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Relapsed and Refractory Multiple Myeloma

Chilean Society of Hematology

October 2014

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida

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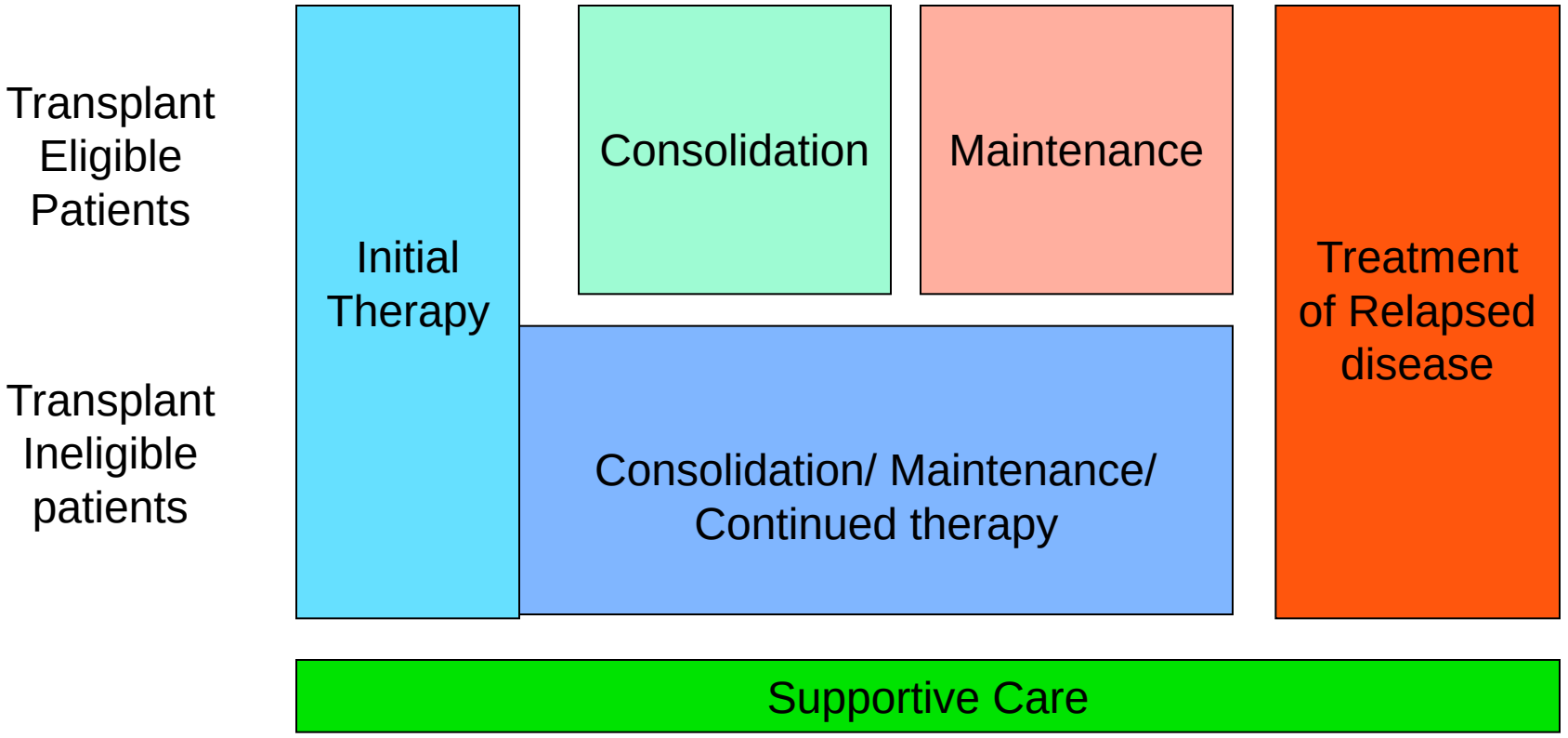
Managing myeloma: the components



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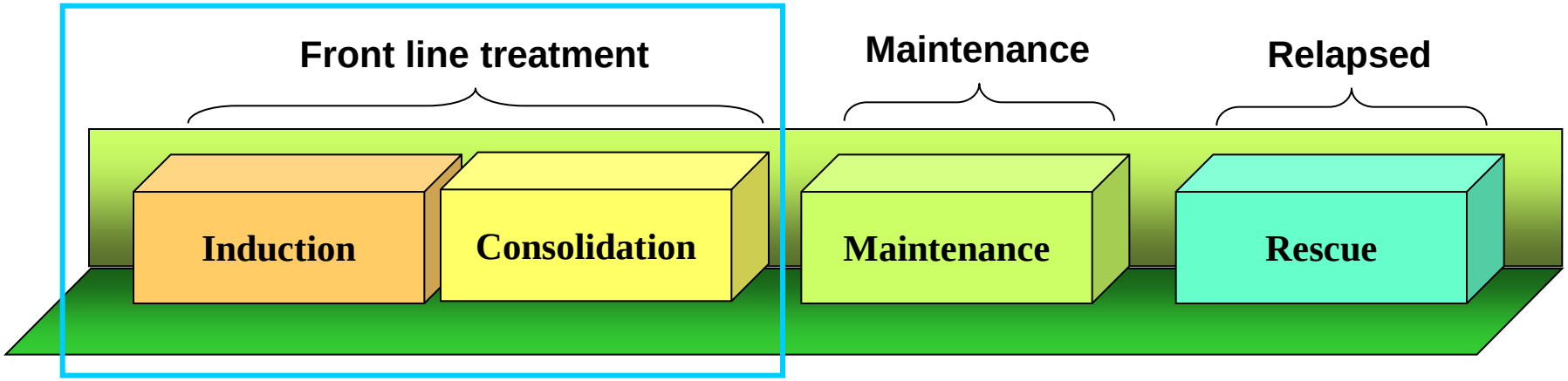
Treatment sequence



VAD DEX	SCT	Nothing Prednisone Thalidomide	Few options

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RELAPSE

- With prolonged survival in most patients with myeloma, relapse therapy is more important than ever
  - Approach must now take into account long term thinking
- Overall approach must be:
  - Evidence based
  - Rational
  - Individualized to patient
- I don’t really believe in “standard second line” therapy
- A strategy to choose the best therapy needs to address multiple issues
- Ask yourself the following questions:

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Question #1: Do I really need to treat this patient?

- Spectrum of MGUS, Asymptomatic (smoldering) MM and true MM
- Recall the importance of
  - Calcium
  - Renal insufficiency
  - Anemia
  - Bone Disease

- But for many patients, this may be too “late” – consider other factors…

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Question #2: Are the Light Chains Elevated or Climbing?

- **Light chains rising often heralds the relapse before clinically apparent**
- **Initiating therapy earlier when light chains are climbing may prevent renal injury**
- **Consider an absolute level of 100 (involved over uninvolved) to be reason to treat**
- **Also consider when 25% rise occurs twice**

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Question #3: Does the patient have High Risk Disease?

- Recall the importance of risk stratification in myeloma and its varied presentation
- Relapse occurs more quickly and aggressively in high risk patients
- Close monitoring and rapid institution of therapy is critical
- More likely require longer term (or even continuous) therapy
- Standard: fewer drugs at once, more likely sequential

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Question #4: What did I use the last time?

- Depth of response
  - How rapidly and successfully did it work
    - CR, VGPR, PR, MR, SD
- Duration of Response
  - How long did it last?
- If depth and duration reasonable, consider retreating with same regimen – knowing it will be less effective

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Question #5: How well tolerated was the previous therapy?

- Key areas of tolerability
  - Neuropathy
  - Cytopenias with sequelae
  - Fatigue
  - Other
- Did it lead to dose reductions or discontinuation?
- To what extent did it impair quality of life?

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Question #6: Have I employed the Big Three?

- **Thalidomide – little cytopenias, ok in renal dz**
  - **Neuropathy, fatigue, thrombosis, constipation**
- **Bortezomib – manageable cytopenias, ok in renal dz**
  - **Neuropathy, IV/SC route (weekly)**
- **Lenalidomide – little neuropathy**
  - **Fatigue, may affect stem cell collection**
  - **Concern of MDS or SPM**

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Question #7: Should I use carfilzomib or pomalidomide?

- **Recently FDA approved agents for relapsed/refractory MM**
- **Highly active, well tolerated**
- **Carfilzomib is novel proteasome inhibitor with minimal neurotoxicity, effective even in bortezomib refractory disease**
- **Pomalidomide is novel immunomodulatory agent, oral and effective even in lenalidomide refractory disease**

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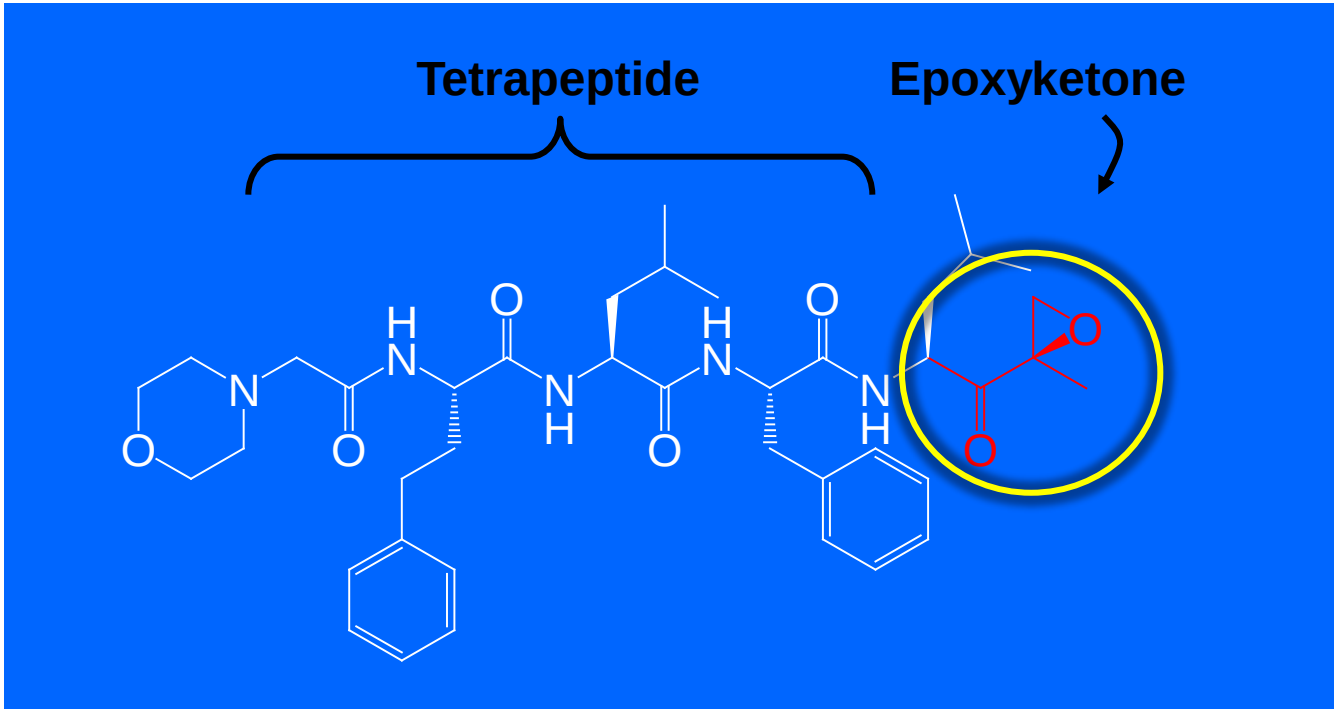
Carfilzomib: A Novel Agent Designed to Promote Selective and Sustained Proteasome Inhibition

- **Carfilzomib is a next-generation, selective proteasome inhibitor**
  - **Potent and sustained target suppression**
  - **Improved antitumor activity**
  - **Minimal off-target activity with low neurotoxicity**



Phase 2 study of single agent CFZ for R/R MM

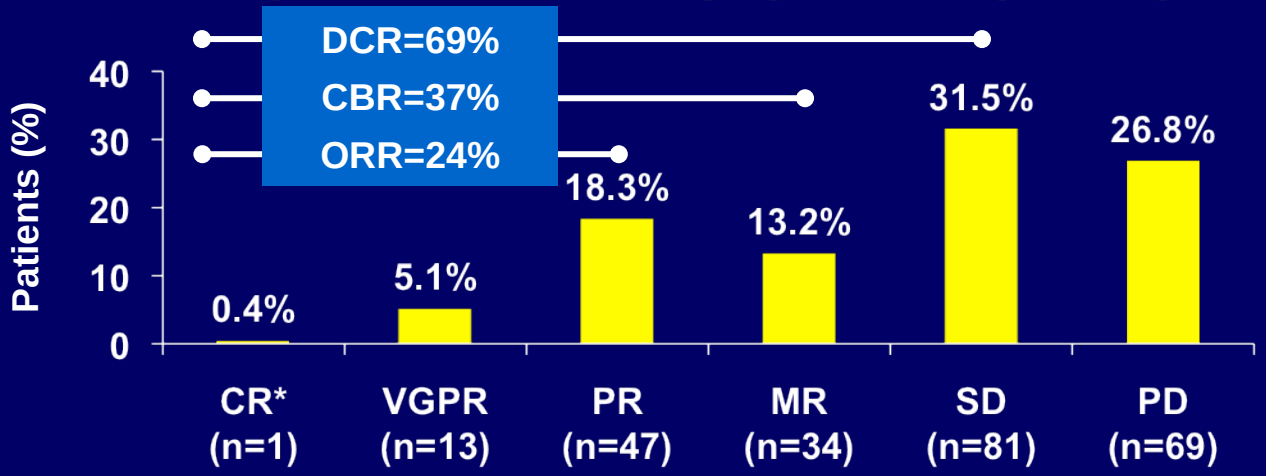
- **Population: ≥2 prior regimens, including BTZ, THAL or LEN; refractory to most recent therapy (median 5 prior therapies [range 1–20]; 99.6% prior BTZ; 94% prior LEN)**
- **Primary endpoint: overall response rate (ORR) (≥ partial response [PR])**

CFZ 20/27 mg/m²* (IV over 2–10 mins)

Cycles 1–12

28-day cycle

Response-evaluable population (n=257)



TTR: 1.9 mo (≥PR) and 1.0 mo (≥MR)

DOR: 7.8 mo (≥PR) and 8.3 mo (≥MR)

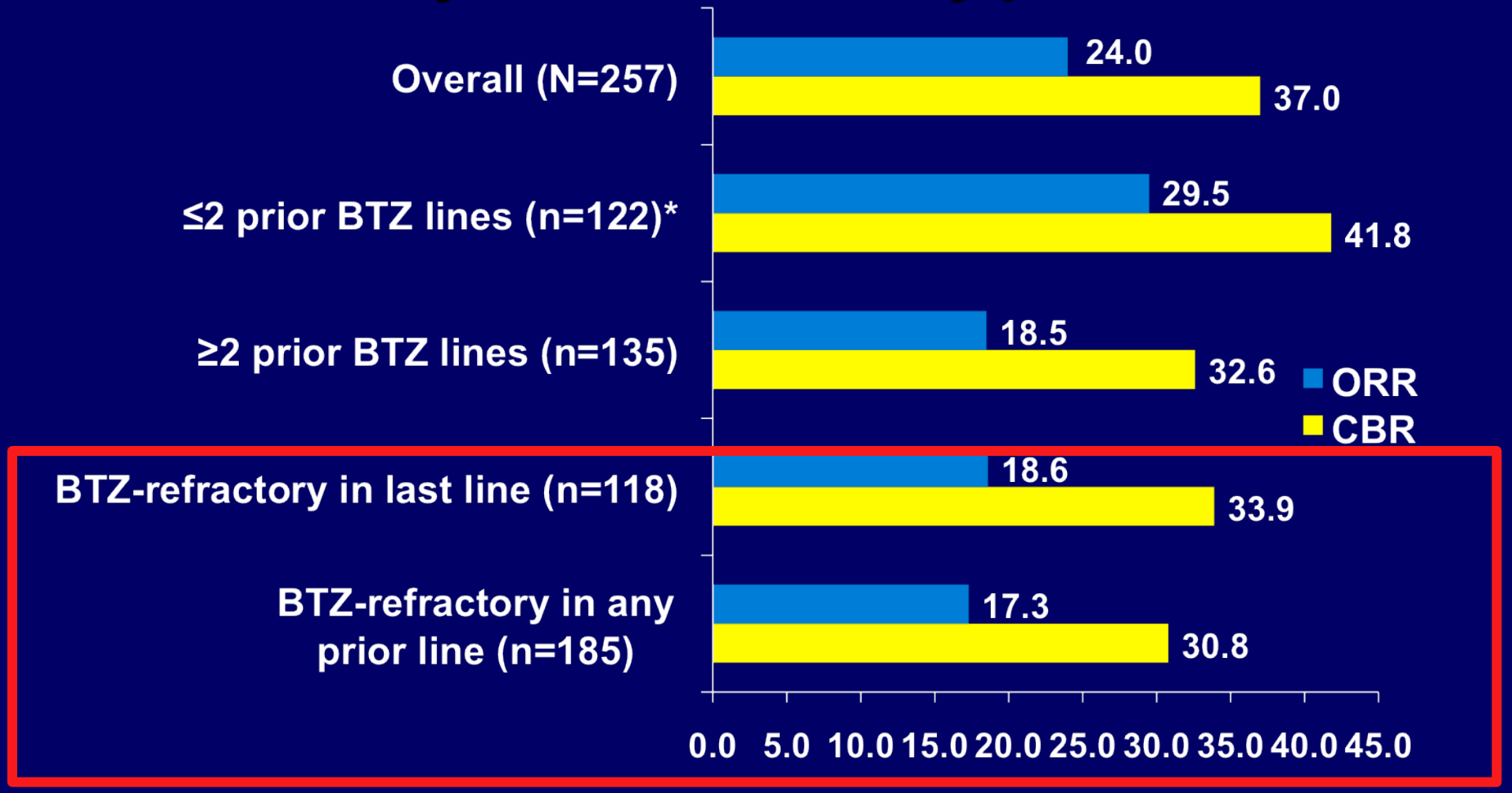
*Cycle 1 dosed at 20 mg/m², CFZ given at 27 mg/m² from Cycle 2 onwards. DEX 4 mg (PO/IV) administered before each CFZ dose in Cycle 1 and thereafter as required to prevent infusion reactions (non-therapeutic dose)

CR, complete response; DOR, duration of response; MR, minimal response; PD, progressive disease; SD, stable disease; TTR, time to response; VGPR, very good partial response

Note: Carfilzomib is an investigational product and is not licensed in the EU

Siegel DS, et al. Blood 2012;120:2817–2825

Phase 2 study of single agent CFZ for R/R MM: activity in BTZ-refractory patients



*1 patient did not receive prior BTZ

Note: Carfilzomib is an investigational product and is not licensed in the EU

Siegel D, et al. Blood 2012;120:2817–2825;
Siegel D, et al. J Clin Oncol 2011;29(Suppl);Abstract 8027 and poster presentation at ASCO 2011
Wang M, et al. Blood 2011;118:Abstract 3969 and poster presentation at ASH 2011

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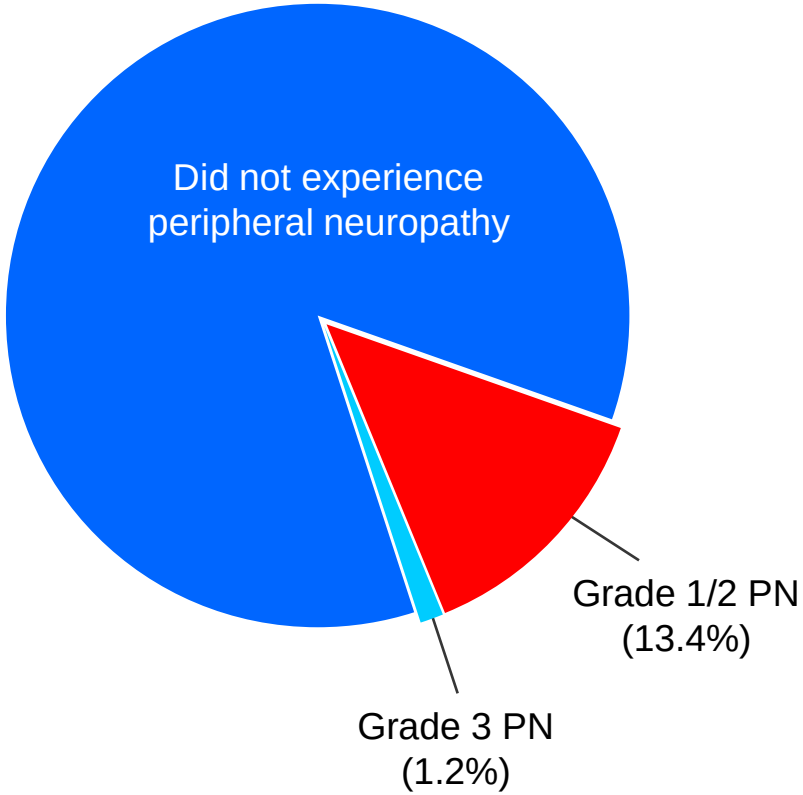
Neuropathy Was Infrequent and Not Dose Limiting

Pooled data from single-agent studies (003 / 004 / 005)

- **Peripheral neuropathy occurred infrequently across all single-agent studies***
  - **Only 6 patients (1.2%) experienced a Grade 3 PN event**
  - **No Grade 4 PN events**
- **Only 1 patient had drug discontinued for PN (study 004; BTZ-treated arm)**



*Includes the terms peripheral neuropathy, neuropathy, peripheral sensory neuropathy, peripheral motor neuropathy

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Phase III ASPIRE Trial

Randomized 1:1

N = 700

Stratification

- Prior bortezomib
- Prior lenalidomide
- β_2m

- Carfilzomib 27 mg/m^2 IV Day 1, 2, 8, 9, 15, 16 (20 mg/m^2 on Days 1, 2 of Cycle 1)
- Lenalidomide 25 mg PO Days 1–21
- Dexamethasone 40 mg PO or IV on Days 1, 8, 15, 22

Cycle = 28 days

- Lenalidomide 25 mg Days 1–21
- Dexamethasone 40 mg PO or IV on Days 1, 8, 15, 22

Cycle = 28 days

Primary End Point: PFS

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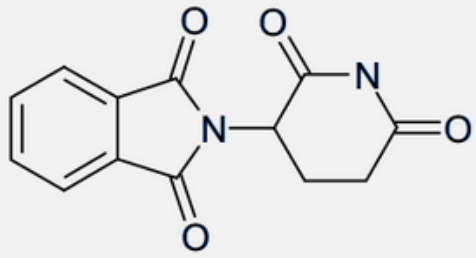
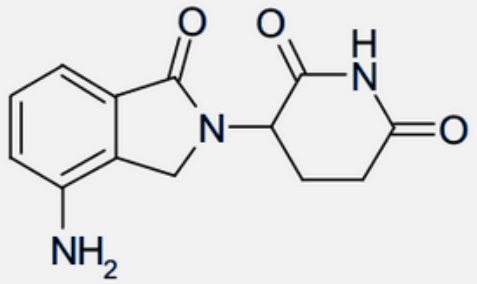
Molecular Structure of Thalidomide, Lenalidomide and Pomalidomide



Thalidomide

100-200 mg/d

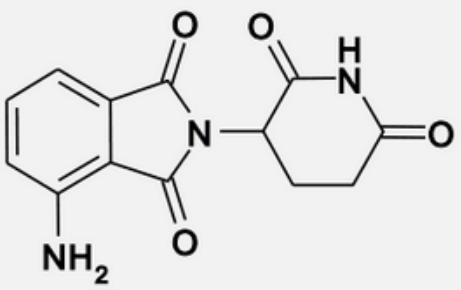
Neuropathy
Constipation
Sedation
DVT



Lenalidomide

15-25 mg/d

Myelosuppression
Skin rash
DVT



Pomalidomide

1-4 mg/d

Structurally similar, but functionally different both qualitatively and quantitatively

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Myeloma Pomalidomide Summary

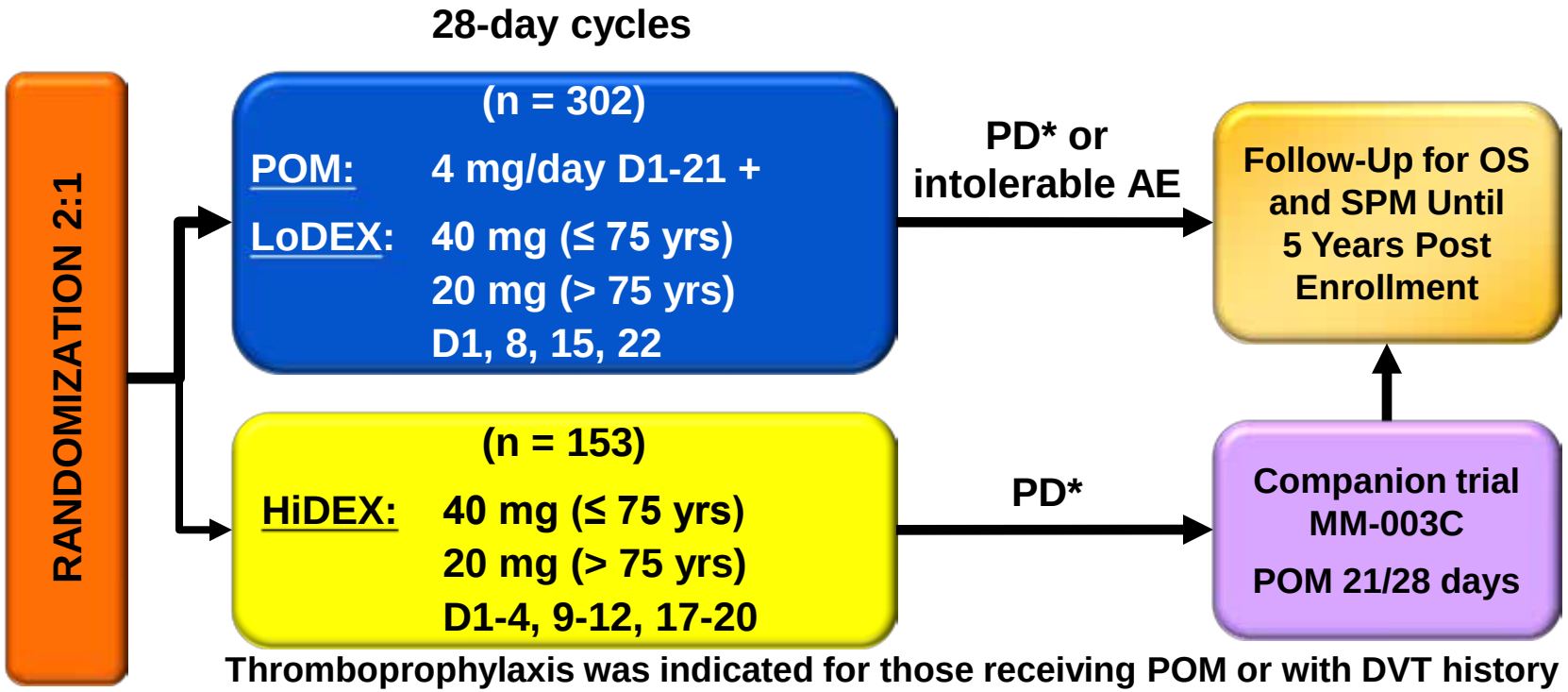
	Lacy Pom/Dex 1-3 reg	Lacy Pom/Dex Len ref	Richardson Pom+/- dex MM-002
[3] PR	63%	32%	28%
[3] MR	82%*	47%	52%

Median 3 prior regimens

Median 4-6 prior regimens

MM-003 Design: POM + LoDEX vs HiDEX

Refractory MM Pts Who Have Failed BORT and LEN



Stratification

- **Age (≤ 75 vs > 75 yrs)**
- **Number of prior Tx (2 vs > 2)**
- **Disease population**

*Progression of disease was independently adjudicated in real-time

Dimopoulos Blood 2012, 120(21): LBA-6

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MM-003: Key Eligibility Criteria

- All pts had to be refractory to last therapy
- At least 2 prior therapies
  - ≥ 2 consecutive cycles of LEN and BORT (alone or in combination)
  - Adequate prior alkylator therapy (SCT or ≥ 6 cycles or PD following ≥ 2 cycles)
- All pts must have failed LEN and BORT
  - Pt progressed on or within 60 days
  - Pt with PR must have progressed within 6 months
  - Intolerant to BORT
- Refractory or relapsed and refractory disease
  - Primary refractory: never achieved > PD to any therapy
  - Relapsed and refractory: relapsed after having achieved ≥ SD for ≥ 2 cycles of Tx to at least one prior regimen and then developed PD ≤ 60 days of completing their last therapy

Dimopoulos Blood 2012, 120(21): LBA-6

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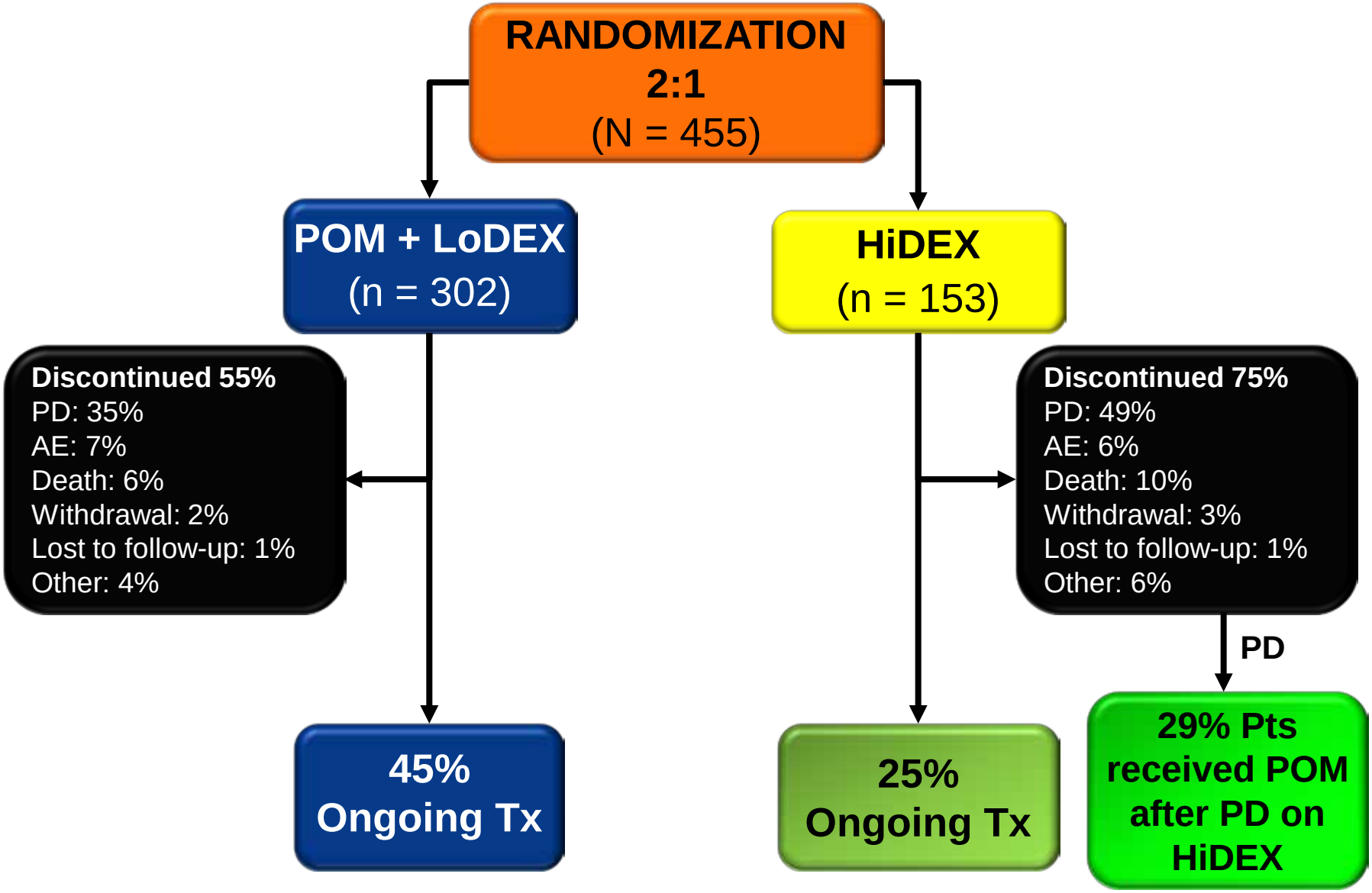
MM-003: Patient Disposition*



*As of final PFS analysis, Sept 7, 2012.

Dimopoulos Blood 2012, 120(21): LBA-6

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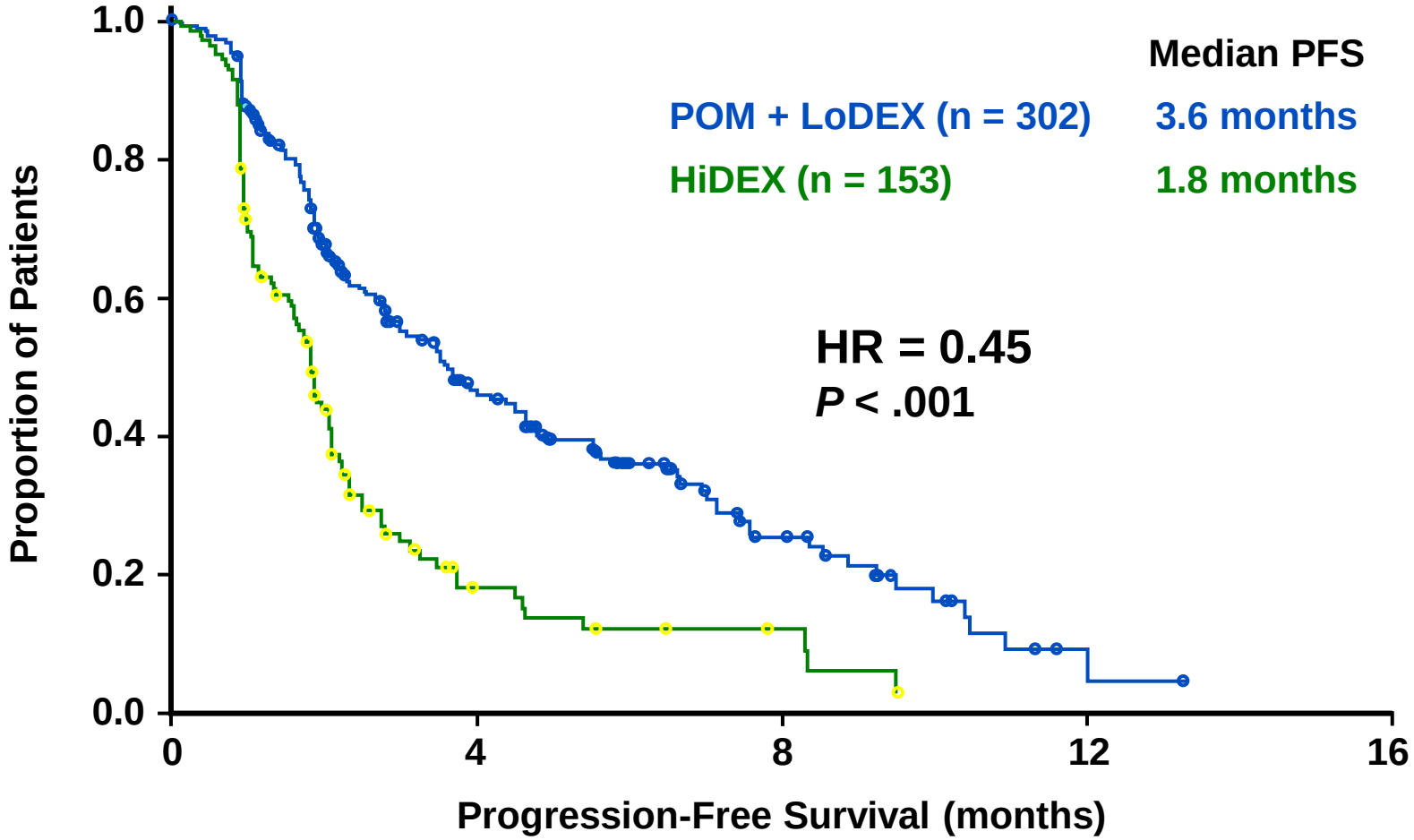
MM-003: Progression-Free Survival *ITT Population*



Based on adjudicated data; IMWG criteria

Dimopoulos Blood 2012, 120(21): LBA-6

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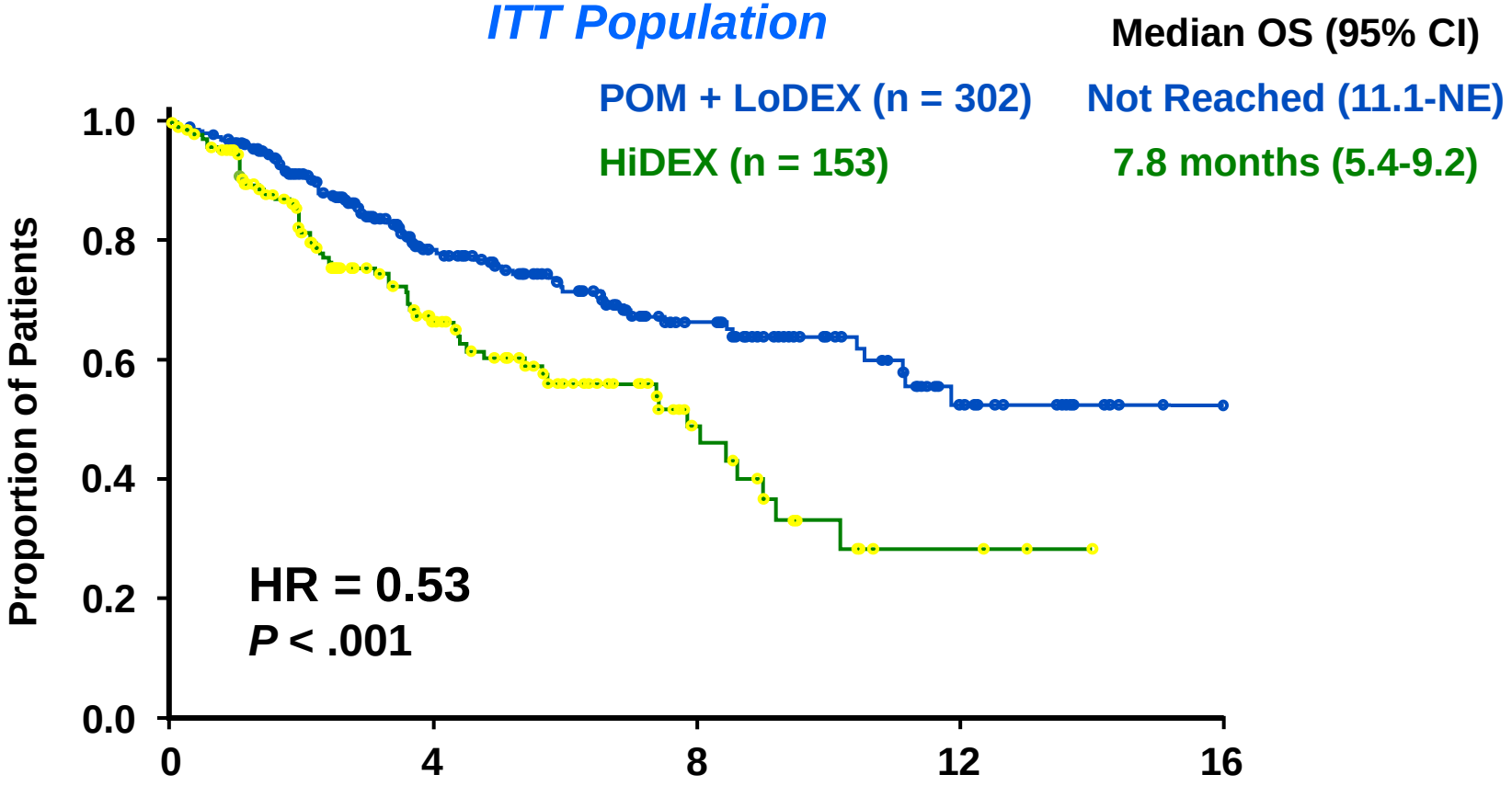
MM-003: Overall Survival

ITT Population



29% of pts received POM after progression on HiDEX

NE, not estimable

Dimopoulos Blood 2012, 120(21): LBA-6

MM-003: Ongoing Evaluation of Response
ITT Population

Response, %	POM + LoDEX (n=302)	HiDEX (n=153)	P value
ORR (≥ PR)	21	3	< .001
VGPR	3	1	—
≥ MR	37	8	—
≥ SD	81	60	—
Median DOR*, m (95% CI)	10.1 (6.2 – 12.1)	NE	—

As of Nov 9, 2012

- **PFS of ≥ MR in POM + LoDEX: 8.5 months**

Response based on IMWG criteria, except for MR (based on EBMT criteria)
*** KM median, patients with ≥ PR only**
NE, not estimated due to too few responders

Dimopoulos Blood 2012, 120(21): LBA-6

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Pomalidomide - Practical

- **Similar to lenalidomide with slightly less myelotoxicity and fatigue**
- **Dosing range 2-4mg**
- **Thromboprophylaxis necessary**
- **Feasible in combination**

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Factors in the selection of relapsed therapy

Patient Related Factors

- Age
- Performance Status
- Renal insufficiency
- Poor Marrow Reserve (previous myelosuppression)
- Neuropathy (pre-existing)
- Other comorbidities – cardiac, diabetes

Disease Related Factors

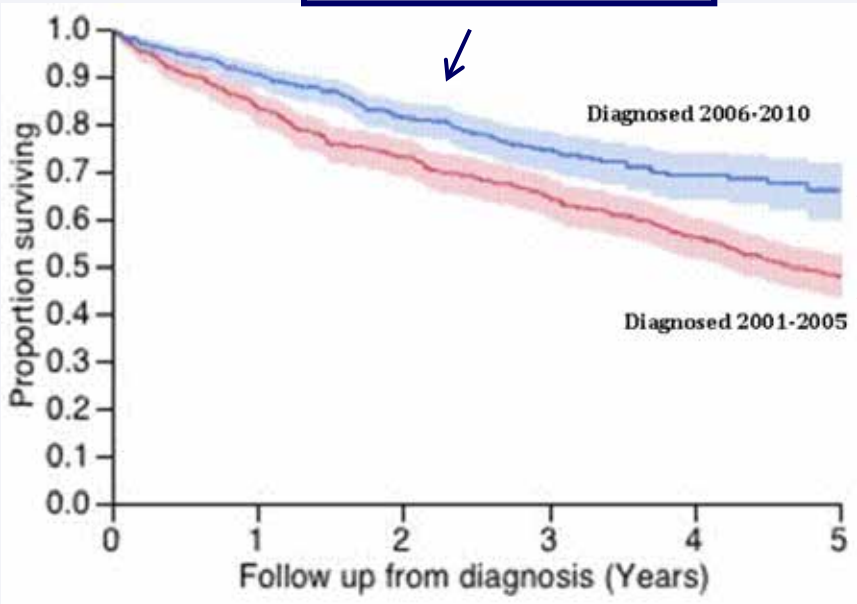
- Risk Status (high, intermediate, standard)
- Aggressivity of relapse (rapid M protein growth, organ damage, plasma cell leukemia)
- Depth and Duration of response to previous therapy

Treatment Related Factors

- Refractoriness to previous therapies
- Single agent vs combination therapies
- Mode of administration (PO, SQ, IV)
- Cost
- Toxicity – myelosuppression, neuropathy, thrombosis, GI tolerance
- Risk of Second Primary Malignancy

IMPACT OF NOVEL THERAPY 2012/2013

Median 7.3 years



5 YEAR SURVIVAL BY AGE

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

2012 ASH Abstract #3972 Kumar et al

Monoclonal Antibodies in MM

Target	mAb	Stage of development
Surface molecules		
CS1/SLAMF7	Elotuzumab	Phase 2/3
CD38	Daratumumab	Phase 1/2/3
	SAR650984	Phase 1/2
	MOR202	Phase 1/2
CD74	Milatuzumab	Phase 1/2
CD40	Dacetuzumab	Phase 1
CD56	Lorvotuzumab mertansine	Phase 1
CD138	BT062	Phase 1
Signaling molecules		
IL-6	Siltuximab	Phase 3
RANKL	Denosumab	Phase 3
B cell activating factor (BAFF)	Tabalumab	Phase 2/3
VEGF	Bevacizumab	Phase 2
DKK1	BHQ880	Phase 2

Richardson et al. et al. IMW 2013 (Abstract P-214), poster presentation
Plesner et al. ASH 2013 (Abstract 1987), poster presentation
Martin et al. ASH 2013 (Abstract 284), oral presentation
http://www.clinicaltrials.gov/ct2/show/NCT00421525
http://www.clinicaltrials.gov/ct2/show/NCT00079716

http://www.clinicaltrials.gov/ct2/show/NCT00346255
http://www.clinicaltrials.gov/ct2/show/NCT01001442
Wong et al. ASH 2013 (Abstract 505), oral presentation
Hageman et al. Ann Pharmacother 2013;47:1069-74

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Anti CD 38 Monoclonal Antibodies

- **Most promising agents for myeloma (according to 80% vote at International Myeloma Working Group)**
- **2 currently in later development – Daratumumab and SAR 650984**
- **Both have significant single agent activity and can be combined**
- **Will this be the “rituximab” of Myeloma??**

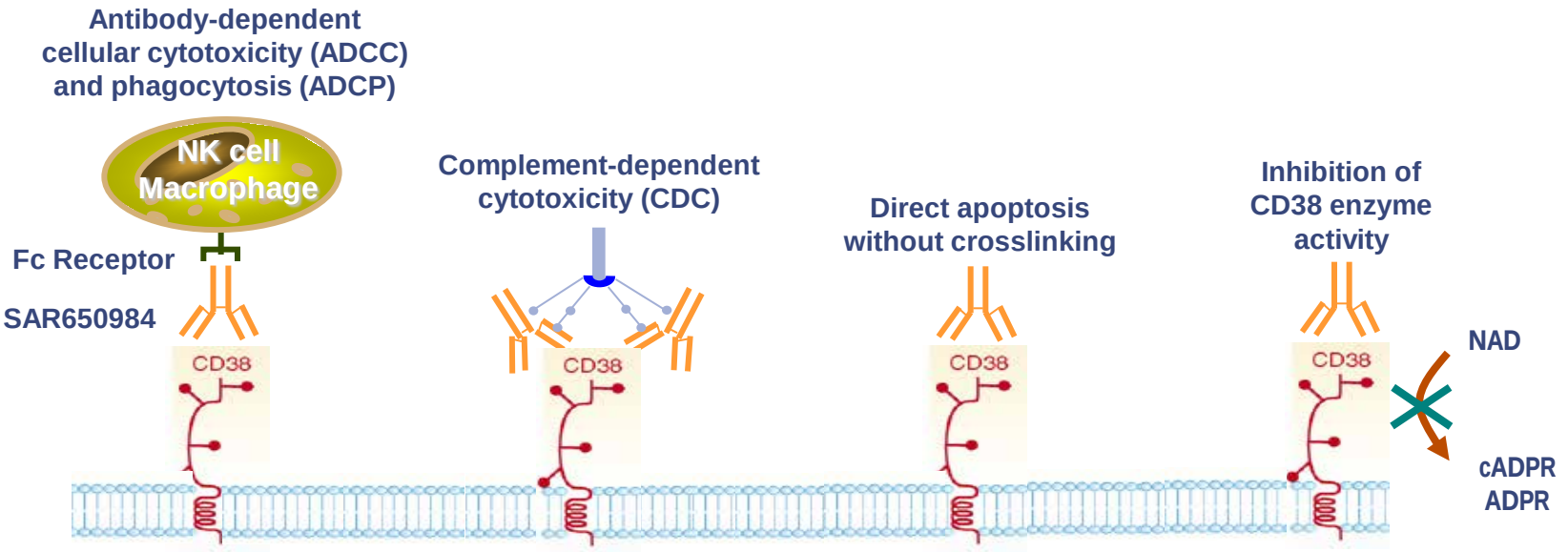
A Phase I trial of SAR650984, a CD38 monoclonal antibody, in relapsed or refractory multiple myeloma

Joseph Mikhael,[1] Stephen Strickland,[2] Martha Glenn,[3] Eric Charpentier,[4] Karl Hsu,[4] Thomas Martin[5]

[1]Mayo Clinic, Scottsdale, AZ, USA; [2]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [3]Huntsman Cancer Institute, Salt Lake City, UT, USA; [4]Sanofi Oncology, Cambridge, MA, USA; [5]University of California at San Francisco, San Francisco, CA, USA

Introduction to CD38 and SAR650984

- CD38 is a 45 kD type II transmembrane glycoprotein which functions as a receptor and an ectoenzyme
- Widely expressed in many hematologic malignancies including multiple myeloma, NHL, AML, and CLL[1-5]
- SAR650984 is a humanized IgG1 monoclonal antibody that binds selectively to a unique epitope on the human CD38 receptor
  - Four potential modes of action:



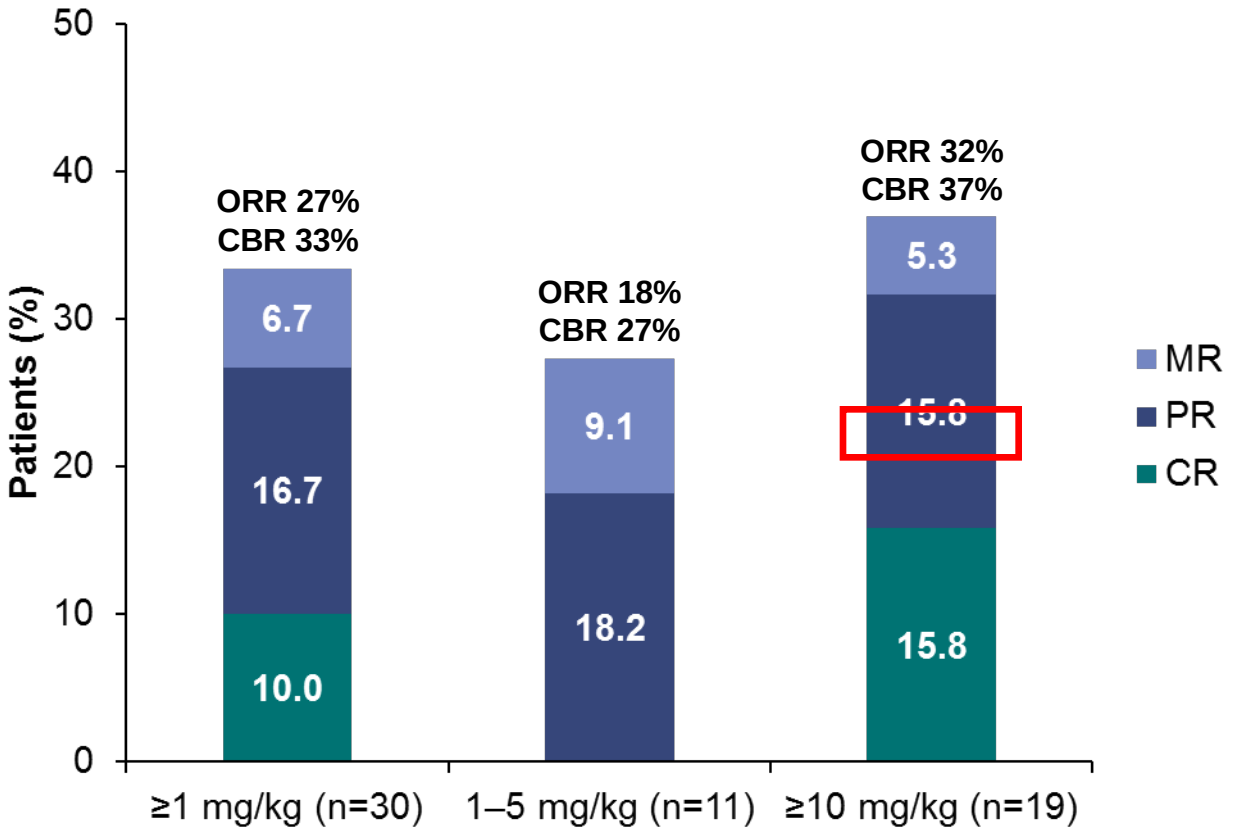
1. Lin, et al. Am J Clin Pathol 2004;121:482–8.
2. Angelopoulou, et al. Eur J Haematol 2002;68:12–21.
3. Schwonzen, et al. Br J Haematol 1993;83:232–9.
4. Keyhani, et al. Leukemia Res 1999;24:153–9.
5. Domingo-Domènech, et al. Haematologica 2002;87:1021–7.

Demographics

	SAR650984 dose level (mg/kg) and schedule								
	≤0.1 q2W	0.3 q2W	1 q2W	3 q2W	5 q2W	10 q2W	10 q1W	20 q2W	Overall
No. of patients	5	5	3	5	3	6	6	7	40
Median age, years (range)	65 (54–77)	62 (41–76)	61 (55–74)	65 (60–74)	64 (58–64)	65 (61–70)	65 (40–76)	68 (49–74)	65 (40–77)
Median time since diagnosis, years (range)	3.7 (2–8)	7.0 (3–12)	8.0 (7–9)	8.0 (3–14)	4.0 (4–10)	5.5 (2–9)	9.5 (4–16)	5.0 (4–8)	6.5 (2–16)
No. of prior therapies	5.0 (3–9)	7.0 (3–12)	8.0 (7–9)	8.0 (3–14)	4.0 (4–10)	5.5 (2–9)	9.5 (4–16)	5.0 (4–8)	6.5 (2–16)
Bortezomib	5 (100)	5 (100)	3 (100)	5 (100)	3 (100)	6 (100)	6 (100)	7 (100)	40 (100)
Carfilzomib	0	0	0	3 (60)	1 (33)	4 (67)	5 (83)	4 (57)	17 (43)*
Lenalidomide	3 (60)	5 (100)	3 (100)	5 (100)	3 (100)	6 (100)	6 (100)	6 (86)	37 (93)
Pomalidomide	0	0	2 (67)	0	2 (67)	0	2 (33)	3 (43)	9 (23)*
Thalidomide	5 (100)	5 (100)	2 (67)	3 (60)	2 (67)	5 (83)	4 (67)	5 (71)	31 (78)

***66% of patients had received Carfilzomib and/or Pomalidomide**

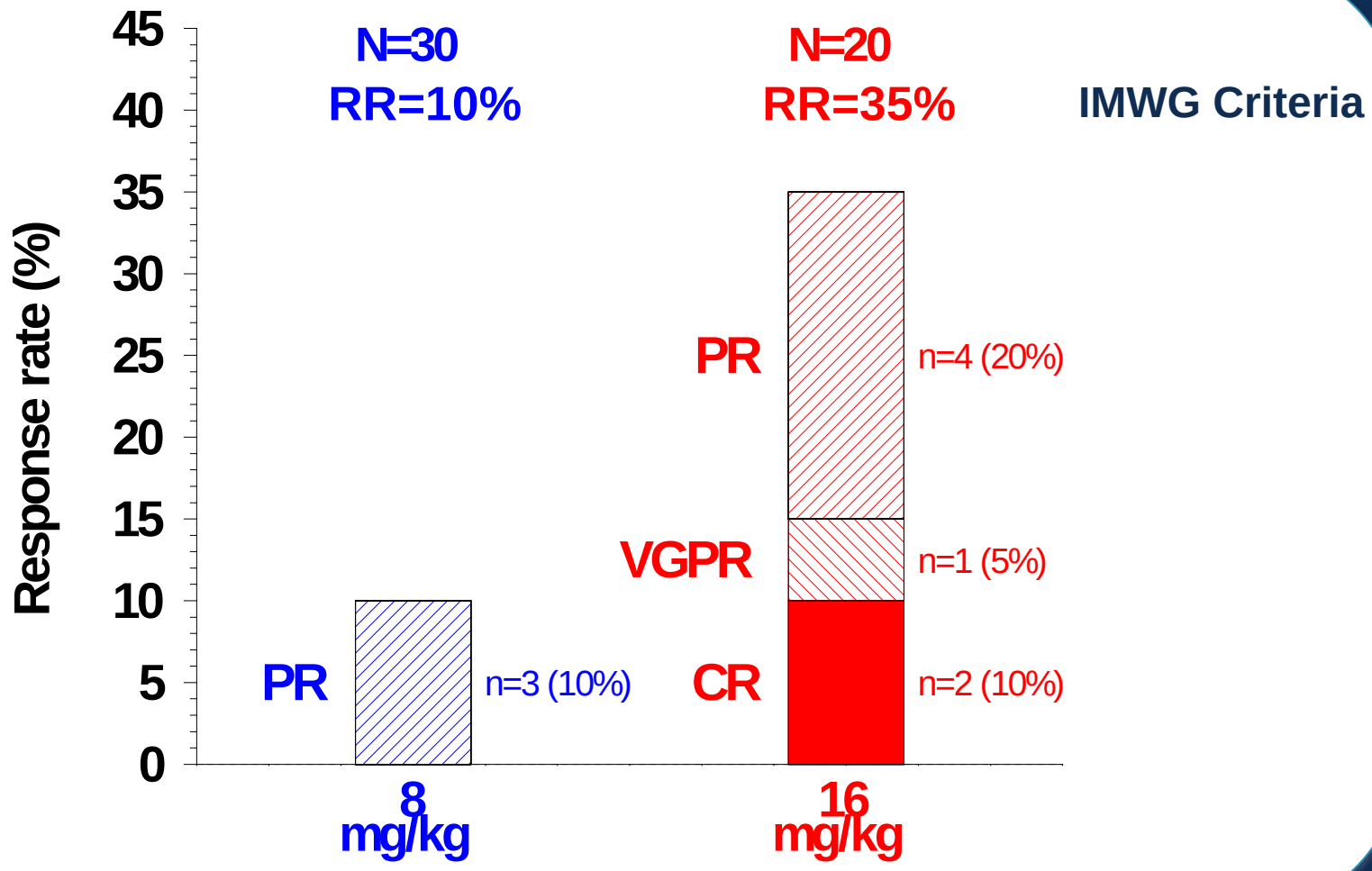
Response Summary*(dose cohorts ≥1 mg/kg)



*According to EBMT/IMWG criteria.

CBR, clinical benefit rate (at least MR); CR, complete response;
MR, minimal response; ORR, objective response rate (at least PR); PR, partial response

DARA - Response



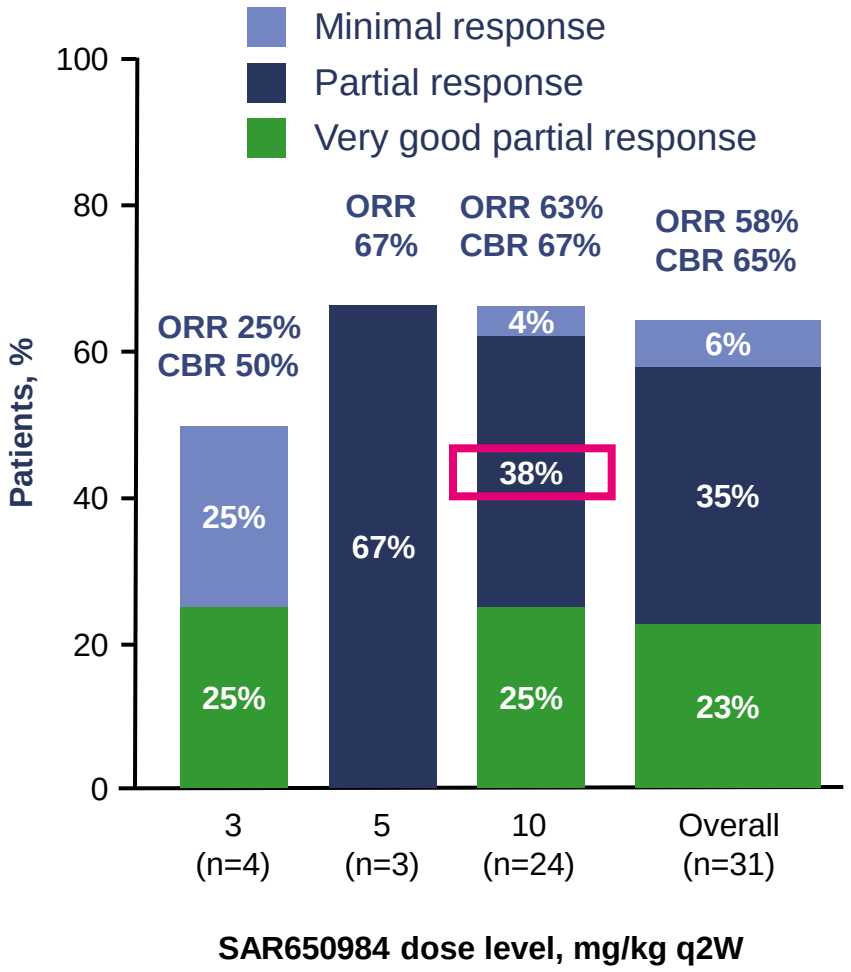
DARA monotherapy: Conclusions

Efficacy

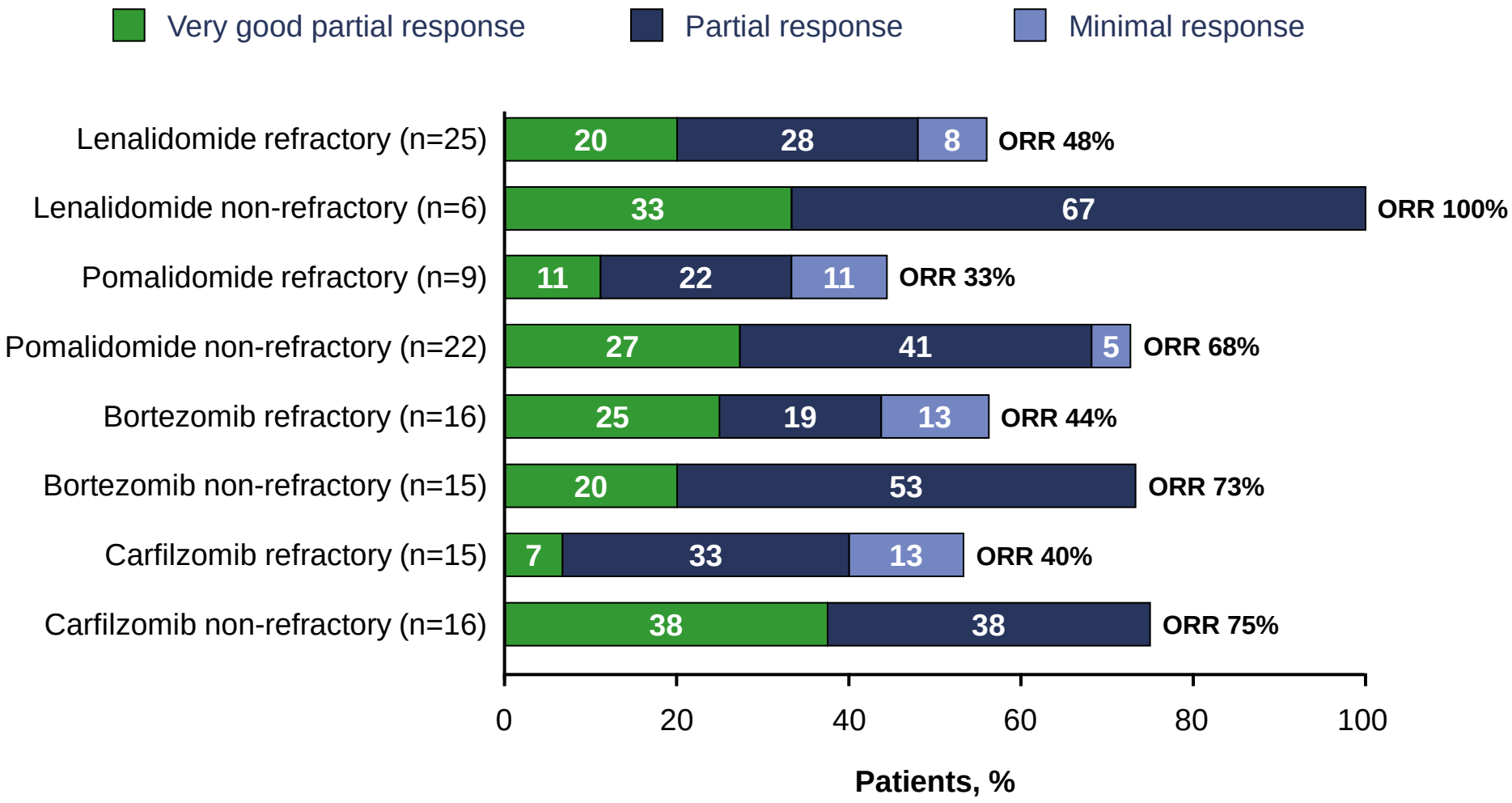
- **Preliminary ORR (PR and better) is very promising in the 16 mg/kg cohort with 35% compared to 10% in the 8 mg/kg cohorts**
- **Response is deeper in the 16 mg/kg cohort in part 2 compared to the 8 mg/kg cohort and the higher dose cohorts (4-24 mg/kg) from part 1**
- **In patients who achieved a clinical response, the bone marrow plasma cells decreased to normal level**
- **16 mg/kg is the dose that should be chosen for further studies of daratumumab as monotherapy**

A Phase Ib dose-escalation trial of SAR650984 (anti-CD38 mAb) in combination with lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: Response summary (IMWG criteria) (Martin et al, ASCO 2014)

Number of patients (%)	All (n=31)
Overall response rate	18 (58)
Very good partial response	7 (23)
Partial response	11 (35)
Minimal response	2 (6)
Clinical benefit (MR or better)	20 (65)
Stable disease	3 (10)
Progressive disease	7 (23)
Not evaluable	1 (3)



Response rate by prior anticancer treatment



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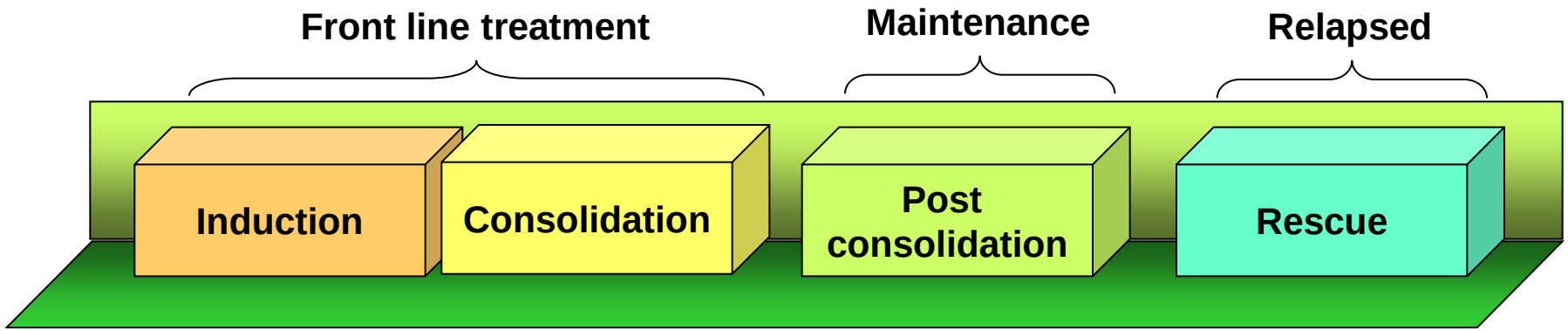
Treatment sequence in Myeloma

Now

Induction	Consolidation	Post consolidation	Rescue
VD Rev/Dex CyBorD VTD VRD	SCT	Nothing Thalidomide? Bortezomib Lenalidomide	Bortezomib Lenalidomide Thalidomide Carfilzomib Pomalidomide



New

Induction	Consolidation	Post consolidation	Rescue
Carfilzomib Combos	“more” induction Lenalidomide 2 mths	Bortezomib ? Ixazomib	Ixazomib Monoclonal Ab (CD38) Elotuzumab Panobinostat Bendamustine ++++++++

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More to Come!!

Classes of Agents in Development for Myeloma

1. *Oral Proteasome Inhibitors* – ixazomib (MLN 9708), oprozomib
2. *Monoclonal antibodies*
    a. SLAMF7 (Signaling Lymphocytic Activation Molecule F7) (formerly CS-1) – elotuzumab
    b. Anti CD38 – daratumumab, SAR650984
    c. Anti CD 138 – indatuximab, ravatansine
3. *KSP Inhibitors* – filanesib
4. *Histone Deacetylase Inhibitors* – panobinostat, ACY-1215
5. *Akt inhibitors* - afuresertib
6. *BCL Family Inhibitors* – ABT-199
7. *CDK inhibitors* - dinaciclib
8. *Nuclear Transport* – CRM/XPO1 - selinexor
9. *IAP antagonists* – LCL161
10. *PIM kinase inhibitors* – LGH447
11. *Bromodomain and Extra-Terminal (BET) inhibitors*- GSK525762
12. *Immune Therapies* – programmed cell death protein 1 (pd1), programmed death-ligand 1 (pdl1)

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What is in the Future of Myeloma? Joe the Prophet speaks…

1. Less Transplant
2. More Risk Stratification
3. Longer Treatments
4. More Combinations
5. Monoclonal Antibodies! (esp CD38)
6. More convenient regimens
7. MRD
8. Quality of Life

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