Carfilzomib Weekly plus Melphalan and Prednisone in Newly Diagnosed Transplant-Ineligible Multiple Myeloma (IFM 2012-03)

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Statement of significance.

The IFM2012-03 study demonstrated that the MTD of carfilzomib weekly is 70 mg/m2 in eNDMM, and 56 mg/m2 for patients older than 75 years.

Response rates, and especially CR rate, were remarkable in this population, and would benefit from being assessed on a larger scale study.

Statement of translational relevance.

Carfilzomib (K) is a novel generation proteasome inhibitor with a different safety profile from bortezomib. The Carmysap trial demonstrated that twice-weekly KMP (carfilzomib, melphalan, prednisone) might challenge the MPV (melphalan, prednisone, bortezomib) standard. We sought to demonstrate that KMP with carfilzomib weekly can provide a good efficacy and improve convenience and safety profile.

IFM 2012-03 is a phase 1 multicenter study of KMP weekly in newly diagnosed elderly multiple myeloma (eNDMM), aimed to determine the maximum tolerated dose (MTD) of carfilzomib. The MTD dose of carfilzomib was 70mg/m^2. Response rates, and especially CR rate, were remarkable in this population.

Even though KMP might not be approved in eNDMM, it is likely that carfilzomib will be used in other regiments in future studies. This study confirms that carfilzomib used weekly has a good efficacy and safety profile and can be combined with other MM molecules.

ABSTRACT

Purpose. Carfilzomib is a novel generation proteasome inhibitor. The Carmysap trial demonstrated that twice weekly KMP (carfilzomib, melphalan, prednisone) might challenge the MPV (melphalan, prednisone, bortezomib) standard. We sought to study KMP weekly, allowing to increase carfilzomib's dose with maintained efficacy and improved safety profile.

Experimental design. IFM2012-03 is a phase 1 multicenter study of KMP weekly in newly diagnosed elderly multiple myeloma (eNDMM), aimed to determine the maximum tolerated dose (MTD) of carfilzomib. Carfilzomib was given IV at 36, 45, 56 and 70mg/m^2/day on days 1,8,15,22 with melphalan and prednisone, for nine 35-days induction cycles, followed by carfilzomib maintenance for 1 year. Three dose limiting toxicities (DLT) determined MTD at the lower dose.

Results. 30 eNDMM were treated, 6 per cohort at 36, 45, 56mg/m^2 and 12 at 70mg/m². There was one DLT at 36mg/m^2 (lymphopenia), one at 45mg/m^2 (lysis syndrome), two at 56mg/m^2 (cardiac insufficiency and febrile neutropenia) and two at 70mg/m^2 (vomiting and elevated liver enzymes). The safety profile was acceptable, however, specific attention must be paid to the risk of cardiovascular events especially for elderly patients. The overall response rate was 93.3% with 46.6% complete response.

Conclusions. The MTD dose of carfilzomib was 70mg/m^2 in this KMP weekly study in eNDMM. Response rates, and especially CR rate, were remarkable in this population, and would benefit from being assessed on a larger scale study.

INTRODUCTION

Bortezomib in combination with melphalan and prednisone (MPV) is one of the most widely used standard of care regimens in previously untreated transplant-ineligible multiple myeloma (eNDMM) (1, 2). Significant improvements were made to the MPV regimen design in the last 15 years, such as sub-cutaneous administration of bortezomib and weekly instead of twice-weekly schedule (3). MPV regimens modified with weekly bortezomib induced similar responses rates and survival than twice-weekly, because the actual delivered dose of bortezomib was similar or even higher than the actual delivered dose in the MPV regimen with twice-weekly bortezomib (4-7). Despite these advances, toxicity issues remain, that hamper the ability to administer MPV optimally and for a prolonged treatment period (2, 8).

Carfilzomib is an epoxyketone proteasome inhibitor that binds selectively and irreversibly to the constitutive proteasome and immunoproteasome (9). In a preclinical model, carfilzomib was shown to produce more potent anti-myeloma activity than bortezomib (10). Furthermore, this new generation proteasome inhibitor has a different safety profile from bortezomib, with a very low incidence of neuropathy (11, 12). Carfilzomib's favorable safety profile allows the use of an increased dose and prolonged duration of treatment, resulting in a more potent proteasome inhibition than with bortezomib.

The Intergroupe Francophone du Myélome (IFM) Carmysap phase 1/2 trial of twice-weekly carfilzomib plus MP (KMP) identified the maximum tolerated dose (MTD) of carfilzomib at 36 mg/m² in eNDMM patients (13). Efficacy was remarkable with an overall response rate of 90% across 50 evaluable patients treated at the MTD, a median progression free survival of 21 months (95% CI [18.2; 23.1]) and a projected 3-year overall survival rate of 80%. The safety profile appeared acceptable in this transplant-ineligible population at the MTD. Similarly to what has been observed with bortezomib, it has been hypothesized that a weekly administration of carfilzomib, more convenient, would improve patients' compliance and result in a longer time on treatment than the twice-weekly schedule. The administration of carfilzomib has thus then been evaluated on a weekly schedule. The phase 1/2 Champion study of weekly carfilzomib with dexamethasone was performed in relapsed or refractory MM. In this study, carfilzomib at 70 mg/m^2 had an acceptable safety profile, and led to an ORR of 77% and a median progression-free survival of 12.6 months (14).

Based on these data, we hypothesized that in the KMP regimen, carfilzomib could be as effective weekly as the twice-weekly standard in eNDMM patients. Given its positive safety profile, the dose of carfilzomib weekly could be increased compared to twice-weekly.

METHODS

Study. IFM (Intergroupe Francophone du Myelome) 2012-13 (Carmysap weekly) is a phase 1, multicenter, single-arm, dose-escalation study investigating carfilzomib administered on a weekly schedule in combination with melphalan and prednisone for transplant-ineligible patients with untreated MM (eNDMM). Two Belgian and 42 French IFM centers participated in this study.

This study was conducted in accordance to the Conference on Harmonization Guidelines for Good Clinical Practice. Institutional Review Board approval was obtained and the study was registered at ClinicalTrials.gov under the following number: NCT02302495. The sponsor designed the study in collaboration with the investigators, and collected, analyzed, and interpreted the data in conjunction with the investigators.

Objectives. The primary objective of the study was to determine the incidence of dose-limiting toxicities (DLTs) during the first cycle of carfilzomib weekly in KMP and to define the maximum tolerated dose (MTD) of carfilzomib.

Secondary objectives were to determine the safety profile (incidence and severity of adverse events) of carfilzomib weekly at each dose level, to evaluate the response rate during the first 9 cycles and during maintenance, to evaluate the progression free survival (PFS, defined as the time from enrollment until disease progression or death from any cause) and overall survival (OS, defined as the time from enrollment until the date of death or the date the patient was last known to be alive).

Study design. In this dose-escalation study, 6 patients were to be included per cohort. 4 cohorts were initially planned at 36, 45, 56 and 70mg/m^2 of carfilzomib weekly, and per DMC request (Data Monitoring Committee, or DSMB Data and Safety Monitoring Board) a second cohort was recruited upon protocol amendment. The amendment was aimed at increasing hypertension and fluid overload awareness on carfilzomib treatment. Rules to better manage these adverse events were provided. In particular, hydration was limited to 250 to 500 mL intravenously at each administration of carfilzomib, and oral and intravenous hydration were adapted to the risk of renal insufficiency and to the risk of fluid overload. Blood pressure was monitored during each carfilzomib administration and corrected if needed, with reintroduction of carfilzomib upon normalization of blood pressure.

If $\leq$ 2 DLTs were observed at a dose level, 6 patients were subsequently enrolled at the next dose level. If > 2 DLTs were observed at a dose level, the previous dose level was identified as the MTD.

DLTs. DLTs were defined as any hematologic toxicity of grade 4 intensity or preventing administration of 2 or more of the 4 carfilzomib doses of the first treatment cycle, grade 3 febrile neutropenia, grade $\geq$ 3 gastrointestinal toxicities, any other grade $\geq$ 3 non-hematologic toxicity considered related to KMP by the principal investigator and grade $\geq$ 3 peripheral neuropathy persisting for more than 3 weeks after discontinuation of study drugs.

Treatment. The KMP regimen was given in induction and maintenance. During the induction, patients received oral melphalan (0.25 mg/kg) and oral prednisone (60 mg/m^2) on days 1 to 4, in combination with carfilzomib IV weekly on days 1, 8, 15, 22 of a 35-day cycle. Patients received up to

9 cycles of induction treatment. Carfilzomib was administered as 30-minute IV infusion, and the first dose (first cycle day 1) was fixed at 20 mg/m². During maintenance patients received carfilzomib monotherapy, 36 mg/m^2 every two weeks for one year.

Patients. Eligible patients were 65 years of age or older and presented with symptomatic, measurable, previously untreated MM**.** Additional eligibility criteria included: be able to understand and voluntarily sign an informed consent form and be able to adhere to the study visit schedule and other protocol requirements, Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2, absolute neutrophil count ≥ 1 x10^9/L, spontaneous platelet count > 75 x10^9/L and hemoglobin ≥ 8.5 g/dL.

The main exclusion criteria included terminal renal failure that required dialysis or clearance creatinine < 30 ml/min, history of other cancer, heart failure class 3 and 4 according to the NYHA criteria, past history of myocardial infarction within the last 6 months or uncontrolled cardiac conduction abnormalities, left ventricular ejection fraction below 45% (LVEF < 45%), patients known positive for HIV or active infectious type B or C hepatitis, and female of childbearing potential. Male subjects must understand the potential teratogen risk of melphalan and the potential genotoxic risk of carfilzomib if engaged in sexual activity with a pregnant female or a female of childbearing potential.

Assessments. Efficacy assessments occurred on a 35-days basis for the first 9 induction cycles then on a monthly basis during the maintenance phase, then on a 2-months basis during the follow up phase until progression. Response to therapy was assessed according to the International Myeloma Working Group (IMWG) Uniform Response Criteria (15). The incidence and severity of adverse events (AEs) were assessed at each patient visit and were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (version 4.0).

Statistical analyses. Analyses were done on an Intent to Treat (ITT) basis, including for analysis all patients that received day 1 cycle 1. All survival end points were evaluated through the Kaplan-Meier estimates and compared through the Log-rank test. The estimate of the relative risk of event and its 95% confidence interval (95%CI) were estimated through a proportional hazard model. All analyses were done by the unit of biostatistics, CHRU Lille.

RESULTS

Patients. Thirty-two eNDMM patients were recruited and 30 were treated across 5 cohorts (6 patients per cohort at 36, 45, 56 mg/m^2 and 12 patients at 70 mg/m²) during this phase 1 study (**Figure 1**). The median age was 73 years, with 43.3% of patients older than 75 years. 58.6% of patients had a R-ISS score of 2 or 3. Patients' characteristics are summarized in **Table 1**, and patients' characteristics by cohort are presented in Supplementary Table 1. At data cut-off, 10 patients had completed therapy and 8 patients were still on therapy. The remaining patients stopped therapy during induction or maintenance (**Figure 1**).

Determination of MTD of carfilzomib in the KMP regimen. There was one DLT at 36 mg/m^2 (grade 4 lymphopenia), one at 45 mg/m^2 (tumor lysis syndrome with grade 4 renal insufficiency), two at 56 mg/m^2 (cardiac insufficiency grade 4 and febrile neutropenia grade 4) and two at 70 mg/m^2 (vomiting grade 3 and elevated liver enzymes grade 3). DLTs are summarized in **Table 2**.

The MTD of carfilzomib weekly in KMP was thus 70 mg/m² in this study.

Response rate. For the 30 treated patients, the overall response rate (ORR) was 93.3%, including 70% of patients achieving ≥ VGPR (very good partial response) and 46.6% ≥ CR (complete response). Response rates are summarized in **Table 3**. Response rates by cohort are presented in Supplementary Table 2. Median time to best response was 3 months, and median duration of response was 17.5 months (Supplementary Figure 1).

Progression-free survival (PFS) and overall survival (OS). At data cut-off, 8 patients had progressed and 3 had died of whom one of cardiac dysfunction considered related to carfilzomib at 56 mg/m². With a median follow-up of 28 months, median PFS was 35.8 months, median OS was not reached. The estimated OS was 90% at 2 years. Survival curves for PFS and OS are presented in **Figure 2A and 2C**. Of note, progression was observed across all cohorts (at 45, 56 and 70 #1) except the last cohort at 70 (70 #2), which had a shorter follow-up. Event-free survival (EFS) and time to new treatment (TTNT) are presented in Supplementary Figure 1.

We also wanted to assess whether prognosis factors impacted survival on KMP weekly. Patients with high-risk cytogenetic MM seemed to have a shorter median PFS and OS than low-risk patients, even though no conclusion should be drawn given the low number of high-risk patients. In that regard, this data might point out that replacing bortezomib with carfilzomib in an MP-based combination did not improve outcome of MM patients with high-risk features. However, it should be noted that the high-risk MM were treated in the 45 and 56 mg/m^2 cohorts, and no data is available at the maximum tolerated dose of 70 mg/m^2. Even though we did not find a clear dose effect of carfilzomib in our study, one could wonder whether their outcome would have been improved with a higher dose. Survival curves according to cytogenetic risk are presented in Supplementary Figure 2A for PFS and 2B for OS. Interestingly, PFS and OS were quite prolonged even in these elderly MM patients.

Furthermore, it has been extensively demonstrated that depth of response is of key importance for survival in MM, including in elderly patients. We therefore thought to compare patients according to depth of response, and we found that patients in CR expectedly performed better than patients in VGPR. Survival curves according to depth of response are presented on **Figure 2B for PFS and 2D for OS**. The lack of statistical significance could be explained by the limited number of patients included in this phase 1 study.

This data acknowledge that patients with poor prognosis according to cytogenetics remain so on KMP weekly, and similarly, less sensitive patients characterized with lower deep response rates also

perform poorly on KMP weekly. However, PFS and OS might be considered interestingly prolonged compared to other standard of care in this frail eNDMM population.

Safety profile. For the whole cohort, 33 serious adverse events (SAEs) were reported for a total of greater than 200 cycles administered of KMP. Of particular interest, 20 SAEs were reported across the carfilzomib 56 and 70 mg/m^2 cohorts, 6 of which were of cardiovascular origin, in 4 patients (3 cardiac failures (including 1 associated with pulmonary edema and 1 associated with pulmonary embolism), and 1 myocardial infarction). To note, all 4 patients presented uncontrolled elevated blood pressure before the beginning of carfilzomib therapy. At least 2 cases of cardiac failure occurred during hyperhydration administered around carfilzomib infusion. These events led the DMC to request a second carfilzomib 70 mg/m^2 KMP cohort. Interestingly, with special attention drawn around hyperhydration and monitoring blood pressure, no grade 3/4 adverse events were recorded in this second 6-patients KMP cohort at 70 mg/m² of carfilzomib, nor any DLT.

Safety profile appeared otherwise acceptable. Adverse events observed in ≥ 10% of patients are presented in **Table 4**, and severe adverse events are presented in Supplementary Table 3. Serious adverse events by cohort are presented in Supplementary Table 4. The most frequent non-hematological toxicities were gastro-intestinal, including nausea, vomiting, transit disorders and appetite loss. Hematological toxicities were also common, although only one febrile neutropenia was reported. Among cardio-vascular toxicities, hypertension was the most frequent reported adverse events.

Dose reductions and discontinuation. Overall, 12 patients discontinued the treatment among which 7 during induction and 5 during maintenance (**Figure 1**). Among these 12 patients, 7 patients stopped treatment because of toxicity, 3 patients because of progression, 1 patient because of lack of efficacy and 1 by patient decision. The toxicities leading to interruption of carfilzomib treatment were mainly of cardiovascular origin (two cardiac failures, one myocardial infarction, one pulmonary edema), along with one case of grade 4 tumor lysis syndrome, one grade 4 neutropenia and thrombocytopenia, and one grade 3 nausea/vomiting.

Interestingly, while no dose reduction was observed at 36 mg/m², one patient required a dose reduction at 45 mg/m², 4 at 56 mg/m², and 8 at 70 mg/m². Causes for dose reductions were: vomiting (4 cases), hypertension (2 cases), neutropenia (2 cases), thrombocytopenia, elevated liver enzymes, renal amyloidosis, aortic valve dysfunction, and anxiety.

DISCUSSION

This IFM 2012-03 study aimed to evaluate the KMP weekly regimen (Carfilzomib Weekly plus Melphalan and Prednisone) in eNDMM. The primary objective of this phase 1 study was to determine the MTD of carfilzomib in weekly KMP, which we demonstrated to be 70 mg/m² in this study.

The DMC recommended use of carfilzomib at 70 mg/m^2 for patients aged below 75 years, and 56 mg/m^2 for patients older than 75 years, despite the observed good safety profile of the second cohort at 70 mg/m^2. However, we did not observe that toxicity correlated with the dose of carfilzomib and we believe that increased attention around hyperhydration and monitoring blood pressure is a better way to reduce toxicity, than to lower the dose of carfilzomib.

Independently of the regimen used, bortezomib administered once weekly has a better safety profile and similar efficacy to the initial twice-weekly schedule (5, 16). It was shown that the twice-weekly administration of bortezomib introduced unnecessary accumulation of adverse events, especially for symptomatic and elderly MM patients, without improving efficacy. We therefore sought to demonstrate that similarly to bortezomib, carfilzomib could be safely used once weekly. Indeed, we were able to increase the dose of carfilzomib with a manageable safety profile up to 70mg/m^2, and we observed responses, and particularly deep responses at all dose levels.

Although cross-trial comparisons should be interpreted with caution, the CR rate of KMP weekly is remarkable in this study, as compared with previously reported CR rates with MPV and twice weekly KMP regimens. In our study, ORR and CR rates were 90% and 46.6%, that compared favorably to 90% and 12% respectively in the Carmysap study (KMP with twice weekly carfilzomib) (13). For the MPV regimens, ORR and CR rates ranged from 74% to 89% and 20% to 39% after maintenance (by bortezomib and thalidomide), respectively (2) (Supplementary Table 5). Our study has limitations, the main limitation being the small number of patients per cohort along with a small number of high-risk patients. However, we believe that the results of this phase 1 study are promising, possibly at least partially due to the addition of one year carfilzomib maintenance, as median PFS was 35.8 months compared to 21 months in the Carmysap study (13). The favorable safety profile and the convenience of a weekly administration of carfilzomib could have allowed patients to remain on treatment for a longer period of time.

In this study, safety profile was acceptable with mostly grade 1-2 adverse events (AEs). The most common grade 3-4 AEs were hematological, especially thrombocytopenia and neutropenia as expected, with only one reported case of febrile neutropenia. As previously described, the main toxicities observed with carfilzomib were cardio-vascular, with 4 cases of grade 3-4 hypertension, 2 cardiac failures, 1 myocardial infarction, and 1 acute pulmonary edema. The cardiotoxicity profile as observed in our study is now well reported, and similar to the cardiac toxicity previously reported with carfilzomib, both as a single agent (11) and in combination [Champion (14), Arrow (17) and Clarion (#NCT01818752) studies]. This particular toxicity profile needs to be acknowledged, as preventive measures can dramatically reduce the incidence of cardio-vascular AEs. Indeed, no grade 3-4 cardio-vascular adverse events were recorded in the additional 70 mg/m² cohort when special attention was drawn to the prevention of these toxicities. Dose modifications of carfilzomib were necessary in approximately 43% of patients with only 23% patients that discontinued therapy because of toxicity, during induction or maintenance.

The Clarion trial, a randomized multicenter international phase 3 study of KMP versus MPV in transplant-ineligible newly diagnosed MM patients (#NCT01818752) failed to demonstrate a superior median PFS with KMP as compared with MPV, which was the primary objective. Carfilzomib was administered twice-weekly at 20/36 mg/m². Median PFS were indeed similar at 22.3 months for KMP and 22.1 months for MPV (HR=0.91, 95% CI: 0.75-1.10). This data might not allow an approval of KMP in eNDMM, however, carfilzomib can still be approved in other regimens. Several other carfilzomib triplet-based studies are expected, particularly with lenalidomide and low-dose dexamethasone (Rd). For instance, ECOG E1A11 is an ongoing trial comparing RVD to KRd in NDMM (#NCT01863550), with twice-weekly carfilzomib.

Several studies have now confirmed that carfilzomib used weekly at 56 or 70 mg/m² has a good efficacy and safety profile: in the relapse setting associated with dexamethasone in the phase 1/2 Champion study (14) and the randomised phase 3 Arrow study (17), in the relapse setting associated with lenalidomide and dexamethasone (18), or upfront associated with melphalan and prednisone in eNDMM in this IFM2012-03 study. It is thus likely that independently of the regimen used, carfilzomib will be used weekly in future studies.

In conclusion, the IFM2012-03 study demonstrated that the MTD of carfilzomib weekly is 70 mg/m^2 in eNDMM for all patients. The DMC recommended use of carfilzomib at 70 mg/m^2 for patients aged below 75 years, and 56 mg/m^2 for patients older than 75 years, despite the observed good safety profile of the second cohort at 70 mg/m^2 for K.

Safety profile was acceptable, but special attention should be drawn to the prevention of cardio-vascular adverse events through monitoring and particularly treating hypertension and careful hydration.

Response rates, and especially CR and sCR rates, were remarkable in this population when compared with current standards of care. The Carfilzomib Weekly plus Melphalan and Prednisone regimen thus shows promising efficacy compared to other regimens available for eNDMM, and would benefit from being assessed on a larger scale study.

Table 1. Patients characteristics (n=30).

	n (%) unless specified
Age, median (range)	73 (65 – 81)
Age > 75 years, n (%)	13 (43.3)
Sex ratio male/female	1.5
ISS stage[1]	
ISS 2, n (%)	9 (31)
ISS 3, n (%)	8 (27.6)
Renal insufficiency (creatinine clearance < 60 ml/min), n (%)	13 (43.3)
Anemia (hemoglobin < 10 g/dL), n (%)	12 (40)
Thrombocytopenia (platelets < 100.10^9/L), n (%)	2 (6.7)
Beta2 microglobulin (mg/L), median (range)[1]	3.7 (2.2 - 9)
Extra-medullary disease, n (%)	1 (3.3)
High-risk cytogenetics [del(17p) or t(4;14)], n (%)[2]	3 (11.1)

[1] 1 missing data ; [2] 3 missing data

Table 2. Dose Limiting Toxicities (DLTs).

n=6 per cohorts, mg/m^2	Dose Limiting Toxicities
36	Grade 4 lymphopenia
45	Grade 4 tumor lysis syndrome
56	Grade 4 febrile neutropenia
	Grade 4 heart failure
70, cohort #1	Grade 3 nausea/vomiting
	Grade 3 elevated liver enzymes
70, cohort #2	None

DLTs were defined as any hematologic toxicity of grade 4 intensity or preventing administration of 2 or more of the 4 carfilzomib doses of the first treatment cycle, grade ≥3 febrile neutropenia, grade ≥3 gastrointestinal toxicities, any other grade ≥3 nonhematologic toxicity considered related to KMP by the principal investigator and grade ≥3 peripheral neuropathy persisting for more than 3 weeks after discontinuation of study drugs.

Table 3. Response rates (n=30).

	n (%)
≥ CR	**14 (46.7)**
iCR	4 (13.3)
sCR	7 (23.3)
CR	3 (10)
VGPR	**21 (70)**
≥ CR	14 (46.7)
VGPR	7 (23.3)
ORR	**28 (93.3)**
PR	7 (23.3)
SD	0 (0)
PD	0 (0)
NA*	2 (6.7)

iCR: immunophenotypic complete response; sCR: stringent complete response; CR: complete response
VGPR: very good partial response; PR: partial response; PD: progressive disease; * No available response assessment

Table 4. Summary of adverse events occurring in ≥10% of patients across cohorts, by organ and severity (n=30).

AEs, n (%)	Any grade	Grade 3-4
Blood and lymphatic system disorders		
Anemia	15 (50.0)	5 (16.7)
Lymphopenia	12 (40.0)	11 (36.7)
Neutropenia	9 (30.0)	9 (30.0)
Thrombocytopenia	11 (36.7)	7 (23.3)
Gastrointestinal disorders		
Diarrhea	6 (20.0)	2 (6.7)
Nausea	20 (66.7)	1 (3.3)
Vomiting	16 (53.3)	2 (6.7)
General disorders and administration site conditions		
Asthenia	14 (46.7)	0
Edema limbs	3 (10.0)	1 (3.3)
Fever	8 (26.7)	2 (6.7)
Infections and infestations		
Bronchitis	6 (20.0)	1 (3.3)
Urinary infection	3 (10.0)	1 (3.3)
Weight loss	4 (13.3)	0
Musculoskeletal disorders: Bone pain	3 (10.0)	1 (3.3)
Renal and urinary disorders : Acute renal failure	4 (13.3)	3 (10.0)
Respiratory, thoracic and mediastinal disorders		
Cough	4 (13.3)	1 (3.3)
Dyspnea	4 (13.3)	3 (10.0)
Vascular disorders : Hypertension	6 (20.0)	5 (16.7)
Neurological toxicities : Sensitive neuropathy	10 (33.3)	0

Figures' legends.

Figure 1. Study flow chart

Figure 2. Progression Free Survival and Overall Survival.
(A) Progression Free Survival (PFS); (B) PFS according to depth of response.
(C) Overall Survival (OS); (D) OS according to depth of response.

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Conduction of Trial: XL, TF, MOP

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Data analysis and interpretation: XL, MOP, AD, FM

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