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Running head: **Once-weekly KPd for Relapsed/Refractory Myeloma**

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Despite the progress made in the past two decades, multiple myeloma (MM) remains an incurable disease and the prognosis of patients relapsing after first-generation novel agents is extremely poor (1). Pomalidomide and carfilzomib, respectively second-generation immunomodulatory drug (IMiD) and proteasome inhibitor (PI), proved to be effective in patients previously exposed to both lenalidomide and bortezomib(2–4) and received approval for the treatment of relapsed/refractory MM (RRMM).

Synergism between IMiDs and PIs has been demonstrated (5–7): twice-weekly carfilzomib in combination with pomalidomide and dexamethasone (KPd) was well tolerated and effective in patients refractory to lenalidomide (8).

Currently, carfilzomib is approved with the twice-weekly schedule at a dose of 27 mg/m^2; however, higher doses of weekly carfilzomib, up to 70 mg/m^2, could be safely administered, with similar efficacy as compared to the twice-weekly schedule [11-12].

Herein, we report the results of a phase I/II trial with once-weekly KPd (wKPd) in RRMM patients.

Patient eligibility, study design and statistical analysis are summarized in Supplementary Appendix.

Briefly, patients with relapsed MM, or RRMM to the last line of therapy, who received 1 to 3 previous anti-myeloma therapies, and were primary refractory or relapsed and refractory to lenalidomide were eligible. Patients could be either pre-treated with bortezomib or bortezomib-naïve.

In the phase 1 portion, the primary endpoint was the maximum tolerated dose (MTD) of wKPd (Table S1).

In the phase 2 portion, patients received the MTD of carfilzomib; the primary endpoint was the partial response (PR) rate.

Treatment with wKPD consisted of a fixed induction (eight 28-day cycles) with weekly carfilzomib (20 mg/m^2 intravenously on day 1 cycle 1, then at a higher dose according to cohort level on days 8 and 15), pomalidomide (4 mg orally on days 1-21) and dexamethasone (20 mg on days 1, 8, 15 and 22; Figure S1). Afterwards, patients could receive maintenance treatment (28-day cycles) with carfilzomib (according to the assigned dose level, on days 1, 8 and 15), pomalidomide (4 mg, on days 1-21/28) and dexamethasone (20 mg on days 1, 8, 15 and 22), until progression or intolerance. According to physician's discretion, patients could proceed to wKPd until progression or to maintenance with pomalidomide alone. Adverse event (AE) assessment and response criteria are described in Supplementary Appendix.

The institutional review board at each participating centre approved the study in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Between July 2014 and December 2015, 57 patients were enrolled at 6 Italian centres: 15 patients in the phase 1, 42 in the phase 2. Patient characteristics are listed in Table S2, dose levels and the observed DLTs are in Table S3.

Five DLTs were observed: 2 with carfilzomib at the dose of 45 mg/ m^2 (1 grade 3 hypertension and 1 sudden death) and 3 with carfilzomib at the dose of 36 mg/ m^2 (1 grade 3 atrial fibrillation, 1 grade 3 hypertension and 1 grade 5 heart failure). Four of 5 DLTs in the first 9 patients were considered related to hypertension.

In light of the cardiovascular events observed, the safety committee established new safety procedures for both screening and treatment: all patients underwent a cardiovascular screening before starting treatment, and a strict blood-pressure control before and after carfilzomib infusion.

As per protocol, 6 additional patients were enrolled at dose level -1 (carfilzomib 27 mg/ m^2) and no DLTs were reported. The MTD of carfilzomib in combination with pomalidomide and dexamethasone was then determined to be 27 mg/m^2.

Forty-eight patients were assigned to the MTD of carfilzomib; 47 of them were evaluable for safety and efficacy, 1 patient did not start treatment due to a protocol violation and, consequently, was not included in the analysis.
Twenty-five (53%) patients completed the induction phase and proceeded to maintenance, while 22 patients discontinued treatment before maintenance: 17 (36%) due to progressive disease (PD), 2 (4%) for toxicity, 2 (4%) to proceed to allogeneic stem-cell transplantation and 1 (2%) for other reasons.
Patients received a median of 8 cycles (range, 1-21 cycles) of study treatment. The overall response rate (ORR) reported after induction in patients treated at the MTD of carfilzomib was 62% (Table S4); 18 patients achieved PR (38%), 9 very good partial response (VGPR; 19%), 1 near complete response (nCR; 2%) and 1 complete response (CR; 2%). Taking into account 11 patients who had a stable disease (23%), the clinical benefit rate was 85%.
Responses were rapid, with median time to PR of 2.1 months (95% CI, 1.9 – 6.8), and were not affected by previous therapies: the ORR was 54% among patients refractory to lenalidomide only and 71% in patients refractory to both lenalidomide and bortezomib, with equal VGPR rate (19%).
After a median follow-up of 12.8 months, median PFS was 10.3 months, whereas median OS was not reached and the 1-year OS was 67% (Figure 1).
Patients with standard-risk fluorescence in situ hybridization (FISH) had a significantly higher ORR rate in comparison with those with high-risk fluorescence in situ hybridization (80% vs 40%, respectively; p= 0.04). However, median PFS (11.4 vs 10.7 months, HR 0.61; p=0.3) and OS (median not reached in both groups; 1 year-OS: 74% vs 60%, HR 0.54, p=0.3) were similar in the two risk groups.
Similar outcomes were reported in patients refractory to lenalidomide or lenalidomide and bortezomib (median PFS: 9.8 vs 10.3 months, HR: 1.16, p=0.68.
Any grade haematological treatment-emergent adverse events (AEs) occurred in 37 (79%) patients, grade 3-4 haematological AEs occurred in 30 (64%) patients, including neutropenia in 30 (64%), thrombocytopenia in 6 (13%) and anaemia in 5 (11%) patients (Table 1).
Any grade non-haematological treatment-emergent AEs were observed in 36 (77%) patients, grade 3-4 non-haematological AEs were reported in 11 (23%) patients, and the most frequent were infections in 5 (11%), vascular events in 4 (9%), cardiac events and fatigue in 2 (4%) patients each; no grade 5 AE was reported.
Any grade cardiovascular AEs occurred in 9 patients (19%), grade 3-4 events occurred in 5 (11%) patients, including cardiac AEs in 2 (4%) and hypertension in 3 (6%) patients.
Nine (19%) patients needed at least one dose reduction due to AEs: 1 (2%) reduced both carfilzomib and dexamethasone doses due to dyspnea, 4 (9%) reduced pomalidomide dose (2 for fever, 1 for pneumonia and 1 for thrombocytopenia) and 4 (9%) reduced dexamethasone dose (1 for infection, 1 hypertension, 1 steroid-related myopathy and 1 for hepatic toxicity).
In patients treated at the MTD of carfilzomib (27 mg/m^2), wKPd proved to be safe and effective, inducing an objective response in 62% of patients, that translated into a median PFS of 10.3 months. Of note, wKPd was active in double refractory patients, with comparable ORR (54% vs 71%) and median PFS (10 months in both groups) to patients refractory to lenalidomide only.
Despite the limitations of cross-trial comparisons, wKPd in our study induced higher ORR (62% vs 20-30%) and longer PFS (median, 10 vs 4-5 months) compared with pomalidomide or carfilzomib plus dexamethasone (2,3,10,11).
Furthermore, the ORR and median PFS reported with wKPd in our study were not inferior to those observed with twice-weekly KPd (ORR 50%; PFS 7 months), with a lower rate of dose reductions (19% vs 37%) and treatment discontinuations (4% vs 19%) due to AEs (8). Yet,

caution is needed when interpreting these data, as patients enrolled in the above-mentioned trials were more heavily pre-treated than patients in our trial.
In our study, the protocol did not allow investigators to re-escalate the dose of carfilzomib in the phase 1; we do not know whether the new safety cardio-vascular procedures might have allowed an additional carfilzomib dose escalation to improve the efficacy of the regimen.
Once-weekly KPd was well tolerated in the present trial: myelosuppression was the major toxicity reported but AEs were mainly limited to grade 1-2.
During the dose escalation phase, 5 DLTs were observed, all cardio-vascular in nature and mainly related to hypertension. The adoption of safety procedures, during screening and treatment, together with a lower dose of carfilzomib (27 mg/m2), led to a significant reduction of any grade (78% vs 19%; p=0.001) and grade 3-4 (56% vs 6%; p=0.003) cardiovascular AEs.
The rates of any grade and grade 3-4 hypertension (6%) and cardiac events (4%) in patients treated at the MTD of carfilzomib were consistent with previously published data (4,7,12).
In conclusion, once-weekly carfilzomib at the MTD of 27 mg/m^2, pomalidomide (4 mg) and dexamethasone (20 mg) is a safe and effective treatment option for RRMM patients after lenalidomide and bortezomib. A baseline screening for cardiovascular risk factors and blood pressure monitoring are recommended to guarantee treatment tolerability and compliance.
The promising ORR and PFS support further investigation of higher doses of once-weekly KPd, and a formal comparison of once- versus twice-weekly KPd in future trials for RRMM patients.

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AUTHORSHIP
Contribution: S.B., R.M., A.P., P.S., and M.B. designed the study and supervised its conduct and the data analysis; S.B., R.M., A.M.C., A.M.L., A.B., G.G., F.P., R.F., L.D.P., G.R., A.L., P.B., and M.B recruited patients in the source studies and provided relevant data; S.B., R.M., R.T. collected, assembled, and analyzed the data; S.S. performed the statistical analysis; S.B. and R.M. drafted the initial manuscript; and all authors were given unrestricted access to the data, critically reviewed the manuscript drafts, approved the final version, and made the decision to submit the manuscript for publication.

Conflict-of-interest disclosure: S.B. has received honoraria from BMS, Celgene, Janssen-Cilag, and served on the advisory boards for Amgen and Janssen-Cilag; G.G. has served on the advisory boards for Roche, AbbVie, Janssen, Gilead, and Morphosys; F.P. has received lecturing fees from MSD Italia and served on the advisory board for Janssen; L.D.P has served on the advisory boards for AbbVie, Amgen, Celgene, and Janssen; G.R. has served on the advisory boards for Celgene and Amgen; A.P. is currently a Takeda employee; P.S. has received research support from Amgen, Celgene, Janssen, Karyopharm, and honoraria from Amgen, Celgene, Janssen, Karyopharm and BMS; and M.B. has received research funding from Amgen, BMS, Celgene, Janssen, Mundipharma, Novartis, Sanofi, and honoraria from AbbVie, Amgen, BMS, Celgene, Janssen, Novartis, Sanofi. The remaining authors declare no competing financial interests.

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Figure legend

Figure 1. Time-to-event analysis.
PFS (A) and OS (B) in patients treated with wKPd at the MTD