Carfilzomib vs low-dose corticosteroids and optional cyclophosphamide in patients with relapsed and refractory multiple myeloma: A phase 3 study (FOCUS)

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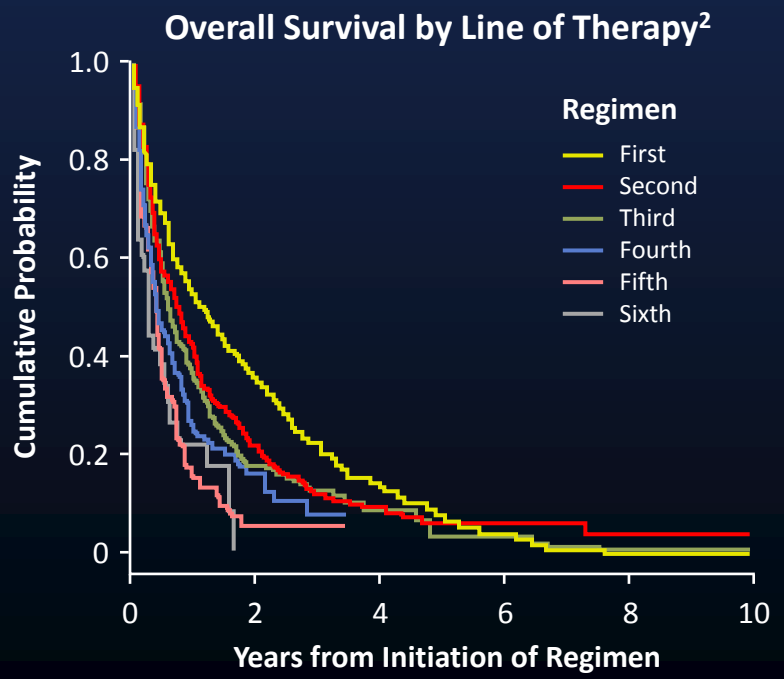
Disclosures

- **Honoraria:** Celgene, Janssen-Cilag, Bristol Meyers, Biotest
- **Research funding:** Celgene, Janssen-Cilag, Millennium

Background

- Survival and response rates decrease with each line of therapy received by patients with multiple myeloma
- In a retrospective cohort study conducted by the IMF (2007–2010)
  - 383 patients were included at first relapse and followed throughout the course of their disease[1]

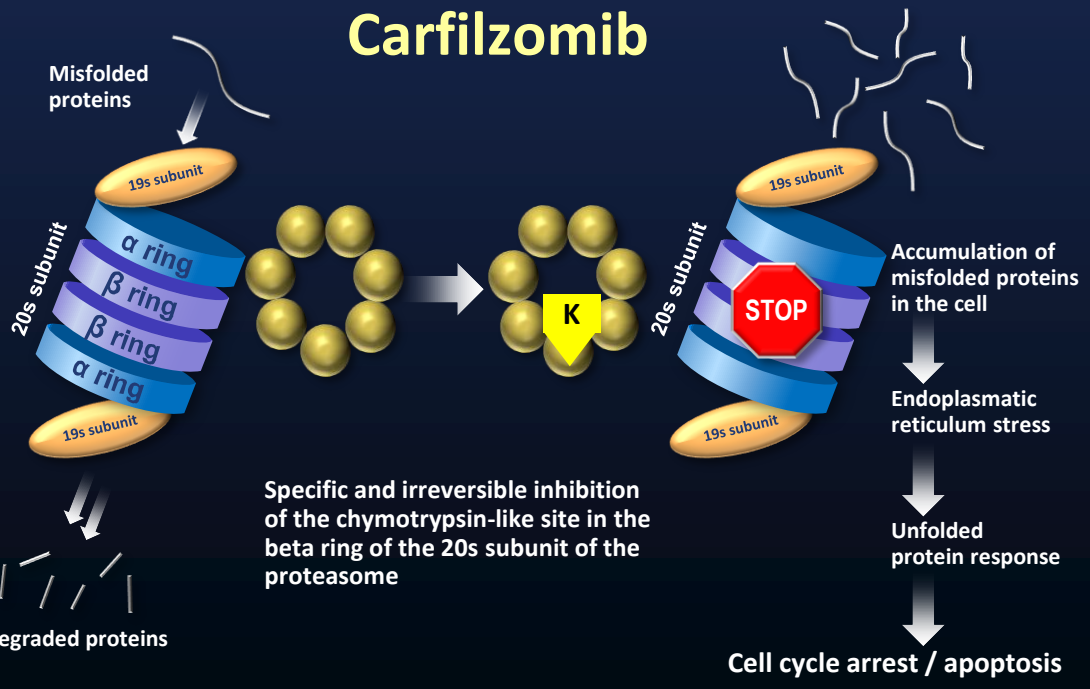
Relapse	Line of therapy	Patients treated	ORR, %
1st	2nd	383	58
2nd	3rd	207	45
3rd	4th	86	30
4th	5th	27	15
5th	6th	PX-171-003-A1 and PX-171-011 (FOCUS) study populations	



[1]Durie et al. *J Clin Oncol*. 2012. [2]Kumar et al. *Mayo Clin Proc*. 2004.

Carfilzomib (K)

- Second generation proteasome inhibitor[1]
- Irreversibly binds to the constitutive proteasome (β5 subunit) and the immunoproteasome (LMP7 subunit)
- Able to overcome bortezomib resistance
- Less off target activity than bortezomib



[1]Kuhn et al. *Blood* 2007.

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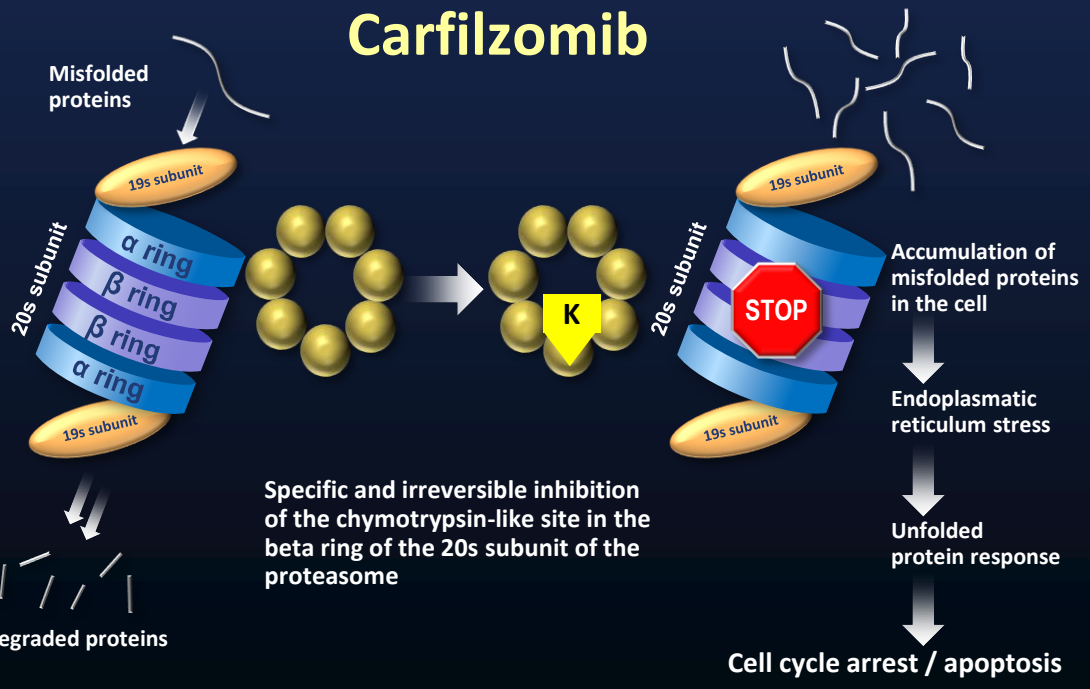


[1]Kuhn et al. *Blood* 2007.

FOCUS: A Randomized Comparison of Single-agent K vs Low-Dose Corticosteroids and Optional Cyclophosphamide

- **Objectives**
  - **Primary endpoint: OS**
  - **Secondary endpoints: PFS, ORR, DOR, CBR, DCR, and safety**
- **Designed in 2008 to show overall survival benefit in end-stage patients**
- **Design based on an estimated median OS of 8.6 mo for K vs 6.0 mo for the control (based on historical reports)[1]**

CBR, clinical benefit rate; DCR, disease control rate; DOR, duration of response; PFS, progression-free survival; ORR, overall response rate; OS, overall survival

[1]Anderson et al. *Leukemia* 2008.

FOCUS Study Design

Inclusion Criteria

- Measurable disease
- Relapsed and refractory multiple myeloma
- ≥3 prior regimens
- Mandatory prior treatment
  - Bortezomib
  - IMiDs
  - Alkylating agent
  - Corticosteroid
- Refractory to the most recent regimen
- Platelets ≥30 × 10^6
- Creatinine clearance ≥15 mL/min

Carfilzomib Arm

- IV [10-min infusion]
  - Days 1, 2, 8, 9, 15, and 16 of 28-day cycles for cycles 1–9
    - 20 mg/m^2 on days 1 and 2 of cycle 1
    - 27 mg/m^2 thereafter
  - Days 1, 2, 15, and 16 of 28-day cycles for cycles ≥10

Control Arm

- Corticosteroid (prednisone 30 mg PO, dexamethasone 6 mg PO, or equivalent) every other day)
- Optional cyclophosphamide (50 mg PO every day)

- 1:1 randomization
- Stratified by:
  - Number of prior therapies
  - Geographic region
- Multicenter (81 sites): Europe, Asia-Pacific

Patient and Disease Characteristics at Baseline

Characteristic	Carfilzomib (n=157)	Control (n=158)
Median age, years (range)	63 (32–85)	66 (43–81)
≥65 years, %	47.8	56.3
ECOG performance status, %		
0–1	80.9	78.5
2	18.5	20.9
3	0.6	0.6
Cytogenetic risk category by FISH, %		
High	14.0	18.4
Standard	43.3	48.1
Unknown	42.7	33.5
ISS stage at baseline, %		
I–II	49.7	46.2
III	48.4	51.9
Measurable disease category, %		
Light chain proteinuria/ UPEP-positive	53.5	41.1

ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; ISS, International Staging System; UPEP, urine protein electrophoresis

Patient and Disease Characteristics at Baseline (continued)

Characteristic	Carfilzomib (n=157)	Control (n=158)
Number of prior regimens, median (range)	5 (3–15)	5 (3–17)
>6 prior regimens, %	28.7	27.8
Time from initial diagnosis to start of FOCUS, median years (range)	6 (1.6–20.4)	5.4 (1.5–23.5)
Prior therapies, %		
Bortezomib/IMiD/alkylator/corticosteroid	100	100
Transplant	68.2	64.6
Anthracycline	74.5	77.2
Refractory, %		
Bortezomib (any prior regimen)	65.6	68.4
Bortezomib (last prior regimen)	22.9	25.9
IMiD (any prior regimen)	93.0	91.8
Bortezomib and IMiD (any prior regimen)	61.8	63.3
Creatinine clearance, %		
<30 mL/min	10.8	8.9
30–<50 mL/min	17.8	22.8

IMiD, immunomodulatory agent

Treatment Received

Treatment	Carfilzomib (n=157)	Control (n=153)
Median number of cycles (range)	5 (1–35)	3 (1–35)
Median K relative dose intensity†, %	99.87	-
Median corticosteroid relative dose intensity, %	-	99.86
Received optional cyclophosphamide, %	-	94.8
Median cyclophosphamide dose received, mg/cycle**	-	1083.3

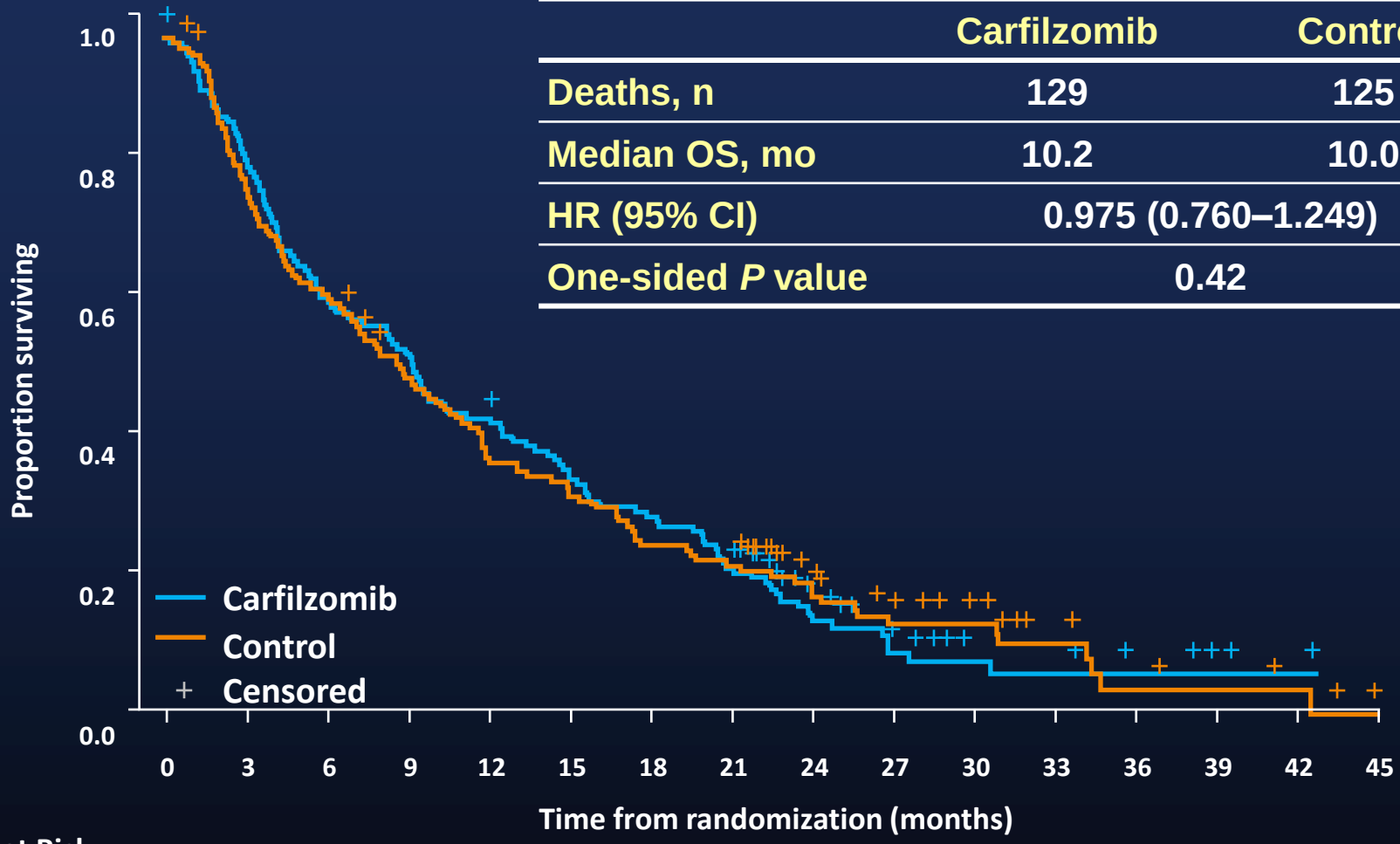
†Relative dose intensity = actual dose intensity / planned dose intensity

*Maximal dexamethasone dose per cycle: 84 mg

**Maximal cyclophosphamide dose per cycle: 1400 mg

Primary Endpoint: Overall Survival

	Carfilzomib	Control
Deaths, n	129	125
Median OS, mo	10.2	10.0
HR (95% CI)	0.975 (0.760–1.249)	
One-sided *P* value	0.42	



No. at Risk															
Carfilzomib	157	129	101	89	75	61	53	42	21	13	8	7	5	3	1	0
Control	158	121	100	79	62	55	45	41	26	19	15	9	5	4	3	0

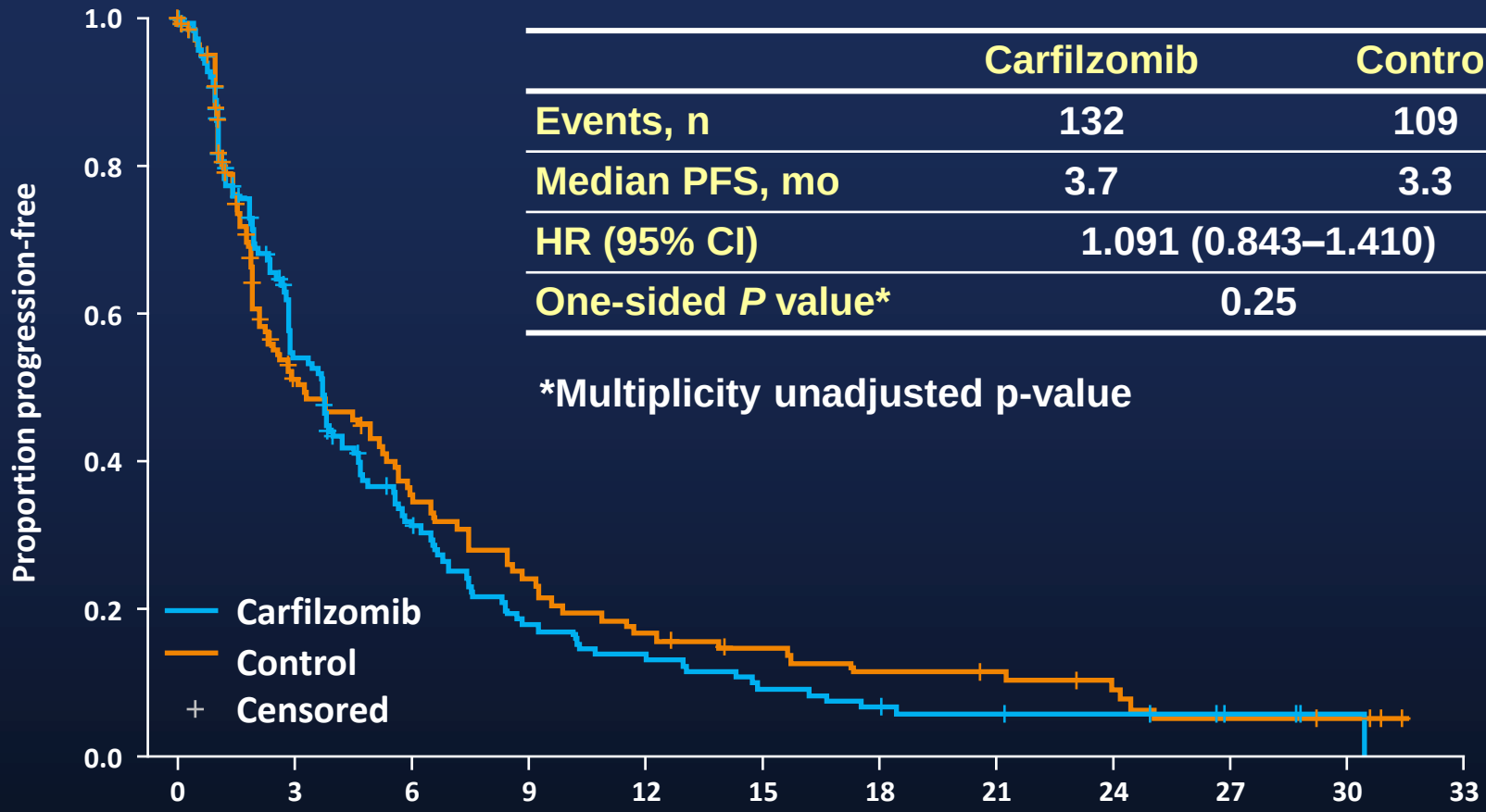
Secondary Endpoints: Response

Response, n (%)	Carfilzomib (n=157)	Control (n=158)	One-sided *P*-value*
Best overall response			
≥VGPR	6 (3.8)	5 (3.2)	-
PR	24 (15.3)	13 (8.2)	-
MR	19 (12.1)	15 (9.5)	-
ORR	30 (19.1)	18 (11.4)	0.03
CBR	49 (31.2)	33 (20.9)	0.02
DCR	119 (75.8)	107 (67.7)	0.05
Median DOR, months (95% CI)	7.2 (4.6–12.0)	9.5 (3.7–NE)	-

*Multiplicity unadjusted p-value

CI, confidence interval; DCR, disease control rate; DOR, duration of response; MR, minimal response; NE, not estimable; ORR, overall response rate; PR, partial response; VGPR, very good partial response

Secondary Endpoint: Progression-Free Survival



	Carfilzomib	Control
Events, n	132	109
Median PFS, mo	3.7	3.3
HR (95% CI)	1.091 (0.843–1.410)	
One-sided *P* value*	0.25	

*Multiplicity unadjusted p-value

No. at Risk												
Carfilzomib	157	76	41	23	18	12	9	7	6	3	1	0
Control	158	57	38	26	18	14	11	10	7	4	3	0

More censoring due to non-protocol therapy in the control arm (32; 20.3%) compared with the K arm (12; 7.6%) in the PFS analysis

Time-to-Event : Progression, Death, or Start of Next Therapy

- On the control arm, more patients switched to next therapy sooner (i.e., more patient censoring)

	Carfilzomib (median)	Control (median)	HR (95% CI)
Censoring due to start of next therapy, n (%)	12 (7.6)	32 (20.3)	-
Time to next anti-myeloma therapy	7.1 mo	5.7 mo	0.918 (0.693-1.216)
Time to treatment failure (both PFS events and non-protocol therapy considered as events)	3.4 mo	2.2 mo	0.923 (0.730–1.169)

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

Adverse events, Treatment Discontinuations, and Deaths

Adverse Event Category, %	Carfilzomib (n=157)	Control (n=153)
Any AE*	98.1	93.5
Grade ≥3 treatment-emergent AE	75.2	71.2
Deaths within 30 days of last dose	18.5	22.2
Deaths due to disease progression	8.9	9.2
Serious adverse event	58.6	51.0
AE leading to discontinuation of ≥1 study drug	14.6	20.3

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute Common Terminology for Adverse Events

Grade ≥3 AEs Occurring in ≥3.5% of Patients in an Arm

Adverse event*, %	Carfilzomib (n=157)		Control (n=153)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Hematologic adverse events				
Anemia	56.1	25.5	49.0	30.7
Thrombocytopenia	37.6	24.2	30.1	22.2
Neutropenia	14.6	7.6	17.0	12.4
Non-hematologic adverse events				
Pneumonia	7.6	6.4	13.1	12.4
Renal failure acute	9.6	7.6	3.9	3.3
Renal failure	6.4	5.1	2.0	1.3
Hypercalcemia	10.8	3.8	6.5	4.6
Renal impairment	7.0	3.8	3.3	0.7

- **More grade ≥3 acute renal failure events (grouped terms)† were observed with K (17.2%) vs control (5.2%)**

†Azotemia, oliguria, renal failure, renal failure acute, and renal impairment

Other AEs of Interest

Adverse event*, %	Carfilzomib (n=157)		Control (n=153)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Other AEs of interest				
Cardiac failure	4.5	1.9	0.7	0.7
Cardiac failure congestive	1.3	1.3	2.6	2.0
Dyspnea	14.6	1.3	8.5	0
Peripheral neuropathy	4.5	0.6	3.9	0

*AEs were coded according to MedDRA version 15.1; AE severity was graded according to NCI-CTCAE version 4.0. All AEs listed were treatment-emergent.

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute Common Terminology for Adverse Events

Renal Adverse Events

- In both arms, renal impairment or acute renal failure events occurred more often in patients with lower baseline CrCL

Baseline CrCl	Incidence of renal failure
<30 mL/min	35.5%
30 to <50 mL/min	23.4%
≥50 mL/min	12.0%

- More patients with renal impairment or acute renal failure events had light chain proteinuria/ UPEP-positivity
  - More light chain proteinuria was present at baseline in the K arm (54% vs 41%)
- Of patients with renal impairment or acute renal failure, 42% of cases occurred with myeloma progression in the K arm and 36% in the control arm
- Less renal impairment events were observed with K in the phase 2 setting[1]

[1]Siegel et al. *Haematologica* 2013.

Conclusions

- **Study did not meet its primary endpoint of prolonging overall survival**
  - **Control arm performed better than predicted**
- **ORR was higher with single-agent carfilzomib (19.1% vs 11.4%)**
- **The carfilzomib and control arm had a similar median PFS (3.7 mo vs 3.3 mo)**
- **Both arms had a median OS of approximately 10 months**
- **Safety profile of single-agent carfilzomib was consistent with previous studies in heavily pretreated patients with MM[1,2] except for renal impairment events**

[1]Siegel et al. *Blood* 2012; [2]Siegel et al. *Haematologica* 2013.

Future Directions

- K-based combinations are promising
- Previously untreated MM
  - KRd in elderly patients[1]
    - ORR of 100% (91% achieved ≥VGPR), a 3-yr OS rate of 100%, and a 3-yr PFS rate of 79.6%
- Relapsed/refractory MM
  - Kd (20/45 or 20/56 mg/m^2 of K)
    - ORR of 55%[2]
- Relapsed MM
  - KRd vs Rd (phase 3 ASPIRE study)
    - 8.7-month improvement in median PFS for KRd[3,4]

[1]Dytfeld et al. *Haematologica* 2014; [2]Papadopoulos et al. *J Clin Oncol*. 2014; [3]Press release, Amgen 2014., [4]Submitted to ASH 2014

Backup Slides

Next Anti-Myeloma Therapy

Next therapy received, %	Carfilzomib (n=157)	Control (n=158)
Patients who received next therapy	66.9	62.0
Median number of regimens (range)	1 (0–8)	1 (0–6)
Bortezomib	14.6	20.3
IMiD	32.5	26.6
Lenalidomide	8.9	7.0
Thalidomide	19.1	16.5
Pomalidomide	8.9	5.7
Bortezomib and an IMiD	8.3	9.5
Anthracycline	7.6	8.2
Alkylating agent	40.8	36.7
Corticosteroids	56.1	51.3

IMiD, immunomodulatory agent