

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



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ABSTRACT

Despite remarkable advances in the treatment of multiple myeloma (MM) 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 have been 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 MM receiving upfront carfilzomib cyclophosphamide and dexamethasone followed by carfilzomib maintenance. The aim of this analysis was to compare treatment outcomes in patients with standard-risk *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-risk *versus* high-risk patients, we observed similar progression-free survival (PFS) (3-year PFS: 52% *vs.* 43%, respectively; $P=0.50$), overall survival (OS) (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 PFS was observed between patients with or without del17p. Carfilzomib, used both as induction and maintenance agent for transplant-ineligible newly diagnosed MM patients, mitigated the poor prognosis carried by high-risk cytogenetics and resulted in similar PFS and OS as in standard-risk patients. (Registered at clinicaltrials.gov identifiers: NCT01857115 [IST-CAR-561] and NCT01346787 [IST-CAR-506].)

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Introduction

Multiple myeloma (MM) is a plasma cell dyscrasia with a heterogeneous prognosis ranging from a few years to over a decade, according to both disease-related factors (such as albumin and β -2 microglobulin 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 CA detected by fluorescence *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 with a dismal prognosis.⁴ Another adverse CA is t(4;14), which is carried by 12-15% 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 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 three 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 (ASCT). In this patient 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) patients (HR:1.29).^{12,13} In the FIRST study, among patients receiving continuous Rd, the median PFS was 8.4 months in HiR patients *versus* 31.1 in SR patients.^{14,15}

Carfilzomib is a second-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) elderly MM patients (NDMM).^{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 SR and HiR patients.

Methods

Study design and treatment

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

Details of study procedures have been published previously.¹⁸⁻²⁰ Briefly, in both trials treatment consisted of nine 28-day cycles of KCyD followed by maintenance with single-agent carfilzomib until disease progression or intolerance. Carfilzomib was administered once weekly (70 mg/m²) in the IST-CAR-561 study and twice weekly (36 mg/m²) in the IST-CAR-506 study. The same doses and schedules of cyclophosphamide (oral 300 mg on days 1, 8 and 15) 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 *versus* 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 (CI). 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).

Table 1. Patients' 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 [U/mmol]			
Median (range)	282.5 (168-361)	288 (198-359)	274 (154-386)
Missing	18 (19%)	13 (23%)	5 (14%)

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

Results

Among the 121 patients 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 patients in the HiR group, t(4;14) was present in 12 patients (13%), t(14;16) in four 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% (range: 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 or 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 of 57 in the SR and 36 of 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; $P=0.47$). In addition, 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 and in 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 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 (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, $P=0.70$) (Figure 2). When adopting a higher cut-off for del17p positivity (>20%), no significant difference in PFS was reported between del17p-negative and del17p-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

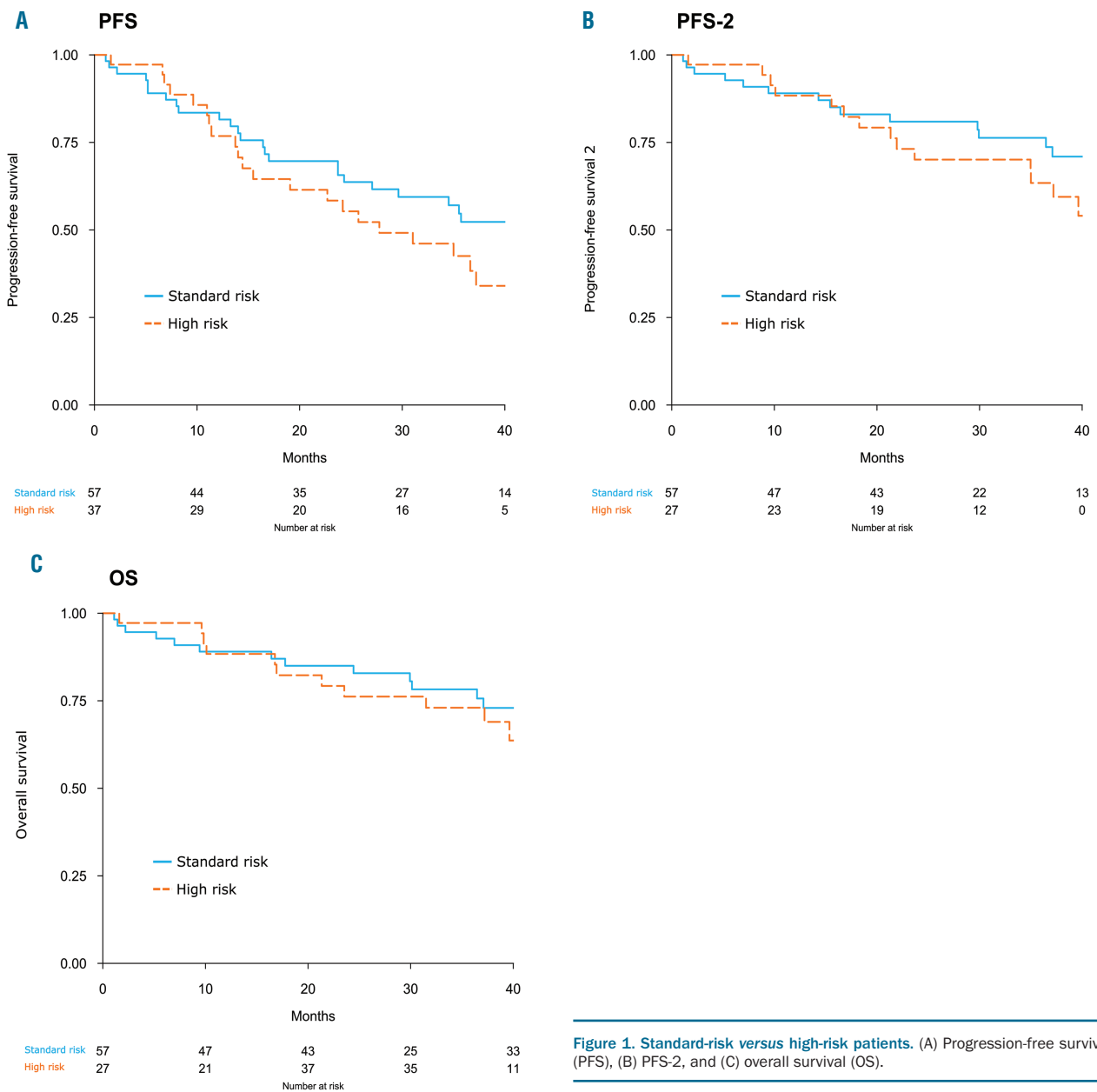


Figure 1. Standard-risk versus high-risk patients. (A) Progression-free survival (PFS), (B) PFS-2, and (C) overall survival (OS).

negative impact of HiR cytogenetics and ameliorate the prognosis of transplant-ineligible MM patients carrying HiR CA.

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 (*clinicaltrials.gov* identifier: NCT03829374). 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 approximately 10 months compared to Rd in patients with HiR cytogenetics, although median PFS in HiR patients treated with KRd (23 months) remained approximately 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 versus 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,

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%)

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.

respectively).²⁴ The efficacy of newer PI 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 (\geq VGPR) or a CR was similar to that of SR patients.²⁵ In the phase II FORTE study, similar \geq VGPR rates (79% vs. 86%) and minimal residual disease negativity (62% vs. 49%) were obtained with eight 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 PI, especially those of the second generation such as carfilzomib, can at least partially abrogate the adverse impact of high-risk CA 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 trial¹⁵ (PFS: 8.4 months; OS: 29.3 months) and VMP in the VISTA study¹² (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 patients ineligible for transplant. 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

PFS according to del17p

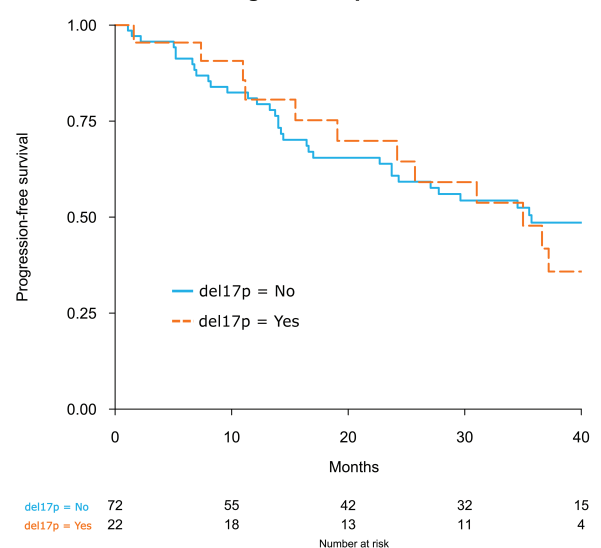


Figure 2. Median progression-free survival (PFS) according to del17p status.

number of patients analyzed does not allow definite conclusions to be drawn on this issue, 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 slightly 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 same time as 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 be of particular benefit to HiR patients. However, continuous therapy is not sufficient to overcome the poor prognosis of adverse CA. For example, 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.

Disclosures

RM has received honoraria from Sanofi, Celgene, Takeda and Janssen; has served on the advisory boards for Sanofi, Takeda, and Janssen; has received consultancy fees from 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, and Servier, has received clinical trial support from Novartis, AbbVie, Roche, Amgen, and Celgene, has served on the advisory boards for AbbVie, Amgen, Takeda, and 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 boards for Janssen; MB has received honoraria from Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol-Myers Squibb, and AbbVie; has served on the advisory boards for Janssen and GSK; 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 have no conflicts of interest to disclose.

Contributions

RM, FB, PO, MB and SB made substantial contributions to the conception or design of the analysis; all authors are responsible for the acquisition, analysis or interpretation of data; RM, FB, AC, MG, PO and SB made the first draft of the manuscript; AC carried out the statistical analysis; MB and SB supervised the analysis; all authors critically revised the manuscript for important intellectual content; all authors gave their final approval of the version to be published; all authors agree 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.

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