A Phase I/II Study of the Combination of Panobinostat and Carfilzomib in Patients with Relapsed or Relapsed/Refractory Multiple Myeloma

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Background and Rationale

- Preclinical data demonstrate synergistic anti-MM activity with the combination of HDAC inhibition and proteasome inhibition in part through dual inhibition of the proteasome and aggresome pathways.
- Panobinostat (PAN) is an oral pan-HDACi which was recently FDA approved in combination with bortezomib and dexamethasone largely as a result of the PANORAMA1 study findings (San Miguel et al. Lancet Oncology, 2014)
- Carfilzomib (CFZ) is an epoxyketone-based selective proteasome inhibitor
  - FDA approved for R/R MM at the stepped up dose of 20mg/m2 up to 27 mg/m2 infused over 2-10 mins twice weekly (Siegel et al. Blood, 2012)
  - Increasing infusion times to 30 mins has allowed further dose escalation up to 56 mg/m2 twice weekly. (Papadopoulos et al. JCO 2015)

Background

- We have previously reported the combination of PAN and CFZ in pts with relapsed and relapsed/refractory MM with encouraging results*
- Four dose levels were explored
  - PAN 30mg PO TIW QOW + CFZ 20/45mg/m^2 IV twice weekly was expanded.
  - The ORR was 67%
- The maximum tolerated dose (MTD) of CFZ and PAN was never reached and we extended our original study to investigate higher dose levels – results are presented here

*Berdeja et al. Haematologia, 2015

Treatment Plan

Dosing (28-day cycle)
Panobinostat PO D1, 3, 5, 15, 17 & 19
Carfilzomib 20/56 mg/m^2 IV D1, 2, 8, 9, 15 & 16

Response Evaluation every 4 weeks*

Patients with SD or better will continue treatment until progression or intolerable toxicity

Dose Level	Panabinostat	Carfilzomib
5	30 mg	20/56 mg/m^2
6	20 mg	20/56 mg/m^2

*International Myeloma Working Group Uniform Response Criteria with addition of MR as per the EBMT criteria (Kyle and Rajkumar, Leukemia 2009)

Key Eligibility

Inclusion

- Diagnosis of multiple myeloma that has progressed during or after one previous treatment regimen
- ECOG PS 0-2
- Measurable disease
  - Serum M-protein: ≥ 0.5 g/dL
  - Urine light chain excretion ≥ 200 mg/24hr
  - Serum free light chain assay: involved free light chain level ≥ 10 mg/dL provided the serum free light chain ratio is abnormal
- Absolute neutrophil count (ANC) ≥1000/μL
- Platelets ≥70,000/μL
- Patients with adequate organ function as measured by serum creatinine and LFTs

Exclusion

- Grade > 2 peripheral neuropathy within 14 days prior to enrollment
- Previous treatment with HDAC, DAC, HSP90 inhibitors or valproic acid for treatment of cancer

Study Objectives

Primary

- To determine the overall safety and tolerability of the combination of panobinostat and carfilzomib that can be administered to patients with relapsed and relapsed/refractory MM and to determine the optimal dose for the expansion phase II portion
- To evaluate the overall response rate (≥PR)

Secondary

- To evaluate time-to-progression (TTP) defined as the date of 1st protocol treatment to date of tumor progression
- To evaluate progression-free-survival (PFS) defined as the date of 1st protocol treatment to date of documented tumor progression or date of death
- To evaluate overall-survival (OS) defined as the interval from the first study treatment until the date of death

Patient Characteristics (N=36)

Median age, years (range)	64 (49-91)
Gender, n (%)	
Female	13 (36%)
Male	23 (64%)
Ethnicity, n (%)	
Caucasian	32 (89%)
African American	3 (8%)
Asian	1 (3%)
ECOG Status, n (%)	
0	21 (58%)
1	15 (42%)
Stage, n (%)	
ISS ≥ 2	18 (50%)
Durie-Salmon Stage ≥ 2	28 (78%)
Risk, n (%)	
Poor Risk Patients	15 (42%)
17p del	11 (31%)

Prior Therapy (N=36)

Median number of prior therapies, (range)	3 (0-9)
Prior Treatments, n (%)	
Prior Prot Inhibs	36 (100%)
Prior IMiDs	29 (81%)
Prior Stem Cell Trans	20 (56%)
Refractory to Prior Treatments, n (%)	
Refractory to prior Prot Inhibs	17 (47%)
Refractory to prior IMiDs	18 (50%)
Refractory to both prior IMiDs and Prot Inhibs	9 (25%)

Treatment Summary (N=36)

Median number of cycles completed, (range)	5 (0-19)
Patients on Active Treatment, n (%)	12 (33%)
Patients Off Treatment, n (%)	24 (67%)
Disease progression	10 (28%)
Toxicity*	5 (14%)
Other (5 of 6 underwent ASCT)	6 (17%)
Patient request	2 (6%)
Death on study**	1 (3%)

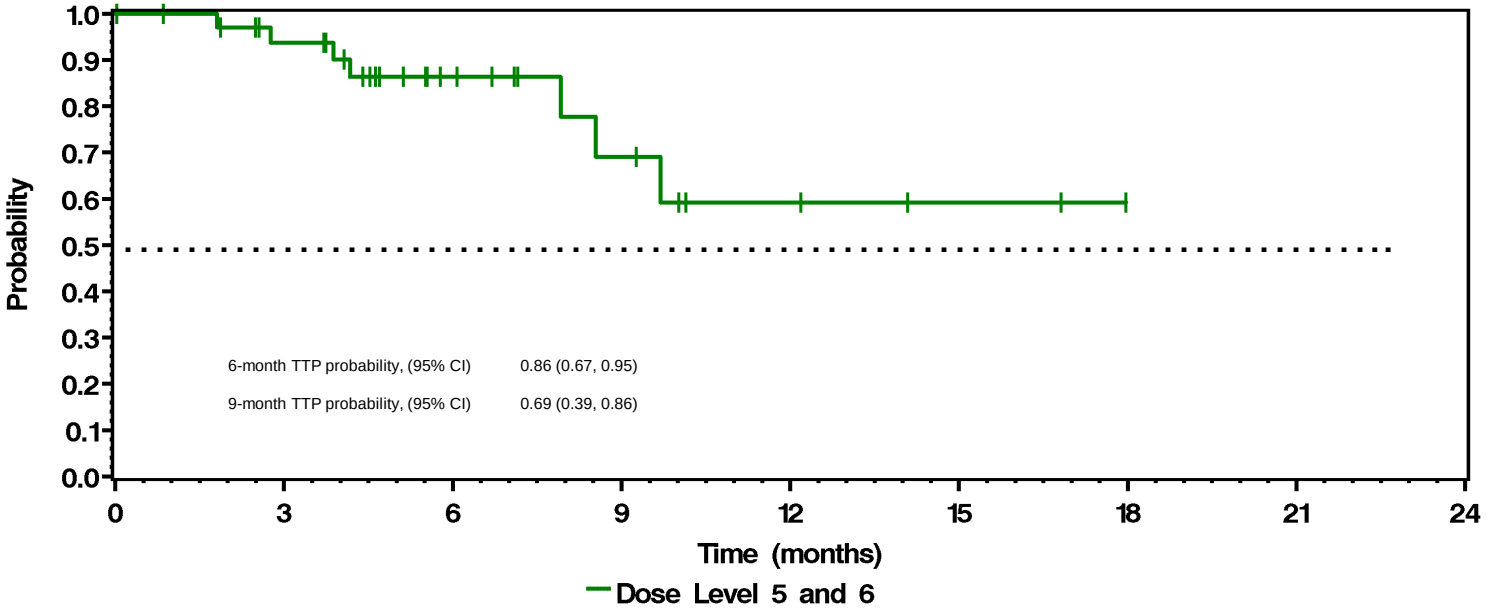
*G4 TTP (1pt); G3 pruritus (1pt); G3 diarrhea (1pt); G3 fatigue (1pt); G3 weakness (1pt)
**Pt died of unrelated upper respiratory infection

Response to Treatment

Response Assessment	All Pts (n=35)	DL 6 (n=32)
Overall Response Rate (ORR)	27 (77%)	24 (75%)
Clinical Benefit Rate (CBR)	31 (88%)	28 (87%)
Complete Response (CR)	1 (3%)	1 (3%)
Very Good Partial response (VGPR)	10 (29%)	9 (28%)
Partial response (PR)	16 (45%)	14 (44%)
Minimum response (MR)	4 (11%)	4 (13%)
Stable disease (SD)	4 (11%)	4 (13%)
Unevaluable (UE)*	1	1
Median Time to Best Response, weeks (Range)	4.1 (0-27.3)	4.4 (0-23)

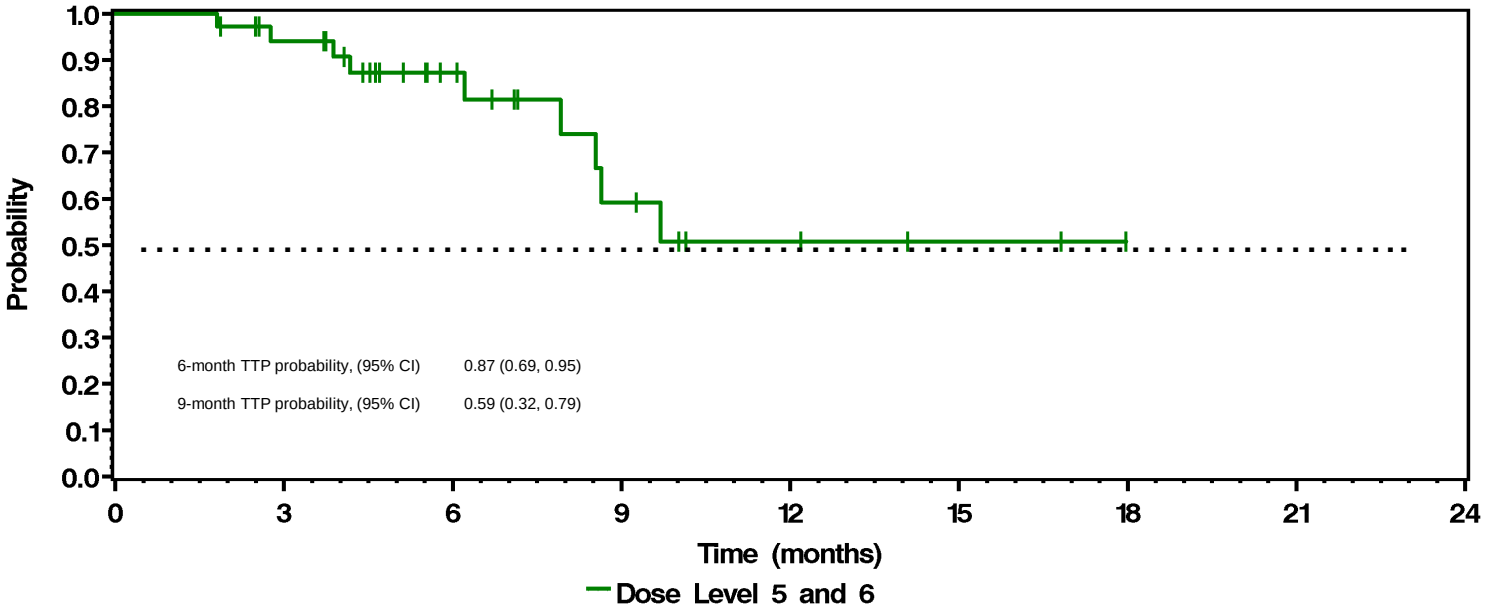
* UE: 1 patient died prior to response assessment

TTP All Patients (N=36)



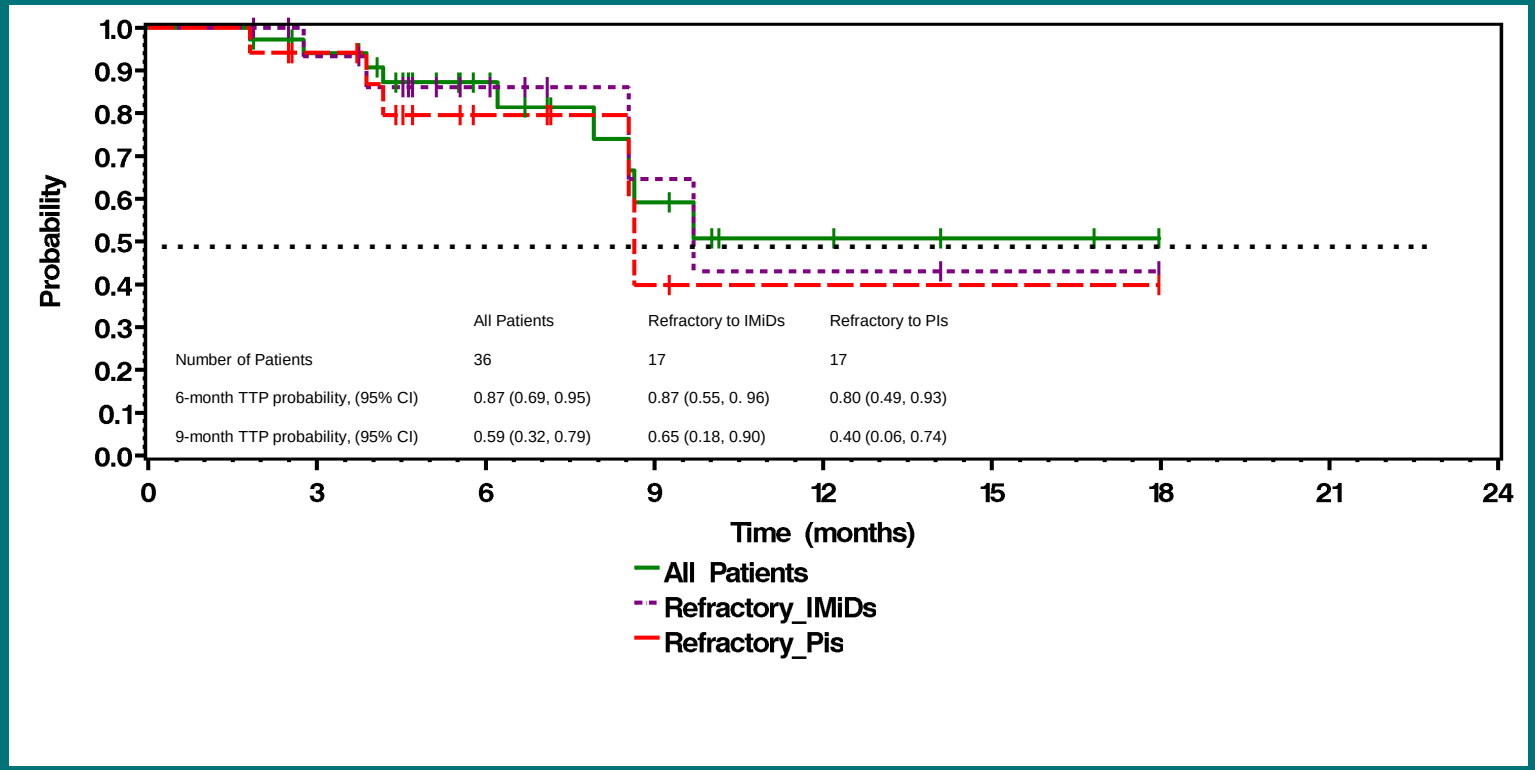
With a median follow up time of 7.9 months, the median TTP has not been reached.

PFS All Patients (N=36)



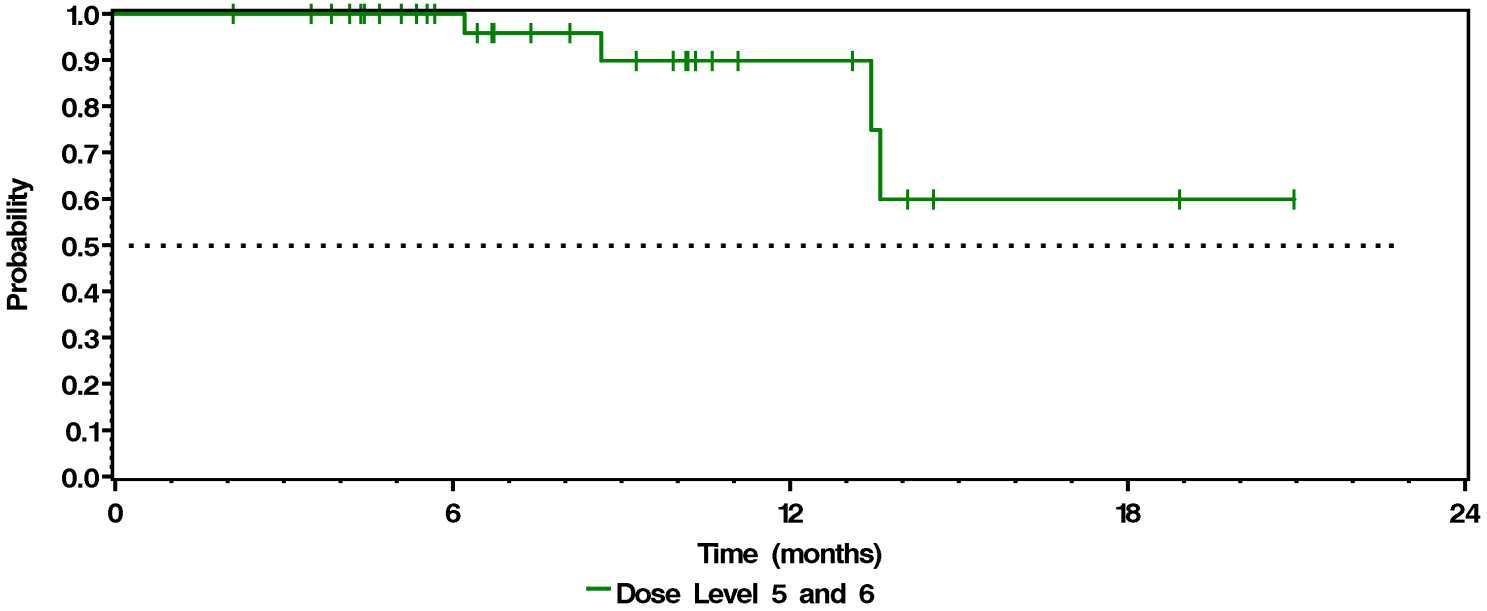
With a median follow up time of 7.9 months, the median PFS has not been reached.

PFS (Refractory to prior PI or IMiD)



	All Patients	Refractory to IMiDs	Refractory to PIs
Number of Patients	36	17	17
6-month TTP probability, (95% CI)	0.87 (0.69, 0.95)	0.87 (0.55, 0. 96)	0.80 (0.49, 0.93)
9-month TTP probability, (95% CI)	0.59 (0.32, 0.79)	0.65 (0.18, 0.90)	0.40 (0.06, 0.74)

OS All Patients (N=36)



With a median follow up time of 7.9 months, the median OS has not been reached.

Grade 3/4 Treatment-Related Toxicity Seen in >5% of Patients* (N=36)

Number of Patients (%)

	Grade 3	Grade 4	Total
Hematologic			
Thrombocytopenia	11 (31%)	6 (17%)	17 (47%)
Neutropenia	3 (8%)	0	3 (8%)
Anemia	1 (3%)	1 (3%)	2 (6%)
Non-Hematologic			
Fatigue	4 (11%)	0	4 (11%)
Diarrhea	2 (6%)	0	2 (6%)**
Confusion	2 (6%)	0	2 (6%)
Creatinine Levels Increased	2 (6%)	0	2 (6%)

- *Per CTCAE 4.03

All Grade Non-Heme Toxicities of Interest

	Grade 1	Grade 2	Grade 3	Grade 4	Total
Nausea	11 (31%)	11 (31%)	1 (3%)	0	23 (64%)
Diarrhea	9 (25%)	7 (19%)	2 (6%)	0	18 (50%)
Vomiting	11 (31%)	7 (19%)	0	0	18 (50%)
Fatigue	9 (25%)	3 (8%)	4 (11%)	0	16 (44%)
Dyspnea	3 (8%)	4 (11%)	2 (6%)	1 (3%)	10 (28%)
Cardiac Events*	3 (8%)	1 (3%)	1 (3%)	1 (3%)	6 (17%)
Neuropathy	0	1 (3%)	1 (3%)	0	2 (6%)

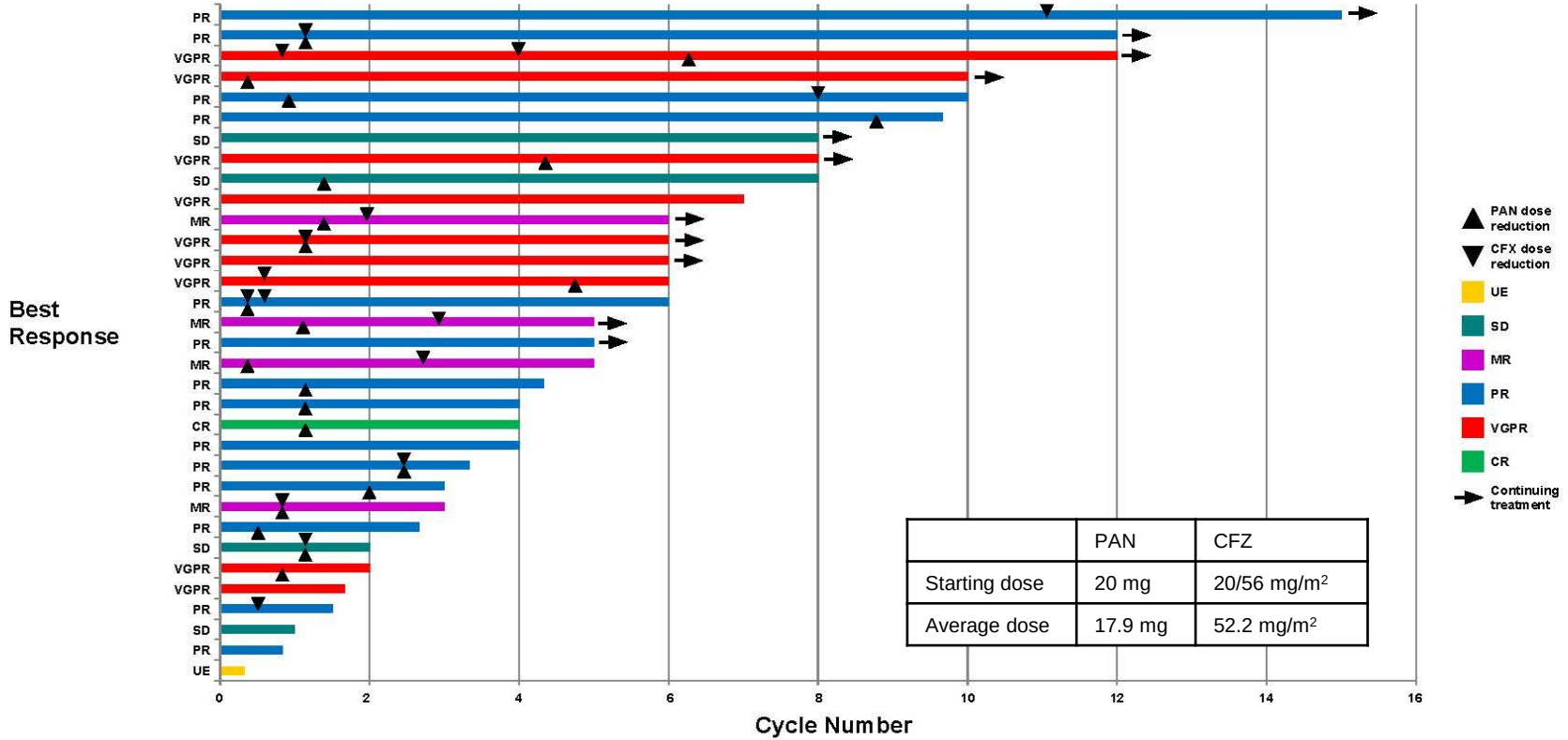
*G1 sinus tachycardia (1pt); G1 premature ventricular contractions (1pt); G1 palpitations (1pt); G2 cardiac chest pain (1pt); G3 congestive heart failure (1pt); G4 atrial fibrillation (1pt)

All Serious Adverse Events (N=36)

SAEs	Number of patients
Dehydration and Platelet Count Decreased	1
Thrombotic Thrombocytopenic Purpura/Hemolytic-Uremic Syndrome, Interstitial Pneumonitis and Fever	1
Pneumonia	1
Fever	1
Acute Renal Failure	1
Atrial Fibrillation and Pancreatitis	1
Hypercalcemia	1
Acute Kidney Injury	1
Anemia	1
Fluid Volume Overload and Respiratory Failure	1
Fluid Volume Overload	1
Total SAEs	17
Patients with SAEs	11

There were no treatment-related deaths

DL 6 responses and dose reductions (N=33)



	PAN	CFZ
Starting dose	20 mg	20/56 mg/m^2
Average dose	17.9 mg	52.2 mg/m^2

Conclusions

- PAN 20 mg PO TIW every other week in combination with CFZ 20/56 mg/m^2 twice weekly is safe and effective in this relapsed/refractory MM population.
- The ORR of 77% compares favorably to other reported PAN/PI combinations.
- In contrast to PANORAMA 1, GI toxicity was mostly grade ½ and very manageable [Grade ¾ diarrhea 6% v 26%]
- 90% of the intended PAN and CFZ dose was delivered
- PAN/CFZ at this dose and schedule merits further exploration.

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