Approaches to the Patient with "Double-Refractory" Myeloma

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Learning Objectives

- Define the patient population and their unmet medical need
- Review data about current and emerging agents that show promise in this setting
- Provide a framework for future approaches to overcome resistance in a molecularly adapted fashion

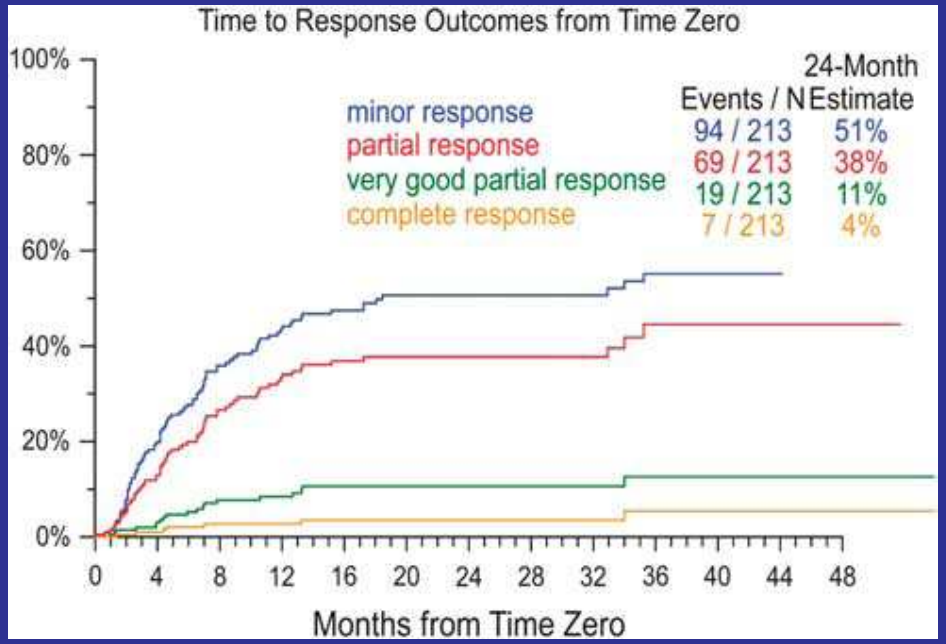
Defining the Population

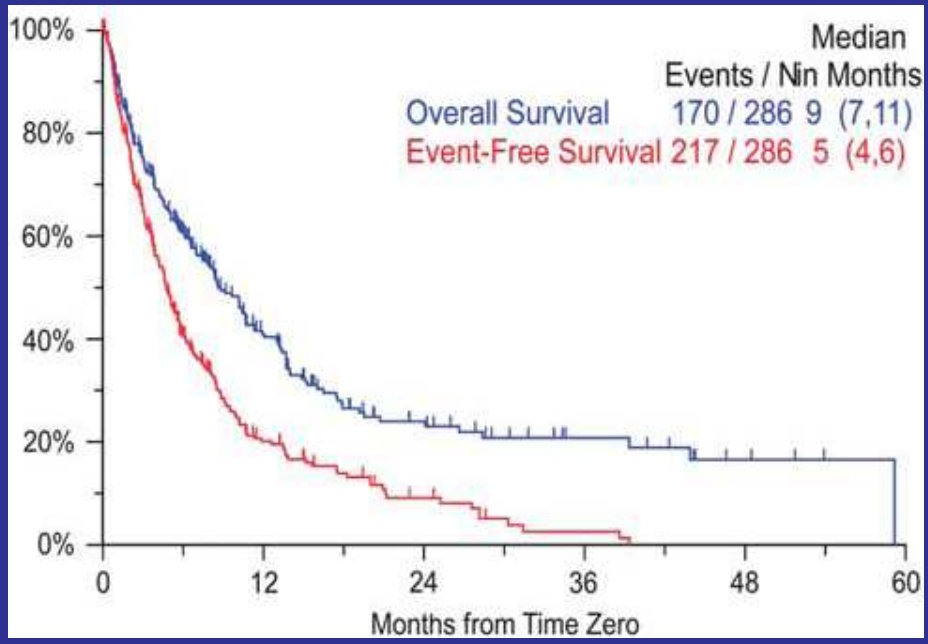
- Refractory myeloma[1]
  - Progression on current therapy
  - Progression within 60 days of last therapy
  - Stable disease as best response to last therapy
- Double refractory myeloma
  - Refractory to bortezomib
  - Refractory to lenalidomide

[1]Rajkumar, SV et al. Blood 117:4691, 2011.

An Unmet Medical Need

- Patients with disease that is refractory to bortezomib, and relapsed after, or refractory to, or ineligible for an IMiD

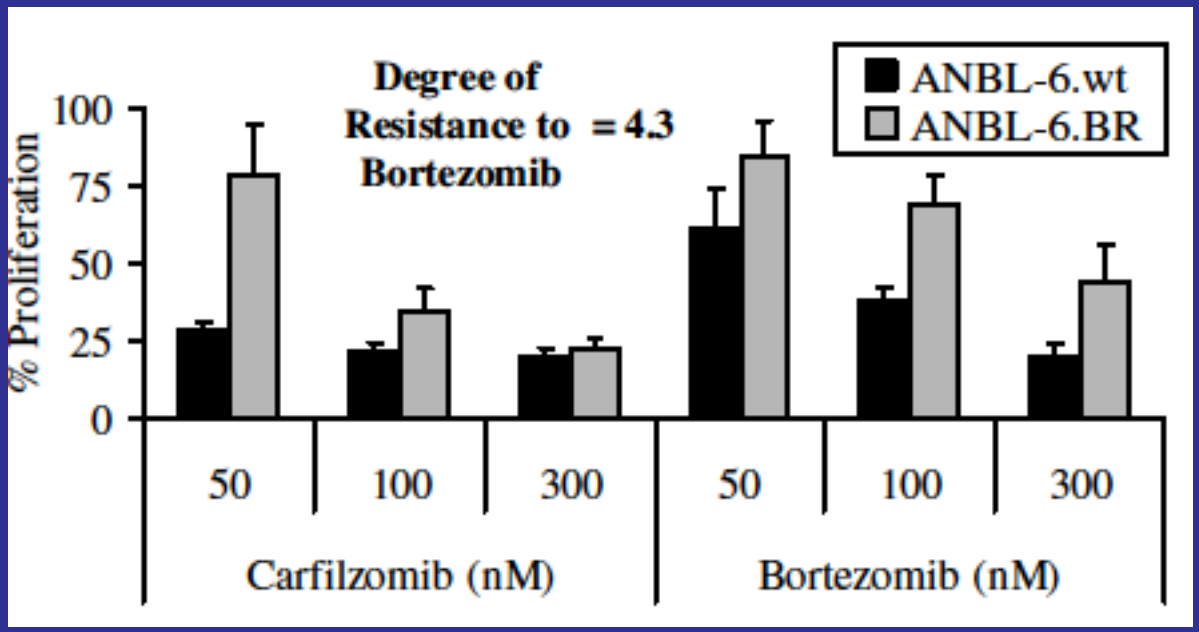




Kumar, S et al. Leukemia 26:149, 2012.

Carfilzomib: Pre-clinical Data

- Irreversible epoxyketone proteasome inhibitor specific for the chymotrypsin-like activity
- Active against bortezomib-resistant myeloma models



Kuhn, DJ et al. Blood 110:3281, 2007.

Carfilzomib: Phase I Data

- Safety profile notable for less treatment-emergent PN
- Evidence of activity in patients with bortezomib-refractory myeloma

Adverse event	All patients (*N* = 29)				
	Grade 1 *n* (%)	Grade 2 *n* (%)	Grade 3 *n* (%)	Grade 4 *n* (%)	All Grades *n* (%)
Any	4 (14)	11 (38)	11 (38)	3 (10)	29 (100)
Fatigue	10 (35)	3 (10)	1 (3)	0 (0)	14 (48)
Nausea	11 (38)	3 (10)	0 (0)	0 (0)	14 (48)
Diarrhea	7 (24)	3 (10)	0 (0)	0 (0)	10 (35)
Cough	8 (28)	0 (0)	0 (0)	0 (0)	8 (28)
Dyspnea	6 (21)	0 (0)	1 (3)	1 (3)	8 (28)
Hypoesthesia	5 (17)	3 (10)	0 (0)	0 (0)	8 (28)
Pyrexia	5 (17)	3 (10)	0 (0)	0 (0)	8 (28)
Headache	7 (24)	0 (0)	0 (0)	0 (0)	7 (24)
Peripheral edema	7 (24)	0 (0)	0 (0)	0 (0)	7 (24)
Constipation	5 (17)	1 (3)	0 (0)	0 (0)	6 (21)
Exertional dyspnea	6 (21)	0 (0)	0 (0)	0 (0)	6 (21)
Paresthesia	4 (14)	2 (7)	0 (0)	0 (0)	6 (21)

O'Connor, OA et al. Clin Cancer Res. 15:7085, 2009.
Alsina, M et al. Clin Cancer Res. 18:4830, 2012.

Carfilzomib: Phase II Data

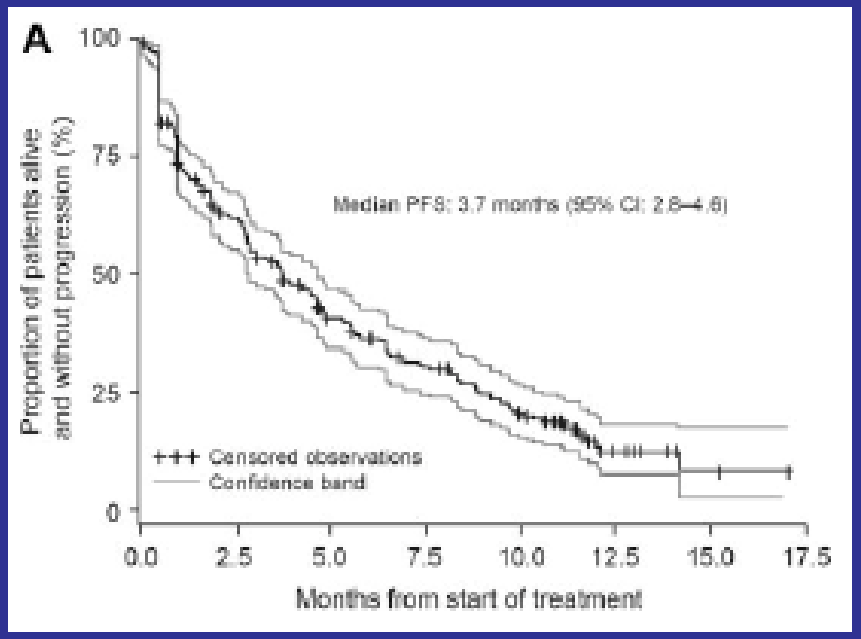
- ORR (≥PR) for entire population with relapsed/refractory disease was 23.7%
- 15.4% in double-refractory patients

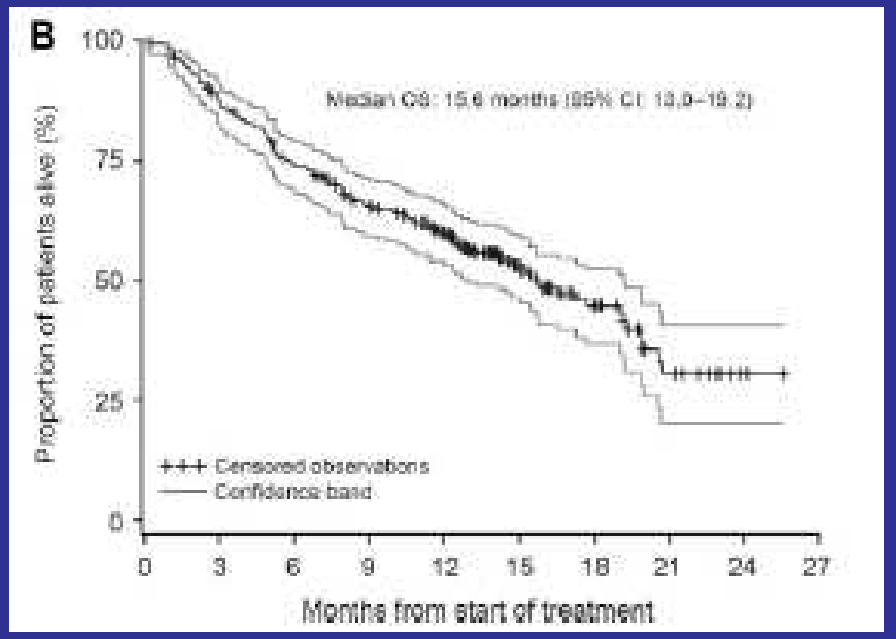
	All patients (n = 257)	Patients with unfavorable cytogenetic/ FISH markers (n = 71)
Response category, n (%)		
Complete response	1 (0.4)	0 (0)
Very good partial response	13 (5.1)	3 (4.2)
Partial response	47 (18.3)	18 (25.4)
Minimal response	34 (13.2)	3 (4.2)
Stable disease	81 (31.5)	28 (39.4)
Progressive disease	69 (26.8)	15 (21.1)
Not evaluable	12 (4.7)	4 (5.6)
Overall response, n (%)	61 (23.7)	21 (29.6)
95% CI	18.7-29.4	19.3-41.6
Clinical benefit rate, n (%)	95 (37.0)	24 (33.8)
95% CI	31.1-43.2	23.0-46.0
PFS, median (95% CI), mo	3.7 (2.8-4.6)	3.6 (2.3-4.6)
Median duration of response, mo (95% CI)†	7.8 (5.6-9.2)	6.9 (3.7-8.5)
Mean treatment duration, mo (range)‡	3.0 (0.03-16.9)	3.6 (0-11.1)

Siegel, DS et al. Blood 120:2817, 2012.

Carfilzomib: Durability

- DOR for entire cohort was 7.8 mos.
- Same for dual-refractory





Siegel, DS et al. Blood 120:2817, 2012.

High Dose Carfilzomib

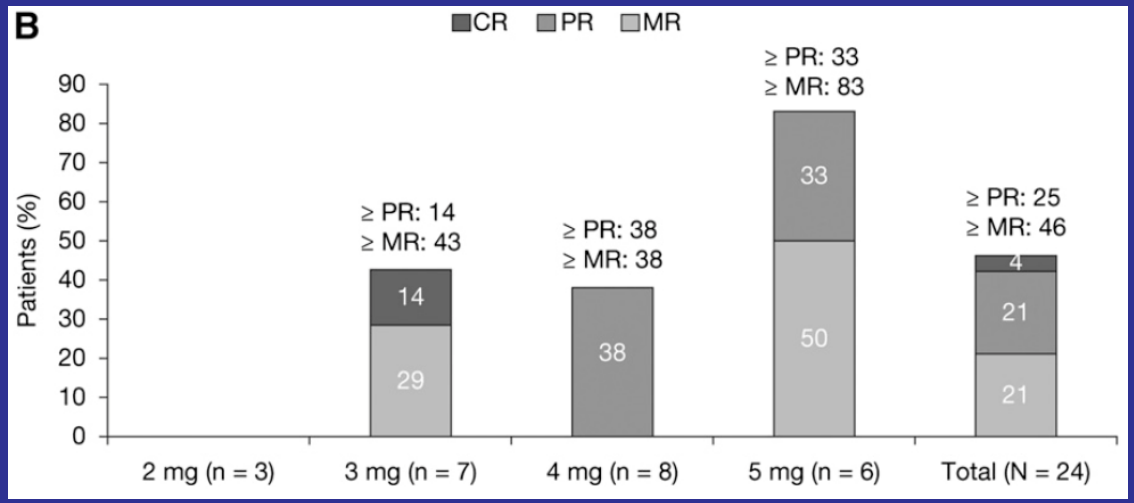
- Higher doses tolerated when given as a prolonged infusion
- Initial phase II data suggest a better response rate and durability

	N=38
Best response, n	
CR	1 (3%)
VGPR	9 (24%)
PR	10 (26%)
MR	1 (3%)
SD	11 (29%)
POD	6 (16%)
ORR	53%

Lendvai, N et al. 2012 ASH Abstract # 947.

Pomalidomide: Phase I Data

- Recommended dose of 4 mg
  - DLTs were grade 4 neutropenia at 5 mg level
- ORR for entire population (≥PR) was 21%
  - 25% (6/24) in dual refractory (27% at MTD or less)



Richardson, PG et al. Blood 121:1961, 2013.

Pomalidomide + Dex

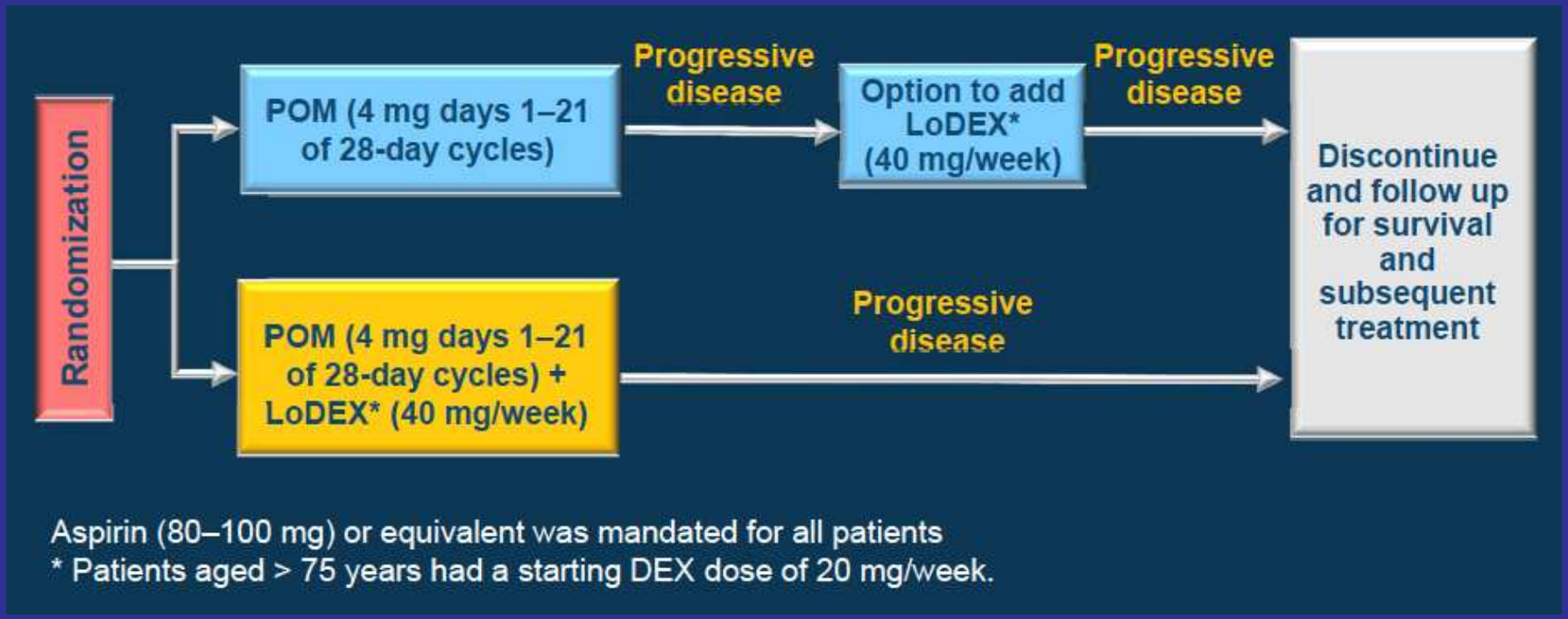
- ORR 34.5% for population as a whole
  - 74% (32/43) and 78% (32/41) on the two arms were double refractory

	21/28 (N = 43)	28/28 (N = 41)	Total
Response rate, n (%)		ITT (N = 84)	
ORR (≥PR)	15 (35)	14 (34)	29 (34.5)
CR*	1 (2)	2 (5)	3 (4)
VGPR	1 (2)	1 (2)	2 (2)
PR	13 (30)	11 (27)	24 (27)
Stable disease	19 (44)	21 (51)	40 (48)
Progressive disease	5 (12)	3 (7)	8 (9.5)
Not evaluable	4 (9)	3 (7)	7 (8)
Median time to first response (95% CI), months	2.7 (0.8, 9.5)	1.1 (0.6, 8)	1.8 (0.6, 9.5)
Median duration of response (95% CI), months	6.4 (4, —)	8.3 (6.5, 16)	7.3 (5, 15)
One year free of relapse, %	42	47	44

Leleu, X et al. Blood 121:1968, 2013.

Pom in Registration Studies

- Design of MM-002 study



Vij, R et al. 2012 ASCO Abstract # 8016.

Overall Response Data

	POM (n = 108)	POM + LoDEX (n = 113)
ORR (≥ PR) (%)	9	30
Median DOR*, months	NR	7.4
≥ MR	25	45
CR	0	1
PR	9	29
MR	16	15
SD	46	35
PD	16	6
Median time to ORR*, months	2.0	1.9

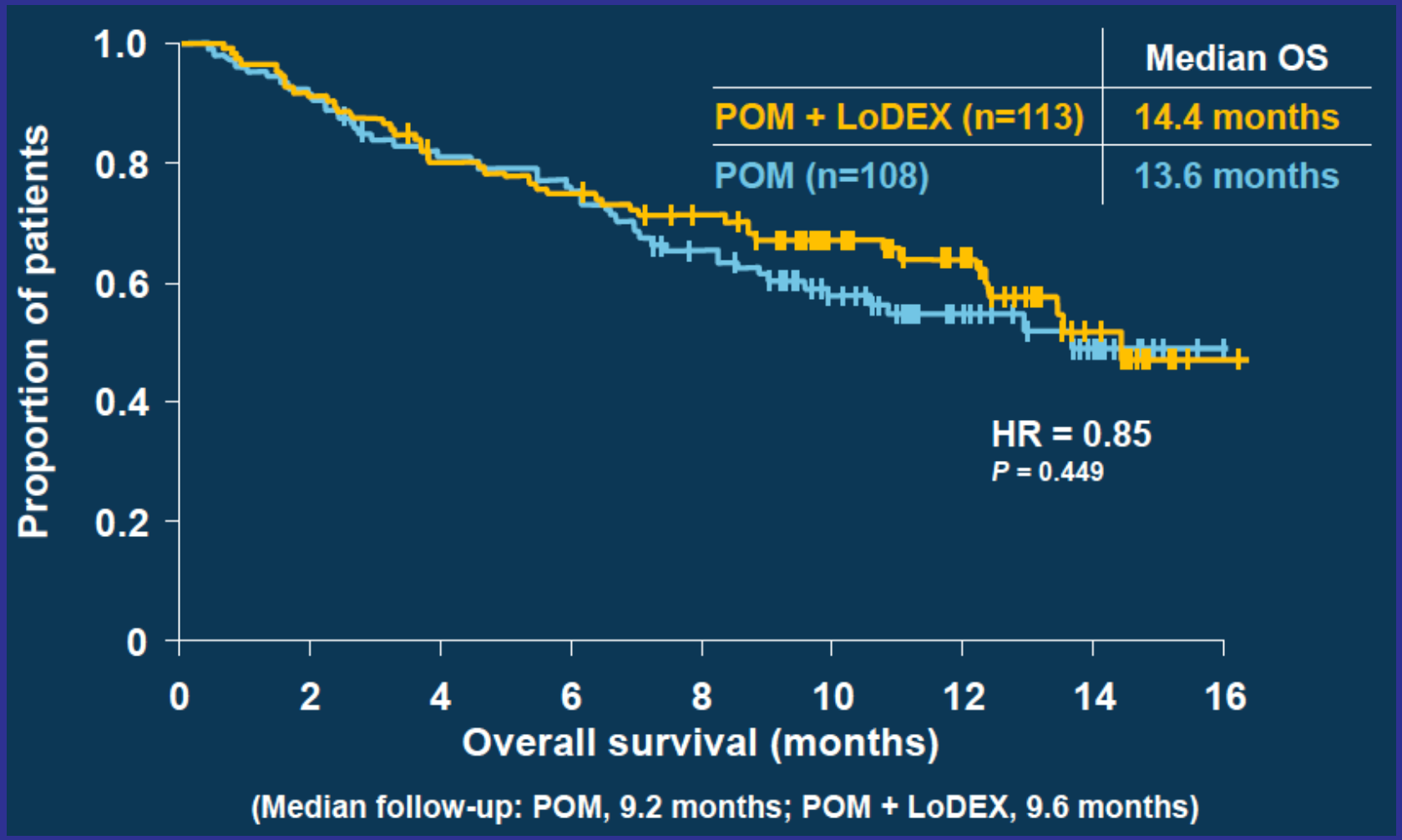
Vij, R et al. 2012 ASCO Abstract # 8016.

Dual Refractory Data

Response	LEN refractory (n = 87)	BORT refractory (n = 82)	LEN-BORT refractory (n = 69)	LEN-BORT refractory + prior transplant (n = 47)
ORR (≥ PR) (%)	25	29	28	34
≥ MR (%)	41	46	46	53
CR (%)	0	0	0	0
PR (%)	25	29	28	34
MR (%)	16	17	19	19
SD (%)	40	33	35	28
PD (%)	7	7	7	6
Time to ≥ PR (mo)	1.9	1.9	1.8	1.6
Median duration of ≥ PR (mo)	7.0	5.8	6.2	5.7
Median duration of MR only (mo)	3.4	3.2	3.0	5.7

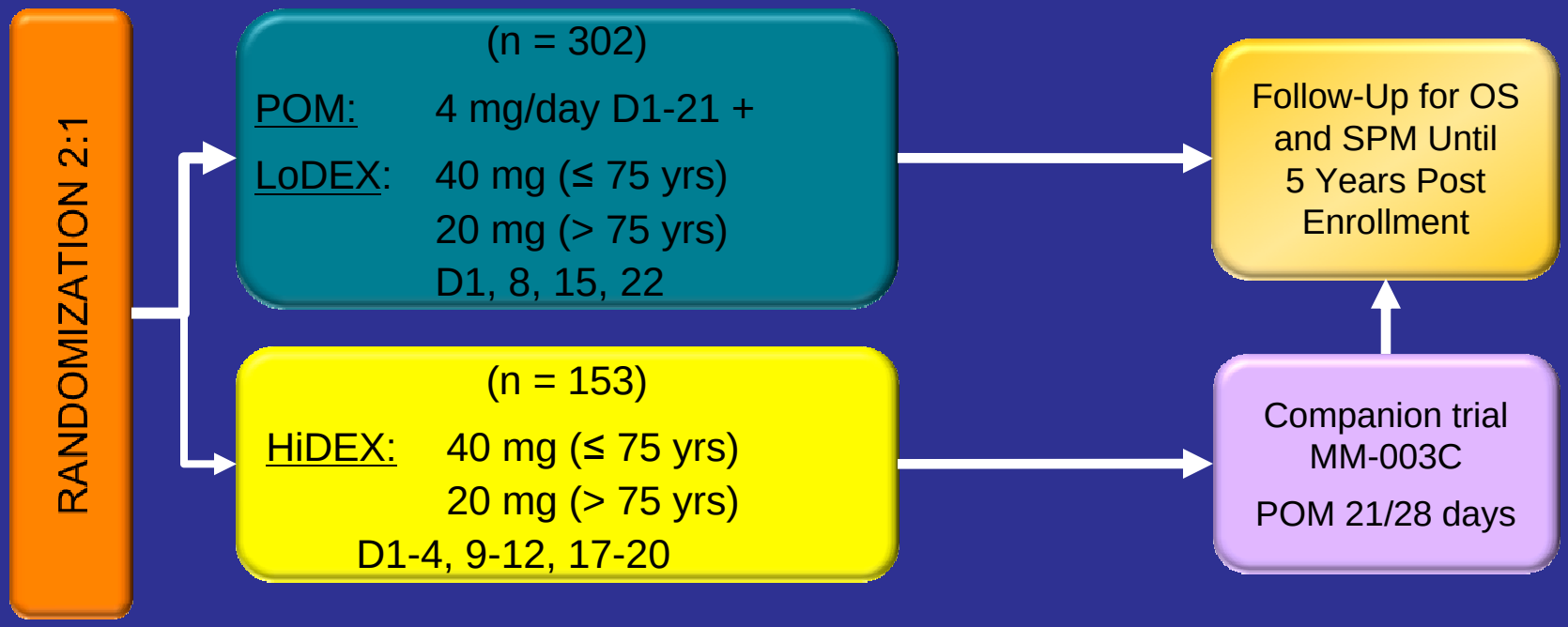
Vij, R et al. 2012 ASCO Abstract # 8016.

Overall Survival Data



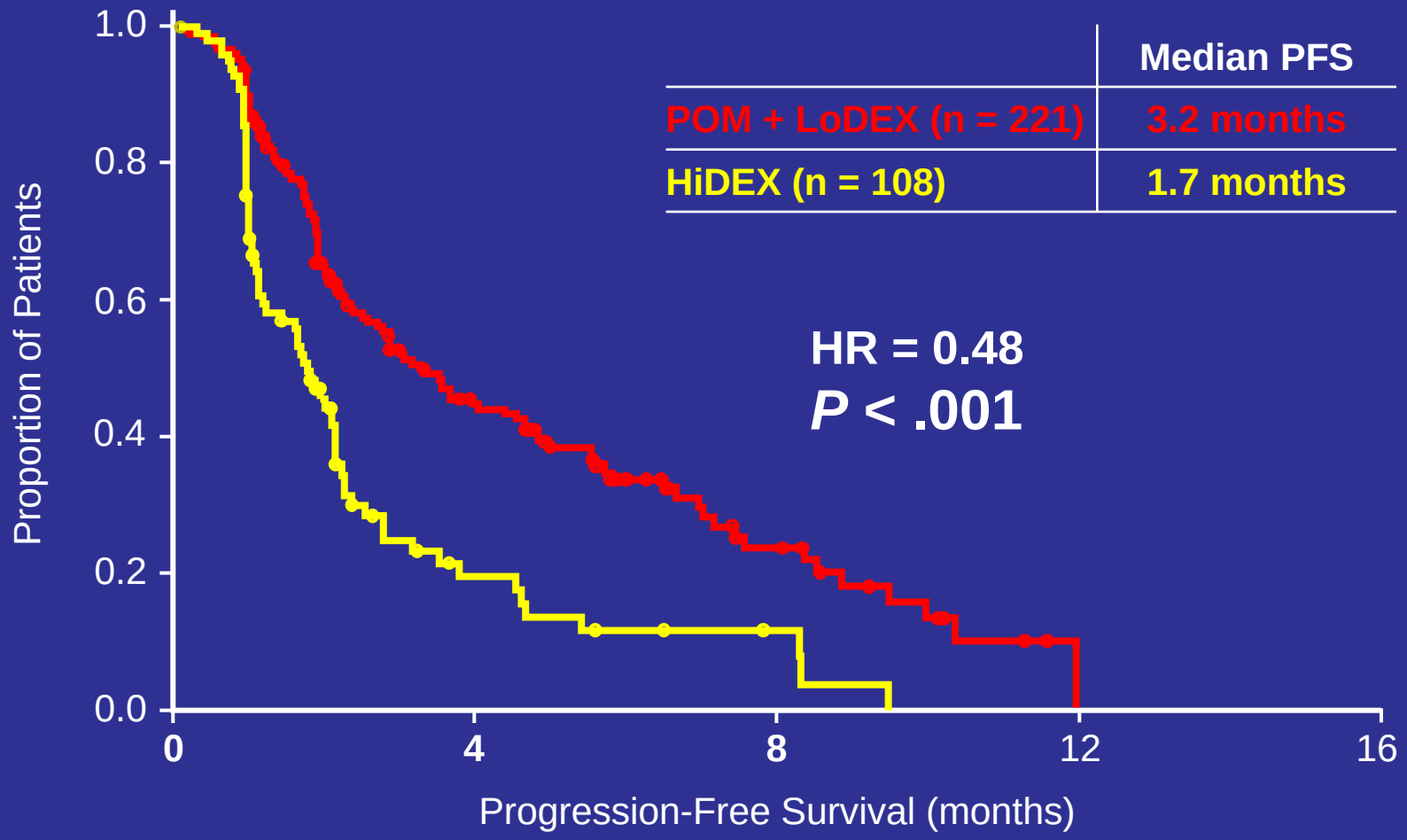
Vij, R et al. 2012 ASCO Abstract # 8016.

Pomalidomide MM-003 Study



Dimopoulos, MA et al. 2012 ASH Abstract # LBA-6.

PFS: Dual-refractory Disease



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

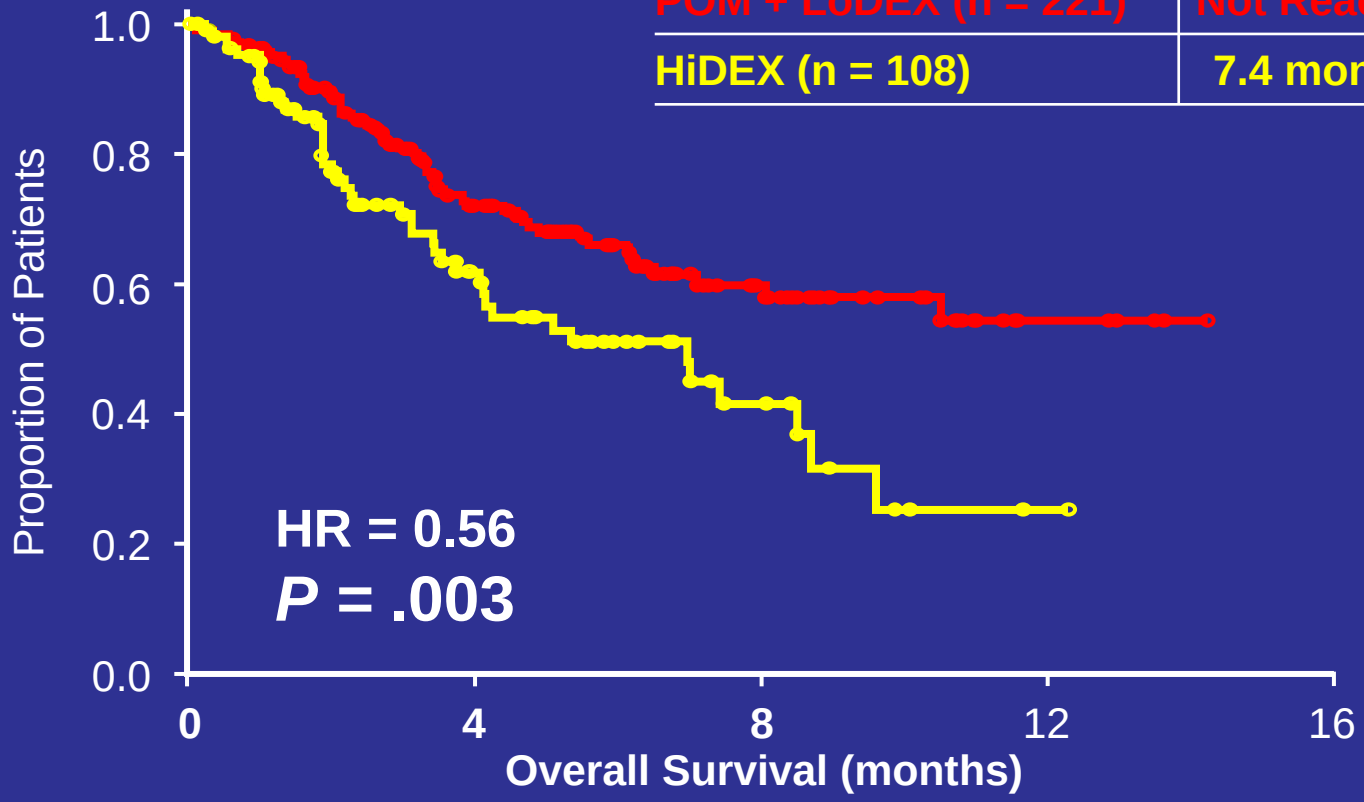
HR = 0.48

***P* < .001**

Dimopoulos, MA et al. 2012 ASH Abstract # LBA-6.

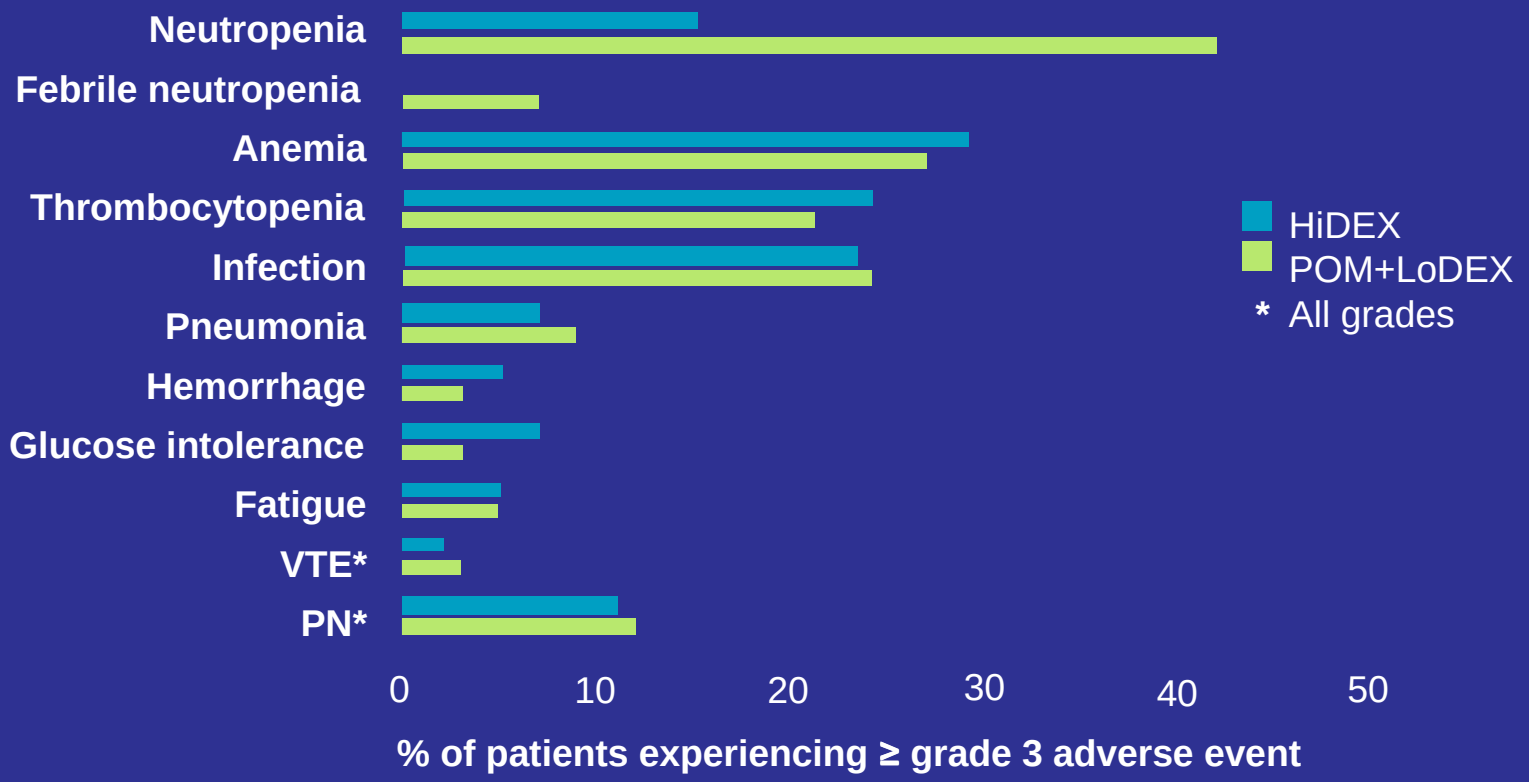
OS: Dual-refractory Disease

	Median OS (95% CI)
POM + LoDEX (n = 221)	Not Reached (8.5-NE)
HiDEX (n = 108)	7.4 months (4.3-9.2)



Dimopoulos, MA et al. 2012 ASH Abstract # LBA-6.

Safety Profile



7% of POM + LoDEX and 6% of HiDEX patients discontinued due to AEs

Dimopoulos, MA et al. 2012 ASH Abstract # LBA-6.

Pom/Bortez/Dex

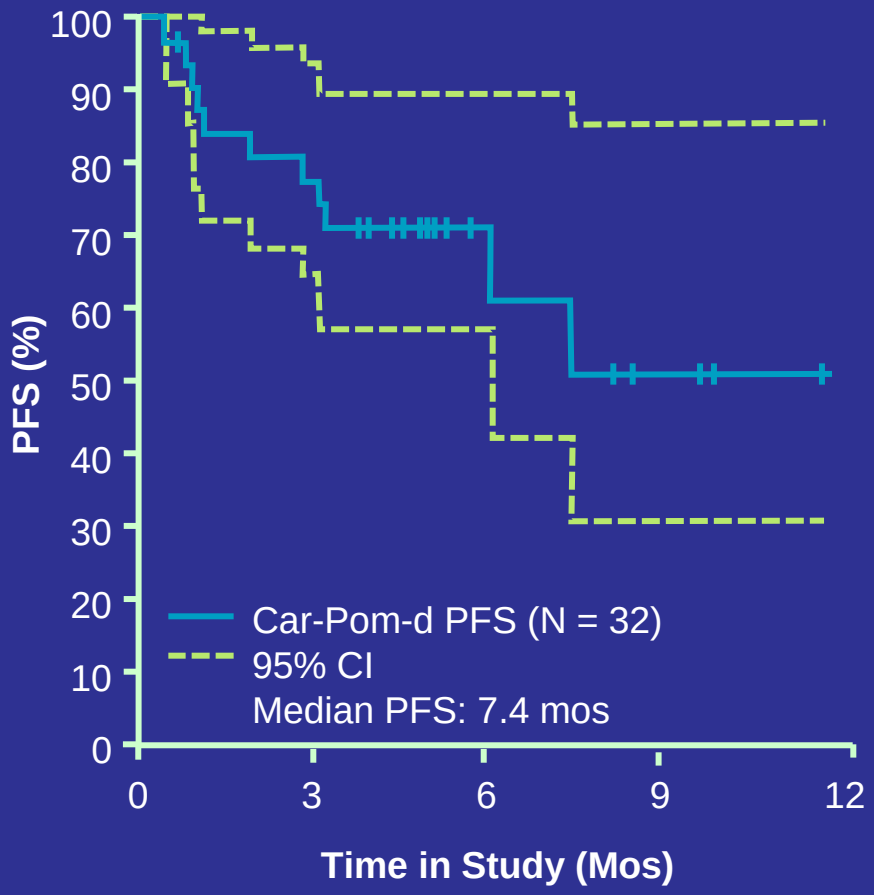
Cohort	Best Response
Cohort 1 (n = 3)	1 VGPR, 1 PR, 1 SD
Cohort 2 (n = 3)	1 PR, 2 SD
Cohort 3 (n = 3)	2 VGPR, 1 PR
Cohort 4 (n = 3)	1 VGPR, 2 PR
Cohort 5 (n = 3)	2 PR, 1 SD

- ORR (≥ PR): 73%; VGPR: 27%; SD: 27%
- Median time to response: 1 cycle (range 1-2)
- Most responses are ongoing

Richardson, PG et al. 2012 ASH Abstract # 727.

Car-Pom-D

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



Shah, JJ et al. 2012 ASH Abstract # 74.

KSP Inhibitor ARRY-520

Adverse Events, %	ARRY-520 (n = 32)		ARRY + Dexamethasone (n = 21)	
	Grade 3	Grade 4	Grade 3	Grade 4
Non-hematologic				
▪ Pneumonia	--	--	10	10
▪ Fatigue	12	3	10	--
▪ Arthralgia	--	--	5	--
▪ Back pain	6	--	--	--
▪ Hypokalemia	3	3	5	--
▪ Upper respiratory tract infection	--	--	5	--
Hematologic				
▪ Neutropenia	19	28	24	38
▪ Thrombocytopenia	22	25	38	19
▪ Anemia	31	6	43	5
▪ Febrile neutropenia	3	--	5	--

Shah, JJ et al. 2012 ASH Abstract # 449.

Response Data

Outcome	ARRY-520 (n = 32)	ARRY-520 + Dexamethasone (n = 18)
Overall best response, %		
▪ PR	16	22
• MR + PR	19	33
▪ SD	44	28
▪ PD	34	28
▪ Not evaluable	3	11
Median duration of response (≥ PR), mos (range)	8.6 (1.4-20.0)	5.4 (2.5-9.0)

- 520 + Dex population was “triple refractory”

Shah, JJ et al. 2012 ASH Abstract # 449.

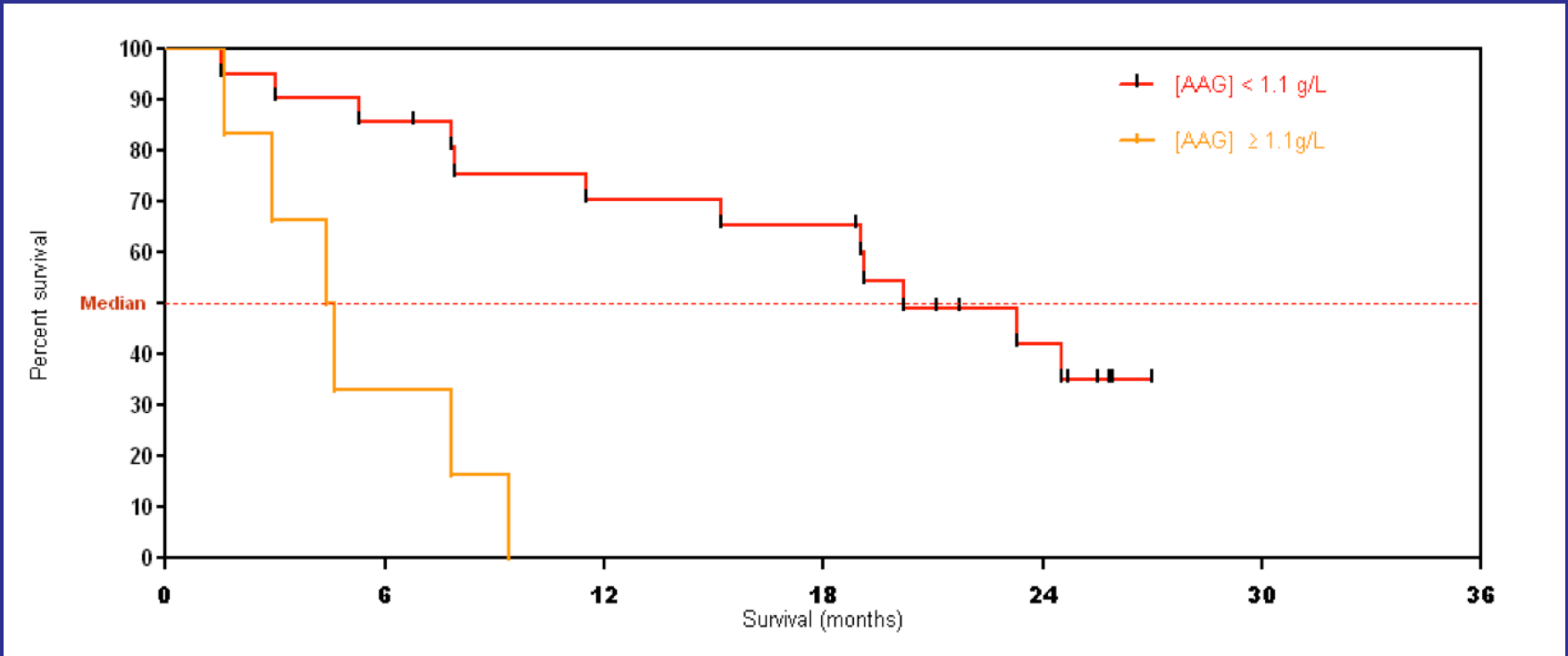
Updated Subgroup Analysis

ARRY-520 Subgroup Analysis for ORR and OS			
Subgroup	N	Median EFS (Months)	Median OS (Months)
All Patients	32	3.7	19.0
AAG ≤1.1 g/L	21	5.3	20.2
AAG > 1.1 g/L	6	2.4	4.5
ISS Stage I at Baseline	10	12.0	20.2
ISS Stage II at Baseline	13	2.3	19.1
ISS Stage III at Baseline	9	1.9	6.2
Bortezomib-Refractory	17	4.8	19.0
Lenalidomide Refractory	24	3.7	19.1
Dual-Refractory	13	4.2	9.9
Refractory to Last Therapy	15	3.0	20.2

Lonial, S et al. 2013 IMW Poster # P-224.

Survival and AAG Level

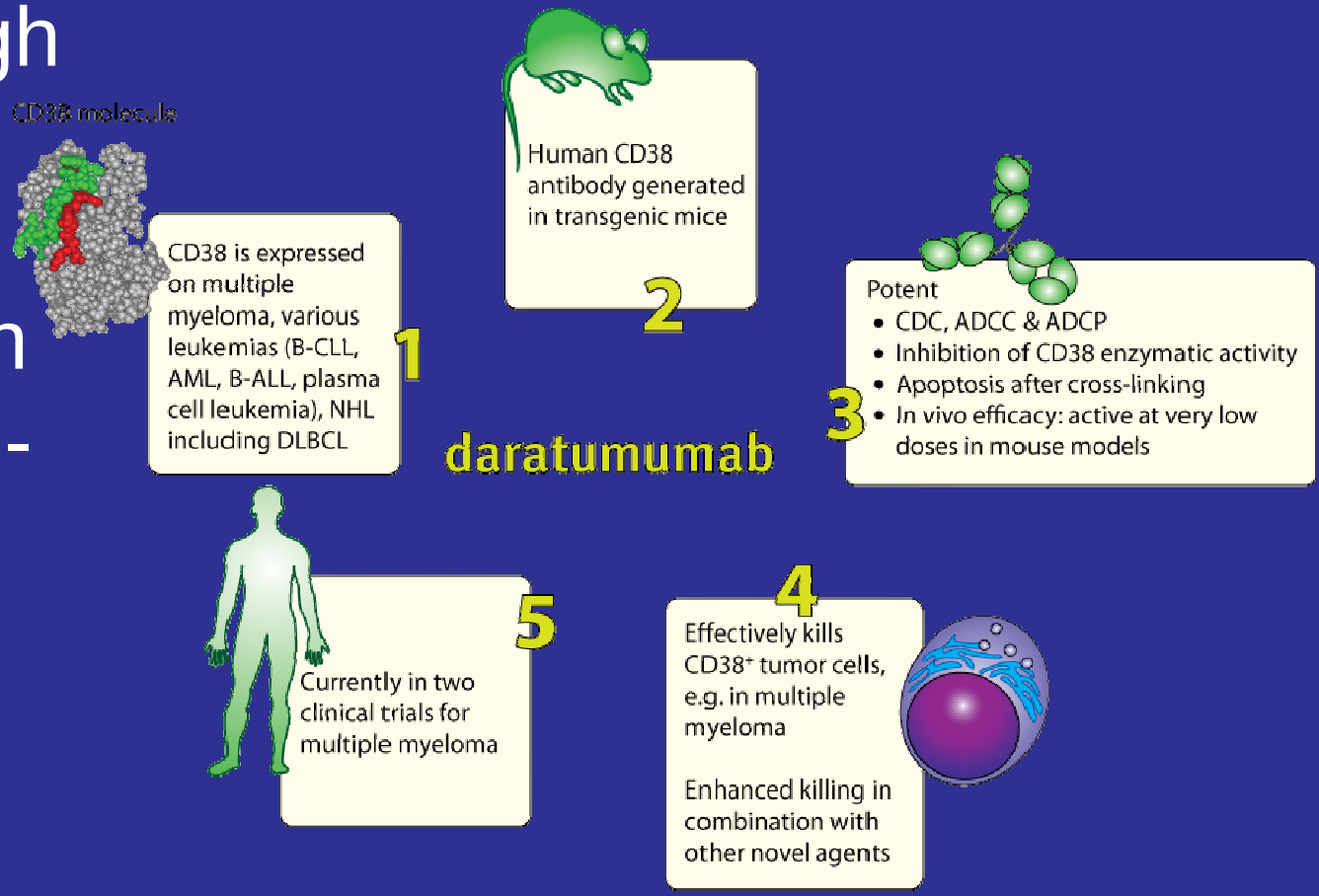
- AAG binds 520, may reduce free fraction



Lonial, S et al. 2013 IMW Poster # P-224.

Daratumumab

- Breakthrough therapy designation from FDA, in part for dual-refractory population



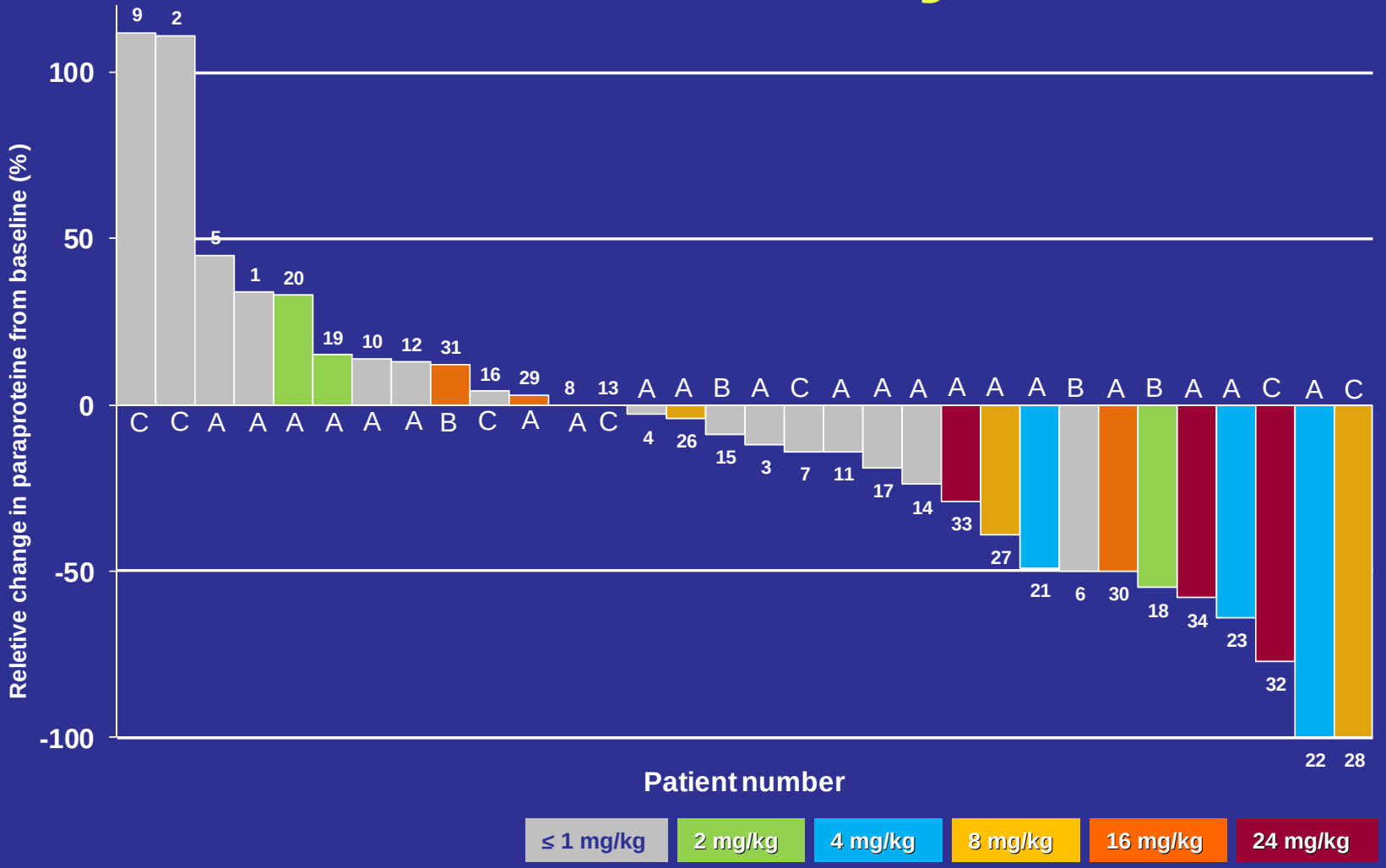
Plesner, T et al. 2012 ASH Abstract # 73.

Daratumumab: Safety

- Infusion-related reactions
  - 26% with first infusion; decreased with later tx
  - Two events were grade 3; others grade 1-2
    - Onset usually within 3-4 hours
    - Five late reactions (2 bronchospasms in patients with prior history of asthma or COPD, 1 each of headache, dyspnea, and fever)
- Dose-dependent decrease in NK cells

Plesner, T et al. 2012 ASH Abstract # 73.

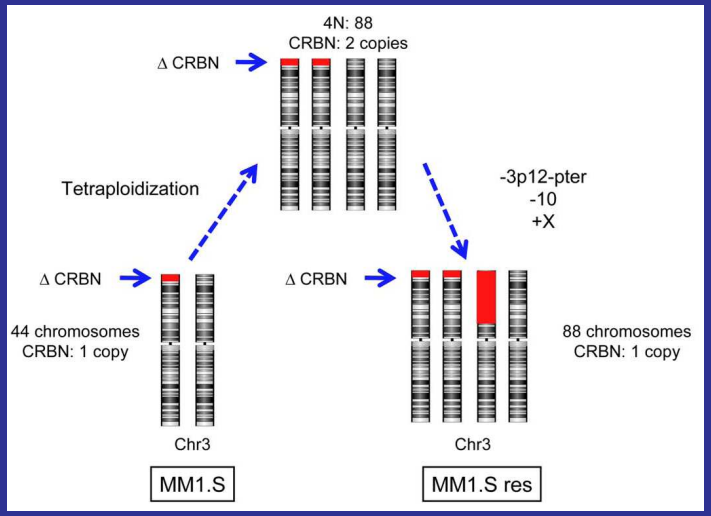
Daratumumab: Efficacy Data

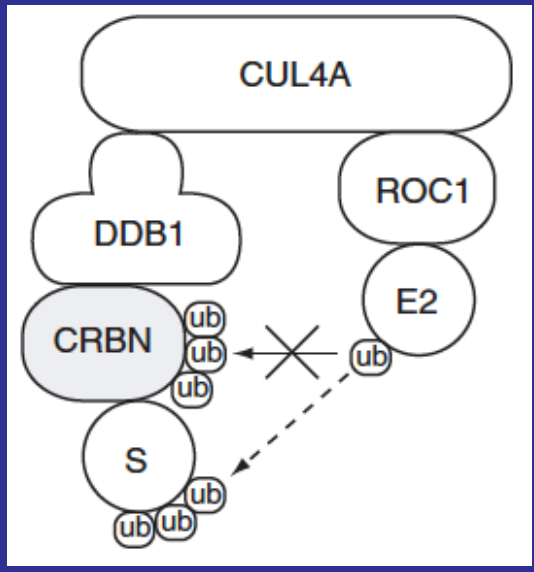


Plesner, T et al. 2012 ASH Abstract # 73.

Need for Biomarker Approaches

- Activity of immunomodulatory drugs is dependent on Cereblon expression
- Reduced expression associated with resistance

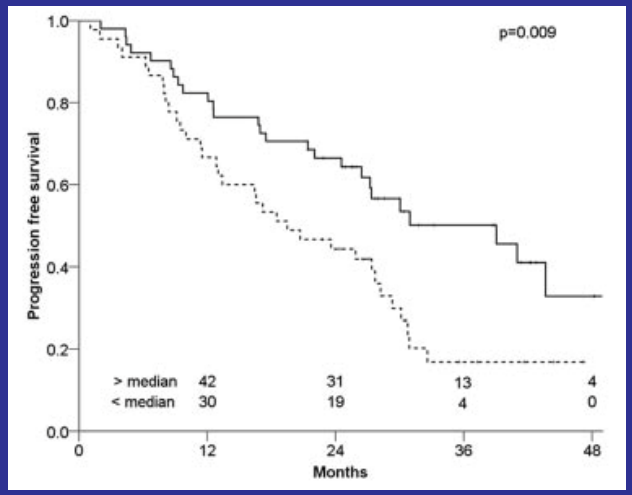


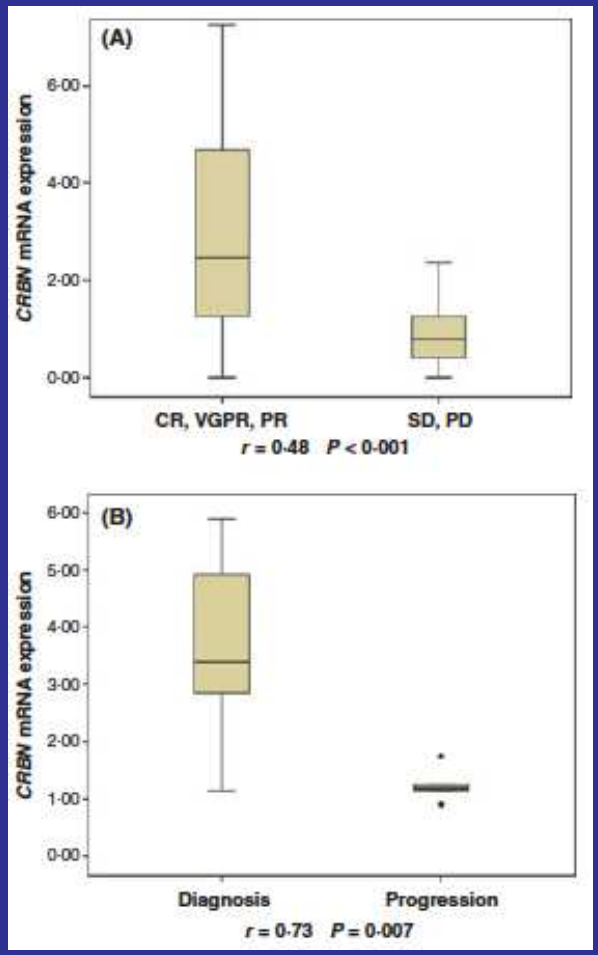


Zu, YX et al. Blood 118:4771, 2011.
Lopez-Girona, A et al. Leukemia 26:2326, 2012.

Cereblon as a Prognostic Marker

- CRBN expression related to outcomes with thal-based maintenance and len/dex-based induction therapies

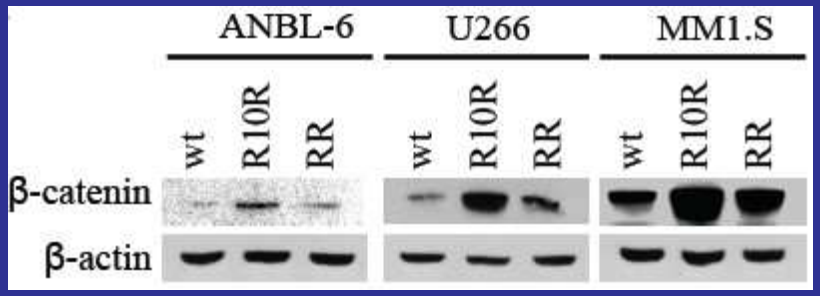


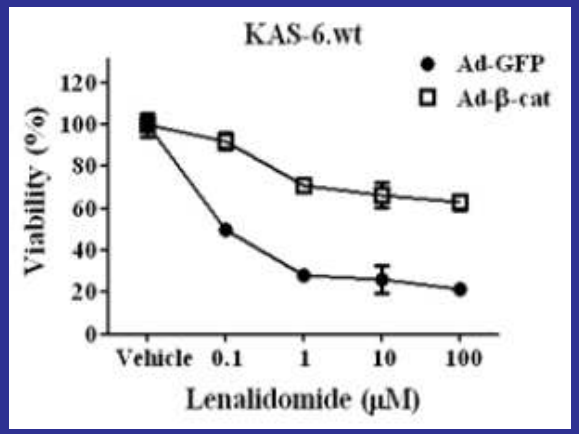


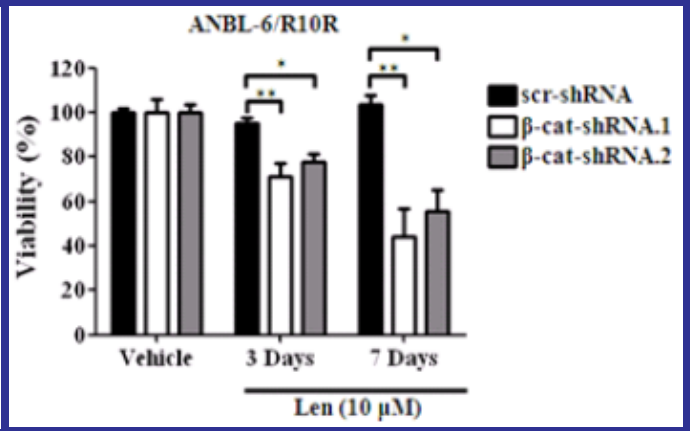
Broyl, A et al. Blood 121:624, 2013.
Heintel, D et al. Br J Haematol. 161:695, 2013.

Is Cereblon the Whole Story ?

- Since some len-refractory patients respond to pom, they must express CRBN
- Wnt/β-catenin activation seen even in the presence of CRBN suppression



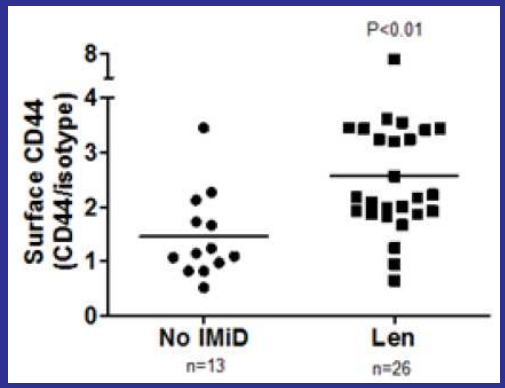


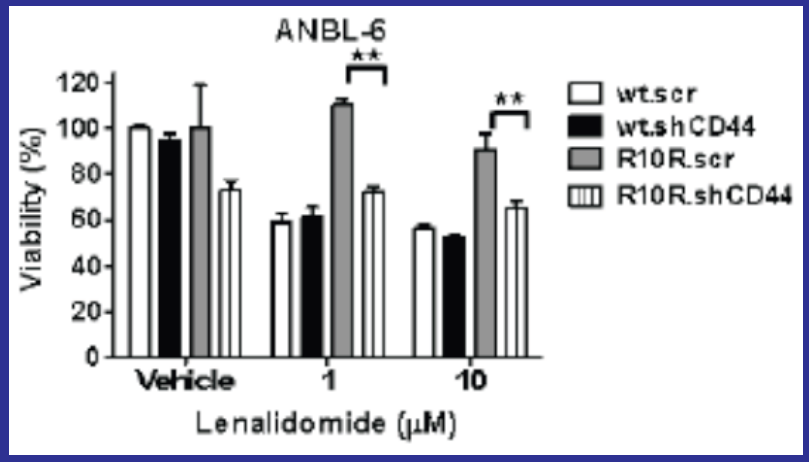


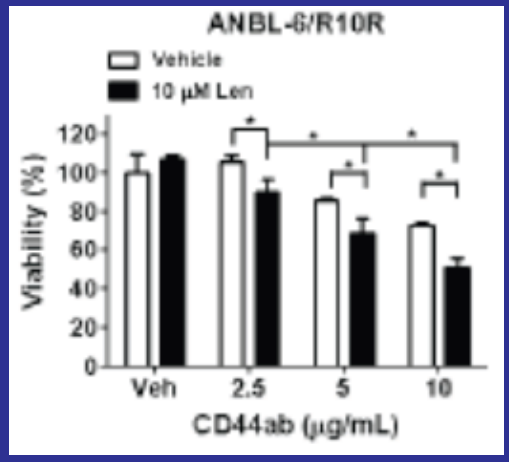
Bjorklund, CC et al. J Biol Chem. 286:11009, 2011.

Role for CD44 and CAM-DR

- The Wnt/β-catenin target CD44 is over-expressed; increases adhesion
- Suppression of CD44 with an shRNA or monoclonal antibody restores len sensitivity

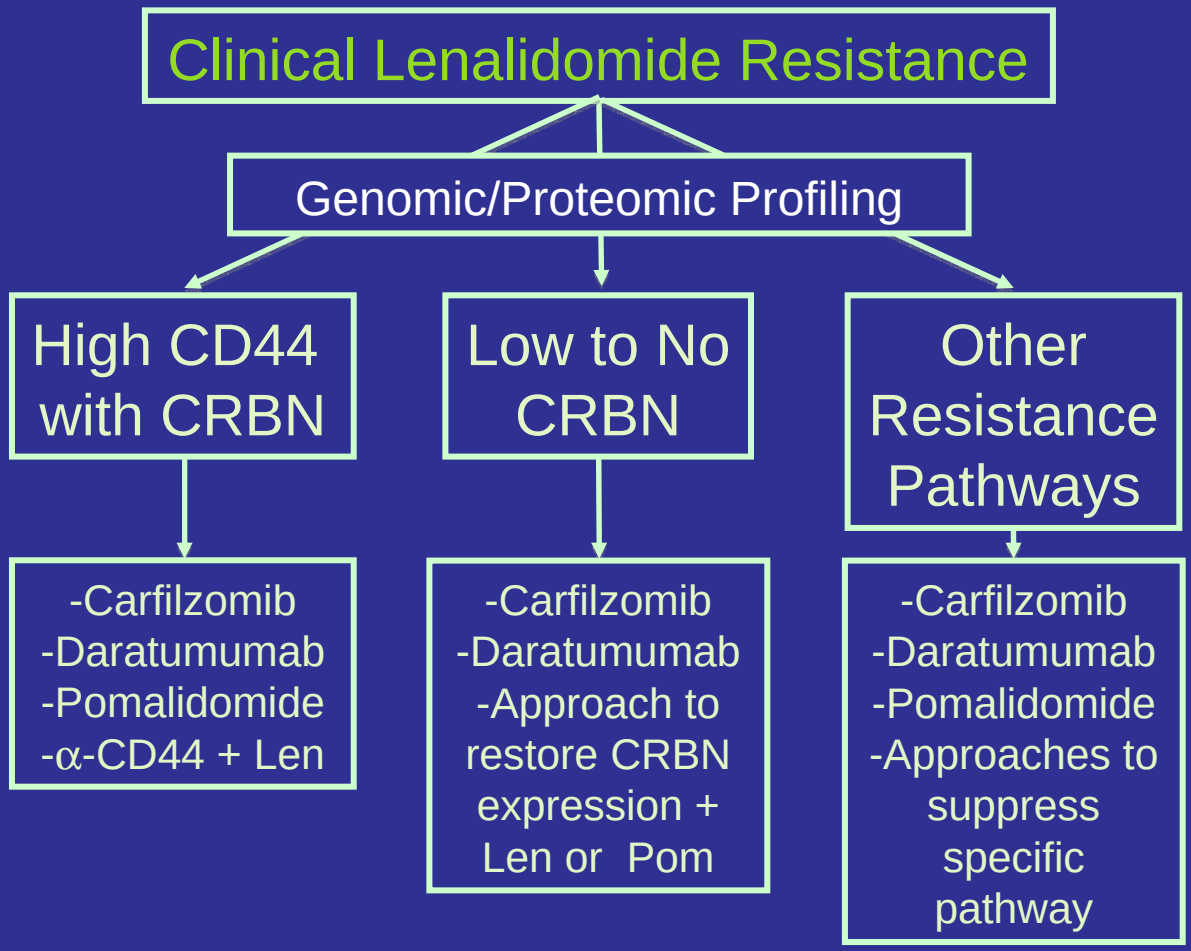




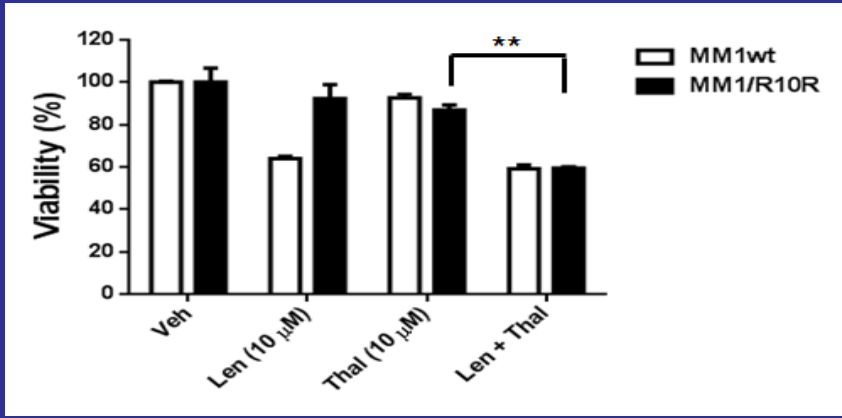


Bjorklund, CC et al. Leukemia *in press*, 2013.

Future Algorithm 1.0



Early Validation Efforts



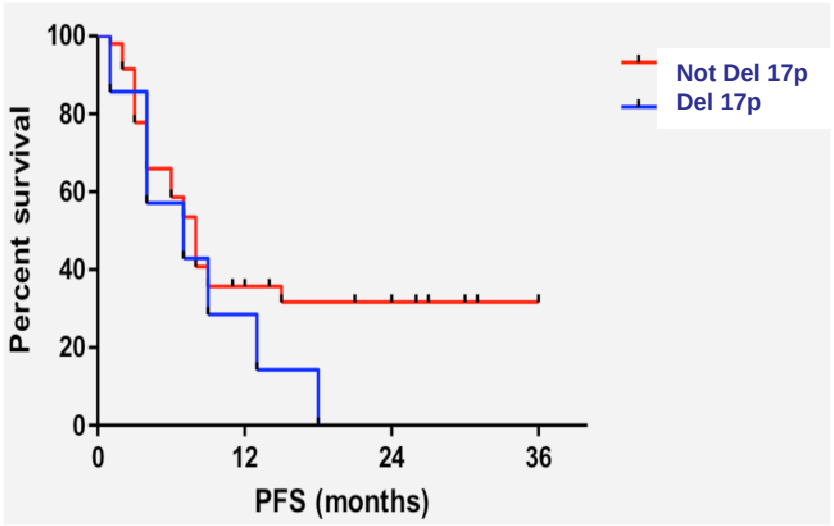
	N = 41*
Overall Response	**13 (34%)**
Stable Disease	12 (29%)
Minimal Response	8 (20%)
Partial Response	11 (27%)
VGPR	1 (2%)
CR / nCR	2 (5%)
Progressive Disease	7 (17%)

- Thal (inhibits Wnt/β-catenin) overcomes len resistance pre-clinically
- CBR 51% in len-refractory disease with len/thal/dex

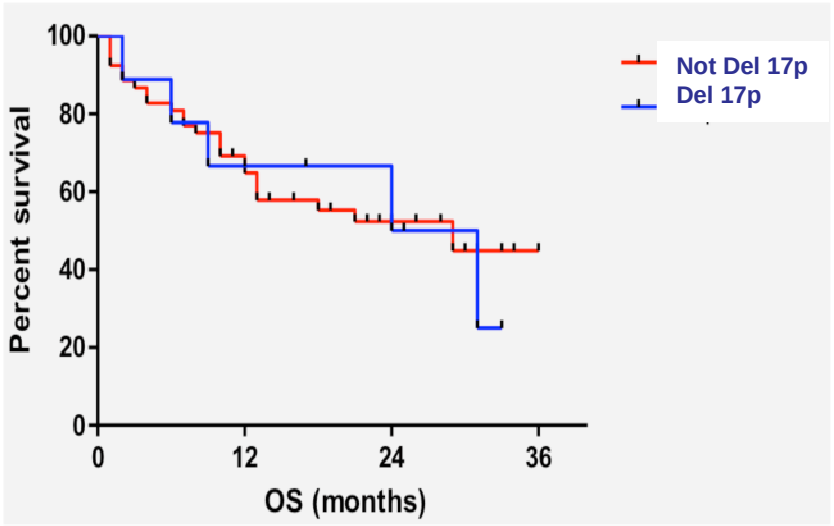
Shah, JJ et al. 2012 ASH Abstract # 75.

Efficacy in High Risk Patients

Progression Free Survival



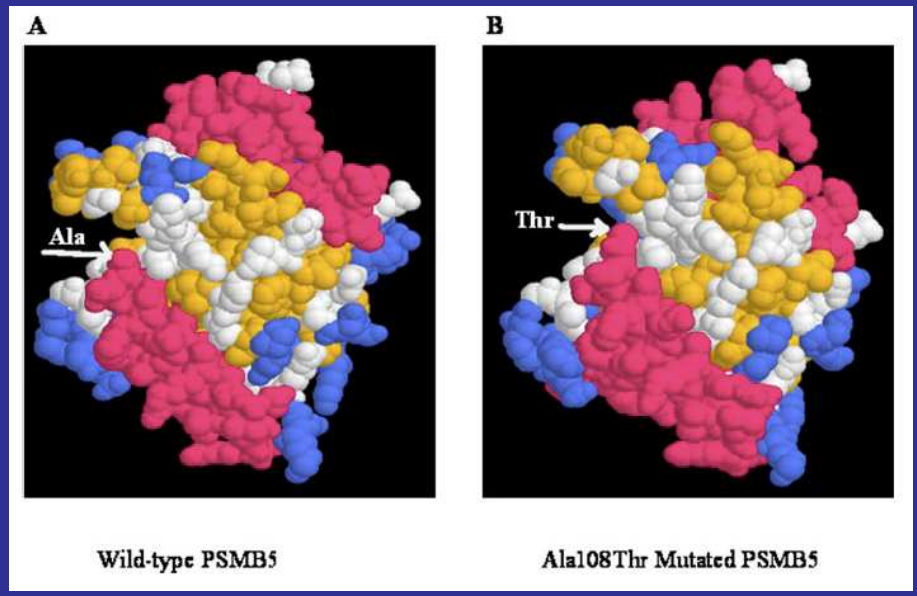
Overall Survival



Shah, JJ et al. 2012 ASH Abstract # 75.

Bortezomib Resistance Models

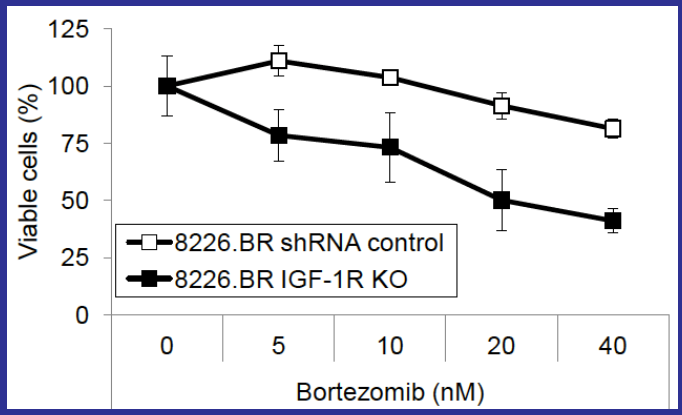
- Initial models suggested role for mutation of PSMB5 bortezomib binding pocket
- However, studies of primary samples have not shown β5 mutations in patients with clinical resistance

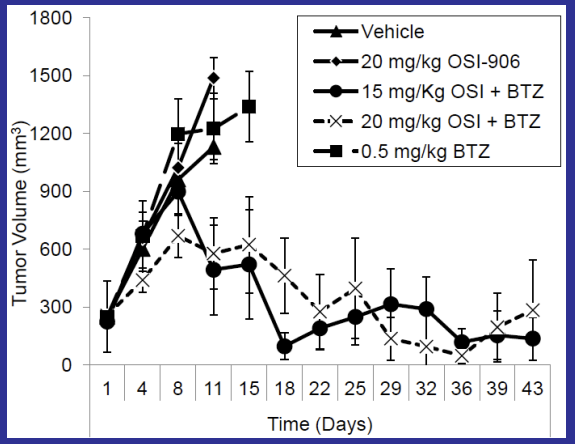


Lu, S et al. J Pharmacol Exp Ther. 326:423, 2008.
Lichter, DI et al. Blood 120:4513, 2012.

Possible Roe for IGF-1/IGF-1R

- Models developed without β5 mutations
- GEP showed prominent dysregulation of autocrine/paracrine IGF-1 loops with over-expression of IGF-1R
- Suppression of IGF-1R overcame bortezomib resistance *in vivo*





Kuhn, DJ et al. Blood 120:3260, 2012.

Conclusions

- Patients with relapsed myeloma that is refractory to bortez & len have a poor prognosis; unmet medical need
- Approvals of carfilzomib & pomalidomide represent important advances; combination regimens will enhance their activity
- Novel drugs with new mechanisms of action are also needed; ARRY-520 & daratumumab represent promising early candidates

Future Directions

- Need to develop more *in vitro* and *in vivo* models of drug resistance to understand the molecular pathobiology
- This will allow for development of novel agents that will work in a rational, biomarker-driven approach, and that can be personalized to the resistance mechanisms that predominate in each patient's disease