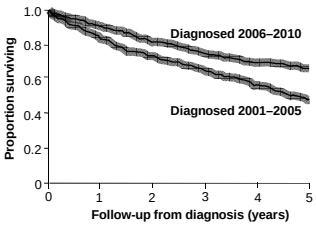
Extending treatment options for patients with advanced multiple myeloma and optimizing the management of relapsed and refractory disease

Paul G. Richardson MD

Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA

Continued Improvement in Survival Since the Introduction of Novel Agents

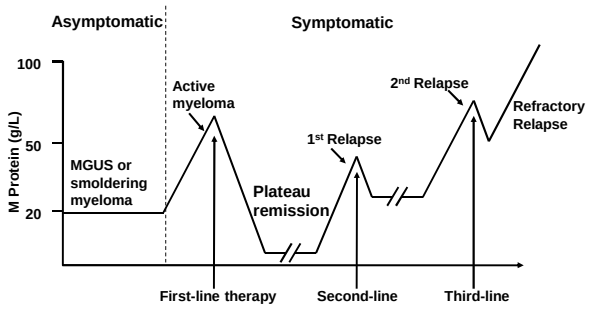
- **1,056 patients grouped into 2001–2005 and 2006–2010 cohorts**
- **Survival improved over time, particularly in patients aged > 65 years (p = 0.001)**



Survival	2001–2005	2006–2010	p
Median OS, years	4.6	NR	0.001
1-year survival, %	83	90	
5-year estimated OS, %			
Overall	48	66	
> 65 years	31	56	0.001
< 65 years	63	73	NS

Kumar SK, et al. Blood. 2012;120:[abstract 3972]. Updated data presented at ASH 2012.

Natural History of Multiple Myeloma: All Patients Experience Relapse….



Durie BGM. Concise review of the disease and treatment options. Multiple myeloma; 2008/2009. Available from: http://myeloma.org/pdfs/cr08-eng_f1web.pdf.

Possible Treatment Approaches for Patients With Aggressive Relapse or Relapse Late in the Disease Course

Aggressive, Rapid, Multiply Relapsed

Clinical trial of a novel agent or a combination should be a priority

Consider combination therapy
Do not wait for symptomatic relapse

Chemotherapy based salvage

- DCEP vs DT-PACE
- Oral vs IV chemo
- PS of patient plays important role

Chemotherapy + novel agent

- Combinations of Lenalidomide and/or bortezomib and other cytotoxic agents

Transplant based salvage

- Likely to be short lived
- Quick disease control
- Reconstitute marrow

Clinical Cancer Research

Lonial S, Mitsiades CS, Richardson PG. Clin Cancer Res 2011;17:1264-77

NCCN Guidelines (USA): Myeloma Therapy (Version 2 2013) – Salvage therapy

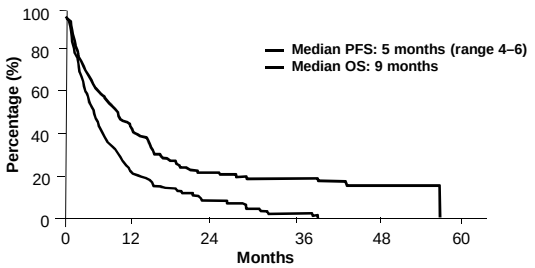
Preferred Regimens	Other Regimens
• Repeat primary induction therapy (if relapse at > 6 mos) • Bortezomib (cat. 1) • Bortezomib / dex • Bortezomib / lenalidomide / dex • Bortezomib / liposomal doxorubicin (cat. 1) • Bortezomib / thalidomide / dex • Carfilzomib [1] • Cyclophosphamide / bortezomib / dex • Cyclophosphamide / lenalidomide / dex • Dex / cyclophosphamide / etoposide / cisplatin • (DCEP) • Dex / thalidomide / cisplatin / doxorubicin / cyclophosphamide / etoposide (DT-PACE) ± bortezomib (VTD-PACE) • High-dose cyclophosphamide • Lenalidomide / dex[2] (cat. 1) • Pomalidomide[1] / dex [2] • Thalidomide / dex[2]	• Bendamustine • Bortezomib / vorinostat • Lenalidomide / bendamustine / dex

*Consideration for appropriate regimen is based on the context of clinical relapse.
[1] Indicated for patients who have received at least two prior therapies including bortezomib and an IMiD and have demonstrated disease progression on or within 60 days of completion of the last therapy.
[2] Consider single agent lenalidomide, pomalidomide, thalidomide for steroid-intolerant individuals.

http://www.nccn.org

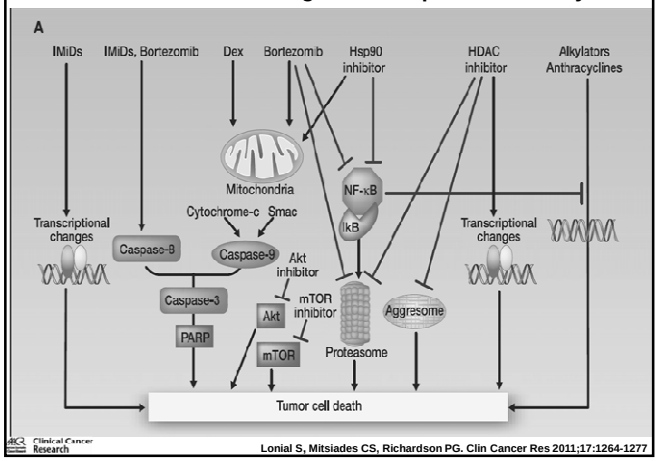
Prognosis for Patients Refractory to Novel Agents Remains Poor

- Patients refractory to bortezomib and relapsed or refractory to or ineligible to immunomodulatory drugs



Kumar SK, et al. Leukemia. 2012;26:149-57.

Rational Combination Strategies in Relapsed Refractory MM

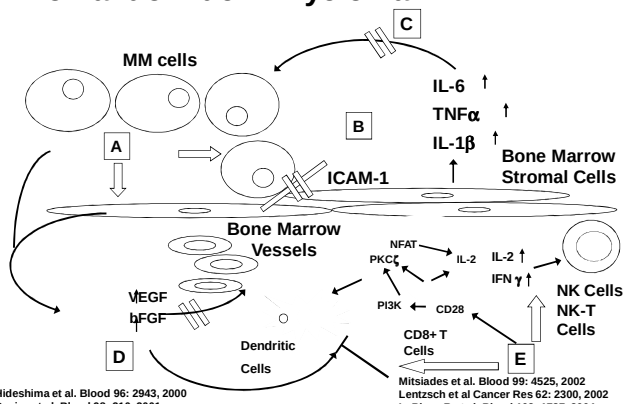


Lonial S, Mitsiades CS, Richardson PG. Clin Cancer Res 2011;17:1264-1277

Selected Novel Agents Currently Available and/or Under Investigation for RRMM

Class	First generation	Next generation
Immunomodulatory drugs	Lenalidomide (p.o.)	Pomalidomide (p.o.)
Proteasome inhibitors	Bortezomib (i.v./s.c.)	Carfilzomib (i.v.) Marizomib [NPI-0052] (i.v.) Ixazomib [MLN9708] (p.o.)
Others including:		
Monoclonal Antibodies	Elotuzumab, Daratumumab	
HDAC Inhibitors	Vorinostat, Panobinostat, Romidepsin, AC1215	
Alkylating Agents	Bendamustine, others (TH 302, melflufen)	

Pomalidomide in Myeloma

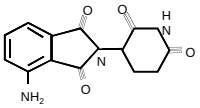


Hideshima et al. Blood 96: 2943, 2000
Davies et al. Blood 98: 210, 2001
Gupta et al. Leukemia 15: 1950, 2001

Mitsiades et al. Blood 99: 4525, 2002
Lentzsch et al Cancer Res 62: 2300, 2002
LeBlanc R et al. Blood 103: 1787, 2004
Hayashi T et al. Brit J Hematol 128: 192, 2005

Pomalidomide: Background

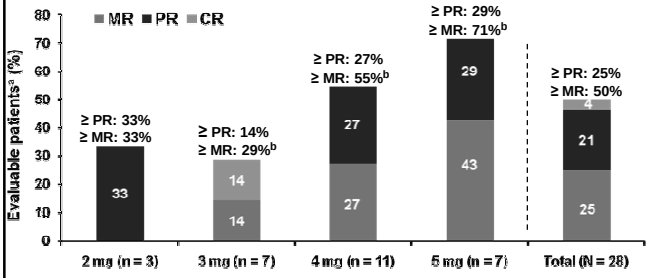
- Pomalidomide is a distinct oral immunomodulatory drug with significant anti-myeloma activity *in vitro*[1,2]
- Pomalidomide has demonstrated promising activity in patients with relapsed/refractory multiple myeloma[3]
- When combined with low-dose dexamethasone, Pomalidomide has clinical efficacy in RRMM patients previously treated with lenalidomide and/or bortezomib[4–6]



Pomalidomide

1. Hideshima T, et al. Blood. 2000;96:2943-50. 2. Mitsiades N, et al. Blood. 2002;99:4525-30.
3. Schey SA, et al. J Clin Oncol. 2004;22:3269-76. 4. Lacy MQ, et al. J Clin Oncol. 2009;27:5008-14.
5. Lacy MQ, et al. Leukemia. 2010;24:1934-9. 6. Lacy MQ, et al. Blood. 2011;118:2970-5.

MM-002 Phase I: Pomalidomide ± Low-dose Dex: Best Response and Clinical Outcome



	2 mg (n = 3)	3 mg (n = 7)	4 mg (n = 11)	5 mg (n = 7)	Total (N = 28)
DOR[c], med wks	20	24	16	Not reached	20
PFS, med wks	31	36	12	20	20
OS, med wks	81	80	Not reached	Not reached	80

a. Includes eligible, treated and evaluable for efficacy assessment. b. Discrepancies in totals due to rounding.
c. Assessed for responders only: 2 mg (1); 3 mg (1); 4 mg (3); 5 mg (2); total (7).

Richardson PG, et al. Blood. 2013;121:1961-7.

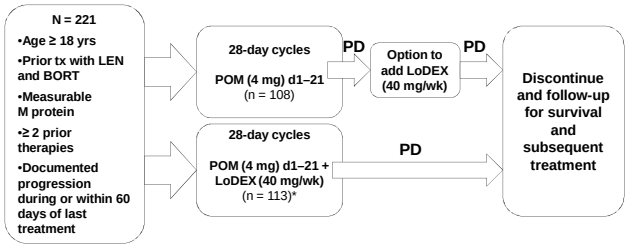
Efficacy Results of Phase 2 Pomalidomide Studies in RRMM

Study	Phase	N	POM schedule	Treatment	Population	Prior lines*	ORR, % (≥ PR)
Jagannath et al. [1]	2	221	21/28	POM: 4 mg DEX: 40 mg/week	LEN- & BORT-refractory	5	34
Leleu[2] et al.	2	84	21/28 vs 28/28	POM: 4 mg + DEX	LEN- & BORT-refractory	5	35 vs 34
Lacy[3] et al.	2	34	28/28	POM: 2 mg DEX: 40 mg/week	LEN-refractory	4	32
Lacy[4] et al.	2	70	28/28	POM: 2 mg & 4 mg DEX: 40 mg/week	LEN- & BORT-refractory	6	25 and 29

*Median number of prior therapies

1. Jagannath S, et al. Blood. 2012;120:[abstract 450]. Updated data presented at ASH 2012.
2. Leleu X, et al. Blood.2013 3. Lacy MQ, et al. Leukemia. 2010;24:1934-9.
4.Lacy MQ, et al. Blood. 2011;118:2970-5.

Phase 2 Trial of Pomalidomide + Low-Dose Dex (MM-002): Study Design

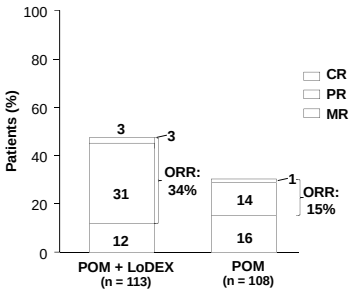


- **Primary endpoint: PFS**
- **Secondary endpoints: ORR, DoR, OS, and safety**

*Pts aged > 75 yrs had a DEX starting dose of 20 mg/wk.

Richardson PG, et al. Blood. 2011;118:[abstract 634].

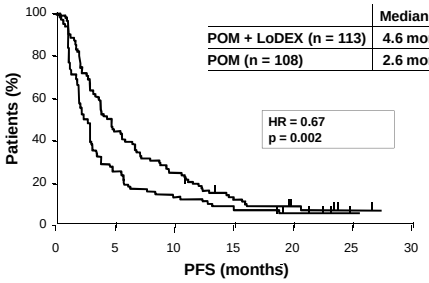
Pomalidomide + Low-Dose Dex (MM-002): Response Rates



- **Median number of cycles received: 5 (range: 1–28)**
- **Disease control (≥ SD) was observed in 81% of patients**

Jagannath S, et al. Blood. 2012;120:[abstract 450]. Updated data presented at ASH 2012.

Pomalidomide + Low-Dose Dex (MM-002): Survival Outcomes



	Median PFS
POM + LoDEX (n = 113)	4.6 months
POM (n = 108)	2.6 months

- **There was no significant difference in OS:**
  - **POM + LoDEX: 16.5 mos; POM*: 13.6 mos (HR = 0.92; p = 0.609)**

* LoDEX added for 64 patients (59%).

Jagannath S, et al. Blood. 2012;120:[abstract 450]. Updated data presented at ASH 2012.

Pomalidomide + Low-Dose Dex (MM-002): Safety Results

- Grade 3 and 4 adverse events were primarily haematological

Grade 3/4 adverse event, %	POM (n = 107)	POM + LoDEX (n = 112)
Haematological		
Neutropenia	47	38
Thrombocytopenia	22	19
Anaemia	22	21
Leukopenia	6	10
Non-haematological		
Pneumonia	14	19
Fatigue	10	10
Back pain	12	9
Dyspnoea	7	13

Vij R. J Clin Oncol. 2012;30(suppl):513s. Updated data presented at ASCO 2012.

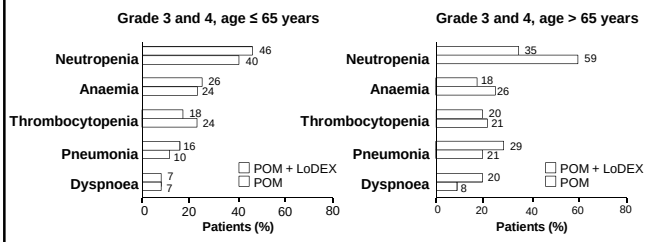
Efficacy of Pomalidomide + Low-dose Dex According to Age (MM-002)

- POM + LoDEX arm (n = 113)
- PFS was significantly longer for POM + LoDEX compared with POM only in patients aged ≤ 65 years (HR = 0.45; $p < 0.001$)

Response	Age ≤ 65 yrs (n = 62)	Age > 65 yrs (n = 51)
≥ PR, %	31	37
≥ MR, %	47	43
Median duration of ≥ PR, mos	10.1	7.7
Median duration of ≥ MR, mos	8.4	7.8
Median PFS, mos	4.7	3.7

Jagannath S, et al. Poster presented at IMW 2013. [Abstract P-210].

Safety of Pomalidomide + Low-dose Dex According to Age (MM-002)



- Other clinically relevant adverse events were febrile neutropenia: 3%; PN: 13% grade 1/2 (no grades 3/4); DVT: 2% all grades
- Only 10% of patients discontinued due to adverse events

Jagannath S, et al. Poster presented at IMW 2013. [Abstract P-210].

Efficacy of Pomalidomide + Low-dose Dex According to Renal function (MM-002)

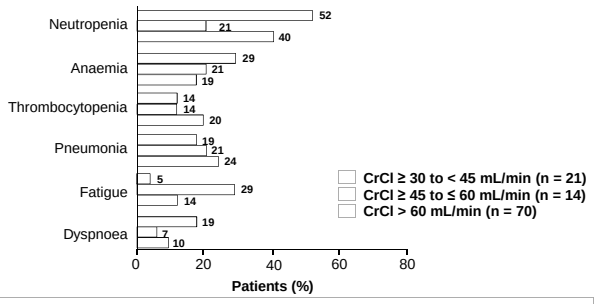
	CrCl, mL/min		
Response	**≥ 30 to < 45 (n = 21)**	**≥ 45 to ≤ 60 (n = 14)**	**> 60 (n = 70)**
ORR (≥ PR), n (%)	**33 (7)**	**43 (6)**	**34 (24)**
Median DoR, mos	**8.3**	**9.2**	**8.3**
Median DoT, mos (range)	**4.2 (0.5–21.6)**	**5.0 (0.9–24.1)**	**5.5 (0.1–28.2)**
Average daily dose,* mg (range)	**4.0 (2.3–4.0)**	**4.0 (2.1–4.0)**	**4.0 (1.6–4.2)**
Median relative dose intensity,† (range)	**0.9 (0.5–1.2)**	**0.9 (0.5–1.0)**	**0.9 (0.2–1.2)**
Patients with ≥ 1 dose reduction, n (%)	**9 (43)**	**4 (29)**	**18 (26)**
Median time to first dose reduction, mos (range)	**1.2 (0.1–11.3)**	**2.3 (1.2–15.9)**	**1.6 (0.9–20.8)**

* Average daily dose = cumulative dose/dose exposure;
† Relative dose intensity = dose intensity (cumulative dose/treatment duration)/planned dose intensity.

Vij R, et al. Poster presented at IMW 2013.[Abstract P-170].

Safety of Pomalidomide + Low-dose Dex According to Renal Function (MM-002)

Grade 3 and 4 treatment-emergent adverse events in ≥ 15% of patients



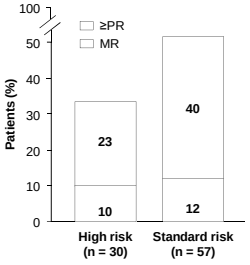
The incidence of grade 3 and 4 AEs was generally comparable across subgroups

Vij R, et al. Poster presented at IMW 2013.[Abstract P-170].

Efficacy of Pomalidomide + Low-Dose Dex in High-Risk Cytogenetics (MM-002)

High-risk cytogenetics was defined as the presence of del (17p13) and t(4;14)

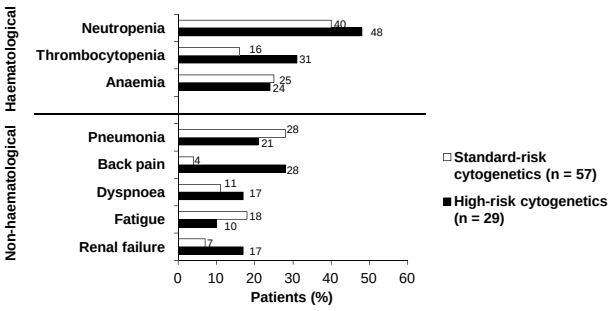
Outcome	High-risk cytogenetics (n = 30)	Standard-risk cytogenetics (n = 57)
Time to response, mos (range)	1.2 (0.9–2.8)	1.9 (0.9–14.4)
Median DoR, mos (95% CI)	4.9 (1.9–13.1)	10.1 (7.7–NR)
Median PFS, mos (95% CI)	3.1 (1.9–3.9)	5.5 (3.7–8.7)
Median OS, mos (95% CI)	13.2 (4.7–19.8)	21.7 (12.4–NR)



Richardson PG, et al. Blood. 2012;120:[abstract 4053]. Updated data presented at ASH 2012.

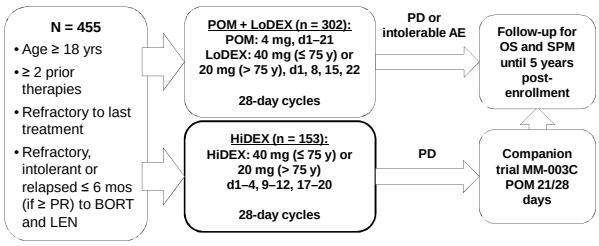
Safety of Pomalidomide + Low-Dose Dex in High-Risk Cytogenetics (MM-002)

Grade 3 and 4 treatment-emergent adverse events in ≥ 15% of patients



Richardson PG, et al. Blood. 2012;120:[abstract 4053].
Updated data presented at ASH 2012.

Phase 3 trial of Pomalidomide + Low-Dose Dex versus High-Dose Dex (MM-003)



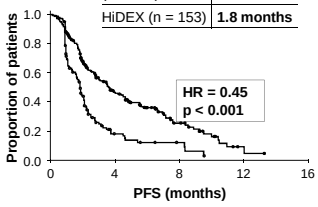
- **Primary endpoint: PFS**
- **Key secondary endpoints: OS, ORR (≥ PR), DoR, safety**

Dimopoulos MA, et al. Blood. 2012;120:[abstract LBA-6].
Updated data presented at ASH 2012.

Pomalidomide + Low-dose Dex (MM-003): Progression-Free Survival

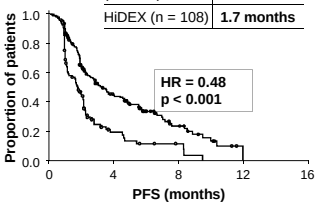
ITT population

	Median PFS
POM + LoDEX (n = 302)	**3.6 months**
HiDEX (n = 153)	**1.8 months**



LEN- and BORT-refractory

	Median PFS
POM + LoDEX (n = 221)	**3.2 months**
HiDEX (n = 108)	**1.7 months**



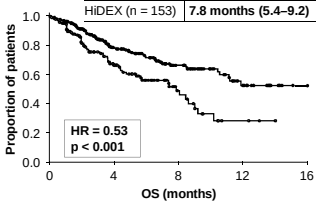
ITT: intent-to-treat.

Dimopoulos MA, et al. Blood. 2012;120:[abstract LBA-6].
Updated data presented at ASH 2012.

Pomalidomide + Low-Dose Dex (MM-003): overall survival

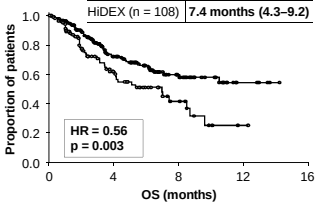
ITT population*

	Median OS (95% CI)
POM + LoDEX (n = 302)	NR (11.1–NE)
HiDEX (n = 153)	7.8 months (5.4–9.2)



LEN- and BORT-refractory*

	Median OS (95% CI)
POM + LoDEX (n = 221)	NR (8.5–NE)
HiDEX (n = 108)	7.4 months (4.3–9.2)



* 29% of pts received POM after progressing on HiDEX.
ITT: intent-to-treat

Dimopoulos MA, et al. Blood. 2012;120:[abstract LBA-6]. Updated data presented at ASH 2012.

Pomalidomide + Low-dose Dex (MM-003): PFS and OS in Double-Refractory Patients by Last Prior Therapy

- PFS and OS results were consistent with those of the overall ITT population

	POM + LoDex (n = 221)	HiDEX (n = 108)	HR	p value
Progression-free Survival (mos)				
Lenalidomide	3.9	1.7	0.38	0.002
Bortezomib	3.1	1.6	0.53	0.002
Overall Survival (mos)				
Lenalidomide	NR	7.4	0.45	0.036
Bortezomib	NR	5.4	0.52	0.027

Moreau P, et al. Poster presented at IMW 2013 [abstract P-189].

Pomalidomide + Low-dose Dex (MM-003): Response Rates

- Short median follow-up (4 months)
- Median DoR of POM + LoDEX was 10.1 months
- ≥ PR was significantly higher with POM + LoDEX (24%) vs HiDEX (3%) for patients randomized ≥ 6 months ($p < 0.001$)

Response*	POM + LoDEX (n = 204)	HiDEX (n = 99)
≥ PR, %	24	3
VGPR, %	3	0
≥ MR, %	38	7
≥ SD, %	79	55

* IRAC for evaluable patients randomized ≥ 6 mos

Dimopoulos MA, et al. Blood. 2012;120:[abstract LBA-6]. Updated data presented at ASH 2012.

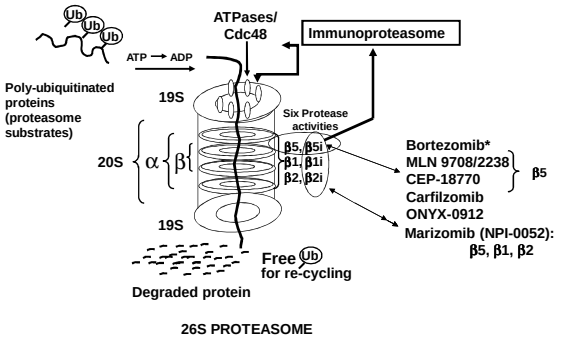
Pomalidomide + Low-dose Dex (MM-003): Safety

- Discontinuation due to AEs: 7% POM + LoDEX; 6% HiDEX
- VTE, all grades: 3% POM + LoDEX; 2% HiDEX

Grade 3 and 4 AEs, %	POM + LoDEX (n = 300)	HiDEX (n = 149)
Neutropenia	42	15
Febrile neutropenia	7	0
Anaemia	27	29
Thrombocytopenia	21	24
Infections	24	23
Pneumonia	9	7
Haemorrhage	3	5
Glucose intolerance	3	7
Fatigue	5	5

Dimopoulos MA, et al. Blood. 2012;120:[abstract LBA-6]. Updated data presented at ASH 2012.

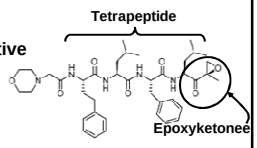
Proteasome Inhibition: Second Generation Inhibitors and Their Targets



*Bortezomib: first -in-class/first generation proteasome inhibitor

Lawasut P, Chauhan D et al. Curr Hematol Malig Rep. 2012: 258-66.

Carfilzomib: A Novel Proteasome (Chymotryptic) Inhibitor



- Novel chemical class with highly selective irreversible proteasome binding
- Minimal neurotoxicity in animals
- Durable responses in relapsed and relapsed, refractory MM (ORR 23%) with reduced neuropathy (G1-2 15%,G3 1%)
- Carfilzomib Lenalidomide Dex versus Lenalidomide Dex ongoing (phase III trial for new drug approval – ASPIRE Study)
- Escalating dose trials in relapsed MM and combination trial with Len/Dex as initial therapy promising (CRd in ND MM: ORR 94%, Jakubowiak et al, Blood 2012)

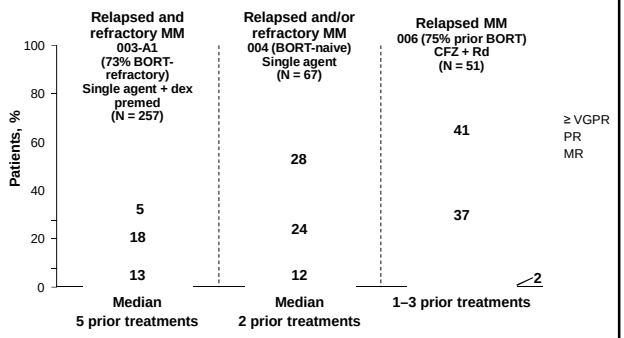
Demo et al. (2007), Cancer Research, 67:6383
Kirk et al, (2008) Blood, 112: 2765; Vij et al, Blood 2012; Siegel et al, Blood 2012

Carfilzomib Clinical Development in RRMM

Relapsed and refractory MM		Relapsed and/or refractory MM	Relapsed MM
003-A0 **(N = 46)** **20 mg/m²** **Relapsed from ≥ 2 prior therapies (must include prior BORT and LEN or THAL)** **Refractory to last treatment**	**003-A1** **(N = 266)** **Amendment to 003-A0** **20/27 mg/m² (step-up dosing)** **Dexamethasone premed** **Sample size increased to 266**	**004** **(N = 164)** **1–3 prior regimens, responded to first-line therapy** **BORT naive and BORT treated** **2 cohorts: 20 & 20/27 mg/m²** **1º endpoint: ORR** **2º endpoints: CBR, DoR, PFS, TTP, OS, safety**	**006** **(N = 92)** **Phase 1b trial in combination with Rd (Six-dose cohorts plus expansion)** **Relapsed after 1–3 prior therapies** **1º endpoint: safety, MTD** **2º endpoints: efficacy, PK**
1º endpoint: ORR **2º endpoints: CBR, DOR, PFS, OS, safety**			

Jagannath S, et al. Clin Lymphoma Myeloma Leuk. 2012;12:310-8. Siegel D, et al. Blood. 2012;120: 2817-25.
Vij R, et al. Blood. 2012;119:5661-70. Wang M, et al. J Clin Oncol. 2011; 29:[abstract 8025]. Updated data presented at ASCO.

Efficacy Results of Carfilzomib in RRMM Across Phase 2 Studies (Response Rate)



Direct comparisons across studies are not possible, given differences in study design and patient populations.

Siegel D, et al. Blood. 2012;120:2817-25. Vij R, et al. Blood. 2012;119:5661-70.
Wang M, et al. J Clin Oncol. 2011; 29:[abstract 8025]. Updated data presented at ASCO 2011.

Safety Profile of Carfilzomib from the 003-A1 Study

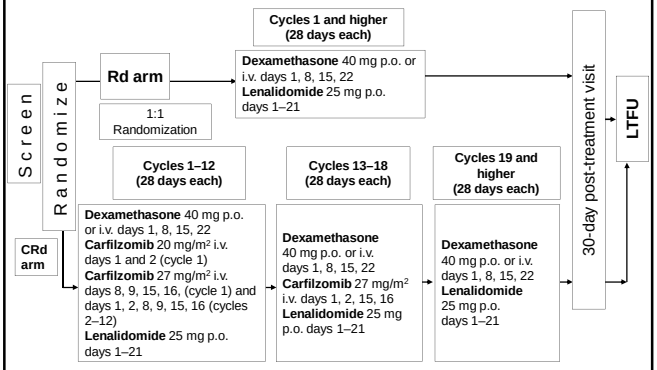
Incidence and severity of treatment-emergent adverse events (≥ 25%) and carfilzomib-related adverse events (n = 266)

Adverse events	All grades, n (%)	Grades 3 or 4, n (%)	All grades carfilzomib-related, n (%)
Haematological			
Anaemia	122 (46)	63 (24)	59 (22)
Thrombocytopenia	103 (39)	77 (29)	77 (29)
Lymphopenia	62 (23)	52 (20)	44 (17)
Neutropenia	48 (18)	29 (11)	40 (15)
Leukopenia	37 (14)	18 (6.8)	31 (12)
Non-haematological			
Fatigue	130 (49)	20 (7.5)	98 (37)

- **Other important toxicities included transient renal impairment and shortness of breath as well as hypertension and rare cases of significant cardiac dysfunction**

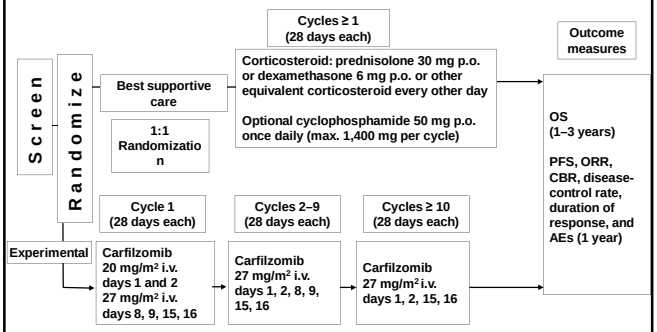
Siegel D, et al. Blood. 2012;120:2817-25.

Carfilzomib Phase 3 ASPIRE Trial in RRMM Patients with 1–3 Prior Therapies



www.clinicaltrials.gov/ct2/show/NCT01080391.

Carfilzomib Phase 3 FOCUS Trial in RRMM Patients with ≥ 3 Prior Therapies



Hajek R, et al. BMC Cancer. 2012;12:415.

Novel Proteasome Inhibitors Show *in vitro* and *in vivo* Activity

Marizomib and Ixazomib: 2nd generation proteasome inhibitors with promising activity in RRMM:

- **Marizomib (NPI-0052):**
  - **induces apoptosis in cell lines resistant to conventional and bortezomib-based therapies[1]**
  - **in animal models, NPI-0052 was well tolerated and prolonged survival[1]**
  - **active in RRMM patients (ORR ~ 25% at MTD +/- dex)[3]**
- **Ixazomib (MLN9708):**
  - **shows selective anti-MM activity in cell lines and an animal model[2]**
  - **is currently being tested in clinical trials, with promising activity, esp. in combination, and has favourable tolerability[4]**

1. Chauhan D, et al. Cancer Cell. 2005;8:407-19. 2. Chauhan D, et al. Clin Cancer Res. 2011;17:5311-21; 3. Richardson et al, Blood 2011. 4.Kumar et al., Blood. 2012;120:[abstract 332].

Conclusions and Future Directions

- **Pomalidomide + low-dose dex (4 mg – 21/28 days) demonstrated an ORR of 25–35% in phase 2 trials and has a well-characterized safety profile**
- **A prolonged PFS, OS, and improved ORR was shown for Pomalidomide + low-dose dex vs high-dose Dex in a randomized phase 3 trial**
- **Efficacy and safety of Pomalidomide was generally not affected by age, renal function, and high-risk cytogenetics**
- **Carfilzomib shows promising efficacy in phase 2 trials and was generally well tolerated in RRMM patients**
- **Current advances in the clinical investigation of Pomalidomide, Carfilzomib, and other new agents (e.g. Ixazomib, Marizomib) are extending treatment options for patients with advanced disease, with combinations showing great promise**