Supplemental tables

Table S1. Key inclusion and exclusion criteria for ASPIRE, ENDEAVOR, and FOCUS trials

Study	ASPIRE	ENDEAVOR	FOCUS
Inclusion Criteria			
Disease Related			
Prior lines of therapy	1-3	1-3 and ≥ partial response to at least 1 line of prior therapy	≥ 3
Prior Treatments	bortezomib, lenalidomide, dexamethasone	Prior bortezomib and carfilzomib therapy allowed if patient achieved ≥partial response, had ≥6-month PI-free interval, and PI therapy was not discontinued due to toxicity	bortezomib, lenalidomide, thalidomide, alkylating agent, corticosteroid
Demographics			
Gender	Males and females	Males and females	Males and females
Age	≥18 years	≥18 years	≥18 years
Eastern Cooperative Oncology Group performance status	0-2	0-2	0-2
Laboratory			
Serum alanine aminotransferase	≤3.5 times ULN	<3 times ULN	<4 times ULN
Serum bilirubin	≤2 mg/dL	<1.5 times ULN	<2.5 mg/dL
Hemoglobin	≥8.0 g/dL	≥8.0 g/dL	≥7.5 g/dL
Platelet count	≥50 × 10^9/L	≥50 × 10^9/L	≥30 × 10^9/L
Absolute neutrophil count	≥1.0 × 10^9/L	≥1.0 × 10^9/L	≥1.0 × 10^9/L
Creatinine Clearance	≥50 mL/min ≤21 days prior to randomization	≥15 mL/min ≤21 days prior to randomization	≥15 mL/min ≤21 days prior to randomization
Left ventricular ejection fraction	Not captured	≥40%	Not captured
Exclusion criteria			
Disease related			
	If previously treated with bortezomib, progression during treatment		Refractory to all prior therapies
	If previously treated with lenalidomide+dexamethasone, progression during first 3 months of treatment		
	Prior carfilzomib treatment	—	Prior carfilzomib treatment
	POEMS syndrome	POEMS syndrome	POEMS syndrome
	Waldenstrom macroglobulinemia	Waldenstrom macroglobulinemia	Waldenstrom macroglobulinemia
	Plasma cell leukemia	Plasma cell leukemia	Plasma cell leukemia
Concurrent or recent treatments			
	Chemotherapy ≤3 weeks prior to randomization	Chemotherapy ≤21 days prior to randomization	Chemotherapy ≤14 days prior to randomization

	Antibody therapy ≤6 weeks prior to randomization	Immunotherapy ≤21 days prior to randomization	Immunotherapy ≤28 days prior to randomization
	Radiotherapy to multiple sites ≤28 days prior to randomization	Focal radiation therapy ≤7 days prior to randomization	Radiotherapy ≤28 days prior to randomization
Concurrent conditions			
	NYHA class III or IV congestive heart failure	NYHA class III or IV congestive heart failure	NYHA class III or IV congestive heart failure
	Grade 3 conduction system abnormalities	Symptomatic ischemia or uncontrolled conduction abnormalities	Uncontrolled conduction system abnormalities
	Myocardial infarction ≤4 months prior to randomization	Myocardial infarction ≤4 months prior to randomization	Myocardial infarction 3 months prior to randomization
	Severe coronary disease and severe uncontrolled ventricular arrhythmias		
	HIV	HIV	HIV
	Uncontrolled hypertension or diabetes ≤14 days prior to randomization	–	–
	Active hepatitis B or C	Active hepatitis B and or C	Active hepatitis A, B, or C
	Grades 3 or 4 neuropathy ≤14 days prior to randomization	Grades 3 or 4 neuropathy ≤14 days prior to randomization	Grades 3 or 4 neuropathy at time of randomization
	Pregnant/lactating females	Pregnant/lactating females	Pregnant/lactating females

HIV, Human Immunodeficiency Virus; NYHA, New York Heart Association; PI, proteasome inhibitor; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; ULN, upper limit of normal.

Figure S1. Carfilzomib clinical trials and dosing

BSC, best supportive care; K, carfilzomib; Kd, carfilzomib and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; MM, multiple myeloma; RRMM; relapsed or refractory multiple myeloma; Vd, bortezomib and dexamethasone.

Figure S2. QTcF change from baseline vs carfilzomib plasma concentration*

QTcF, QTc interval using Fridericia's correction.
*Integrated analysis from the PX-171-005 and PX-171-007 trial

Supplemental methods

Carfilzomib Trials

This study was based on the phase 1 or 1b/2 trials (PX-171-001, PX-171-002, PX-171-006, PX-171-007, and PX-171-008), the phase 2 trials (PX-171-003-A0 and A1, PX-171-004, PX-171-005, and 2011-002), and the phase 3, ASPIRE (PX-171-009), ENDEAVOR (2011-003), and FOCUS (PX-171-011) trials. PX-171-001 and PX-171-002 evaluated the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of carfilzomib in patients with RRMM. The phase 1b/2 PX-171-006 trial examined the relationship between carfilzomib dose and response in patients with RRMM treated with KRd. The phase 1b/2 PX-171-007 trial examined the safety and activity of carfilzomib in patients with relapsed solid tumors, MM, or lymphoma. PX-171-008 trial (phase 1b) examined the effects of carfilzomib on pharmacokinetics of midazolam in patients with solid tumors. The phase 2 trials PX-171-003-A0 and PX-171-003-A1 examined the safety and efficacy of single-agent carfilzomib at the 20 or 20/27 mg/m^2 doses in patients with RRMM who had ≥2 lines of therapy, respectively. PX-171-004 was a single-arm phase 2 trial in patients with RRMM who had 1 to 3 prior lines of therapy. In this trial, two groups of patients were evaluated– bortezomib-treated patients who received carfilzomib at the 20 mg/m^2 dose and bortezomib-naïve patients who received carfilzomib at the 20 and 20/27 mg/m^2 doses. The phase 2 trial PX-171-005 evaluated the safety and pharmacokinetics of carfilzomib in patients with RRMM who were grouped according to renal function. The phase 2 trial 2011-002 extended upon the safety assessment of carfilzomib by providing expanded access to patients with RRMM who were unable to enroll in any other carfilzomib trials. ASPIRE (PX-171-009) was a randomized phase 3 trial comparing KRd vs Rd in patients with relapsed MM with 1 to 3 prior lines of therapy. ENDEAVOR (2011-003) was a randomized phase 3 trial comparing Kd vs Vd in patients with RRMM with 1 to 3 prior lines of

therapy. FOCUS (PX-171-011) was a randomized phase 3 trial comparing K with BSC including cyclophosphamide and steroids in RRMM with ≥3 prior lines of therapy.

Patients

In the ASPIRE trial, patients previously treated with bortezomib were eligible to participate in the study as long as they did not have disease progression during treatment with bortezomib. Patients who had prior lenalidomide and dexamethasone exposure were also eligible to participate if they did not discontinue therapy as result of adverse effects, did not have disease progression during the first 3 months of treatment, or did not have progression at any time during treatment if Rd was their most recent treatment. In the ENDEAVOR trial, patients who had prior bortezomib or carfilzomib treatment were eligible provided they had achieved at least a partial response to treatment, had at least a 6-month interval without bortezomib or carfilzomib treatment prior to enrollment, and did not discontinue bortezomib or carfilzomib because of toxicity. Patients with prior bortezomib (<4 cycles of treatment), immunomodulatory agent, and alkylating agent exposure were allowed to participate in the FOCUS trial.

Patients in FOCUS, ASPIRE, and ENDEAVOR were required to have Eastern Cooperative Oncology Group Performance Status of 0 to 2. Patients with uncontrolled hypertension within 14 days prior to randomization were allowed to enroll in ENDEAVOR trial. Each study center's institutional review board approved informed consent forms. Investigators notified the institutional review board of any significant AEs encountered during these studies.

Study design

In the ASPIRE trial, 792 patients were randomized (1:1) to receive KRd (n=396) or Rd (n=396). Treatments were administered in 28-day cycles until withdrawal of consent, disease progression, or appearance of toxicity. Patients received carfilzomib (10-minute intravenous infusion) on days 1, 2, 8, 9, 15, and 16 (20 mg/m^2 on days 1 and 2 of cycle 1; 27 mg/m^2

thereafter) during cycles 1 to 12. Carfilzomib was omitted on days 8 and 9 of cycles 13-18 and was discontinued after 18 cycles. Lenalidomide (25 mg) was given on days 1 through 21, and dexamethasone (40 mg) was administered on days 1, 8, 15, and 22.

In the ENDEAVOR trial, 929 patients were randomly assigned (1:1) to receive Kd (n=464) or Vd (n=465). Patients randomized to the Kd arm received carfilzomib (30-minute IV infusion) on days 1, 2, 8, 9, 15, and 16 (20 mg/m^2 on days 1 and 2 of cycle 1; 56 mg/m^2 thereafter) and dexamethasone (20 mg/m^2) on days 1, 2, 8, 9, 15, 16, 22, and 23 of a 28-day cycle. Patients on the Vd arm received bortezomib (1.3 mg/m^2) on days 1, 4, 8 and 11 and dexamethasone (20 mg) on days 1, 2, 4, 5, 8, 9, 11, and 12 of a 21-day cycle. In all three trials, the treatment was not blinded to patient or the investigator.

In the FOCUS trial, 310 patients were randomized in a 1:1 ratio to receive carfilzomib (n=157) or BSC (n=153). BSC began on cycle 1 day 1 and included corticosteroid treatment (prednisone 30 mg every other day, dexamethasone 6 mg every other day, or equivalent), with optional cyclophosphamide 50 mg orally once daily. Carfilzomib was administered in 28-day cycles at 20 mg/m^2 IV on days1 and 2 of cycle 1, increasing to 27 mg/m^2 on days 8, 9, 15, and 16 of cycle 1 and continued on days 1, 2, 8, 9, 15, and 16 of cycle 2 through 9. For cycles ≥10, carfilzomib was administered at 27 mg/m^2 IV on days 1, 2, 15, and 16.

Analysis of cardiac AEs and benefit-risk assessment

AEs that continued 30 days after the last dose therapy were specified in the source document by the investigator that the event had stabilized or was not expected to improve. If the patient had repeat episodes of the same AE, the event with the highest severity grade and/or strongest causal relationship to each treatment was used to tabulate incidence. No definitions were specified in the protocol for the cardiac failure outcome categories of resolved, resolved with

sequelae, and not resolved. Cardiac failure outcomes were collected on the case report form according to principal investigator's judgment.

Safety assessments for ASPIRE were performed at 21 days prior to randomization, at baseline, and on days 1, 2, 8, 9, 15, and 22 of treatment cycles 1 to 12, days 1, 8, 15, and 22 of cycles 13 to 18, and days 1, 8 15, and 22 of cycles ≥19. Safety assessments for ENDEAVOR were performed at 21 days prior to randomization, at baseline, on days 1, 2, 4, 8, 9, 15, and 16 of treatment cycles and repeated every 28 days for the Kd arm, on days 1, 2, 4, 5, 8, 9, 11, and 12 of treatment cycles and repeated every 21 days for the Vd arm, and at the end of treatment. Safety assessments for FOCUS were performed at screening, baseline, and on days 1, 2, 8, 9, and 15 of cycle 1 for the carfilzomib arm, on day 1 and 15 of cycles 2 to 9 for the carfilzomib arm or cycles 1 to 9 for the BSC arm, on day 1 of cycles ≥10 for the carfilzomib and BSC arms, and at the end of treatment

The exposure-adjusted AE incidence rate was defined as the number of patients with a particular CV event of interest divided by the total person-time of exposure among patients that were at risk of an initial occurrence of the event. If a patient had multiple events, the person-time exposure was the duration of the exposure at the time of the first CV event. If a patient had no events, the person-time was treatment duration.

Benefit-risk: analysis of time to first event of cardiac failure and PFS or OS in ASPIRE and ENDEAVOR trials.

In this study, only data from the ASPIRE and ENDEAVOR trials were included in the benefit-risk analysis because the clinical outcomes reported in in these trials led to the approval of KRd and Kd for the treatment of RRMM).[1,2] The cumulative incidence of grade ≥3 cardiac failure and death or disease progression was analyzed at 18 months from randomization as KRd patients

were treated with carfilzomib for up to 18 months, after which carfilzomib was discontinued. In addition, the choice of analyzing outcomes at 18 months was based on the median PFS for ASPIRE and ENDEAVOR, which was 26.3 months for KRd and 17.6 months for Rd, and 18.7 months for Kd and 9.4 months for Vd. To assess benefit-risk profile of carfilzomib treatment in the ASPIRE and ENDEAVOR trials, the cumulative incidence of grade ≥3 cardiac failure events, deaths, or deaths or progression was calculated for each arm in the two trials. In order to calculate cumulative incidence of grade ≥3 cardiac failure events, time to first onset of grade ≥3 cardiac failure events was calculated as time from the first dosing date to the start date of the first grade ≥3 cardiac failure event. Patients without grade ≥3 cardiac failure events were censored at the earliest date of 30 days following treatment termination, date of death or last known date alive. The cumulative incidence of grade ≥3 cardiac failure events and deaths, and grade ≥3 cardiac failure events and deaths or progression was plotted over time and overlaid in the same plots to visualize the risk and benefit of carfilzomib treatment vs control.

Benefit-risk: NNT and NNH.

Exposure-adjusted NNT for PFS and exposure-adjusted NNH were calculated for cardiac failure and hypertension based on SMQN.

QTc Analysis

The formal QTc assessment was based on triplicate ECG collection and central blinded reading of ECGs from clinical studies PX-171-005 and PX-171-007. QTc was evaluated in 154 patients with MM or solid tumors following treatment with single or multiple carfilzomib doses ranging from 15 to 70 mg/m^2 in cycles 1 and 2. Time-matched triplicate ECGs and plasma data were used to assess the relationship between carfilzomib plasma concentration and QTc interval change using a linear mixed-effects model for the concentration–QTc analyses.

Phase 1

PX-171-001 (N=29): RRMM
Single-agent K; K dose cycle 1 = 1.2–20 mg/m^2 and K dose cycle 2 and beyond = 1.2–20 mg/m^2

PX-171-002 (NCT00150462) (N=48): RRMM
single agent K at dose escalation then dose expansion including K or Kd; K dose cycle 1 = 1.2–27 mg/m^2 and dose cycle 2 and beyond = 1.2–27 mg/m^2

Phase 1b/2

PX-171-006 (NCT00603447) (N=84): relapsed or progressive MM
KRd; K dose cycle 1= 15 or 20 mg/m^2 on days 1 and 2, then 27 mg/m^2 thereafter (dose-escalation); 20 mg/m^2 on days 1 and 2, then 27 mg/m^2 thereafter (dose-expansion); K dose cycle 2 and beyond= 15, 20, or 27 mg/m^2 (dose-escalation) or 27 mg/m^2 (dose expansion) through cycle 12, then biweekly for subsequent cycles

PX-171-007 (NCT) (N=189): relapsed solid tumors, RRMM, refractory lymphoma
Patients with solid tumors received K at doses of 36 mg/m^2, 45 mg/m^2, 20/45 mg/m^2, and 20/70 mg/m^2 for up to 12 cycles. Patients with MM were enrolled to receive K at doses of 20/36 mg/m^2, 20/45 mg/m^2, 20/56 mg/m^2, and 20/70 mg/m^2

PX-171-008 (N=17): non-randomized study on the effects of K on pharmacokinetics of midazolam in patients with solid tumors.
Trial consisted of 2 periods; a 1-week wash-out followed by one 28-day cycle. Midazolam (2 mg) on period 1, day 7 (+ up to 3 days). Six doses of K during period 2 on cycle 1 on days 1, 2, 8, 9, 15, and 16. Midazolam (2 mg) on cycle 1, days 1 and 16 during period 2. K dose = 27 mg/m^2 during period 2, cycle 1 on days 1, 2, 8, 9. 15, and 16.

Phase 2

PX-171-003-A0 (N=46) and **PX-171-003-A1 (NCT00511238)** (N=266); RRMM
K dose cycle 1= 20 mg/m^2; K dose cycle 2 and beyond = 20 (**A0**) or 27 mg/m^2 (**A1**)

PX-171-004 (NCT00530816) bortezomib-treated (N=35) **and bortezomib-naïve** (N=129): RRMM
K dose cycle 1= 20 mg/m^2; K dose cycle 2 and beyond = 20 (**bortezomib-treated**) or 20, 27 mg/m^2 (**bortezomib-naïve**)

PX-171-005 (NCT00721734) (N=50); RRMM
K dose cycle 1= 15 mg/m^2; K dose cycle 2 and beyond = 20 or 27 mg/m^2, if tolerated

2011-002 (NCT01410500) (N=338); Kd; RRMM
K dose cycle 1= 20 mg/m^2 days; K dose cycle 2 and beyond = 27 mg^2

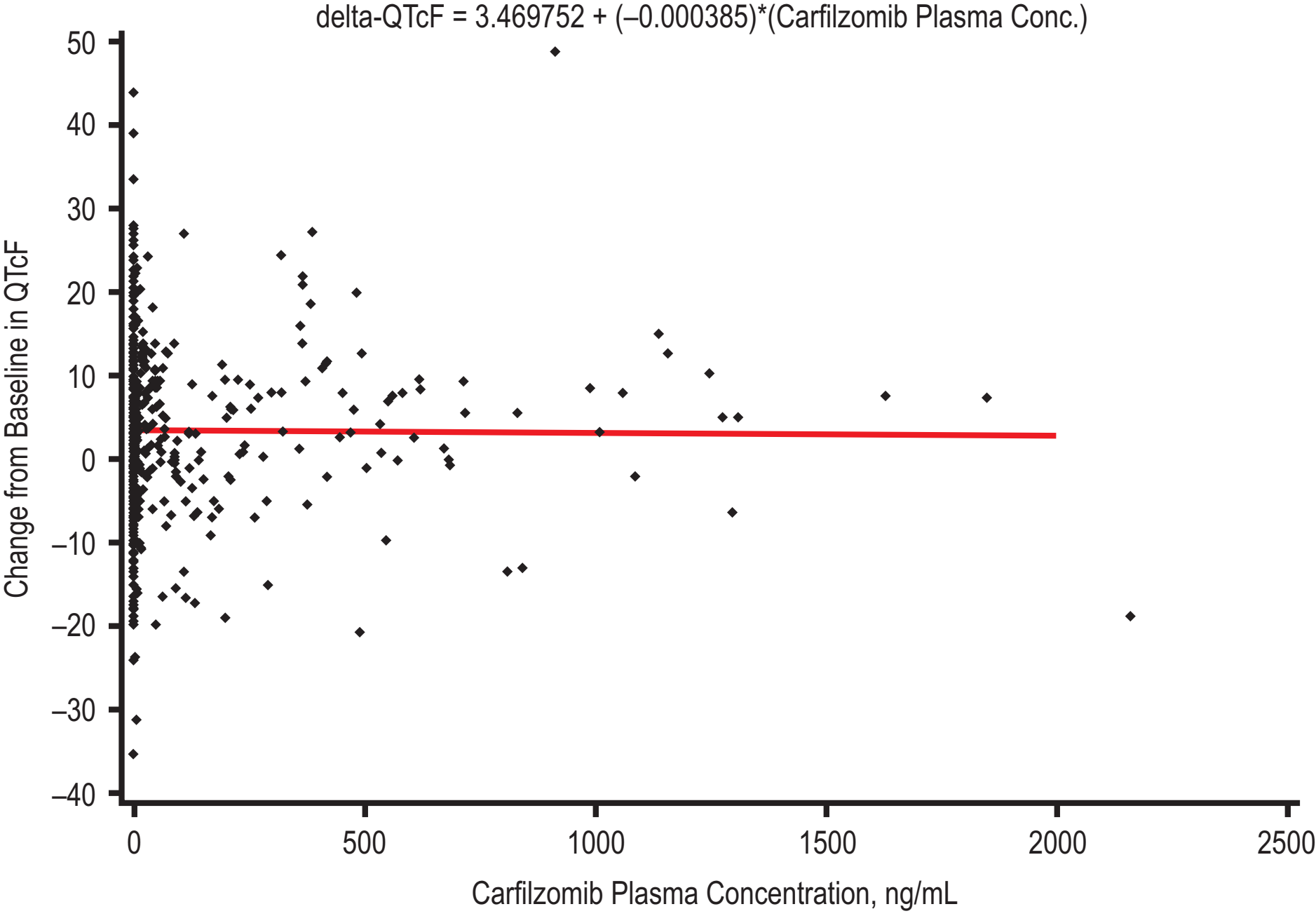
Phase 3

ASPIRE (NCT01080391) (N=751): KRd, 392; Rd, 389; relapsed MM
K dose = 20/27 mg/m^2
Mean cycles = 14.2
Mean dose = 26.1 mg/m^2

ENDEAVOR (NCT01568866) (N=919): Kd, 463; Vd, 456; relapsed MM
K dose = 20/56 mg/m^2
Mean cycles = 10.0
Mean dose = 53.9 mg/m^2

FOCUS (NCT01302392) (N=310): K, 157; BSC, 53; RRMM
K dose = 20/27 mg/m^2
Mean cycles = 6.9
Mean dose = 25.7 mg/m^2

BSC, best supportive care; K, carfilzomib; Kd, carfilzomib and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; MM, multiple myeloma; RRMM; relapsed or refractory multiple myeloma; Vd, bortezomib and dexamethasone.



QTcF, QTc interval using Fridericia's correction.
*Integrated analysis from the PX-171-005 and PX-171-007 trial