Takeda.
AP is currently a GlaxoSmithKline AG employee.
VM has received speaking fees from and served on the advisory boards for Amgen, Celgene, Janssen, and Takeda.
GG has served on the advisory boards for Janssen, AbbVie, Astra-Zeneca and Sunesys; has served on the speakers' bureaus for Janssen, Gilead and AbbVie.
PO has served on the advisory board for Janssen.
MB has received honoraria from Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol-Myers Squibb, and AbbVie; has received research funding from Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol-Myers Squibb, and Mundipharma.
SB has received honoraria from Bristol-Myers Squibb, Celgene, Amgen and Janssen; has served on the advisory boards for Amgen, Karyopharm, Janssen and Celgene; and has received consultancy fees from Takeda and Janssen.
The remaining authors declare no competing financial interests.

References

1. Greipp PR, San Miguel J, Durie BGM, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23(15):3412-3420.
2. Palumbo A, Bringhen S, Mateos M-V, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. Blood. 2015;125(13):2068-2074.
3. Larocca A, Dold SM, Zweegman S, et al. Patient-centered practice in elderly myeloma patients: an overview and consensus from the European Myeloma Network (EMN). Leukemia. 2018;32(8):1697-1712.
4. Fonseca R, Bergsagel PL, Drach J, et al. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. Leukemia. 2009;23(12):2210-2221.
5. Moreau P, Attal M, Garban F, et al. Heterogeneity of t(4;14) in multiple myeloma. Long-term follow-up of 100 cases treated with tandem transplantation in IFM99 trials. Leukemia. 2007;21(9):2020-2024.
6. Gertz MA, Lacy MQ, Dispenzieri A, et al. Clinical implications of t(11;14)(q13;q32), t(4;14)(p16.3;q32), and -17p13 in myeloma patients treated with high-dose therapy. Blood. 2005;106(8):2837-2840.
7. Fonseca R, Blood E, Rue M, et al. Clinical and biologic implications of recurrent genomic aberrations in myeloma. Blood. 2003;101(11):4569-4575.
8. Avet-Loiseau H, Malard F, Campion L, et al. Translocation t(14;16) and multiple myeloma: is it really an independent prognostic factor? Blood. 2011;117(6):2009-2011.
9. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol. 2015;33(26):2863-2869.
10. Howlader N, Noone A, Krapcho M, et al. Cancer Statistics Review, 1975-2015, National Cancer Institute. Based on November 2018 SEER data submission, posted to the SEER web site, April 2019. https://seer.cancer.gov/csr/1975_2015/ (2018, accessed January 7, 2019).
11. Moreau P, San Miguel J, Sonneveld P, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv52-iv61.
12. 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.
13. San-Miguel JF, Schlag R, Khuageva NK, et al. Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in

patients with previously untreated multiple myeloma. J Clin Oncol. 2013;31(4):448-455.
14. 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.
15. Facon T, Dimopoulos MA, Dispenzieri A, et al. Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. Blood. 2018;131(3):301-310.
16. Chng W-J, Goldschmidt H, Dimopoulos MA, et al. Carfilzomib–dexamethasone vs bortezomib–dexamethasone in relapsed or refractory multiple myeloma by cytogenetic risk in the phase 3 study ENDEAVOR. Leukemia. 2017;31(6):1368-1374.
17. Avet-Loiseau H, Fonseca R, Siegel D, et al. Carfilzomib significantly improves the progression-free survival of high-risk patients in multiple myeloma. Blood. 2016;128(9):1174-1180.
18. 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.
19. Bringhen S, D'Agostino M, De Paoli L, et al. Phase 1/2 study of weekly carfilzomib, cyclophosphamide, dexamethasone in newly diagnosed transplant-ineligible myeloma. Leukemia. 2018;32(4):979-985.
20. Bringhen S, Mina R, Petrucci MT, et al. Once-weekly *versus* twice-weekly carfilzomib in patients with newly diagnosed multiple myeloma: a pooled analysis of two phase I/II studies. Haematologica. 2019;104(8):1640-1647.
21. Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood. 2016;127(24):2955-2962.
22. Larocca A, Mina R, Offidani M, et al. First-line therapy with either bortezomib-melphalan-prednisone or lenalidomide-dexamethasone followed by lenalidomide for transplant-ineligible multiple myeloma patients: a pooled analysis of two randomized trials. Haematologica. 2019 Jun 27.[Epub ahead of print]
23. Sonneveld P, Goldschmidt H, Rosiñol L, et al. Bortezomib-based versus nonbortezomib-based induction treatment before autologous stem-cell transplantation in patients with previously untreated multiple myeloma: a meta-analysis of phase III randomized, controlled trials. J Clin Oncol. 2013;31(26):3279-3287.
24. Avet-Loiseau H, Bahlis NJ, Chng W-J, et al. Ixazomib significantly prolongs progression-free survival in high-risk relapsed/refractory myeloma patients. Blood. 2017;130(24):2610-2618.
25. Gay F, Cerrato C, Scalabrini DR, et al. Carfilzomib-Lenalidomide-Dexamethasone (KRd) Induction-Autologous Transplant (ASCT)-Krd Consolidation Vs KRd 12 Cycles Vs Carfilzomib-Cyclophosphamide-Dexamethasone (KCd) Induction-ASCT-KCd Consolidation: Analysis of the Randomized FORTE Trial in Newly Di. Blood. 2018;132(Suppl 1):121.
26. Gay F, Rota Scalabrini D, Belotti A, et al. Updated Efficacy and MRD Data According to Risk Status in Newly Diagnosed Myeloma Patients Treated with Carfilzomib Plus Lenalidomide or Cyclophosphamide: Results from the FORTE Trial. HemaSphere. 2018;2(S1):6.
27. Facon T, Kumar SK, Plesner T, et al. Phase 3 Randomized Study of Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) in Patients with Newly Diagnosed Multiple Myeloma (NDMM) Ineligible for Transplant (MAIA). Blood. 2018;132(Suppl 1):LBA-2.
28. Facon T, Kumar S, Plesner T, et al. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. N Engl J Med. 2019;380(22):2104-2115.
29. Mateos M-V, Dimopoulos MA, Cavo M, et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. N Engl J Med. 2018;378(6):518-528.
30. Lakshman A, Painuly U, Rajkumar SV, et al. Impact of acquired del(17p) in multiple myeloma. Blood Adv. 2019;3(13):1930-1938.
31. Thakurta A, Ortiz M, Blecua P, et al. High subclonal fraction of 17p deletion is associated with poor prognosis in multiple myeloma. Blood. 2019;133(11):1217-1221.

Tables

Table 1. Patient characteristics at baseline

	ALL PATIENTS n=94	STANDARD-RISK PATIENTS n=57	HIGH-RISK PATIENTS n=37
Age			
median (range)	72 (68-75)	72 (68 -75)	72 (68-74)
≥75 years n (%)	24 (26%)	16 (28%)	8 (22%)
Sex, n (%)			
Male	40 (43%)	24 (42%)	16 (43%)
Female	54 (57%)	33 (58%)	21 (57%)
ISS, n (%)			
I	28 (30%)	19 (33%)	9 (24%)
II	32 (34%)	17 (30%)	15 (41%)
III	34 (36%)	21 (37%)	13 (35%)
FISH, n (%)			
t(4;14)	12 (13%)	-	12 (32%)
t(14; 16)	4 (4%)	-	4 (11%)
del17p	22 (23%)	-	22 (59%)
≥2 CA*	1 (1%)	-	1 (3%)
FRAILTY SCORE, n (%)			
Fit	53 (56%)	34 (60%)	19 (51%)
Intermediate	29 (31%)	18 (32%)	11 (30%)
Frail	12 (13%)	5 (9%)	7 (19%)
LDH [UI/mmol]			
median (range)	282.5 (168-361)	288 (198-359)	274 (154-386)
Missing	18 (19%)	13 (23%)	5 (14%)

Abbreviations: ISS, International Staging System; FISH, fluorescence in situ hybridization; LDH, lactate dehydrogenase; n, number; CA, cytogenetic abnormalities.
*At least 2 cytogenetic abnormalities among t(4;14), t(14;16) and del17p.

Table 2. Best response after induction phase and overall (induction and maintenance).

	ALL PATIENTS n=94	STANDARD-RISK PATIENTS n=57	HIGH-RISK PATIENTS n=37
RESPONSE AFTER INDUCTION			
ORR, n (%)	83 (88%)	49 (86%)	34 (92%)
sCR/CR	19 (20%)	11 (19%)	8 (22%)
VGPR	42 (45%)	25 (44%)	17 (46%)
PR	22 (23%)	13 (23%)	9 (24%)
SD	6 (6%)	4 (7%)	2 (5%)
NA	5 (5%)	4 (7%)	1 (3%)
RESPONSE INDUCTION and MAINTENANCE			
ORR, n (%)	85 (90%)	50 (88%)	35 (95%)
sCR/CR	22 (23%)	13 (23%)	9 (24%)
VGPR	42 (45%)	25 (44%)	17 (46%)
PR	21 (22%)	12 (21%)	9 (24%)
SD	4 (4%)	3 (5%)	1 (3%)
NA	5 (5%)	4 (7%)	1 (3%)

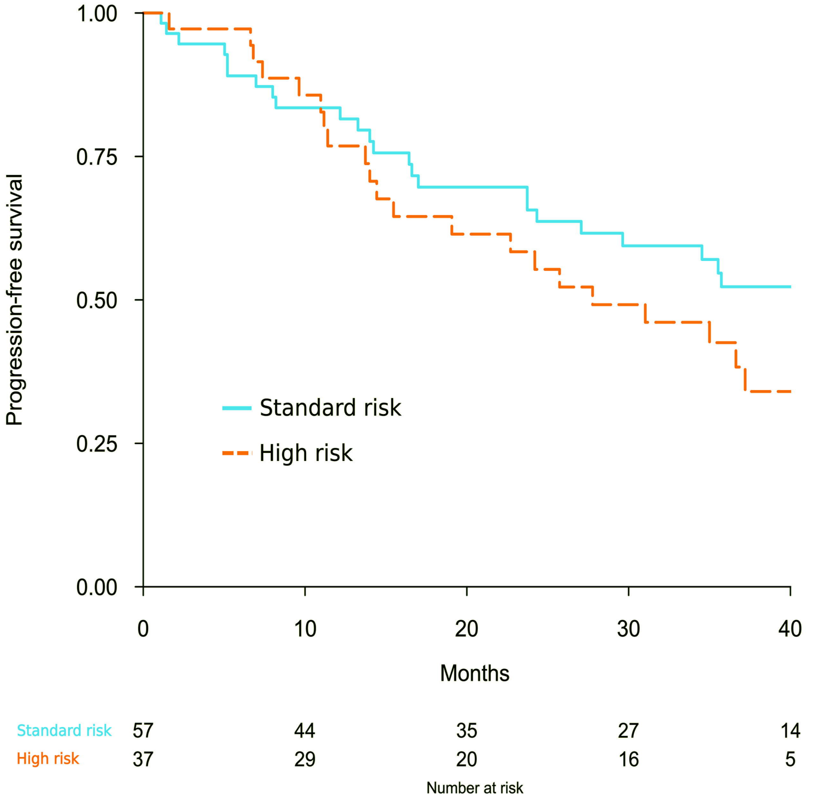
Abbreviations: ORR, overall response rate; CR, complete response; sCR, stringent CR; VGPR, very good partial response; PR, partial response; SD, stable disease; NA, not available; n, number.

Figure titles

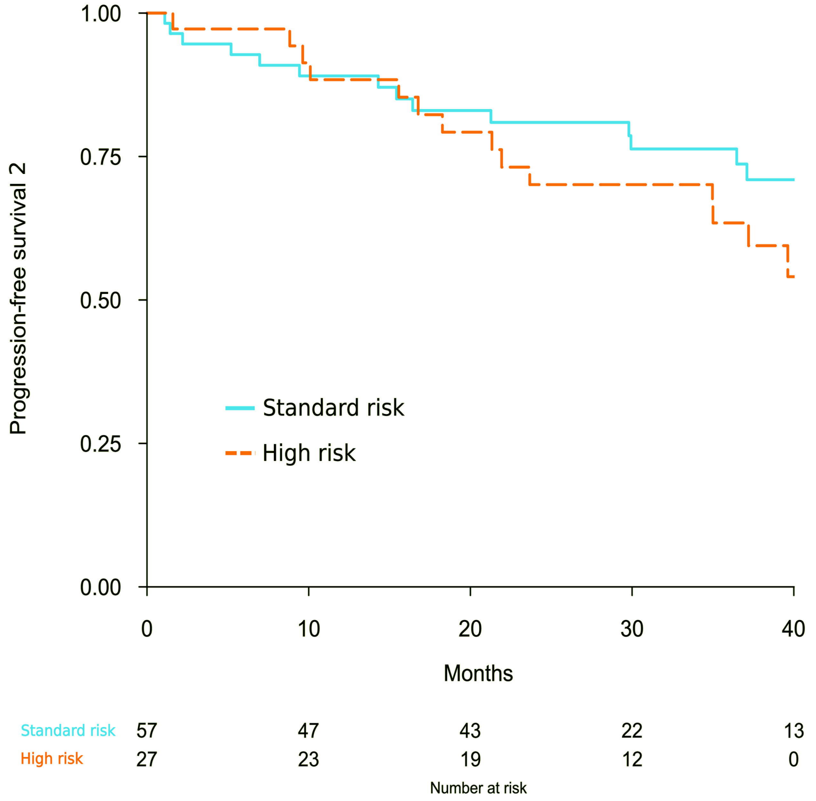
Figure 1. Standard-risk vs high-risk patients. **Panel A**, progression free survival (PFS); **Panel B,** PFS-2; **Panel C,** overall survival (OS)

Figure 2. Median progression-free survival (PFS) according to del17p status

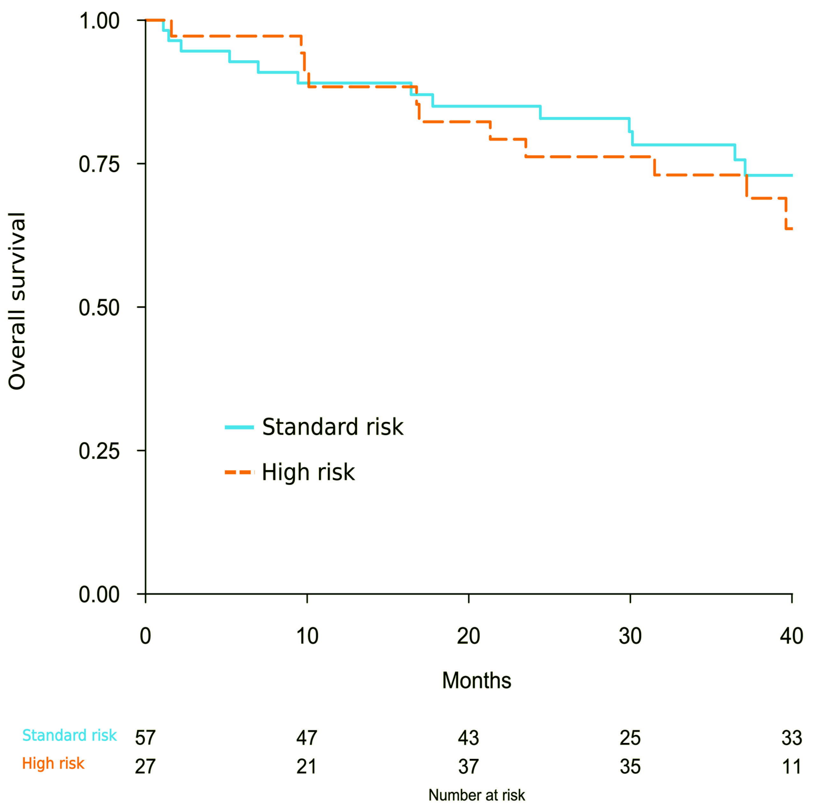
1A. PFS



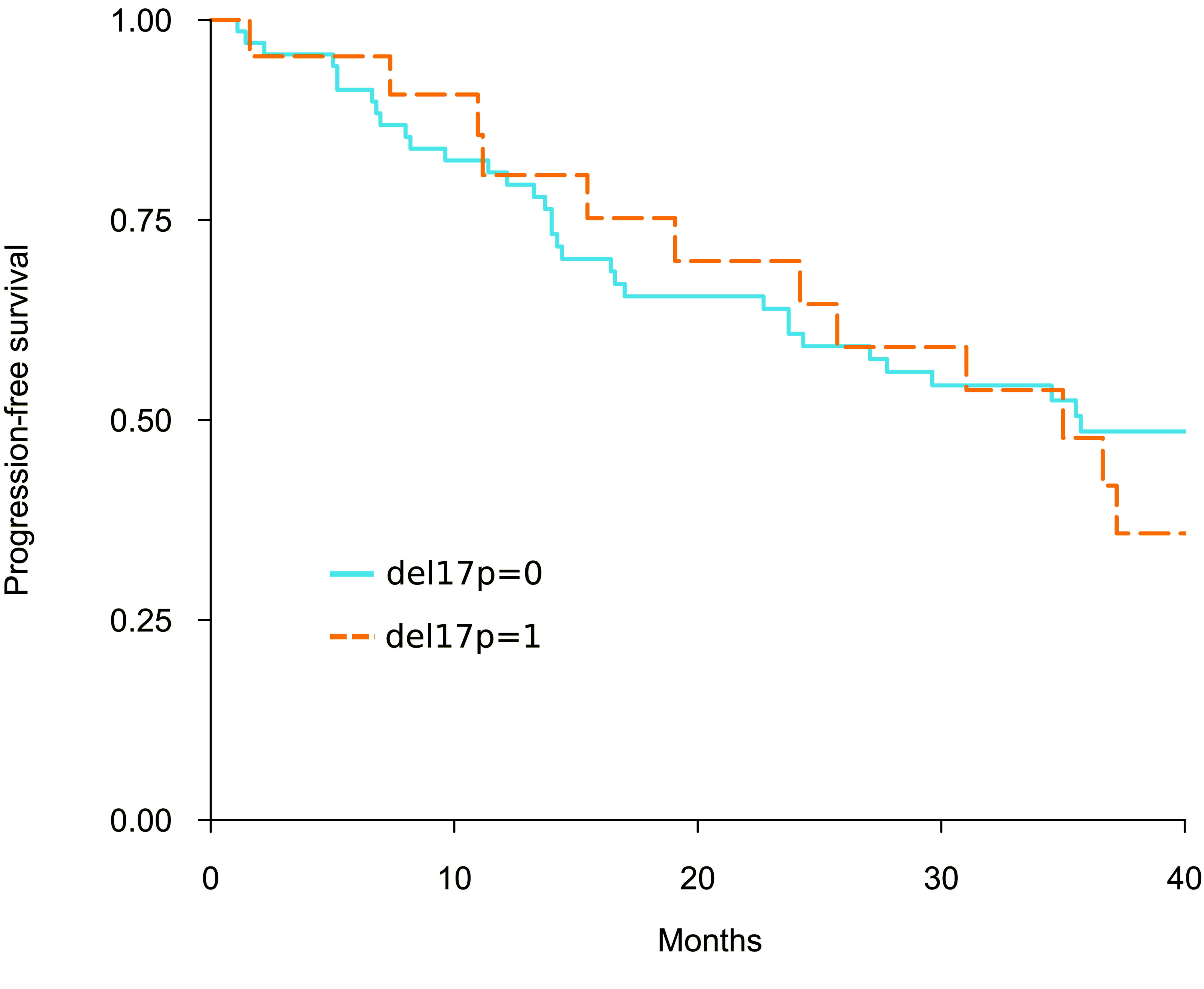
1B. PFS-2



1C. OS



2. PFS according to del17p



	0	10	20	30	40
del17p=0	72	55	42	32	15
del17p=1	22	18	13	11	4

Number at risk