WHAT'S NEW WITH NOVEL THERAPIES?

Thursday, February 21, 2013

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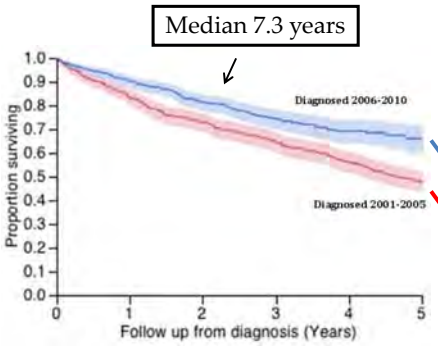
AGENDA FOR TODAY

- Pomalyst® Approval — Brian Durie
- Update On Other Novel Agents — Sagar Lonial
  - Proteasome Inhibitors
  - Monoclonal Antibodies
- Open Q&A

IMPACT OF NOVEL THERAPIES



5 YEAR SURVIVAL BY AGE

	AGE ≤ 65 YRS	AGE > 65 YRS
2006-2010	73%	56%
2001-2005	63%	31%

Kumar et al. ASH Abstract #3972 2012

FDA APPROVAL OF NOVEL THERAPIES

- 2013 ▪ Pomalyst® (pomalidomide)
- 2012 ▪ Kyprolis® (carfilzomib)
- 2006 ▪ Revlimid® (lenalidomide) ▪ Thalomid® (thalidomide)
- 2003 ▪ Velcade® (bortezomib)
- ~ 2000 ▪ Thalidomide available

FDA APPROVAL OF POMALYST

- Pomalyst is a capsule
- FDA approval date was February 8, 2013
- Expected in pharmacies any day now!

Pomalyst is indicated for patients with multiple myeloma who have received at least 2 prior therapies including Revlimid (lenalidomide) and Velcade (bortezomib) and have demonstrated disease progression on or within 60 days of completion of last therapy.

MECHANISM OF ACTION

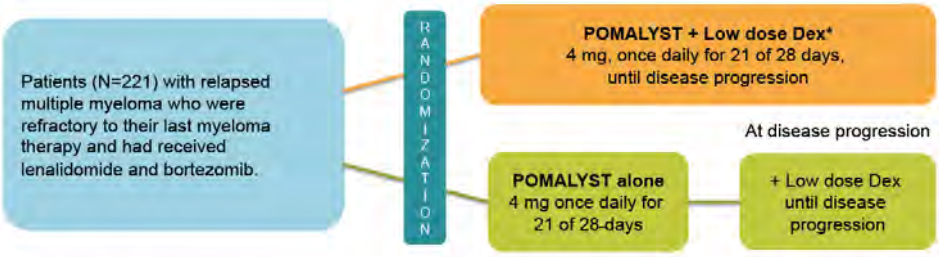
- Pomalidomide is an analogue of thalidomide
- Pomalidomide inhibits growth and causes cell death of myeloma cells in vitro
- Pomalidomide works against thalidomide and lenalidomide (Revlimid) resistant myeloma cells
- Dexamethasone increases the anti-myeloma effects
- Pomalidomide also:
  - Increases T-cell and NK cell immune activity
  - Decreases growth factors such as IL-6/TNF-α

WHY DOES POMALYST, A 3RD IMiD, WORK?

- Why does pomalidomide work when thalidomide and Revlimid stop working?
- Thalidomide and Revlimid bind to cereblon: a direct protein IMiD target, which decreases Interferon Regulatory Factor 4 (IRF4)

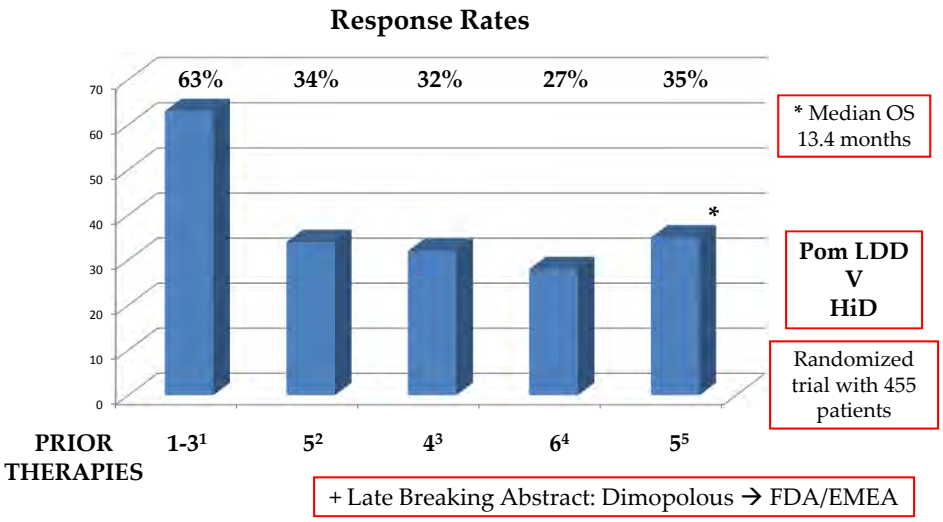
Pomalidomide works even if cereblon is low/absent and so, it has extra mechanism(s) of action.

TRIAL USED AS BASIS FOR FDA APPROVAL



* Low dose Dex = 40 mg per day given only on Days 1, 8, 15 and 22 of each 28-day cycle for patients 75 years or younger, or 20 mg per day on Days 1, 8, 15 and 22 of each 28-day cycle for patients greater than 75 years of age.

POMALIDOMIDE + LOW-DOSE DEX MULTIPLE TRIAL RESULTS



* Median OS 13.4 months

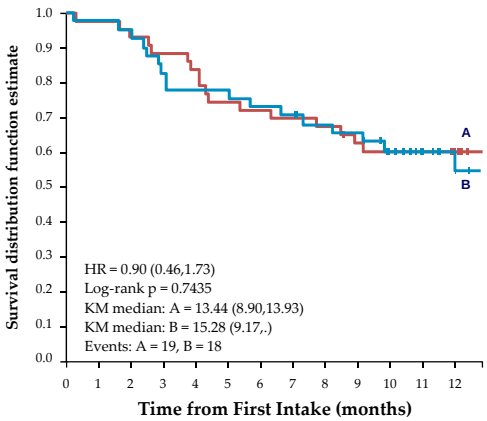
Pom LDD V HiD

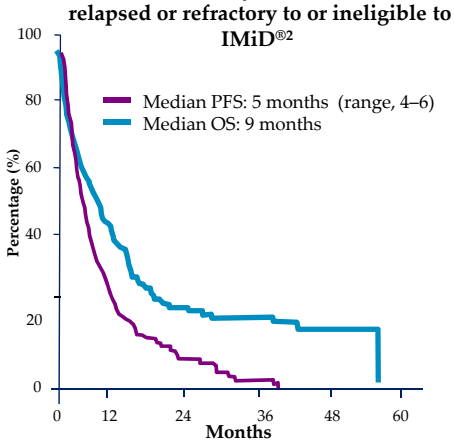
Randomized trial with 455 patients

+ Late Breaking Abstract: Dimopolous → FDA/EMEA

1. Lacy MQ, et al. J Clin Oncol. 2009;27:5008-14. 2. Richardson P, et al. Blood. 2011;118: abstract 634. 3. Lacy MQ, et al. Leukemia.2010;24:1934-9. 4. Lacy MQ, et al. Blood. 2011;118:2970-5. 5. Leleu X, et al. Blood. 2011;118:812. Updated data presented at ASH 2011.

OVERALL SURVIVAL COMPARED WITH HISTORICAL CONTROL IN IFM TRIAL 2009-02 (POMALIDOMIDE)





1. Leleu X, et al. Blood. 2011;118:812. Updated data presented at ASH 2011.
2. Kumar SK, et al. Leukemia. 2012;26:149-57.

CELGENE'S POMALIDOMIDE MEETS MM-003 PHASE III TRIAL ENDPOINTS

	Pom+low-dose dex	High-dose dex
Progression-free survival	**15.7 weeks**	**8.0 weeks**
Overall survival	**Limit not yet reached!**	**34 weeks**

Median number of prior therapies: 5

SAFETY DATA FROM PHASE II POMALIDOMIDE STUDIES IN RRMM

Adverse event Grade 3 or 4, %	IFM 2009-02[1a] Pom + LoDex, all pts N = 84	MM-002[2b] Pom + LoDex arm N = 112
Haematologic		
Neutropenia	62	38
Thrombocytopenia	27	19
Anemia	36	21
Non-haematologic		
Pneumonia	13	19
Dyspnea	12	13
Asthenia/Fatigue	9.5	10

- No grade 3-4 peripheral neuropathy reported
- Incidence of DVT was 4% in IFM 2009-02 and 2–3% in MM-002

[a] Grade 3 or 4 (NCI CTC) AEs that occurred in more than 5% of cases, according to system organ class, ITT population (N = 84).
[b] Grade 3/4 AEs that occurred in ≥ 10% of patients (Safety population) in the pomalidomide plus low dose dexamethasone arm (N = 112).
DVT, deep vein thrombosis; LoDex, low-dose dexamethasone; Pom, pomalidomide; Pts, patients; RRMM, relapsed/refractory multiple myeloma.
1. Leleu X. et al, manuscript in submission. 2. Vij R. *J Clin Oncol.* 2012;30(suppl):513s[abstract 8016].

MOST COMMON SIDE EFFECTS

- In ≥ 30% of patients
  - Fatigue/weakness
  - Low white blood cell count
  - Low red blood cell count
  - Constipation/diarrhea; nausea
  - Breathing problems/resp. infection
  - Fever

- Serious adverse events (grade 3 or 4)
  - Low blood counts
  - Pneumonia
- These require Pomalyst to be held
- Restart with dose 1 mg reduced

BOXED WARNING

Embryo-Fetal Toxicity and Venous Thromboembolism

Embryo-Fetal Toxicity

- **POMALYST is contraindicated in pregnancy. POMALYST is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe birth defects embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting POMALYST treatment.**
- **Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after stopping POMALYST treatment.**

POMALYST is only available through a restricted distribution program called POMALYST REMS.

Venous Thromboembolism

- **Deep Venous Thromboembolism (DVT) and Pulmonary Embolism (PE) occur in patients with multiple myeloma treated with POMALYST. Prophylactic anti-thrombotic measures were employed in the clinical trial. Consider prophylactic measures after assessing an individual patient's underlying risk factors.**

WHAT ARE THE DOSE AND SCHEDULE OF POMALYST?

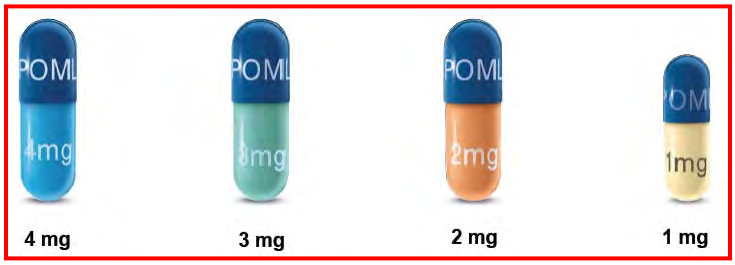
The FDA approved:

- Pomalyst- 4 mg daily, D 1-21
- Dexamethasone- 40 mg daily, one day each week

Cycle repeated every 28 days

Capsules are 4 mg, 3 mg, 2 mg, and 1 mg: color-coded

CAPSULE SIZES



HOW IS POMALYST TAKEN?

- Pomalyst is swallowed with water once a day as a whole capsule. The capsule should be taken two hours before or after a meal.
- Do not break, chew, or open the capsules.
- Do not handle the capsules more than needed.
- If you touch a broken Pomalyst capsule, wash the area of your body that came in contact with the medicine immediately and thoroughly with soap and water.
- If you miss a dose of Pomalyst, and it has been less than 12 hours since your regular time to take it, you should take it as soon as possible. If it has been more than 12 hours since your regular time, just skip your missed dose. Do NOT take two doses at the same time.

HOW THE BODY HANDLES POMALYST

- Elimination from blood stream
  - 50% of pomalidomide is removed within 7.5 hours
- Drug Interactions:
  - Pomalyst is primarily metabolized by CYP1A2 and CYP3A enzyme systems. Pomalyst is also substrate of P-glycoprotein (P-gp).
  - You should not take Pomalyst with drugs that are strong inhibitors of CYP1A2, CYP3A, or P-gp.
  - Cigarette smoking may reduce Pomalyst exposure due to CYP1A2 activation. Patients should be aware that smoking may reduce the efficacy of Pomalyst.
  - Any concerns or questions about possible drug interactions should be discussed with your doctor and pharmacist.

LIVER AND KIDNEY TESTING

- Pomalyst is broken down in the liver
- Pomalyst and metabolites are excreted by the kidneys

Patients should not take Pomalyst

If: > serum creatinine > 3 mg/dl
> serum bilirubin > 2 mg/dl
> AST/ALT > 3 times upper limit of normal

POMALYST INDICATIONS AND USE

- Relapsed myeloma after Revlimid and Velcade
- Approved in combination with dexamethasone
- Full doses: > Pomalyst 4 mg D 1-21
  > Dexamethasone 40 mg Weekly
- Use in other combinations and in earlier disease being explored
  - POM/CYTOXAN/DEX or PRED
  - POM/VELCADE/DEX
  - POM/CARFILZOMIB/DEX

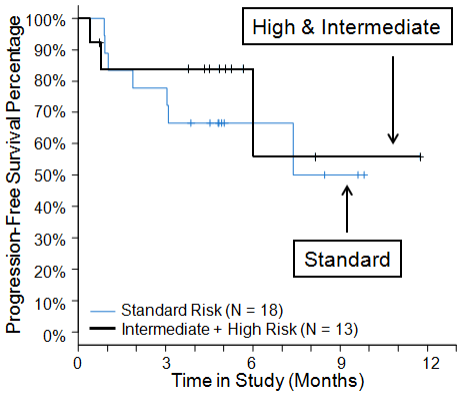
CAR/POM/DEX IN RELAPSED/REFRACTORY MYELOMA

Clinical Benefit Rate (≥ MR) = 67%

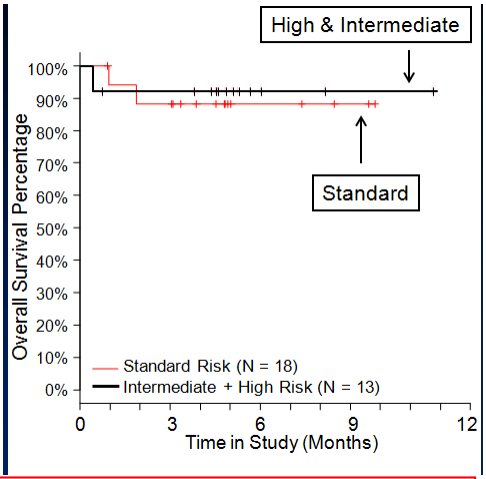
	N = 30
Overall Response Rate (≥ PR)	15 (50%)
VGPR	4 (13%)
PR	11 (37%)
MR	5 (17%)
SD	7 (23%)
PD	3 (10%)

CAR/POM/DEX: SURVIVAL AND RISK STATUS

Progression Free Survival



Overall Survival



Responses & survival are sustained and durable, independent of risk status

POMALYST NEWS UPDATE!

DON WRIGHT
- 71 years old
- Diagnosed 8½ years ago
- On active treatment
- Began running marathons just as he was diagnosed
- In remission on Pomalyst since 2006!

In December 2012, Don achieved his goal of running a marathon in all 50 U.S. states.

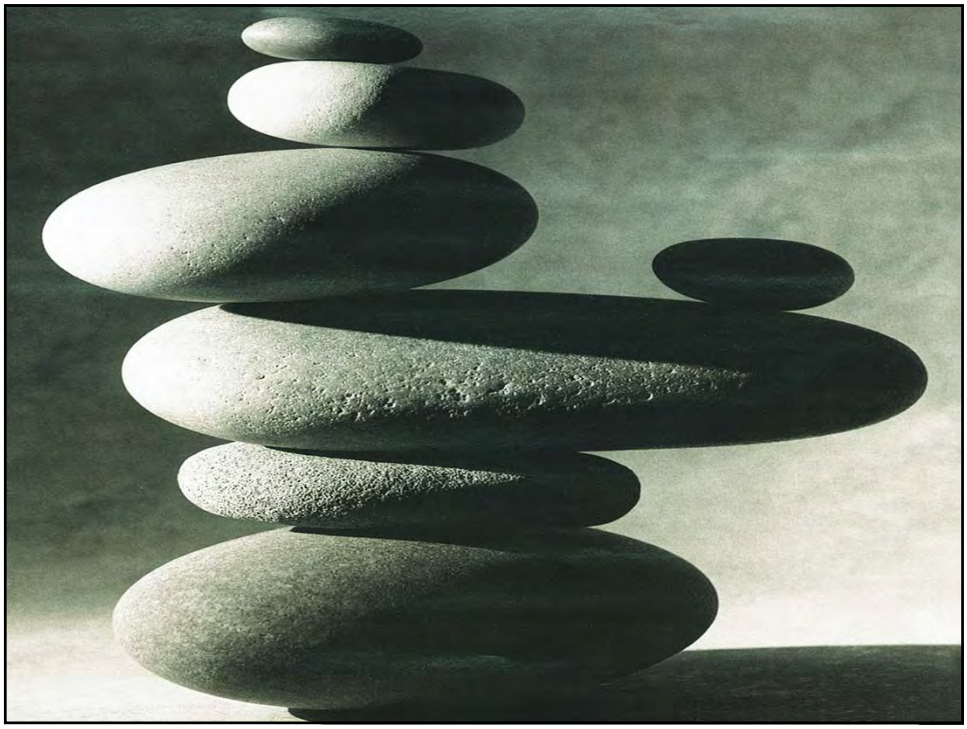
NPR News- February 18, 2013
"Targeted Cancer Drugs Keep Myeloma Patients Up and Running"
www.npr.org/blogs/health/2013/02/18/172098789/targeted-cancer-drugs-keep-myeloma-patients-up-and-running

POMALYST INFORMATION

- NEW Understanding booklet
- NEW Tip Card
- New Myeloma Today Article: Spring Edition

Pomalyst® (pomalidomide) capsules

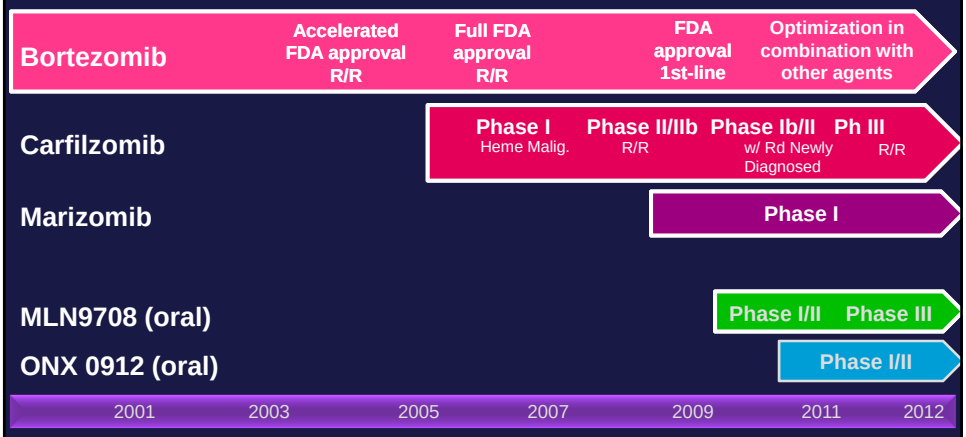
Any questions, contact the Hotline:
call: 1-800-452-CURE (2873)
email: hotline@myeloma.org



Multiple Myeloma: New Approaches

Sagar Lonial, MD
Professor Department of Hematology and Medical Oncology
Winship Cancer Institute
Emory University School of Medicine

Proteasome Inhibitors in MM



R/R, relapsed/refractory.

National Institutes of Health. Available at: www.clinicaltrials.gov. Accessed February 2012.

Alternative Bortezomib Schedule

Regimen	N	ORR	CR	Grade 1/2 PN	≥ Grade 3 PN
CyBorD					
Twice weekly Bz	33	88%	39%	64%	6%
Once weekly Bz	30	93%	40%	56%	0%
VMPT-VT					
Twice weekly Bz	63	86%	35%	29%	14%
Once weekly Bz	190	85%	30%	19%	2%

Bz, bortezomib; PN, peripheral neuropathy; CyBorD, cyclophosphamide, bortezomib, dexamethasone; VMPT-VT, bortezomib, melphalan, prednisone, thalidomide followed by maintenance bortezomib and thalidomide.

Reeder CB, et al. *ASH Annual Meeting Abstracts.* 2009;114(22):616.
Palumbo A, et al. *ASH Annual Meeting Abstracts.* 2010;116(21):620.

3

Alternative Mode of Administration

- MM patients with 1-3 prior therapies

Response / Outcomes	IV, n = 74	SC, n = 148	*P*
ORR after 8 cycles	52%	52%	NS
CR	12%	10%	NS
≥ VGPR	25%	25%	NS
Median TTP	9.4 months	10.4 months	0.39
1-year OS	77%	73%	0.54

Toxicity	IV	SC	*P*
Any grade 3/4 AE	70%	57%	NR
Discontinuation due to AE	27%	22%	NR
Bortezomib dose reduction	43%	31%	NR
Peripheral Neuropathy	53%	38%	0.04
≥ grade 3	16%	6%	0.03
Injection site reaction*	6%	-	NR

*Subcutaneous injection site reactions were reported as an AE in 6% of patients. 57% of investigators reported redness through an investigator-reported local injection-site questionnaire.

NR, not reported; IV, intravenous; SC, subcutaneous; CR, complete response; VGPR, very good partial response; TTP, time to progression; OS, overall survival; AE, adverse event; PN, peripheral neuropathy.

Moreau P, et al. *Lancet Oncol.* 2011;12(5):431-440.

4

Data from Emory Retrospective Review

- Looked back over 1 year of patients who switched form IV to SQ dosing
- Analysis showed:
  - Shorter time in the clinic
  - Fewer side effects
  - Improved patient satisfaction
  - Improved Quality of life
- Conclusion: Use of SQ dosing results in improved patient experience and fewer side effects.

Barbee et al, ASCO 2012

Carfilzomib Monotherapy in Heavily Pre-Treated MM, 003 Trial

	N	ORR	DOR	OS	PFS
All Patients	**266**	**22.9%**	**7.8 mo**	**15.4 mo**	**3.7 mo**
Bz-refractory (≥ imid)	180	15.6%	7.4 mo	12.4 mo	NR
Bz + len-refractory	169	15.4%	7.8 mo	11.9 mo	NR
Bz + len refractory/intolerant	214	20.1%	7.4 mo	13.2 mo	NR
Refractory to 5 approved classes of treatment	44	20.5%	7.8 mo	15.0 mo	NR

Bz, bortezomib; len, lenalidomide; imid, lenalidomide or thalidomide; mo, month; NR, not reported.

Unfavorable cytogenetics did not significantly impact response rates or DOR

Siegel DS, et al. *ASCO Meeting Abstracts.* 2012;30(15S):8035. Siegel DS, et al. *ASCO Meeting Abstracts.* 2011;29(15 suppl):8027. Jakubowiak AJ, et al. *ASH Annual Meeting Abstracts.* 2011;118(21):1875.

Carfilzomib Monotherapy

MM Patients With 1-3 Prior Therapies

Bortezomib-Treated	Cohort 1 (20 mg/m^2 Carfilzomib) n = 34
ORR	21%
CBR (≥ MR)	33%
Median TTP	8.1 months
Median DOR (≥ PR)	11.5 months

Bortezomib-naïve	Cohort 1 (20 mg/m^2) n = 59	Cohort 2 (20→27 mg/m^2) n = 70
ORR	42%	52%
CBR	59%	64%
CR	3%	2%
VGPR	14%	27%
Median TTP	8.3 mo	Not reached
Median DOR	13.1 mo	Not reached
Median PFS	8.2 mo	Not reached

Stewart K, et al. *Hematologica.* 2010;95(S2). Abstract 1099. Vij R, et al. *ASH Annual Meeting Abstracts.* 2011;118(21):813.

Carfilzomib: Toxicity

004, Phase II, Bortezomib-Naïve Patients

≥ Grade 3 AE	Cohort 1 (20 mg/m^2) n = 59	Cohort 2 (20→27 mg/m^2) n = 70
Lymphopenia	14%	19%
Anemia	12%	17%
Thrombocytopenia	15%	11%
Neutropenia	12%	14%
Pneumonia	14%	11%
Fatigue	12%	1%
Dyspenea	5%	6%
Peripheral Neuropathy	**1 patient (grade 3)**	**0**

No treatment discontinuations due to PN

Vij R, et al. *ASH Annual Meeting Abstracts.* 2011;118(21):813. Abstract 1099.

Carfilzomib / Lenalidomide / Dex (CRd) in Relapsed / Refractory MM

MM: 1-3 Prior Therapies
N = 52

→ Carfilzomib
Lenalidomide
Low-dose dex

1º Endpoint
ORR
2º Endpoint
DOR, TTP, OS, PFS, Safety

	CRd N = 51
N	52
Median age	63 years
Median prior therapies	2
Prior bortezomib	85%
Prior lenalidomide	73%
Prior lenalidomide and bortezomib	50%
Prior thalidomide	44%

Wang M, et al. *ASCO Meeting Abstracts.* 2011;29(15 suppl):8025.

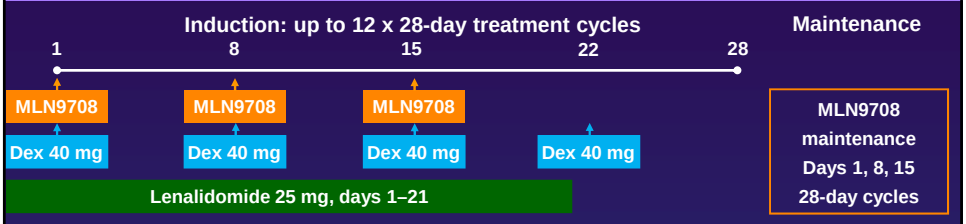
MLN9708

Agent	**MTD**	**N**	**Response**	**Toxicity Notes**
MLN9708 (2x weekly)	2.0 mg/m^2 orally	46	13% ≥ PR 2% CR 2% MR 61% SD	**DLT:** rash, nausea, vomiting **Common:** thrombocytopenia, GI, rash, fatigue **≥ Gr 3:** vomiting, DVT, anemia, rash, thrombocytopenia **PN:** 11% gr 1/2; 0% gr 3
MLN9708 (1x weekly)	2.97 mg/m^2 orally	32	6 % ≥ PR 25% SD	

MTD, maximum tolerated dose; PR, partial response; CR, complete response; MR, marginal response; SD, stable disease; GI, gastrointestinal; Gr, grade; DVT, deep vein thrombosis; DLT, dose-limiting toxicity; PN, peripheral neuropathy; min, minute.

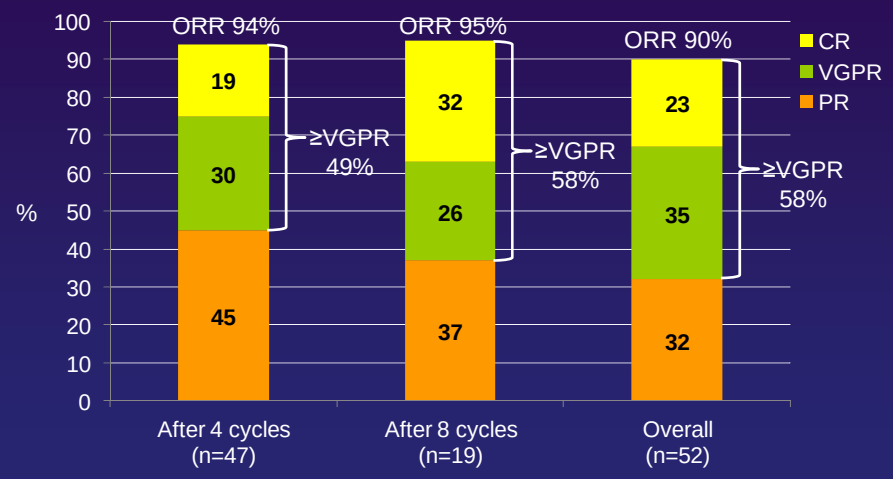
Richardson PG, et al. *ASH Annual Meeting Abstracts.* 2011;118(21):301. Berdeja JG, et al. *ASH Annual Meeting Abstracts.* 2011;118(21):479.

Study design



- Phase 1: oral MLN9708 dose-escalation
  - Standard 3+3 schema, 33% dose increments, based on cycle 1 dose-limiting toxicities (DLTs)
- Phase 2: oral MLN9708 at the RP2D from phase 1
- Stem cell collection allowed after 3 cycles, with autologous stem cell transplantation (ASCT) deferred until after 6 cycles
- MLN9708 maintenance continued until progression or unacceptable toxicity
- Mandatory thromboprophylaxis with aspirin or low-molecular-weight heparin

Preliminary response data over course of treatment – patients treated at RP2D (2.23 mg/m^2 / 4.0 mg)



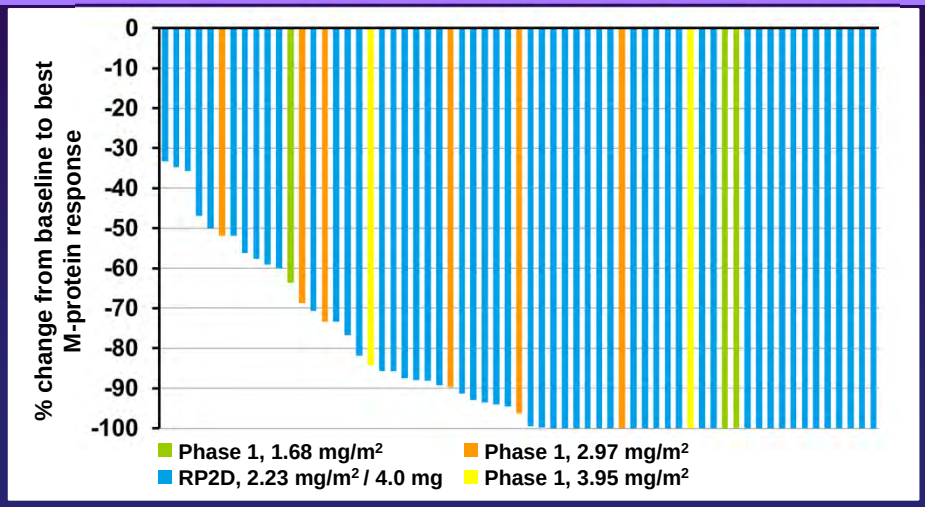
- Of 3 response-evaluable patients who completed 12 cycles, 2 achieved CR and 1 VGPR

Conclusions: Proteasome Inhibitors

- New proteasome inhibitors have good efficacy and improved safety profile
- Oral inhibitors are well tolerated and appear to have good efficacy

Target	Antibody	Company	Type
CS1	**Elotuzumab**	**Abbot/BMS**	**Humanized**
IL-6	**Siltuximab**	**Orthobiotec**	**Chimeric**
CD138	**BT062**	**Biotest**	**Chimeric; conjugated to Maytansinoid**
Anti-KIR	**IPH2101**	**Innate Pharma**	**Fully Human**
CD38	Daratumomab	Genmab	Fully Human
CD56	IMGN901, Lorvotuzumab Meransine	ImmunoGen	Humanized; conjugated to Maytansinoid
CD74	Immu-110	Immunomedics	Humanized; conjugated to Doxorubicin
IGF1-R	CP751,871	Pfizer	Fully Human
RANKL	Denosumab	Amgen	Fully Human
DKK-1	BHQ880	Novartis	Fully Human
FGFR3	PRO-001	Prochon Biotech Genetech	Humanized

Best percent change in M-protein from baseline in response-evaluable patients

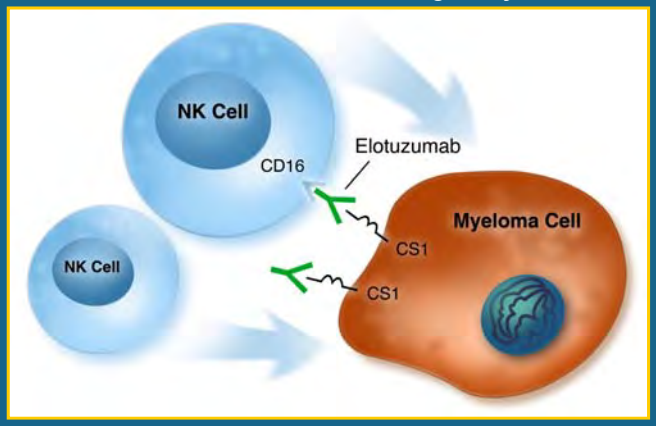


- 48% of patients achieved 100% reduction in M-protein
- Reductions were seen at multiple dose levels

ASH 2012

Elotuzumab

- **Elotuzumab is a monoclonal antibody that targets the CS1 protein, which is highly expressed on the surface of myeloma cells**
- **Elotuzumab enhances NK cell-mediated killing of myeloma cells via ADCC[1,2]**

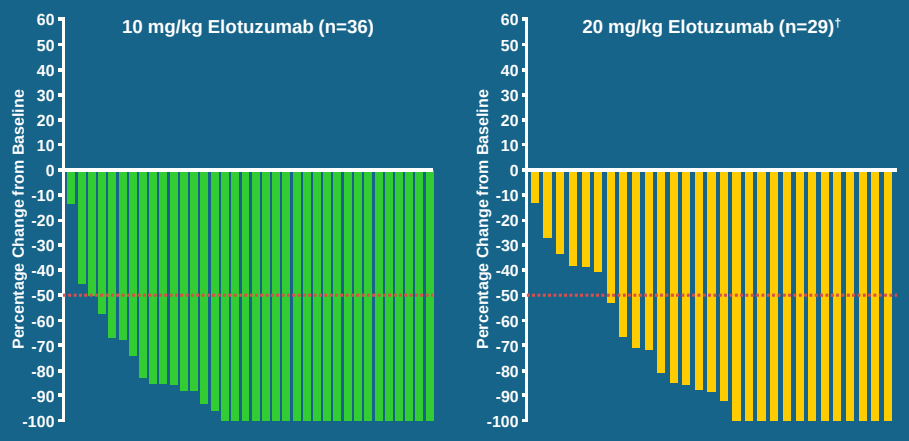


ADCC = antibody-dependent cellular cytotoxicity

1. His et al. *Clin Cancer Res*. 2008; 2. Tai et al. *Blood*. 2008

ASH 2012

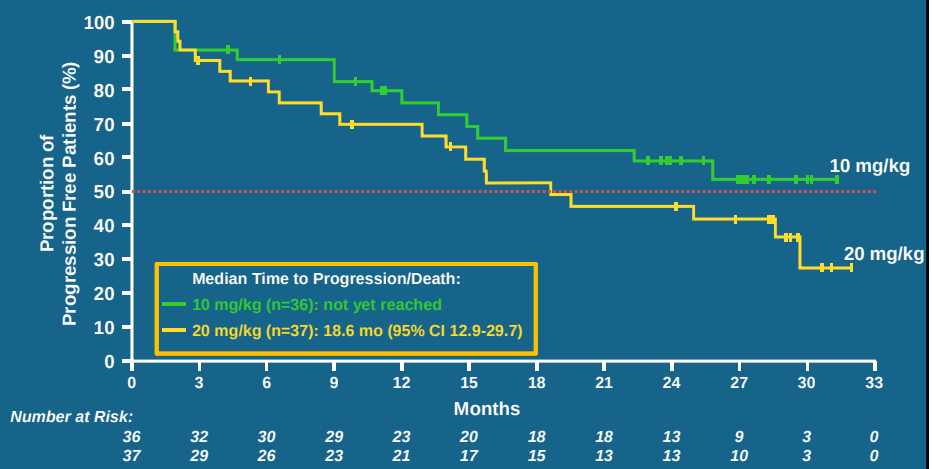
Efficacy: Maximum Percent Reduction in Serum M Protein*



*Maximum percentage decrease from baseline to 60 days after permanent discontinuation of elotuzumab or start of new line of MM therapy.
†Eight patients without measurable disease (baseline and all on-study serum M-protein levels <0.5 g/dL) were not included.

ASH 2012

Progression Free Survival

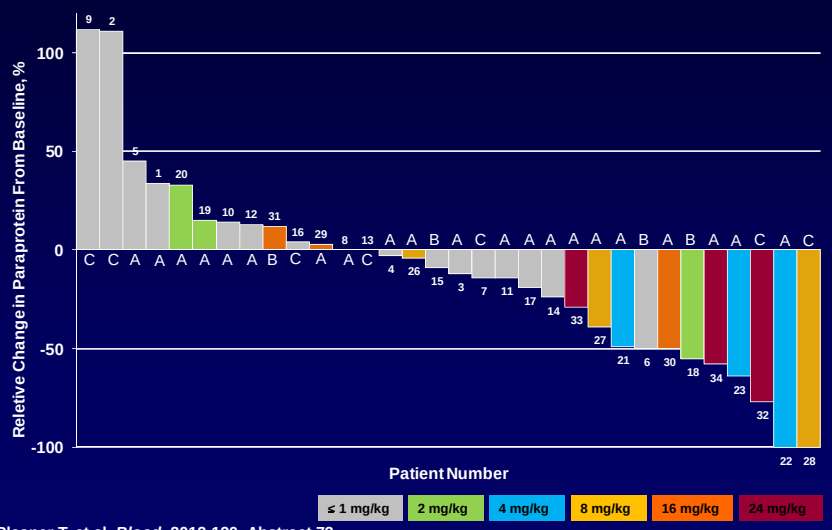


At a median follow-up of 20.8 mo, median PFS has not been reached in the 10 mg/kg arm

- In the abstract, a preliminary median PFS of 26.9 mo was reported; however, after 2.7 mo of additional follow-up, no new progression or death was reported. Therefore, these patients had an increase in their PFS duration, and in the updated analysis, the median PFS was not yet reached

Daratumumab (CD38) Response
Maximal Change in Paraprotein

A: serum M-component B: urine M-component C: FLC



Plesner T, et al. *Blood,* 2012;120: Abstract 73.

New Targets are Close!

- In addition to new proteasome inhibitors and new IMiDs, there are new targets
- These new targets will help to treat relasped disease
- More effective relapsed approaches always move to front line therapy and help us to **eradicate the disease**
- **Eradication Leads to CURE**