Kyprolis (carfilzomib)

Oncologic Drugs Advisory Committee

June 20, 2012

Introduction

Ted W. Love, MD

Executive VP, R&D and Technical Operations
Onyx Pharmaceuticals, Inc.

Onyx Presentation

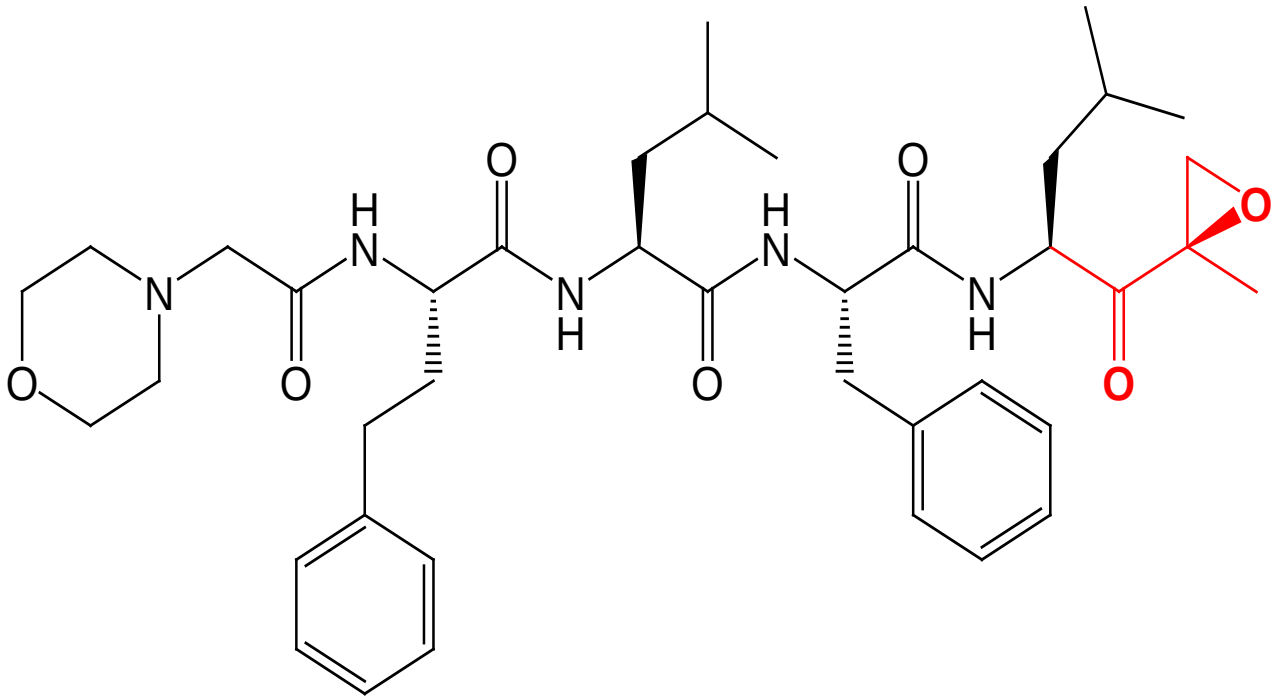
Introduction	**Ted W. Love, MD** EVP, R&D and Technical Operations Onyx Pharmaceuticals, Inc.
Multiple Myeloma Unmet Need	**Kenneth C. Anderson, MD** Program Director and Chief Division of Hematologic Neoplasias, Kraft Family Professor of Medicine, Harvard Medical School
Clinical Efficacy	**Barbara Klencke, MD** Sr. VP, Clinical Development Onyx Pharmaceuticals, Inc.
Clinical Safety	**Natalie Sacks, MD** VP, Clinical Science & Biometrics Onyx Pharmaceuticals, Inc.
Benefit/Risk Summary	**Sagar Lonial, MD** Professor and Vice Chair of Clinical Affairs, Department of Hematology and Medical Oncology Emory University School of Medicine

Consultants

- **David Siegel, MD, PhD**
  Chief, Myeloma Division
  John Theurer Cancer Center, Hackensack University Medical Center

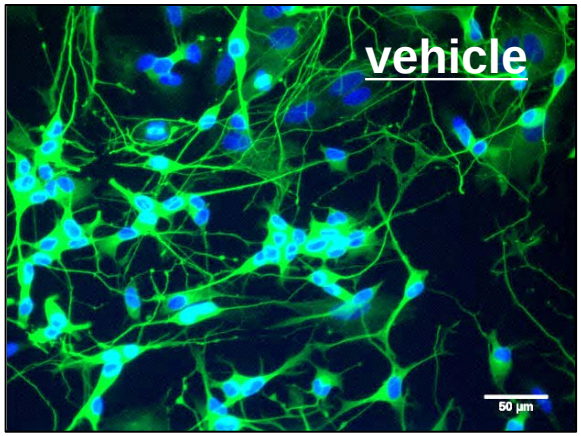
- **Milton Packer, MD**
  Professor & Chairman, Department of Clinical Sciences
  Gayle and Paul Stoffel Distinguished Chair in Cardiology
  UT Southwestern Medical Center

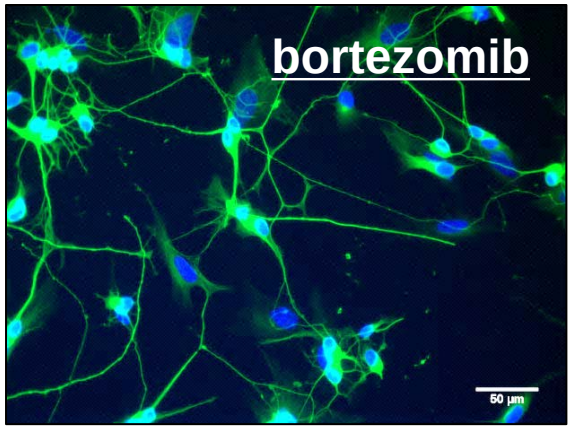
Carfilzomib – A Novel Proteasome Inhibitor

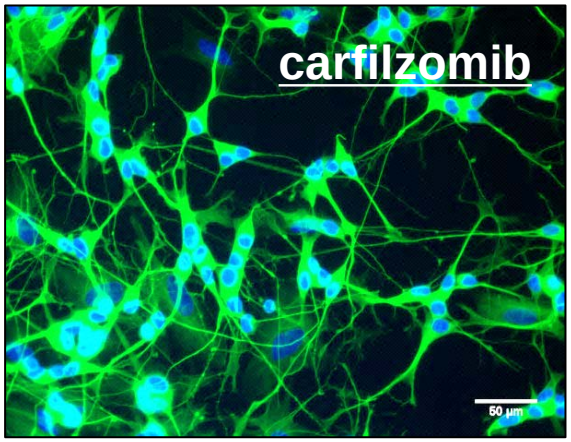


- **Potent and prolonged inhibition**
- **Irreversible and highly specific**

Carfilzomib Does Not Induce Neurodegeneration



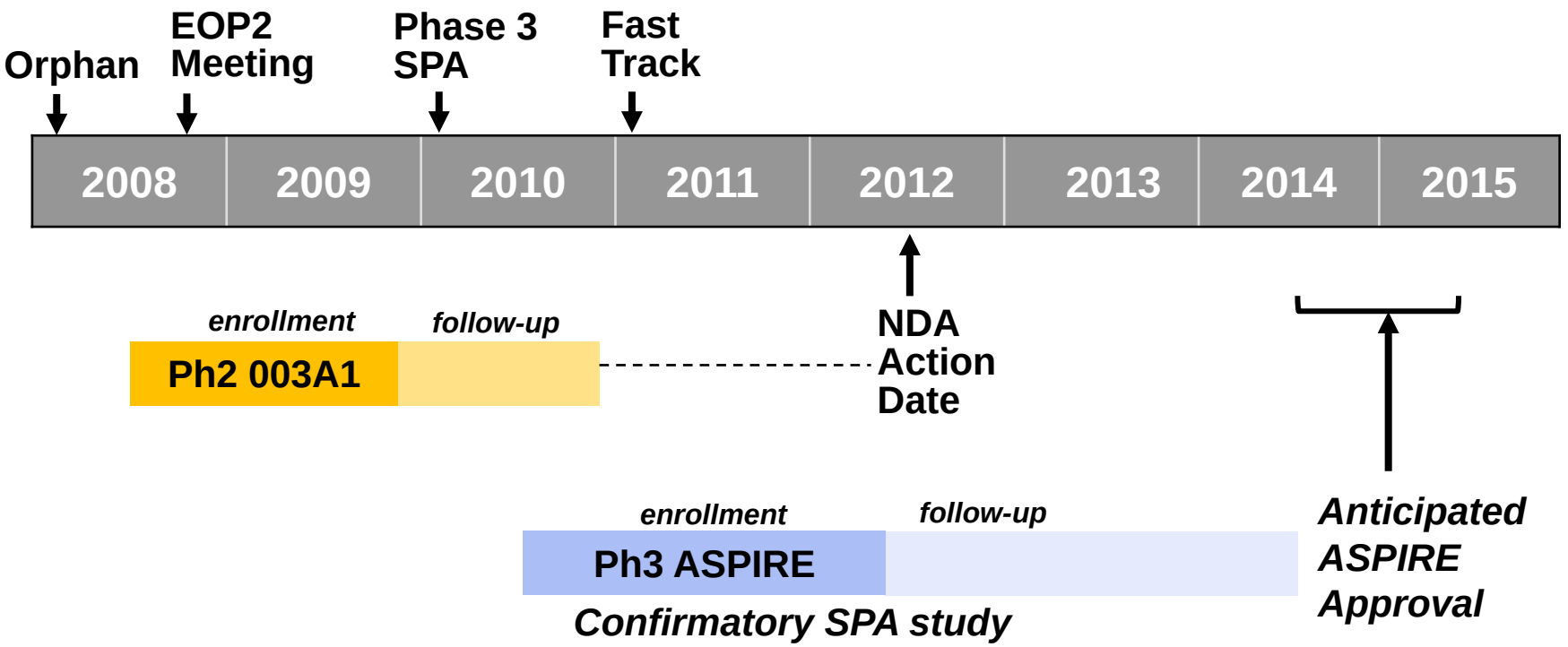




- **Bortezomib induces significant neurite degeneration *in vitro***
- **No neurodegeneration seen with carfilzomib**
  - **Does not inhibit serine protease critical to neuronal cell survival**
  - **Consistent with results from chronic dosing studies in animals**

Arastu-Kapur. *Clin Cancer Res*. 2011.

Carfilzomib Development Milestones



- Nine Phase 1 and 2 studies included in NDA
- Three additional Phase 3 studies underway

Accelerated Approval Sought for Carfilzomib in Relapsed and Refractory Myeloma

- Multiple Myeloma (MM) is a uniformly fatal malignancy
- No treatment options for patients who have exhausted all available therapies
- Carfilzomib monotherapy
  - Meaningful and durable responses
  - Well-characterized safety profile
  - No cumulative toxicity

Proposed Indication

Carfilzomib for the treatment of relapsed and refractory Multiple Myeloma in patients who have received at least 2 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent

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Unmet Need in Relapsed and Refractory Multiple Myeloma

Kenneth C. Anderson, MD

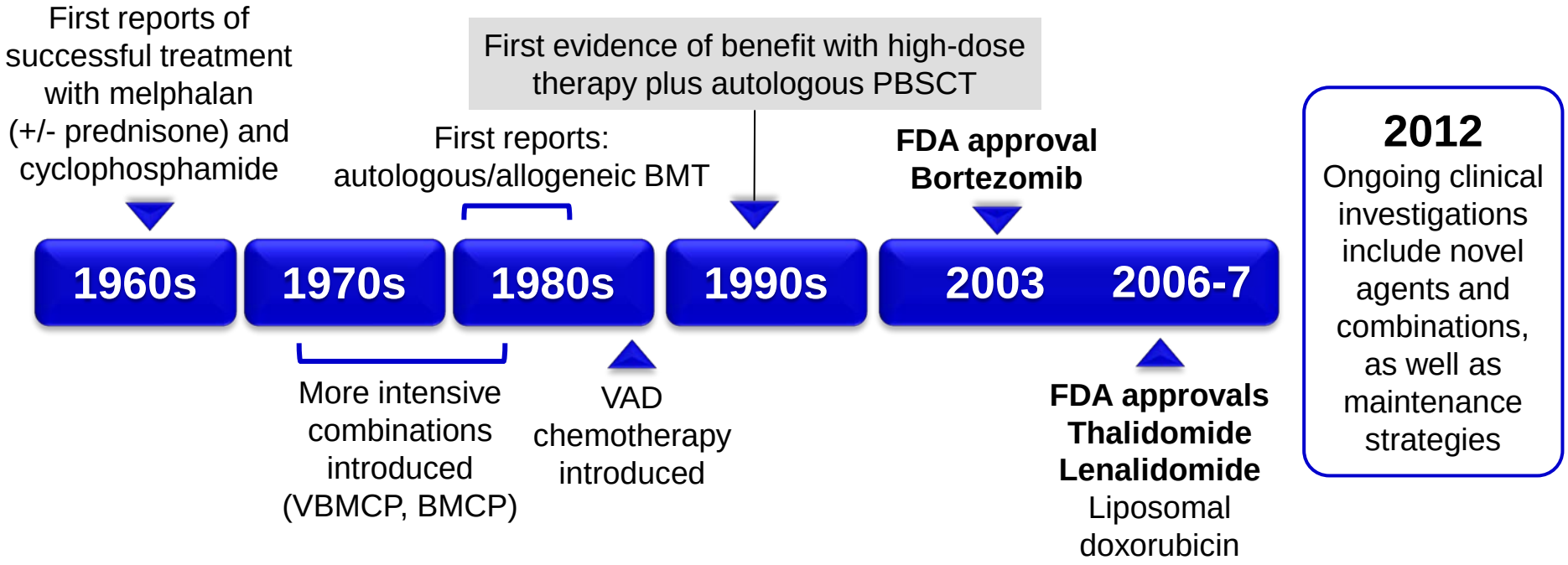
Kraft Family Professor of Medicine, Harvard Medical School

Director, Lebow Institute for Myeloma Therapeutics

Director, Jerome Lipper Multiple Myeloma Center

Dana-Farber Cancer Institute

Historical Perspective of MM Treatment



VBMCP: vincristine, carmustine, melphalan, cyclophosphamide, prednisone
BMCP: carmustine, melphalan, cyclophosphamide, prednisone
VAD: vincristine, doxorubicin, dexamethasone

Adapted from: Durie BGM. Multiple Myeloma. International Myeloma Foundation. 2011/2012 edition.
Laubach JP, et al. *Med Oncol*. 2010;27:S1-S6.

Historical Context – SUMMIT Accelerated Approval Trial for Bortezomib

- **Study Design:**
  - Single arm, Phase 2
  - N = 202 patients; 193 analyzed for efficacy
  - Relapsed myeloma, refractory to last prior therapy
  - Primary endpoint: Response Rate
  - Stat. design: lower limit of 90% CI > 10% defined activity

Patient Characteristics	N = 202
Median prior regimens, n	6
Stem cell transplant	64%
Bortezomib	0%
IMiD	83%
Lenalidomide	0%
Thalidomide	83%
Corticosteroids	> 99%
Alkylating agent	92%
Cyclophosphamide	–
Melphalan	–
Anthracycline	81%

Richardson PG, *et al.* *N Engl J Med.* 2003;348(26):2609-17.

Historical Context – SUMMIT Accelerated Approval Trial for Bortezomib

Efficacy	N = 193
ORR (≥ PR)	27%
CBR (≥ MR)	35%
Duration of response, median	15 months
Overall survival, median	16 months

ORR = overall response rate, CBR = clinical benefit response, DOR = duration of response

- The SUMMIT trial supported the accelerated approval of bortezomib
- Clinical activity confirmed in the subsequent Phase 3 APEX trial

Richardson PG, *et al.* *N Engl J Med.* 2003;348(26):2609-17.

Common Clinical Use of Approved Drugs

	Front Line	Relapsed	Relapsed and Refractory
Alkylating agents			
Melphalan			
Cyclophosphamide	✓	✓	✓
Anthracyclines			
Liposomal doxorubicin		✓	
Nitrosoureas			
Carmustine			
IMiDs			
Thalidomide	✓		
Lenalidomide	✓	✓	✓
Proteasome inhibitor			
Bortezomib	✓	✓	✓

Side Effects Limit the Use of Available Therapies

Class	Limiting Toxicities
Alkylating agents	Myelosuppression
Anthracyclines	Cardiotoxicity, myelosuppression
Nitrosoureas	Pulmonary disease, myelosuppression
Corticosteroids	Hypertension, hyperglycemia, mood disorders
IMiDs	Thromboembolic events, myelosuppression, peripheral neuropathy
Bortezomib	Neuropathy, GI disorders, myelosuppression

There is a Well Defined and Recognized Unmet Need in Multiple Myeloma Treatment

Unmet Need

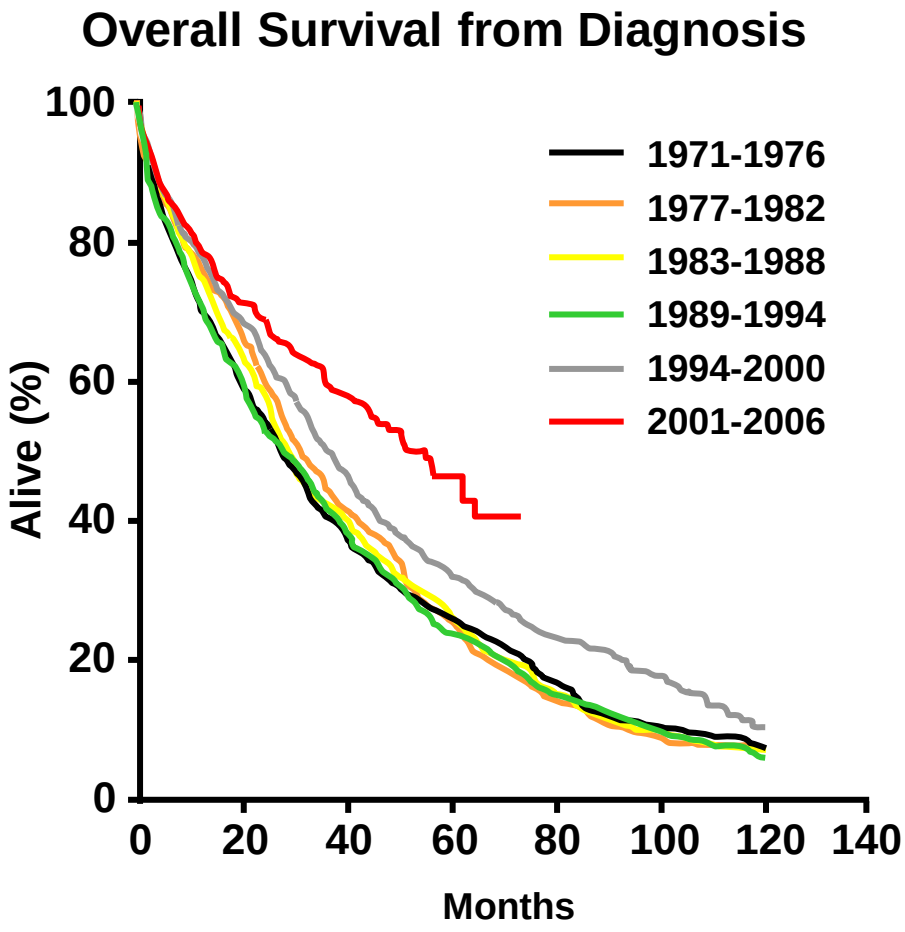
Frontline Treatment → Relapsed → Refractory or Intolerant

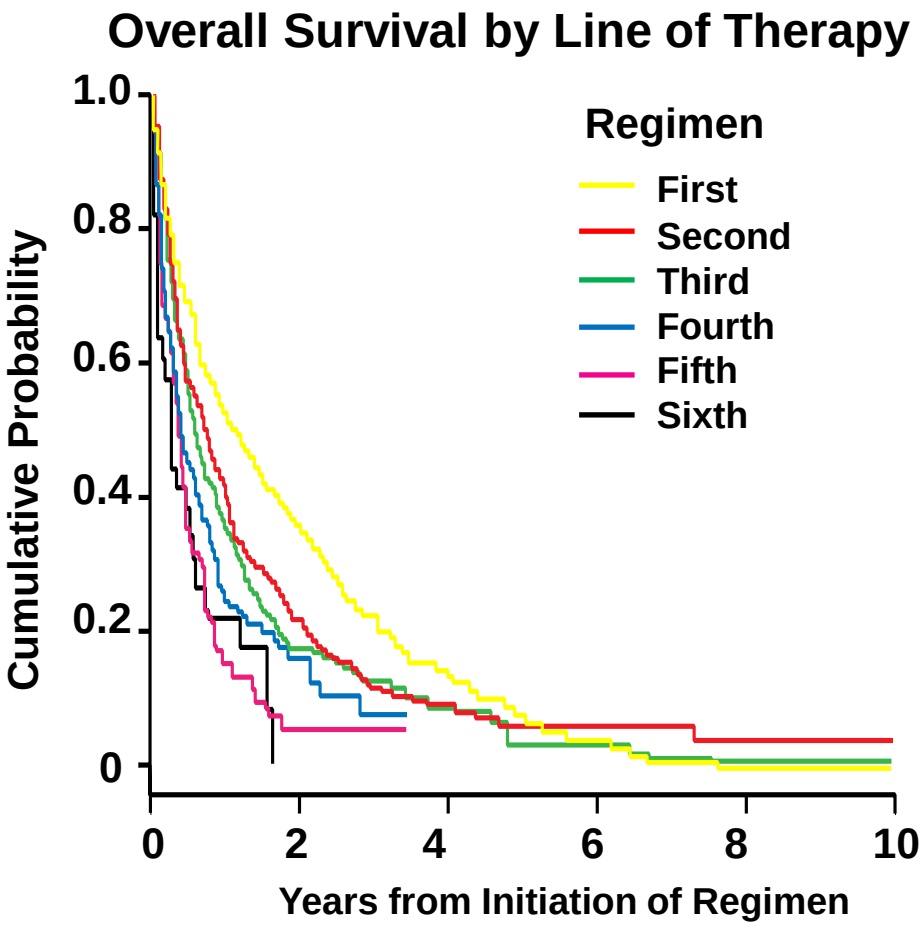
Expected survival (m)	20-50	14-16	6-10
Sensitivity to therapy	Sensitive	Less Sensitive/Resistant	Resistant
Treatment limitations/ comorbidities	Peripheral neuropathy (~15% at diagnosis)	>80% incidence of peripheral neuropathy Compromised marrow reserve Cytopenia	Intolerant to or ineligible for available therapy

Elderly population (↑ risk for heart, lung, renal, liver dysfunction, diabetes)

Adapted from: Durie BGM. Multiple Myeloma. International Myeloma Foundation. 2011/2012 edition.
Jagannath S. *Clin Lymphoma Myeloma*. 2008;8 Suppl 4:S149-S156.

Novel Agents Changing Natural History of Multiple Myeloma but Mortality Remains High





Adapted from Kumar SK, et al. *Blood*. 2008;111:2516-2520.

Kumar SK, et al. *Mayo Clin Proc*. 2004;79(7):867-874.

Poor Survival in Bortezomib and IMiD Refractory MM

- Retrospective review by IMWG in 286 patients refractory to bortezomib and refractory or intolerant to an IMiD
- 4 prior lines of therapy, median
- 3.3 years since diagnosis, median
- No standard treatment
  - 31+ different regimens
  - Combinations with or without novel agents

	Months	95% CI
Median Overall Survival	9	7, 11

Kumar SK, et al. *Leukemia* 2012; 26:149.

Response Rate Decreases with Increasing Lines of Therapy

- Retrospective cohort study by IMWG* (2007-10)
  - 383 patients in 1st relapse identified
  - ORR following each subsequent relapse

Relapse	Line of Therapy	Patients Treated	Response Rate, %
1st	2nd	383	58
2nd	3rd	207	45
3rd	4th	86	30
4th	5th	27	15
5th	6th	003-A1 Study Population	

*Adapted from Durie B et al, *J Clin Oncol* 30, 2012 (suppl; abstr 8095).

Unmet Medical Need in Relapsed and Refractory Multiple Myeloma

- No standard of care and few options
- Trials of repeat single agent/combination novel agents
  - Transient and diminishing responses
  - Short progression-free survival and overall survival
- Urgent need for additional novel agents
  - Clinically meaningful responses
  - Durability of response
  - Associated clinical benefit
- Carfilzomib represents a promising next generation proteasome inhibitor in this clinical setting

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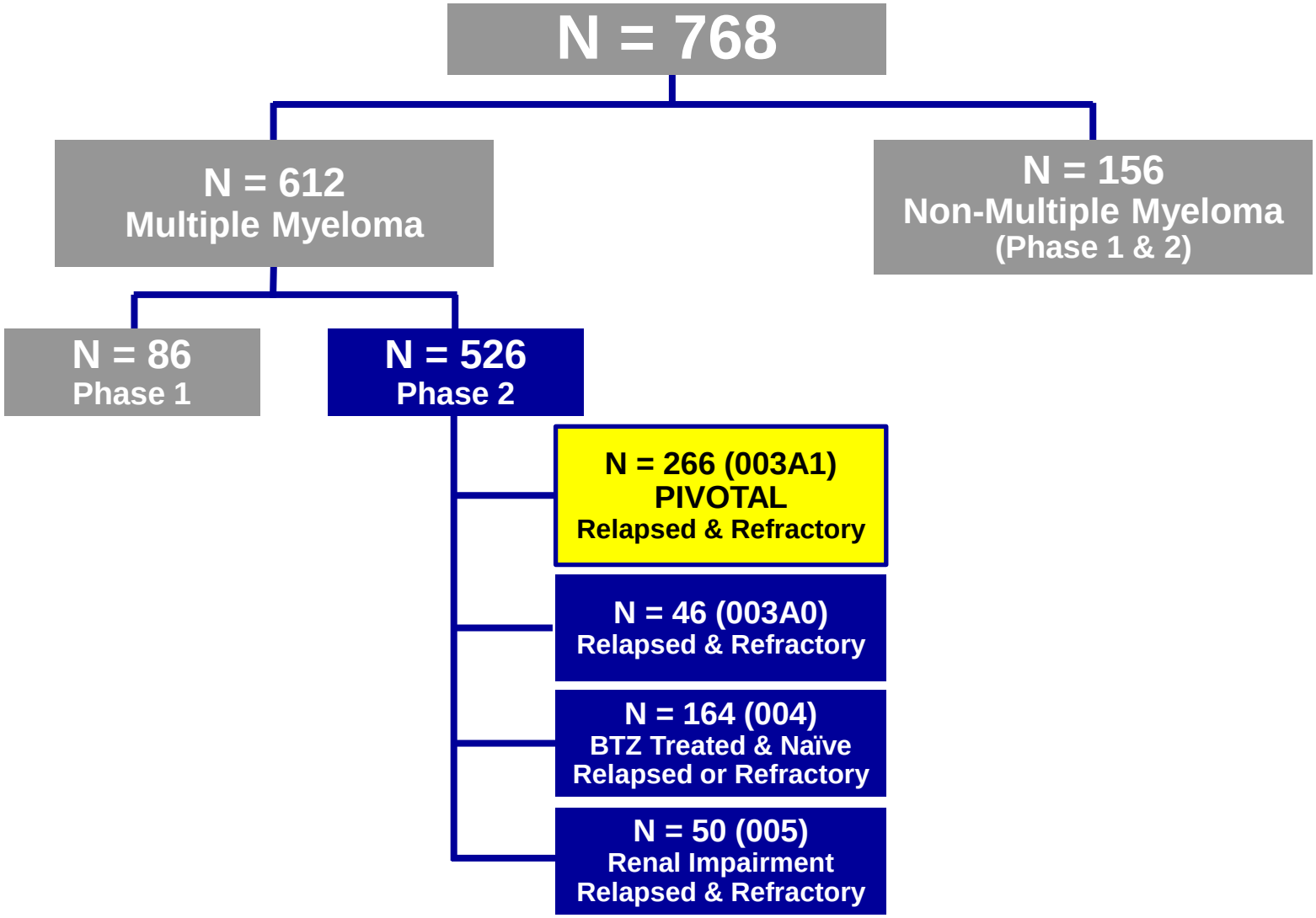
Carfilzomib Efficacy

Barbara Klencke, MD

Senior VP, Clinical Development
Onyx Pharmaceuticals, Inc.

Carfilzomib NDA – Efficacy Database



Carfilzomib
Pivotal Phase 2 Study (003A1)

003A1 – Study Design and Rationale

- Open-label, single-arm, multicenter Phase 2 study
- Assess safety and efficacy of carfilzomib
- Refractory status as defined by the International Myeloma Working Group (IMWG)[1]
  - Progression during treatment or within 60 days of completion of the treatment, or
  - Stable disease (SD) as a best response
- Unmet need population for 003A1:
  - Refractory to the last regimen
  - Consistent with ASH/FDA Workshop on Clinical Endpoints in Multiple Myeloma[2]

[1]Durie. *Leukemia* 2006.
[2]Anderson. *Leukemia* 2008.

003A1 – Key Eligibility Criteria

- Measurable disease by serum and/or urine M protein
- Refractory to last regimen
- Received all 4 classes of approved therapies:
  - Bortezomib
  - Immunomodulatory drug (IMiD): lenalidomide or thalidomide
  - Alkylating agent
  - Anthracycline
- ECOG performance status 0-2
- Permitted entry of patients with compromised organ function:
  - Renal: CrCl ≥ 30 mL/min
  - Hepatic: AST/ALT < 3 × ULN or bilirubin < 2 × ULN
  - Hematologic: ANC ≥ 1000, Hgb ≥ 8, or platelets ≥ 50,000
  - Neuropathy: Grade 1 or 2 neuropathy without pain

003A1 – Primary Efficacy Endpoint of ORR

- ORR defined by IMWG criteria[1]
  - Complete response (CR),
  - Very good partial response (VGPR), or
  - Partial response (PR)
- Rigorously and independently determined
  - Required 2 consecutive assessments
  - Independent Review Committee (IRC)
- Study powered to exclude 10% as lower boundary of the 2-sided 95% CI

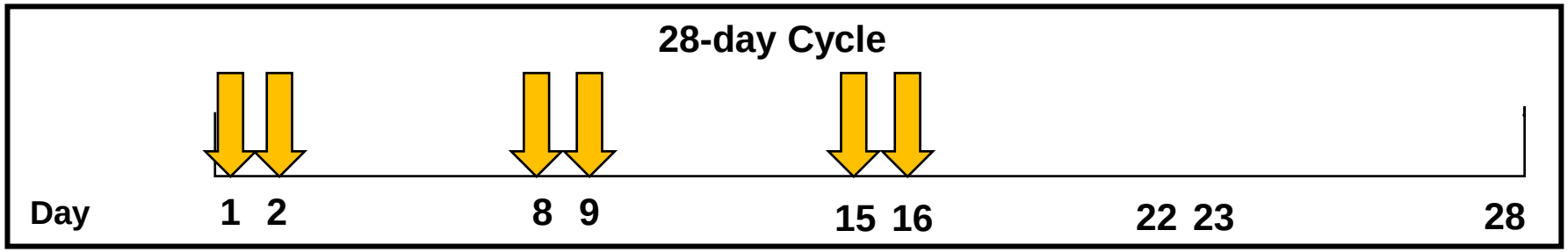
[1]Durie *Leukemia* 2006.

003A1 – Secondary Efficacy Endpoints

- Duration of response (DOR)
- Clinical benefit response (CBR) rate
  - Incorporates minimal response (MR) in addition to CR, VGPR, PR*
- Progression-free survival (PFS)
- Time to progression (TTP)
- Overall survival (OS)

*Blade *Br J Haematol* 1998; Niesvizky *Br J Haematol* 2008; Anderson *Leukemia* 2008.

003A1 – Carfilzomib Monotherapy



Carfilzomib "Stepped-up" Dosing Regimen

- **Cycle 1: 20 mg/m^2 IV**
- **Cycles 2 through 12: 27 mg/m^2 IV**
- **Treatment for up to twelve 28-day cycles**

Hydration

Dexamethasone Premedication

- **4 mg po or IV**
- **Mandatory for Cycle 1 and the 1st carfilzomib dose-escalation (Cycle 2)**
- **Optional thereafter**

003A1 – Demographic Characteristics

Characteristic	Total N = 266
Median age, years (range)	63.0 (37 – 87)
Age group	
< 65 years	55%
≥ 65 years	45%
Gender	
Male	58%
Female	42%
Race	
White	71%
Black	20%
Other	9%

003A1 – Selected Baseline Characteristics

Characteristic	Total, N = 266
Median time from diagnosis (range)	5.4 years (0.5, 22)
Actively progressing (rising M protein in serum or urine)	97%
Refractory to last therapy	94%
Markers of poor prognosis	
Bone marrow plasma cells ≥ 50%	40%
ISS Stage III	31%
Poor prognosis, cytogenetic/FISH	28%
CrCl < 50 mL/min	24%
ECOG = 2	13%
Blood dyscrasias	
Hgb < 10.5 g/dL	57%
Platelets < 75000/mm^3	31%

003A1 – Prior Anti-myeloma Treatment

Prior Therapy	Exposed (N = 266)
Median no. prior regimens (range)	5.0 (1, 20)
Stem cell transplant	74%
Bortezomib	100%*
Immunomodulatory Drug (IMiD)	100%
Lenalidomide	94%
Thalidomide	75%
Corticosteroids	98%
Alkylating agent	93%
Anthracycline	64%

* Actual proportion is 99.6% (265/266 patients)

003A1 – Primary Efficacy Endpoint (IRC)

Response Category	Total N = 266 n (%)
CR	1 (0.4)
VGPR	13 (4.9)
PR	47 (17.7)
MR	34 (12.8)
SD	81 (30.5)
PD	69 (25.9)
Not evaluable	21 (7.9)

ORR = 22.9%
(95% CI: 18.0, 28.5)

Median DOR = 7.8 months (95% CI 5.6, 9.2)

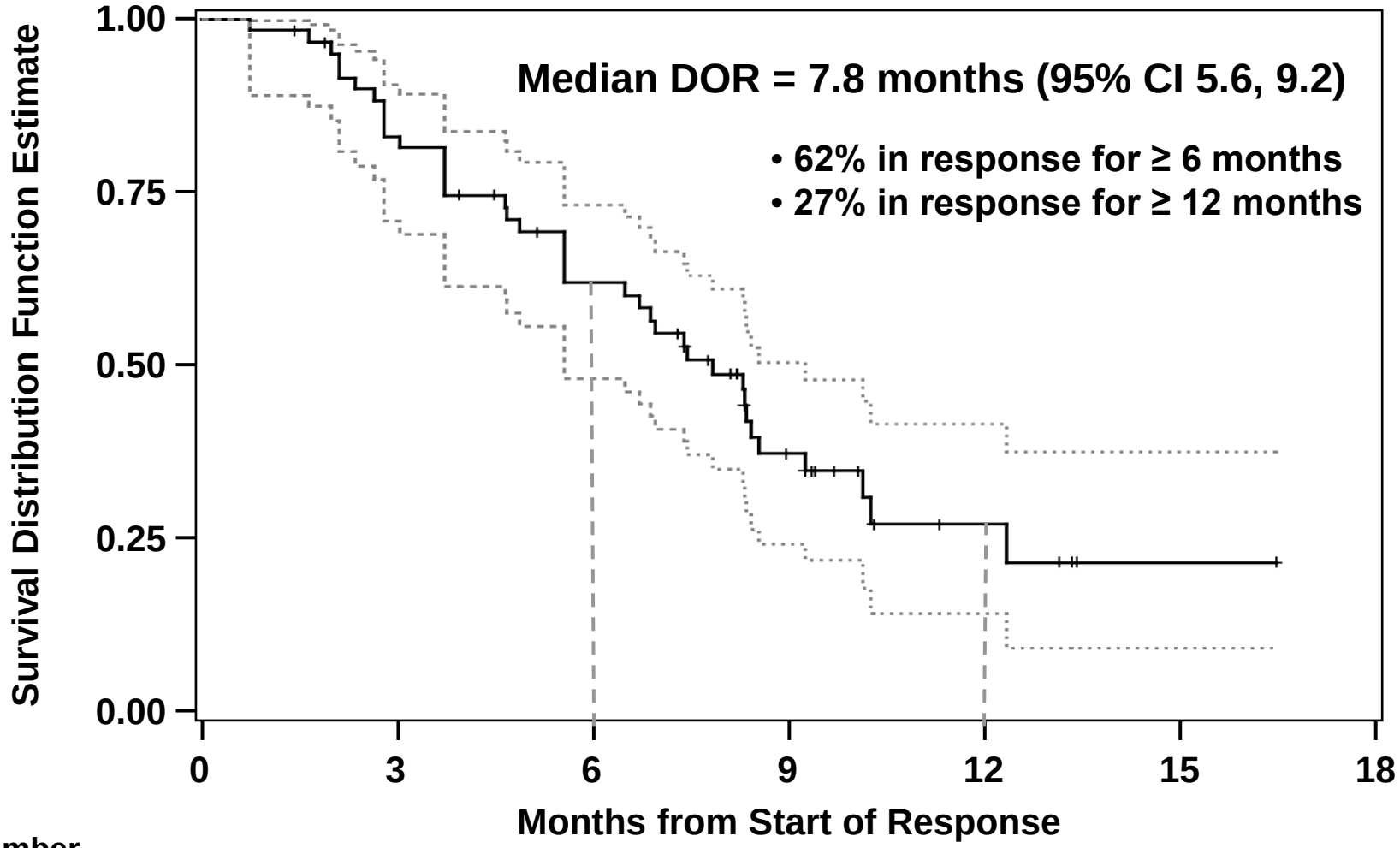
003A1 – Clinical Benefit Response: Secondary Efficacy Endpoint

Response Category	Total N = 266 n (%)
CR	1 (0.4)
VGPR	13 (4.9)
PR	47 (17.7)
MR	34 (12.8)
SD	81 (30.5)
PD	69 (25.9)
Not evaluable	21 (7.9)

CBR = 35.7%
(95% CI: 30.0, 41.8)

Median duration of CBR = 8.3 months (95% CI 6.5, 9.7)

003A1 – Duration of Response



Number at risk:	61	49	34	15	5	1	0

003A1 – Primary Efficacy Endpoint: Concordance by Method of Analysis

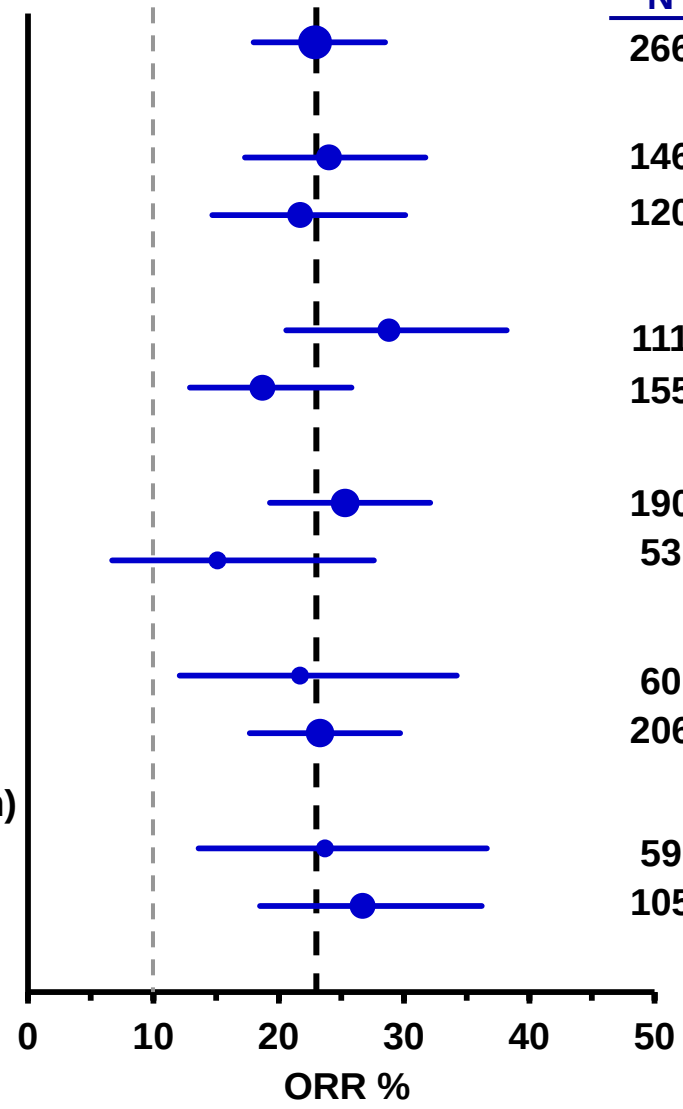
Response Category	IRC	Investigator
CR	1	0
VGPR	13	15
PR	47	45
MR	34	29
SD	81	93
PD	69	69
Not evaluable	21	15

ORR = 22.9%

ORR = 22.6%

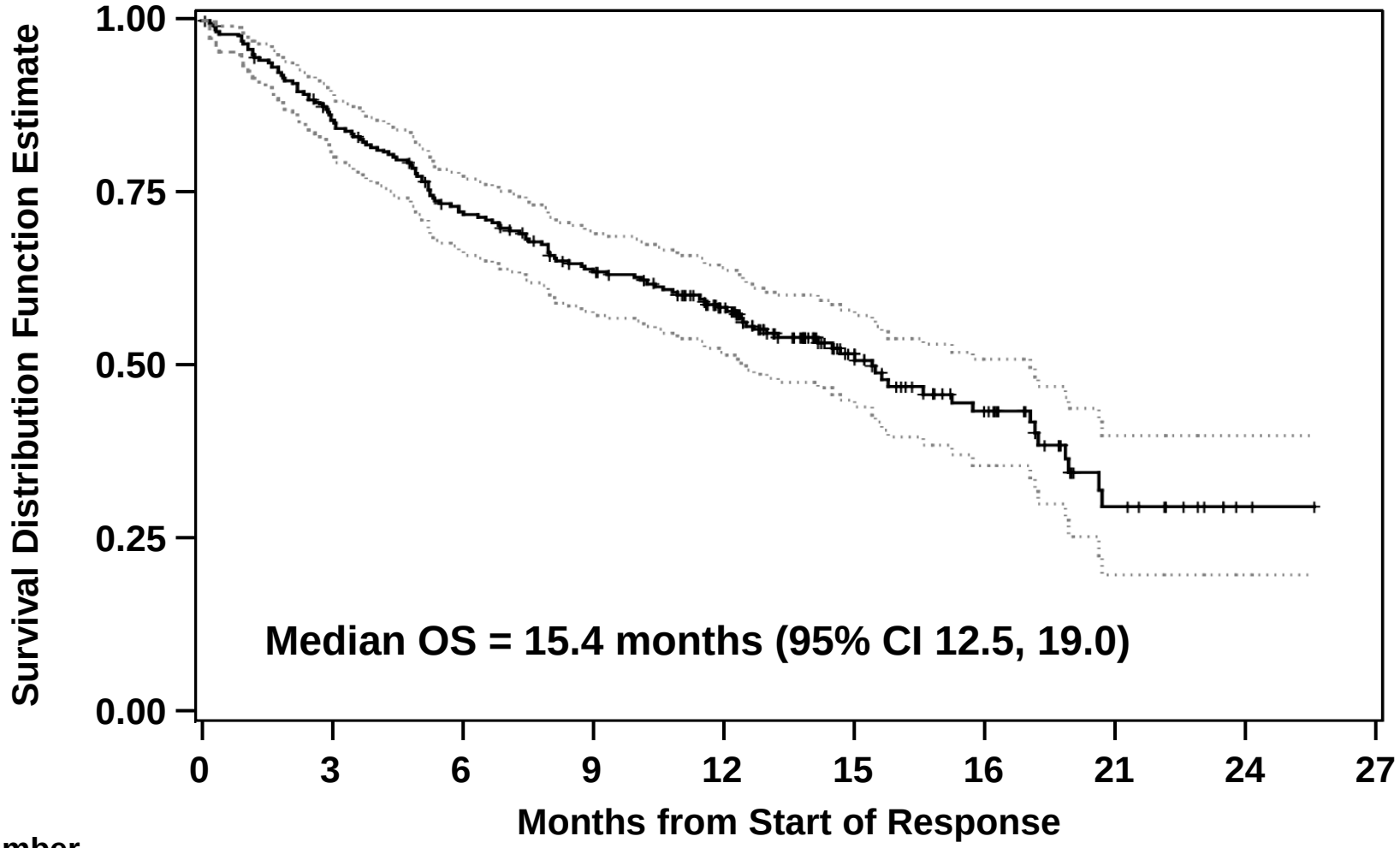
FDA analysis:
ORR = 22.9%

003A1 – Subgroup Analysis of ORR by Key Baseline Characteristics



	N	ORR	95% CI
All subjects	266	22.9	(18.0 – 28.5)
Age (years)			
< 65	146	24.0	(17.3 – 31.7)
≥ 65	120	21.7	(14.7 – 30.1)
Gender			
Female	111	28.8	(20.6 – 38.2)
Male	155	18.7	(12.9 – 25.8)
Race			
White	190	25.3	(19.3 – 32.1)
Black	53	15.1	(6.7 – 27.6)
Baseline neuropathy			
0	60	21.7	(12.1 – 34.2)
≥1	206	23.3	(17.7 – 29.7)
Baseline creatinine clearance (mL/min)			
30 - < 50	59	23.7	(13.6 – 36.6)
50 - < 80	105	26.7	(18.5 – 36.2)

003A1 – Overall Survival (N = 266)



Number at risk:	266	223	185	156	121	58	34	12	2	0

Phase 2 Supportive Myeloma Studies

Population	Study	Number of Patients	Dose of Carfilzomib	ORR %
BTZ-treated	003A0	46	20 mg/m^2	15.2
	003A1	266	20/27 mg/m^2	22.9
	004	35	20 mg/m^2	17.1
	005	50	15/20/27 mg/m^2	20.0
BTZ-naïve	004	59	20 mg/m^2	42.4
	004	70	20/27 mg/m^2	50.0

Carfilzomib Efficacy Summary

- Pivotal 003A1 Study (N = 266)
  - Patients with high unmet medical need
    - Actively progressing, multiply relapsed, and refractory myeloma
  - Objective, durable, and clinically meaningful benefit
    - ORR 22.9%, median DOR of 7.8 months
      - ORR by IRC and investigator highly concordant
    - CBR 35.7%, median DOCBR of 8.3 months
    - Consistent benefit in clinically important subgroups
  - Benefit replicated in supportive Phase 2 myeloma trials

Agenda

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Safety

Natalie Sacks, MD

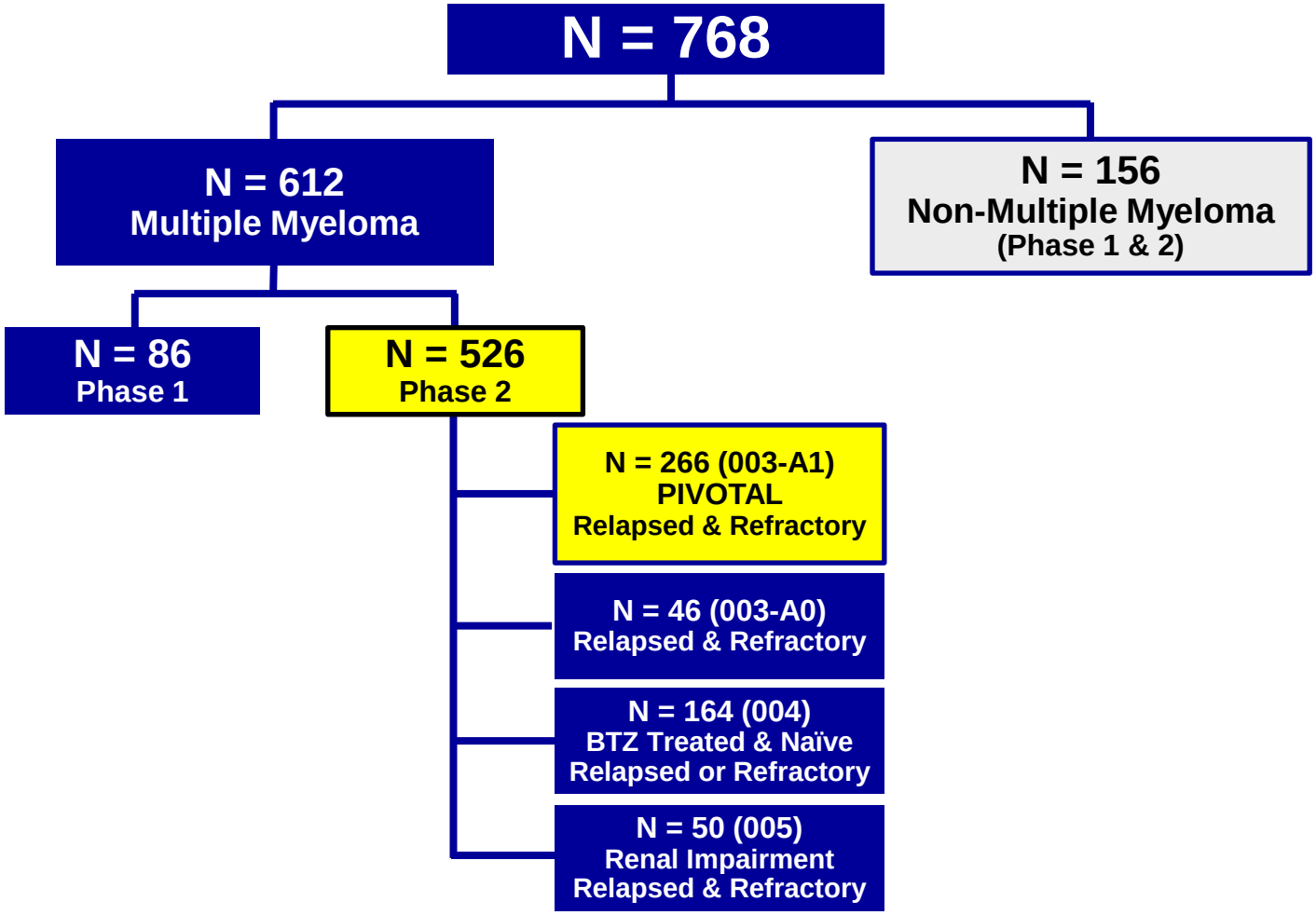
VP, Clinical Science & Biometrics
Onyx Pharmaceuticals, Inc.

Agenda

- Exposure
- Adverse Events
- Serious Adverse Events and Deaths
- Cardiac, Pulmonary and Hepatic Adverse Events
- Conclusion

Carfilzomib NDA Database

- Large number of patients with advanced myeloma



Exposure on 003A1

	Total Patients N = 266
Median number of cycles	4
Patients who completed 6 cycles, %	31
Patients who completed 12 cycles, %	15

Common Hematologic AEs ≥ 20% Study 003A1

AEs Regardless of Relationship	N = 266 %			
	All Grades	Grade 3	Grade 4	Grade 5
Anemia	46	22	2	0
Thrombocytopenia	39	17	12	0
Lymphopenia	23	18	2	0

- 1 patient discontinued
- Clinical sequelae of cytopenias
  - Bleeding (≥ Grade 2) and thrombocytopenia 2%
  - Zoster reactivation 2%
  - Febrile neutropenia 0.8%

Common Non-Hematologic AEs ≥ 20% Study 003A1

AEs Regardless of Relationship	N = 266 %			
	All Grades	Grade 3	Grade 4	Grade 5
Fatigue	49	8	0	0
Nausea	45	2	0	0
Dyspnea	34	3	0	0.4
Diarrhea	32	0.4	0.4	0
Pyrexia	31	2	0	0
Headache	28	2	0	0
Upper respiratory tract infection	27	5	0	0
Blood creatinine increased	25	3	0	0
Cough	24	0.4	0	0
Back pain	24	5	0	0
Peripheral Edema	23	0.4	0	0
Vomiting	22	0.8	0	0
Constipation	21	0	0	0

Peripheral Neuropathy AEs 003A1

AE Regardless of Relationship	N = 266 %			
	All Grades	Grade 3	Grade 4	Grade 5
Peripheral Neuropathy	12	1	0	0

- Baseline neuropathy: 77%
- No patient discontinued
- Consistent with selectivity of carfilzomib proteasome inhibition*

*Arastu-Kapur, 2011.

Summary of AEs
Phase 2 Myeloma Studies

	Pivotal 003A1 N = 266 %	Pilot 003A0 N = 46 %	Relapsed 004 N = 164 %	Renal 005 N = 50 %	Total Phase 2 MM N = 526 %
At least 1 AE	100	100	100	94	99
At least 1 Grade ≥ 3 AE	87	85	65	90	80
At least 1 SAE	47	44	35	66	45
Discontinuation due to AE	12	28	16	12	15
Deaths within 30 days of last dose	9	9	2	10	7

AEs ≥ 1% Leading to Discontinuation

AEs Regardless of Relationship	003A1 N = 266 %	Phase 2 MM Population N = 526 %
All AEs	12.4	14.8
Congestive cardiac failure	1.5	1.5
Dyspnea	1.5	1.3
Cardiac arrest	1.5	1.0

Carfilzomib Long-term Extension Study

- 92 patients enrolled into the extension study
- 78 patients ≥ 1 year, 33 patients ≥ 2 years
  - SAE rate 44%
  - No evidence of unique late onset events

Serious Adverse Events ≥ 2%

SAEs Regardless of Relationship	003A1 N = 266 %	Phase 2 MM Population N = 526 %
Any Event	47.4	44.9
Pneumonia	8.6	9.9
Disease progression	6.0	5.9
Acute renal failure	3.4	4.2
Congestive cardiac failure	3.0	3.4
Pyrexia	3.0	3.4
Pathological fracture	3.0	2.1
Hypercalcemia	2.3	2.1
Spinal cord compression	2.3	1.3

Cardiac Disease in Myeloma Patients

- Cardiac comorbidity common in elderly patients with Myeloma due to:*
  - Age-related cardiovascular risk
  - Chronic anemia
  - Amyloidosis
  - A-V shunt in bony lesions
  - Hyperviscosity
  - Prior anthracycline exposure
  - Prior transplant associated with increased cardiac events and death

*McBride, 1988; Robin, 2008; Inanir, 1998: Kyle, 2003; Chow, 2011.

Cardiac Comorbidities are Common in Multiple Myeloma Patients

Baseline Rate of Cardiac Conditions at Cohort Initiation [1]	Newly Diagnosed MM N = 22,076	≥ 3 Prior Treatment MM N = 1,723
Median age (yrs)	62	61
Any cardiac condition	63%	65%
Cardiac dysrhythmia	14%	17%
Cardiomyopathy	3%	3%
Congestive heart failure	8%	9%
Ischemic heart disease	14%	10%

[1]Claims analysis; United Biosource Corp., 2012.

Cardiac Adverse Events
Phase 2 Myeloma Population

AE Regardless of Relationship	N = 526, %			
	All Grades	Grade 3	Grade 4	Grade 5
Grouped Cardiac Failure Events	7	5	0.8	0
Congestive cardiac failure	4	4	0.4	0
Pulmonary edema	2	1	0.2	0
Cardiac failure	0.6	0.2	0.2	0
Grouped Cardiac Arrhythmia Events	13	1	0.2	0.8
Tachycardia	4	0	0	0
Palpitations	3	0	0	0
Bradycardia	2	0	0	0
Atrial fibrillation	2	0.8	0	0
Cardiac arrest	1	0	0.2	0.8
Grouped Ischemic Heart Disease Events	3	1	0.4	0
Angina pectoris	1	0	0	0
Myocardial ischemia	0.8	0.6	0	0
Myocardial infarction	0.4	0.2	0	0
Troponin increased	0.4	0	0.2	0
Acute coronary syndrome	0.2	0	0.2	0

- 1.7% discontinued from grouped cardiac failure events
- 1.0% discontinued from grouped ischemic heart disease events

Historical Context for Cardiac Failure in Myeloma

AE Regardless of Relationship	Bortezomib N = 331 %	Dexamethasone N = 332 %
Cardiac failure	5	4

[1]APEX Study, Velcade PI 2012.

Causes of Death in Myeloma

Retrospective review myeloma patients, N = 3107*

- **10% (299 patients) died within the first 60 days of diagnosis**
- **Most common causes of death**
  - **Pneumonia (3%)**
  - **Renal failure (3%)**
  - **Cardiac failure (1%)**
  - **Sepsis (1%)**
  - **Sudden death (1% with half occurring at home)**
  - **Vascular (MI or stroke) (0.8%)**

***Augustson, 2005.**

On-Study Deaths
Phase 2 Myeloma Population

Cause of Death	Phase 2 MM Population N = 526 n (%)	
Progressive disease	24 (5)	
Cardiac component	3 (0.6)	
Adverse event reported	13 (3)	8 (1.5)
Cardiac	5 (1)	
Infections	2 (0.4)	
Hepatic failure	2 (0.4)	
Other	4 (0.8)	
Total	37 (7)	

Pre-existing Cardiac Risk Factors and Mortality

	Baseline Cardiac Risk Factors Phase 2 MM Population N = 526	
	Yes N = 368 n	No N = 158 n
Deaths with a cardiac component	9 (2%)	1 (0.6%)
Total on study deaths	26 (7%)	11 (7%)

Deaths Within Two Days of Dosing Phase 2 Myeloma Population

Age, Sex	Number of Prior Anti-MM Regimens	Day of Death	Day from Last Dose	Confounding Factors
66, M	6	92	1	PMH of atherosclerosis, worsening HTN (212/115 mmHg), asthma
53, M	8 anthracycline and transplant	9	0	ECOG 2 at study entry, hyperlipidemia, IDDM, HTN, COPD, A-V block, AF
52, M	2 transplant	4	2	Autopsy: bilateral hypertrophy and ventricular dilatation, pulmonary edema; hyperlipidemia

Historical Context for Overall Deaths in Relapsed and Refractory Myeloma

	Carfilzomib		Lenalidomide	Bortezomib
	003A1 N = 266	Phase 2 MM N = 526	N = 222[1]	N = 202[2]
On study deaths, %	9	7	10	5
On study definition, days	30	30	30	20
Years from diagnosis, median	5.4	4.8	3.7	4.0

[1]MM-014 Study, Richardson, 2009; [2]SUMMIT study, Richardson 2003.

Pulmonary AEs ≥ 10%
Phase 2 Myeloma Population

AEs Regardless of Relationship	N = 526 %			
	All Grades	Grade 3	Grade 4	Grade 5
Dyspnea	42	5	0	0.2
Cough	26	0.2	0	0

- Dyspnea episodes mild, transient
  - 64% of episodes < 2 weeks, 33% ≤ 5 days
  - Median duration 8 days
- 1.5% discontinued from dyspnea

Pulmonary AEs
Phase 2 Myeloma Population

AEs Regardless of Relationship	N = 526 %			
	All Grades	Grade 3	Grade 4	Grade 5
Pleural effusion	4	0.8	0.2	0
Pulmonary hypertension	2	0.4	0	0
Pulmonary embolism	1	0.4	0.4	0
Hemoptysis	0.6	0.2	0	0
Pneumonitis	0.4	0.4	0	0

- Phase 2 and Phase 3: No interstitial lung disease or pulmonary fibrosis

Historical Context for Dyspnea in Myeloma

Dyspnea AEs	Carfilzomib Phase 2 MM N = 526 %	Bortezomib[1] iv N = 228 %	Thalidomide and Dexamethasone[2] N = 102 %	Dexamethasone[2] N = 102 %
All Grade	42	22	42	31
Grade 3	5	3	10	12
Grade ≥ 4	0.2	< 1	3	4

[1]SUMMIT and CREST studies, Velcade PI, 2003.
[2]Thalomid PI, 2006.

Hepatic AEs
Phase 2 Myeloma Population

AEs Regardless of Relationship	N = 526 %			
	All Grades	Grade 3	Grade 4	Grade 5
AST increased	13	3	0.2	0
ALT increased	8	3	0	0
Hepatic failure	0.6	0	0	0.4
Hepatic encephalopathy	0.2	0	0	0
Veno-occlusive liver disease	0.2	0.2	0	0

- 0.8% patients discontinued
- No Hy's law case
- Phase 3: no hepatic failure events

Safety Conclusions

- Large, well-characterized safety database
  - 768 patients in Phase 1/2 trials
  - 1000 patients enrolled in Phase 3
- Patients with comorbidities can be safely treated with carfilzomib
  - Low discontinuation rate
- Serious cardiac event and mortality rates comparable to literature
- Carfilzomib can be used for long-term treatment, even in patients with peripheral neuropathy
- No cumulative toxicity

Agenda

Introduction	**Ted W. Love, MD** EVP, R&D and Technical Operations Onyx Pharmaceuticals, Inc.
Multiple Myeloma Unmet Need	**Kenneth C. Anderson, MD** Program Director and Chief Division of Hematologic Neoplasias, Kraft Family Professor of Medicine, Harvard Medical School
Clinical Efficacy	**Barbara Klencke, MD** Sr. VP, Clinical Development Onyx Pharmaceuticals, Inc.
Clinical Safety	**Natalie Sacks, MD** VP, Clinical Science & Biometrics Onyx Pharmaceuticals, Inc.
Benefit/Risk Summary	**Sagar Lonial, MD** **Professor and Vice Chair of Clinical Affairs,** **Department of Hematology and Medical Oncology** **Emory University School of Medicine**

Benefit/Risk

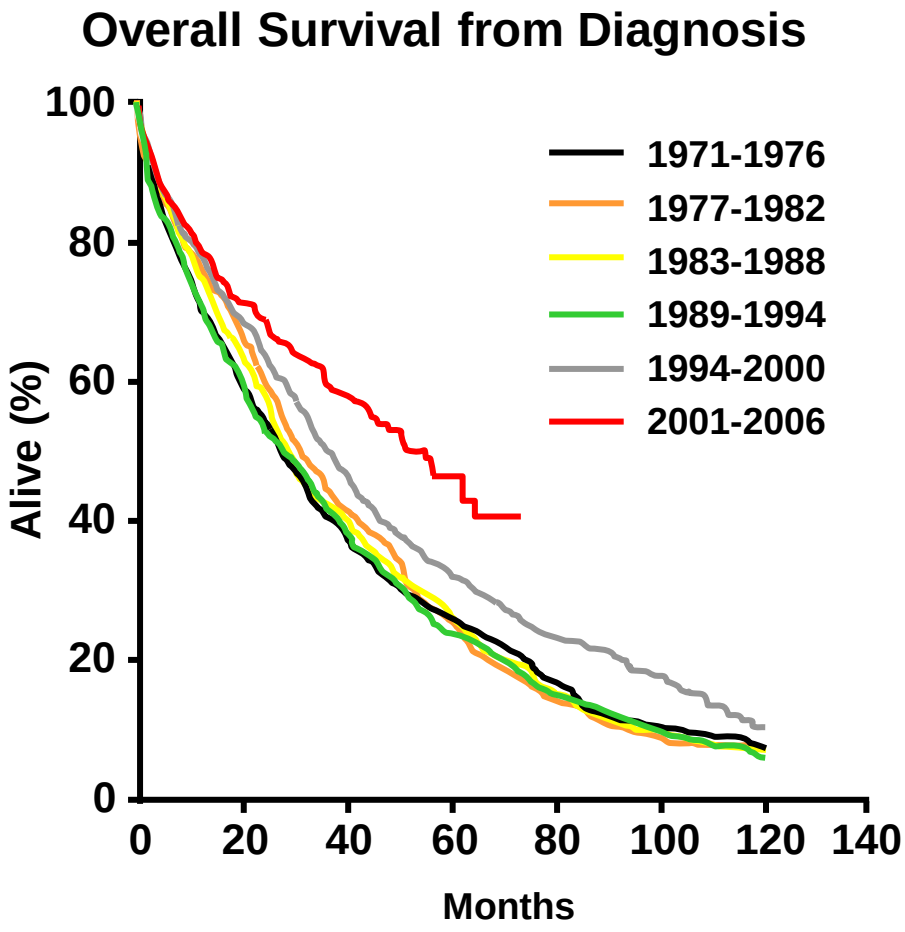
Sagar Lonial, MD

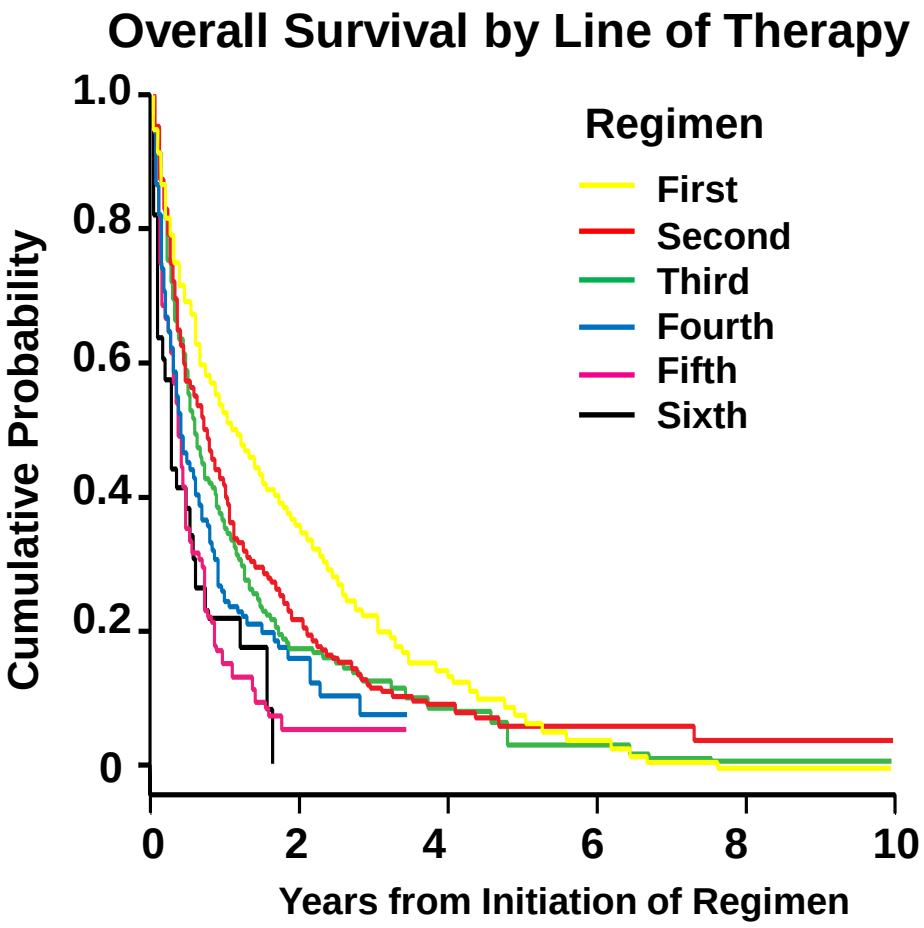
Professor and Vice Chair of Clinical Affairs,

Department of Hematology and Medical Oncology

Emory University School of Medicine

Novel Agents are Changing the Natural History of Multiple Myeloma





Adapted from Kumar SK, et al. *Blood*. 2008;111:2516-2520.

Kumar SK, et al. *Mayo Clin Proc*. 2004;79(7):867-874.

We Have Limited Options for Relapsed and Refractory Patients

- Reuse of agents but with lower ORR and shorter duration
- Combination regimens needed to achieve efficacy but are poorly tolerated
- Experimental therapy with Phase 1 agents
- Supportive, palliative care, hospice

What are the risks we need to balance?

- Will toxicity preclude efficacy?
- What risks should physicians and patients be aware of?
- Are there unexpected toxicities?

Adverse Events Resulting in Discontinuation of Single Agents in Patients with Relapsed and Refractory Multiple Myeloma

Agent	Population (Study)	Median Lines Prior Tx	Any AE Leading to Discontinuation	Drug-related AE Leading to Discontinuation
Bortezomib	Relapsed (SUMMIT)[1, 2]	6	24%	18%
Lenalidomide	Relapsed and Refractory (MM-014)[3]	5	18%	NR
Carfilzomib	Relapsed and Refractory (003-A1)	5	12%	7%

NR, Not reported.

[1]Velcade Package Insert, 2003.

[2]Bortezomib summary for approval.

[3]Richardson, et al. *Blood* 2009 114: 772-778.

What are the risks we need to balance?

- Will toxicity preclude efficacy?
- **What risks should physicians and patients be aware of?**
- Are there unexpected toxicities?

Non-Hematologic Grade 3 and 4 Adverse Events Occurring in ≥ 5% Patients

AEs (by highest incidence)	003A1 (N = 266) Grade 3 and 4 %	BTZ 1.3 mg/m^2 SUMMIT/CREST (N = 228[1]) Grade 3 and 4 %
Non-Hematologic AEs		
Asthenic Conditions*	10	19
Peripheral Neuropathy	1	14
Pneumonia	9	5
Diarrhea	< 1	8
Vomiting	1	7
Pain in Limb	2	7
Dehydration	2	7
Nausea	2	6
URI	5	0
Back pain	5	4
Arthralgia	2	5

[1]Velcade Package Insert, May 2003.

*Asthenic conditions defined as fatigue, malaise and weakness

Incidence of Neuropathy with Carfilzomib, Bortezomib

Neuropathy, %	Relapsed & Refractory†[1] BTZ i.v.	Relapsed & Refractory CFZ	Relapsed SC vs. IV[2] BTZ i.v.	Relapsed SC vs. IV[2] BTZ s.c.
All Grade	37	12.4	53	38
Grade 3	14	1.1	15	5
Grade ≥ 4	0	0	1	1
D/C	5*	0	9	5

Bortezomib neuropathy events in proteasome inhibitor naïve patients, includes neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy.
†Patients from SUMMIT and CREST treated at 1.3 mg/m^2 part of initial bortezomib label (n = 228).
*Drug-related.
[1]Velcade PI. 2003.
[2]Velcade PI., 2012.

What are the risks we need to balance?

- Will toxicity preclude efficacy?
- What risks should the physicians and patients be aware of?
- Are there unexpected toxicities?

Are There Unexpected Toxicities?

- Cannot be excluded
- Large safety database reassuring
  - 768 patients in the NDA database
  - ~1,000 patients in Phase III trials
    - ASPIRE (N = 792) evaluated 4 times by the DSMB to date

On-Study Deaths
Phase 2 Myeloma Population

Cause of Death	Phase 2 MM Population N = 526 n (%)	
Progressive disease	24 (5)	
Cardiac component	3 (0.6)	
Adverse event reported	13 (3)	8 (1.5)
Cardiac	5 (1)	
Infections	2 (0.4)	
Hepatic failure	2 (0.4)	
Other	4 (0.8)	
Total	37 (7)	

Historical Context for Overall Deaths in Relapsed and Refractory Myeloma

	Carfilzomib		Lenalidomide	Bortezomib
	003A1 N = 266	Phase 2 MM N = 526	N = 222[1]	N = 202[2]
On study deaths, %	9	7	10	5
On study definition, days	30	30	30	20
Years from diagnosis, median	5.4	4.8	3.7	4.0

[1]MM-014 Study, Richardson, 2009; [2]SUMMIT study, Richardson 2003.

Benefit – Meaningful ORR, DOR and OS

Response Category	Total N = 266 n (%)	
CR	1 (0.4)	ORR = 22.9%
VGPR	13 (4.9)	
PR	47 (17.7)	
MR	34 (12.8)	CBR = 35.7%
SD	81 (30.5)	
PD	69 (25.9)	
Not evaluable	21 (7.9)	

Duration of Response

Median DOR = 7.8 months

Median DOCBR = 8.3 months

Overall Survival

Median OS = 15.4 months

Benefits of Carfilzomib

- Efficacy in refractory myeloma patients
  - High ORR with durability and prolonged OS
- Risks within expected range for population
- General tolerability experienced by majority of patients
  - Excellent GI and hematologic tolerability
  - No dose limiting peripheral neuropathy
  - Steroid sparing
  - No cumulative toxicity
- Promising overall survival

Carfilzomib Data Supports Accelerated Approval

- Refractory multiple myeloma is a serious and life-threatening disease
- Efficacy demonstrated with good tolerability
- Safety well characterized across a large number of patients
- The benefit / risk profile is favorable
- Urgent need for patients who have refractory MM with limited/no options

Support Slides

Sponsor Presentation

ODAC 6-20-12 PM Session

Neuropathy Assessment on 003A1

- History and Baseline status
  - Highest historical grade history of neuropathy and attribution to prior therapies/disease
  - Baseline neuropathy type and grade by clinical examination
- Repeated on study neurological examinations
  - D1 of Cycles 3, 5, 7, 9 and 11, and at end of study
- Reconciled neurological examination findings with reported AEs during data review

Phase 2 Myeloma Studies – PN AE According to Baseline Neuropathy (N = 526)

Baseline Neuropathy	PN AE reported	No PN AE
Yes-378	47/378 (12%)	330/378 (87%)
No-147	25/147 (17%)	122/147 (83%)

- No increase in frequency of PN AEs for patients with baseline neuropathy
- Of 47 with neuropathy at baseline that had PN AEs, 24 were of an increased grade of severity and 23 were of the same grade

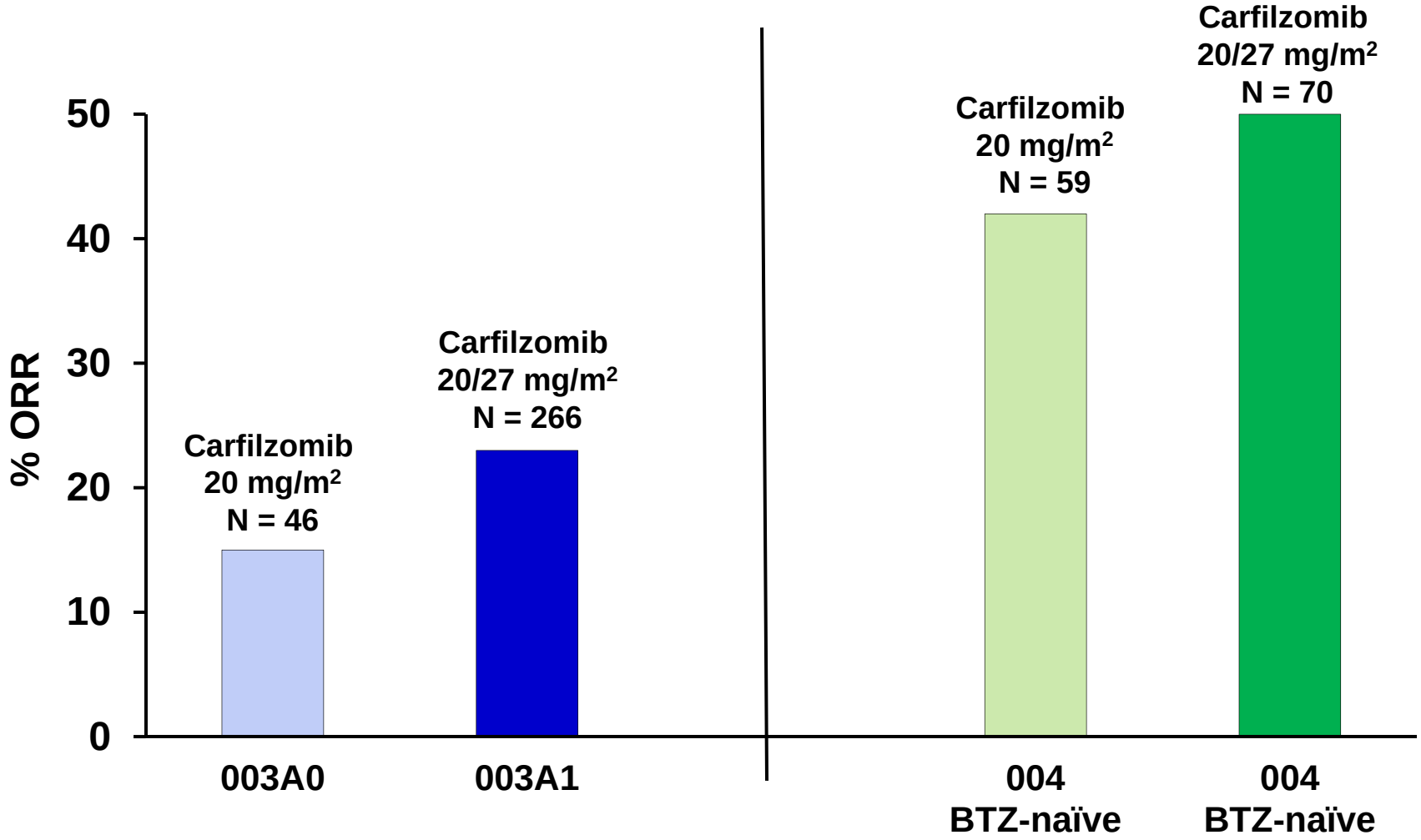
Toxicity Comparison of Proteasome Inhibitors in Rats and Monkeys

Toxicity	Bortezomib	Carfilzomib
Cardiovascular	Acute dose limiting toxicity (cardiac failure)	
Pulmonary	Dyspnea, edema, interstitial inflammation	
GI	Mucosal hyperplasia, hemorrhage, & inflammation	
Renal	Acute: Effects secondary to cardiovascular Chronic: Progressive nephropathy/Pre-renal azotemia	
Hematologic	Anemia, Transient thrombocytopenia	
Neurologic	• Tremors • ↓ conduction velocity • Nerve degeneration	• No neurobehavioral effects • No histologic changes to nerves

Cardiovascular Toxicity in Rats and Monkeys

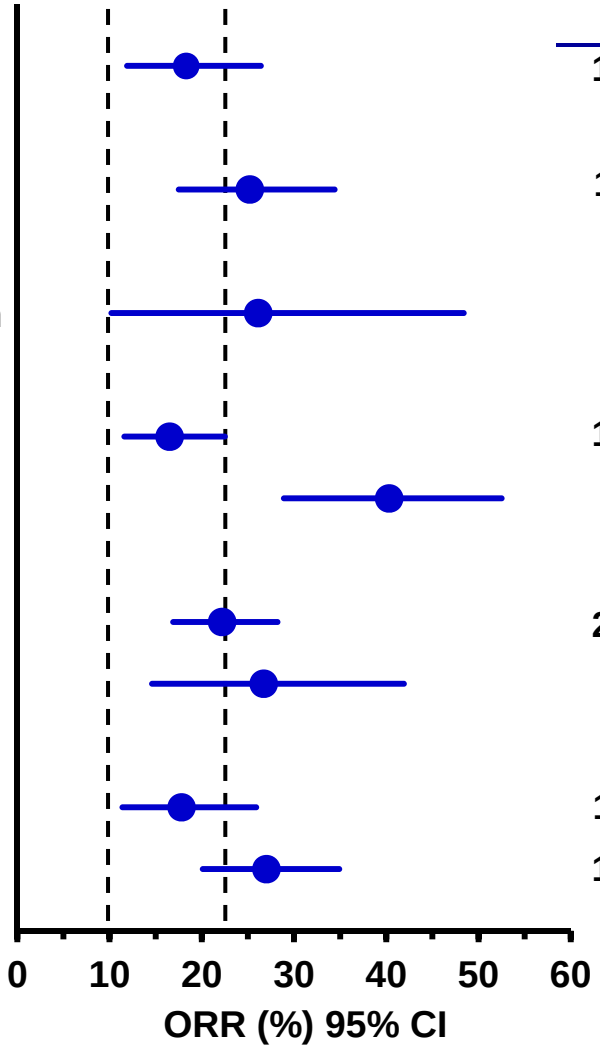
- Bortezomib and carfilzomib induce early mortality due to cardiovascular toxicity
  - Occurs at doses ≤ human equivalent doses
- Acute and repeat dose > MTD
  - Cardiomyopathy, necrosis, fibrosis, hemorrhage, and edema
  - Hypotension with tachycardia
- Repeat dose at MTD
  - Sporadic cardiac inflammation
  - No QTc prolongation in monkeys

Clinical Trial Data – Evidence for Dose Response



	003A0	003A1	004 BTZ-naïve	004 BTZ-naïve
ORR (95% CI)	15.2 % (6.3, 28.9)	22.9% (18.0, 28.4)	42.4% (29.6, 55.9)	50.0% (37.8, 62.2)

003A1 – Subgroup Analysis of ORR: Refractory Status to Novel Agents



	N	ORR	95% CI
BTZ-refractory in Last Prior Regimen	120	18.3	(11. 9 – 26.4)
LEN-refractory in Last Prior Regimen	111	25.2	(17.5 – 34.4)
THAL-refractory in Last Prior Regimen	23	26.1	(10.2 – 48.4)
BTZ-refractory in Any Prior Regimen			
Yes	194	16.5	(11.6 – 22.5)
No	72	40.3	(28.9 – 52.5)
LEN-refractory in Any Prior Regimen			
Yes	221	22.2	(16.9 – 28.8)
No	45	26.7	(14.6 – 41.9)
THAL-refractory in Any Prior Regimen			
Yes	118	17.8	(11. 4 – 25.9)
No	148	27.0	(20.1 – 34.9)

003A1 – Summary of Response According to Prior Bortezomib Therapy

	Number of Patients	ORR (95% CI)	Median DOR (95% CI)
Refractory to bortezomib in last regimen	120	18.3% (11.9, 22.5)	8.4 months (6.7, 12.3)
Refractory to bortezomib in any prior regimen	194	16.5 % (11.6, 22.5)	7.8 months (6.5, 10.2)

003A1 – Summary of Response According to Prior Bortezomib Therapy

	Number of Patients	ORR % (95% CI)
Received bortezomib		
Yes	265	22.6 (17,7. 28.2)
Number of prior bortezomib regimens		
< 2	124	29.0 (21.2, 37.9)
≥ 2	142	17.6 (11.7, 24.9)
Received bortezomib in last line		
Yes	132	18.9 (12.6, 26.7)
No	134	26.9 (19.6, 35.2)
Refractory to bortezomib in last line	120	18.3 (11.9, 26.4)
Refractory to bortezomib in any prior line		
Yes	194	16.5 (11.6, 22.5)
No	72	40.3 (28.9, 52.5)

003A1 – Primary Efficacy Endpoint: Concordance by Method of Analysis

Response Category	IRC	Investigator	Programmatic	Dr. Singhal
CR	1	0	0	0
VGPR	13	15	14	13
PR	47	45	48	48
MR	34	29	27	23
SD	81	93	88	92
PD	69	69	71	69
Not evaluable	21	15	18	21
	ORR = 22.9%	ORR = 22.6%	ORR = 23.3%	ORR = 22.9%

FDA analysis: ORR = 22.9%

Study 003A1 – Refractory and Intolerant Status at Study Entry

	Total N = 266				
Agent	Exposed n (%)	Refractory n (%)	Intolerant n (%)	Refractory and Intolerant n (%)	Neither Refractory nor Intolerant n (%)
Bortezomib	265 (100)	194 (73)	111 (42)	69 (26)	29 (11)
Lenalidomide	249 (94)	221 (83)	59 (22)	46 (17)	15 (6)
Thalidomide	199 (75)	118 (44)	64 (24)	33 (12)	50 (19)

Phase 3 Study 009-ASPIRE Study Design

Relapsed Myeloma
1-3 prior regimens
N = 780
Stratification:
- **Prior bortezomib**
- **Prior lenalidomide**
- **β2-microglobulin**

CRd →

Carfilzomib 20 → 27 mg/m²
- 20 mg/m² on Days 1 and 2 of Cycle 1 only
- 27 mg/m² on Days 8, 9, 15, 16

Lenalidomide 25 mg
Days 1–21

Dexamethasone 40 mg
Days 1, 8, 15, 22

Cycle = 28 days

Rd →

Lenalidomide 25 mg
Days 1–21

Dexamethasone 40 mg on
Days 1, 8, 15, 22

Cycle = 28 days

Primary endpoint: Progression-free Survival

Cardiac Deaths on Study

Baseline characteristic	Cardiac Deaths N = 10, %	Phase 2 MM Population N = 526, %
Median age, yr	64	64
Gender – Male, %	70	57
ECOG-2, %	40	12
β-2 microglobulin ≥ 5.5 mg/L,%	50	30
Poor prognosis cytogenetic markers, %	40	23
Bone marrow plasma cell ≥ 50%, %	70	35
Cardiac History, %	80	66
Current cardiac medication use, %	60	68
Time since diagnosis, yr	5.4	4.8
Median number of prior regimens	7	4
Prior anthracycline, %	40	53
Prior transplant, %	80	75

2 (1%) Hepatic AE On-Study Deaths – 003A1 (N = 266)

Age, Sex	Prior Anti MM Regimens	Day of Death	Days from Last Dose	Confounding Factors
70, M	5	127	13	PD Multiple hepatotoxic concomitant medications Possible liver ischemia
68, M	8	25	9	Concurrent Grade 4 sepsis Liver ischemia PD Multiple hepatotoxic concomitant medications