Risk Stratification in Multiple Myeloma: Putting the Pieces Together

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- Dr. Lee received research support from Daiichi Sankyo, served as a consultant for Takeda Pharmaceuticals and Celgene Corporation and on the Advisory Board of Adaptive Biotechnology.
- Dr. Richards served as a consultant for Celgene Corporation and Takeda Pharmaceuticals.

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Learning Objectives

1. Identify factors to be considered when choosing initial drug therapy for patients with multiple myeloma that minimizes potential limitations in future treatment options.
2. Identify patient, disease, and drug factors to be considered when sequencing therapy for individual patients with multiple myeloma.
3. Identify common toxicities associated with antimyeloma therapies and list monitoring parameters for serious toxicities.
4. Identify reasons for nonadherence to oral myeloma therapies and appropriate strategies to address them.

Audience Response Questions

Please indicate the clinical role that best represents you.

1. Physician
2. PA
3. Nurse practitioner
4. Clinical nurse specialist
5. Nurse
6. Pharmacist
7. Other

Please indicate the practice setting that best represents your practice:

1. Academic medical center, teaching hospital, or comprehensive cancer center
2. Community hospital or community cancer center
3. Private/group practice
4. Government or VA
5. Managed care, insurance, employer, or other payer
6. Pharmaceutical/biotech/device industry
7. Other

Please indicate your clinical specialty:

1. Medical oncology
2. Hematology/oncology
3. Radiation oncology
4. Internal medicine
5. Gynecologic oncology
6. Genetics/genetic counseling
7. Other

Please indicate your years in practice:

1. < 1 year
2. 1–5 years
3. 6–10 years
4. 11–15 years
5. 16–20 years
6. > 20 years

Question #1

Ms. D is a 59-year-old patient with newly diagnosed multiple myeloma. A myeloma FISH panel at diagnosis revealed high-risk disease with deletion 17p and t(4;14). Which therapy would be the preferred treatment option in a newly diagnosed myeloma patient with high-risk cytogenetics?

1. Lenalidomide/dexamethasone
2. Bortezomib/pomalidomide
3. Thalidomide/dexamethasone
4. Bortezomib/lenalidomide/dexamethasone
5. Unsure

Question #2

Ms. D starts carfilzomib, lenalidomide, and dexamethasone as her frontline therapy and develops a pruritic, raised macular rash on her upper torso and face three days after she starts the lenalidomide. What would you advise the patient?

1. Hold lenalidomide and refer to dermatology for skin biopsy
2. Hold lenalidomide, and once rash resolves, restart lenalidomide concurrently with cetirizine, ranitidine, and L-lysine
3. Discontinue lenalidomide permanently and continue carfilzomib and dexamethasone alone
4. Hold lenalidomide, and once rash resolves, restart lenalidomide concurrently with hydrocortisone topical cream
5. Unsure

Question #3

Ms. D completes four cycles of carfilzomib/lenalidomide/dexamethasone, achieving a very good partial response to therapy, followed by high-dose chemotherapy and autologous stem cell transplantation. She returns to clinic and is 2 ½ months post-transplant and is in a near complete remission. She is here to discuss maintenance therapy options with you.

Which therapy would you recommend?

1. Lenalidomide maintenance
2. Bortezomib/lenalidomide/dexamethasone consolidation/maintenance
3. Melphalan/prednisone maintenance
4. Observation
5. Unsure

Question #4

Ms. D starts bortezomib, lenalidomide, and dexamethasone maintenance therapy given her high-risk disease. One year later, she develops a painful vesicular rash on over her left T9 dermatome. A diagnosis of varicella zoster is confirmed. Upon further questioning, she had stopped taking her anti-viral prophylaxis 3 months ago. Which of the following myeloma drugs is varicella zoster prophylaxis mandatory?

1. Daratumumab and bortezomib
2. Lenalidomide
3. Dexamethasone
4. Pomalidomide
5. Unsure

Outline

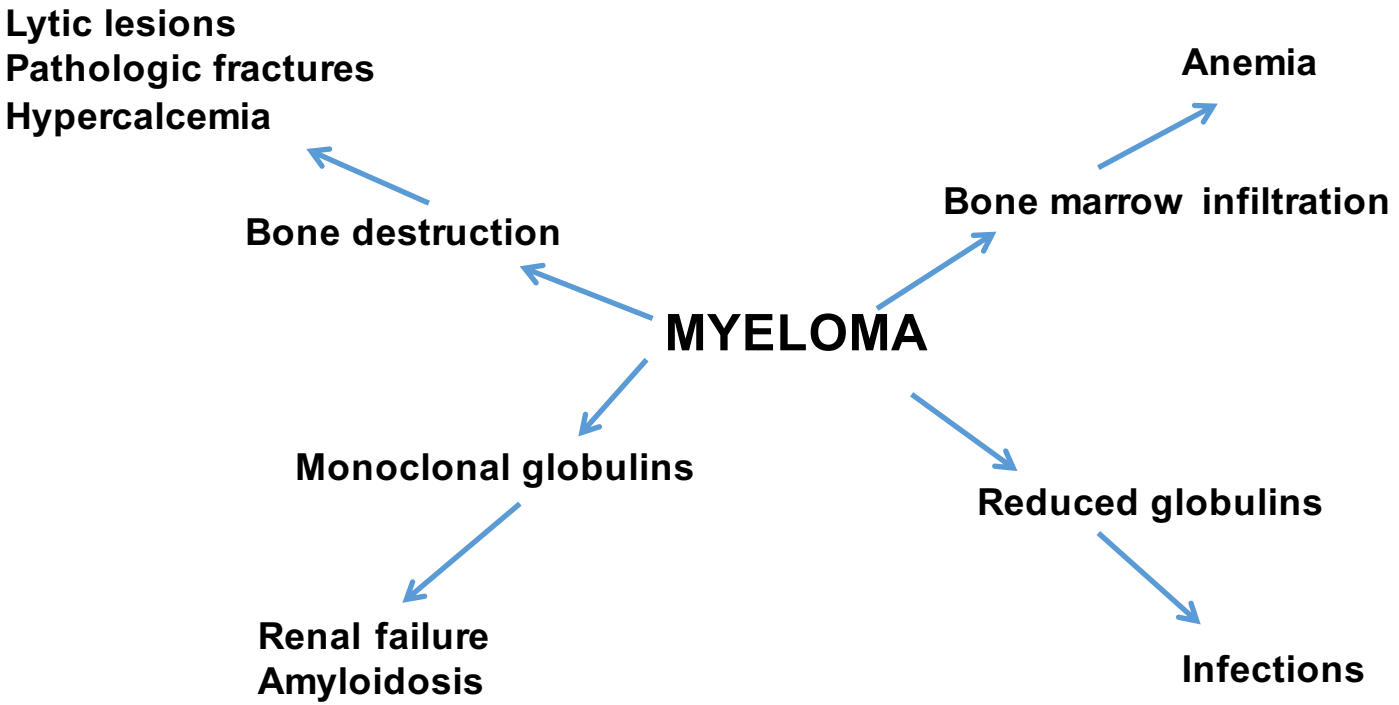
- Myeloma background
- Myeloma risk-stratification
- Treatment considerations for newly diagnosed myeloma
- Treatment considerations for maintenance therapy
- Treatment considerations for relapsed/refractory disease
- Overview of common toxicities to myeloma therapy

Myeloma Epidemiology

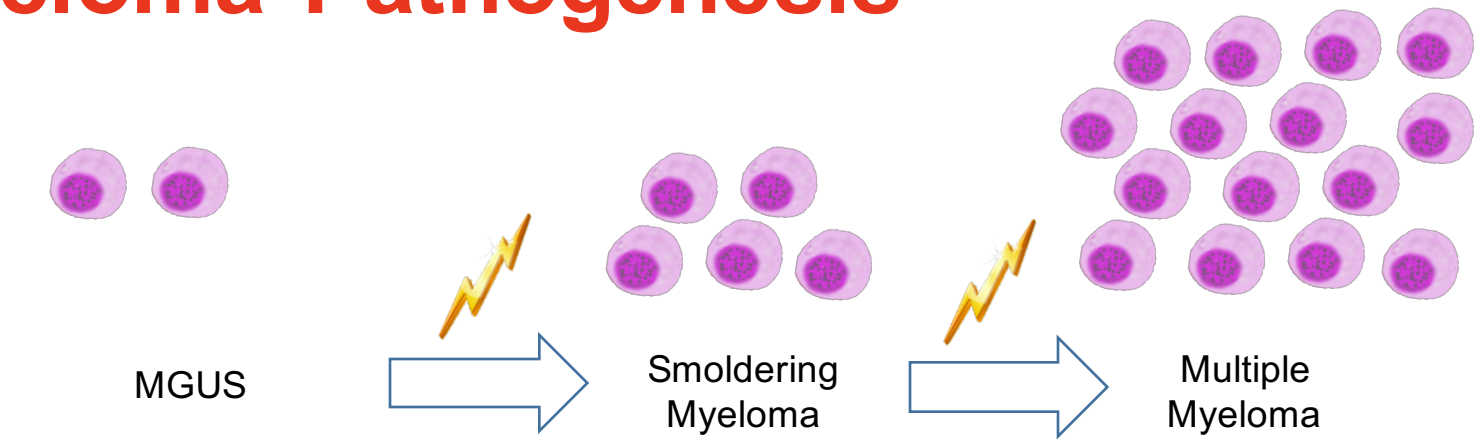
- Second most common hematologic malignancy
- > 24,000 people diagnosed in United States in 2014
- Risk factors
  - Age: 28% (65–74); 25% (75–84)
  - Race: 2x greater risk in African-Americans
  - MGUS
  - Male gender, family history, prior history of inflammatory or autoimmune condition, radiation exposure

MGUS = monoclonal gammopathy of undetermined significance.

Disease Characteristics & Symptoms



Myeloma Pathogenesis



Primary initiating events:
IGH translocations
Hyperdiploidy

Secondary genetic events:
Acquired mutations
Copy number alterations

Morgan GJ, et al. *Nat Rev Cancer.* 2012;12:335-48.

2014 IMWG Myeloma Diagnostic Criteria

	Definition
Multiple Myeloma	▪ Clonal bone marrow plasma cells ≥10% or biopsy- ▪ **START TREATMENT!** cell disorder as defined by CRAB* criteria OR ≥ 1 biomarkers of malignancy which include bone marrow clonal plasmacytosis ≥ 60%, involved:uninvolved serum free light chains ≥ 100, or > 1 focal lesion on MRI studies that is at least 5 mm in size.

New in 2014

CT = computed tomography; IMWG = International Myeloma Working Group; MRI = magnetic resonance imaging; PET = positron emission tomography.

Rajkumar SV, et al. *Lancet Oncol* 2014;15:e538-48.

***CRAB Criteria:**

1) Hyper**C**alcemia: Serum calcium > 1 mg/dL above the upper limit of normal or > 11 mg/dL
2) **R**enal insufficiency: creatinine clearance < 40 mL/min or serum creatinine > 2 mg/dL
3) **A**nemia: hemoglobin < 2 g/dL below the lower limit of normal or < 10 g/dL
4) **B**one lesions: one more osteolytic lesions on skeletal survey, CT scan, or PET-CT

Myeloma Defining Events

SLiM CRAB

- **S**ixty percent or greater clonal plasmacytosis
- **Li**ght chain ratio ≥ 100
- **M**RI changes
- Hyper**C**alcemia
- **R**enal insufficiency
- **A**nemia
- **B**one

2014 IMWG Myeloma Diagnostic Criteria

	Definition	Myeloma Progression Rate
MGUS	▪ Monoclonal protein < 3 grams/dl ▪ Clonal ▪ Absen	1% per year
Smoldering multiple myeloma	▪ Serum monoc marrov ▪ Absen	

OBSERVATION

OBSERVATION (OR TREATMENT ON CLINICAL PROTOCOL)

Rajkumar SV, et al. *Lancet Oncol* 2014;15:e538-48.

Case Study 1

- Ms. D is a 59-year-old female who presented to her primary care physician and was found to have anemia with a hemoglobin of 8.6 and elevated total protein
- Iron studies, vitamin B12, and folate were normal
- Serum protein electrophoresis revealed IgG kappa M protein of 3.6 g/dL
- Presents to an oncologist for evaluation

Case Study 1

Lab/Normal Reference Range	Value
WBC 3.0-11.0 k/µL	6.6
Plt Ct 150-440 k/µL	514 (H)
Hgb 12.0-16.0 g/dL	8.2 (L)
Hct 37.0%-47.0%	22.9 (L)
MCV 82-98 fL	91
RDW-CV 12%-15.5%	14.7
Neut 42%-66.0%	74
ANC 1.00-7.50 k/µL	4.88

Lab/Normal Reference Range	Value
BUN 8-20 mg/dL	48 (H)
Creatinine 0.6-1.0 mg/dL	4.1 (H)
Calcium 8.5-10.5 mg/dL	10.9 (H)
Albumin 3.5-5.0 g/dL	4.1
Alk phos 40-150 U/L	72
$ß_2M$	9.9 (H)
Glucose mg/dL	100

ANC = absolute neutrophil count; alk phos = alkaline phosphatase; BUN = blood urea nitrogen; Hct = hematocrit; Hgb = hemoglobin; MCV = mean corpuscular volume; neut = neutrophil; plt ct = platelet count; WBC = white blood cells.

Case Study 1

24-Hour UPEP: Lab/Normal Reference Range	Value
Total urine protein (50-100 mg/TV)	5565
Urine albumin %	2.9%
Gamma globulin	8.6%
Bence Jones mg/dL per 24 hours	4925
Urine immunofixation	Kappa

Lab/Normal Reference Range	Value
Serum IgG 700-1600 mg/dL	3834
Serum IgA 70-400 mg/dL	20
Serum IgM 40-230 mg/dL	35
Monoclonal protein (serum) g/dl	3.7
Serum immunofixation	GK

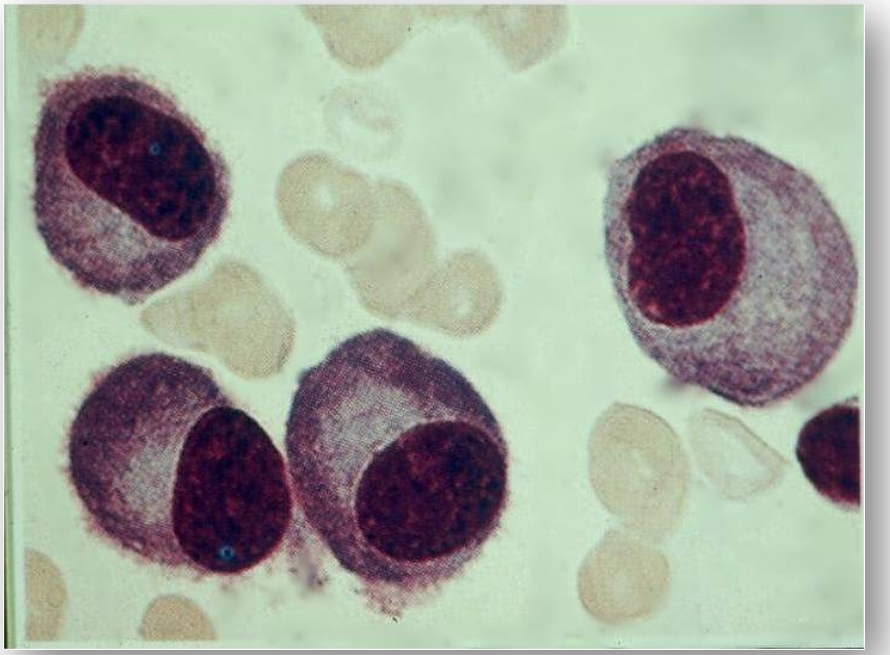
UPEP = urine protein electrophoresis.

Case Study 1

Component	Reference Range	Result
Kappa, free, serum	3.3–19.4 mg/L	15,300 mg/L (H)
Lambda, free, serum	5.7–26.3 mg/L	10.40 mg/L
K/L ratio, serum	0.26–1.65 mg/L	1571(H)

Case Study 1

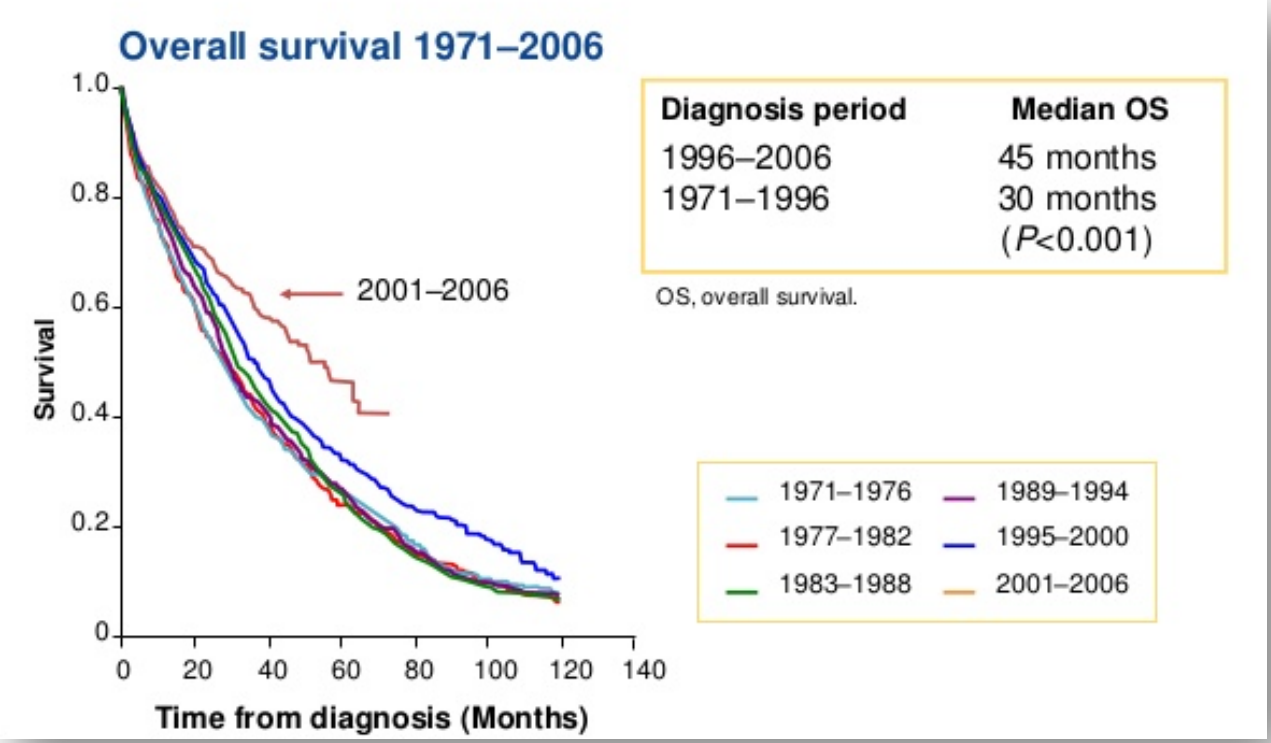
- Bone marrow biopsy reveals 50% plasma cells
  - Positive for kappa, CD138, CD38, CD56
  - Conventional cytogenetics: 46XX
  - FISH: del 17p; t(4;14)
- PET-CT and skeletal survey reveal lytic lesions in the bilateral ribs



How would you risk-stratify this patient?

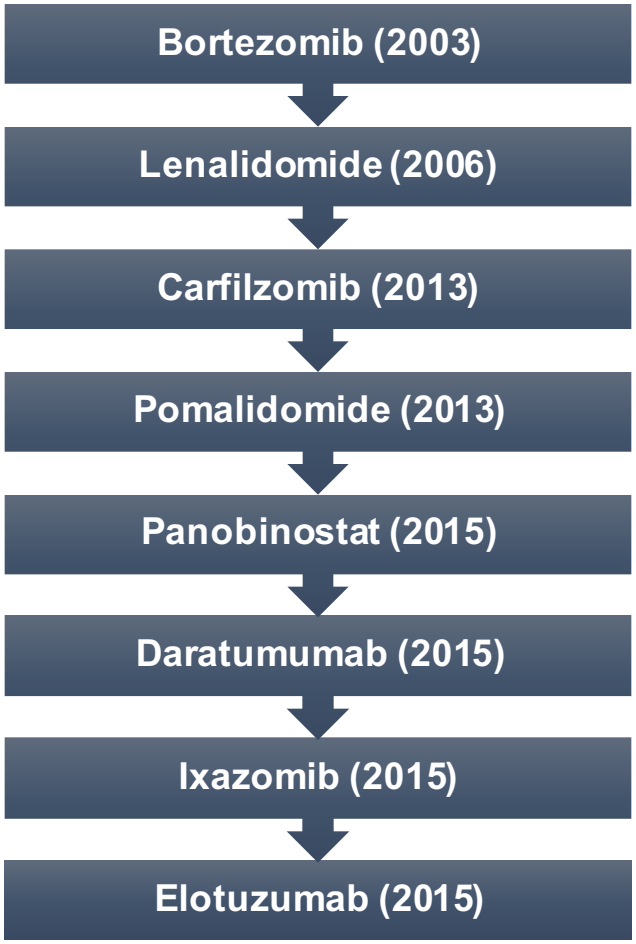
What is the importance of risk stratification?

Impact of Novel Agents in MM



MM = multiple myeloma.

Kumar SK, et al. *Blood* 2008;111:2516-20.



Average life expectancy for standard-risk myeloma patients 10-12 years now!

High-Risk Myeloma
Median Overall Survival 3 years

Standard-Risk Myeloma

Why Risk-Stratify Myeloma?

- Informs prognosis
- Identifies high-risk myeloma patient populations that could be candidates for novel treatment treatment approaches

Defining High-Risk Myeloma

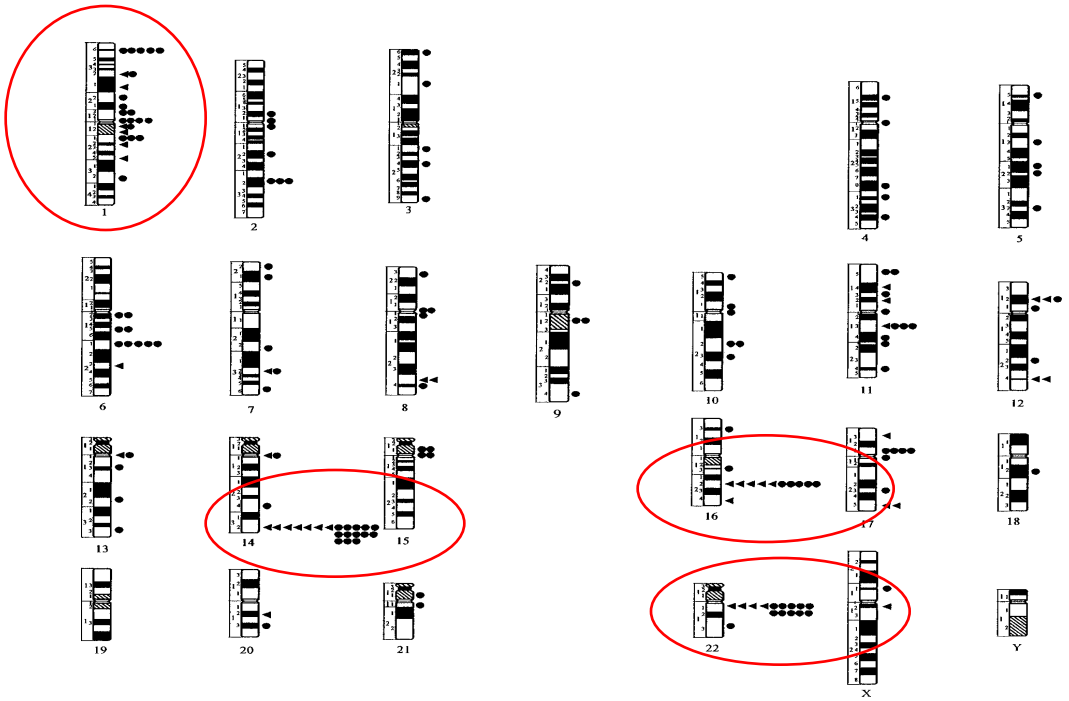
- Disease biology
  - Cytogenetics/FISH
  - GEP
  - Sequencing (emerging)
  - Plasma cell leukemia
  - Extramedullary disease

  } Molecular classification

- Disease burden
  - β2 microglobulin, albumin, LDH
- Response to therapy

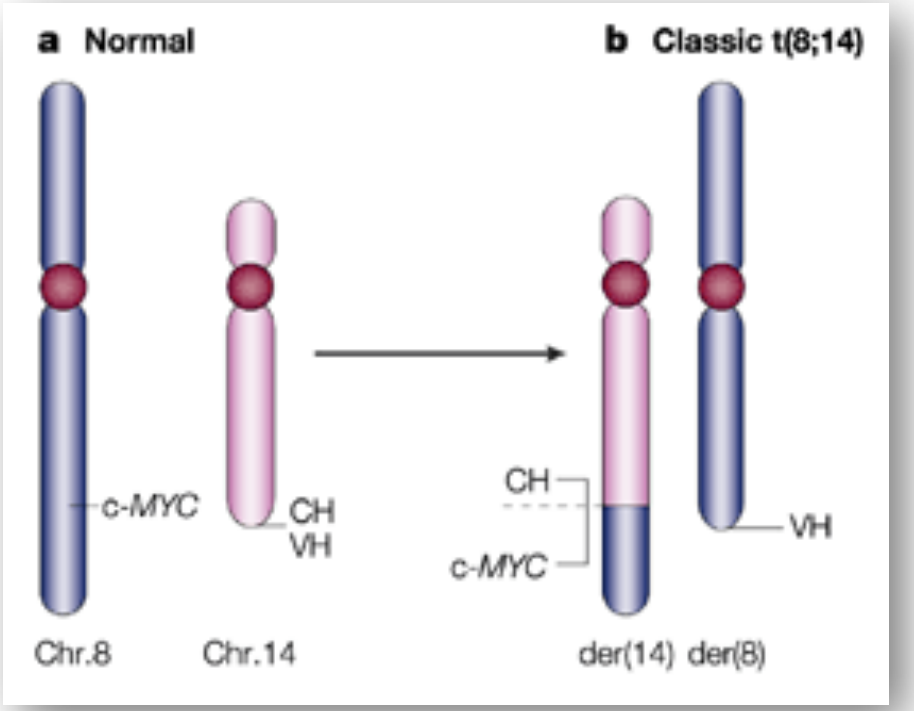
FISH = fluorescence in situ hybridization; GEP = gene expression profiling; LDH = lactate dehydrogenase.

Early Molecular Classification: Conventional Karyotype



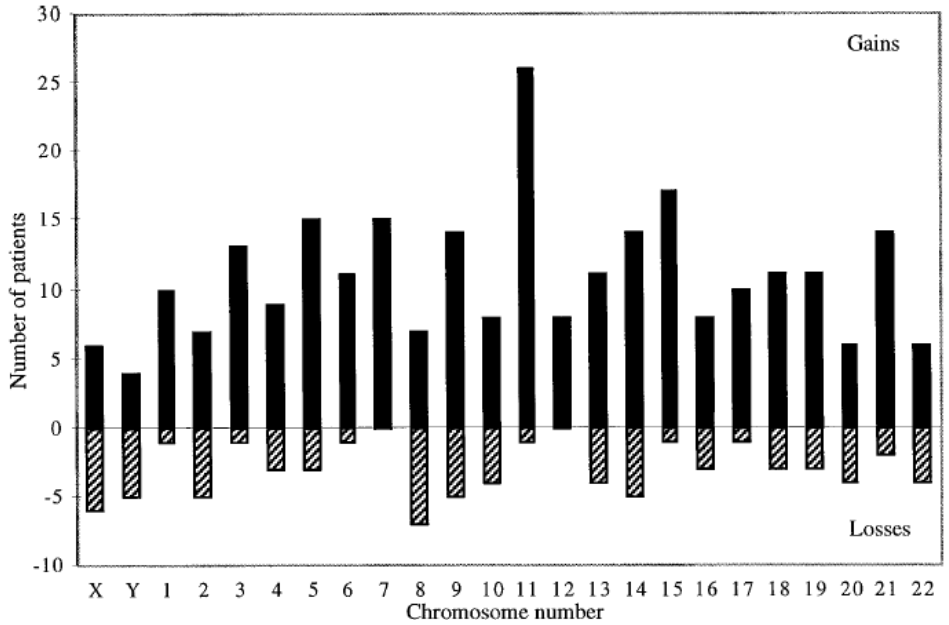
Calasanz MJ, et al. *Genes Chromosomes Cancer* 1997;18:84-93.

IgH Chromosomal Translocations



Kuehl WM, et al. *Nat Rev Cancer* 2002;2:175-87.

Early Molecular Classification: Conventional Karyotype



Frequency of numeric changes in 88 patients with abnormal karoytype

Calasanz MJ, et al. *Genes Chromosomes Cancer* 1997;18:84-93.

Early Molecular Classification: Summary

- Multiple translocations, particularly involving Ig heavy chain locus on chromosome 14q32
- Hyperdiploidy (46% of cases)

Calasanz MJ, et al. *Genes Chromosomes Cancer* 1997;18:84-93.

Molecular Classification: FISH

- **FISH** evaluates chromosomal deletions, amplifications, and translocations which have prognostic significance
  - Deletion 13q14, deletion 17p13 (*TP53*), and deletion of 1p32
  - Amplification of 1q21
  - Translocations involving the immunoglobulin heavy chain locus on chromosome 14q32 and its common gene partners including 11q13 (*CCND1*), 4p16 (*FGFR3* and *MMSET*), 16q23 (*c-MAF*), 6p21 (*CCND3*), and 20q12 (*MAFB*)

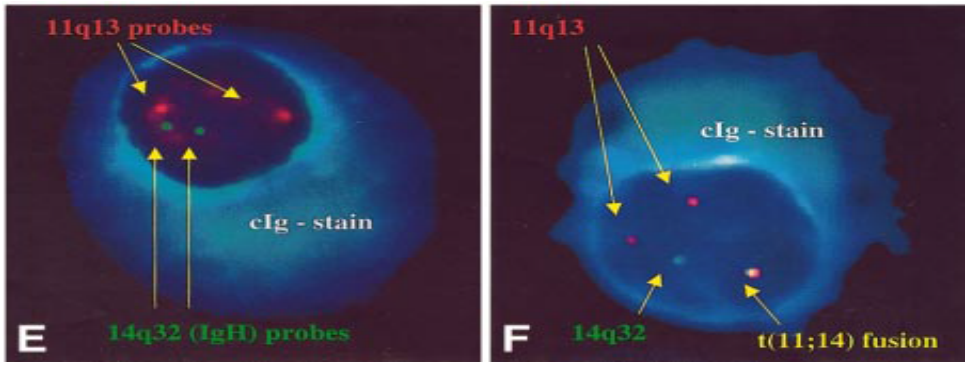
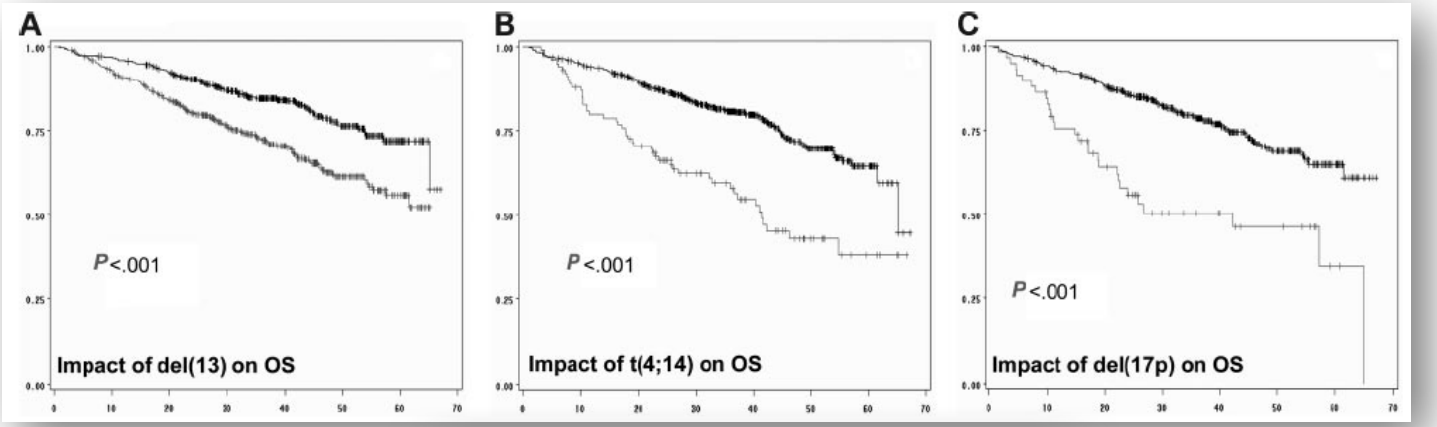
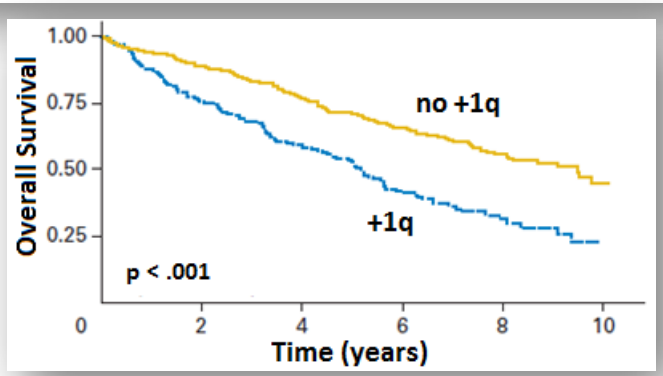


Image from Hayman SR, et al. *Blood* 2001;98:2266-8.

Impact of Cg in Pre-Novel Agent Era

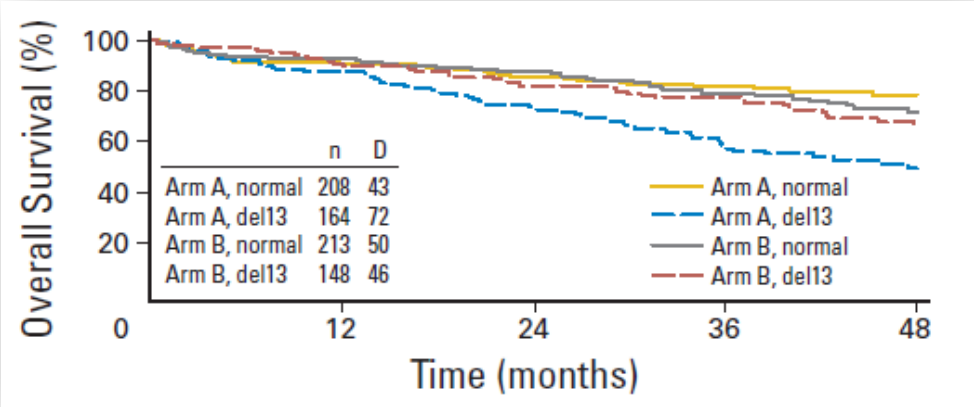


IFM 99 Trials



Avet-Loiseau H, et al. *Blood* 2007;109:3489-95;
Avet-Loiseau H, et al. *J Clin Oncol* 2012;30:1949-52.

Impact of Cg in Novel Agent Era



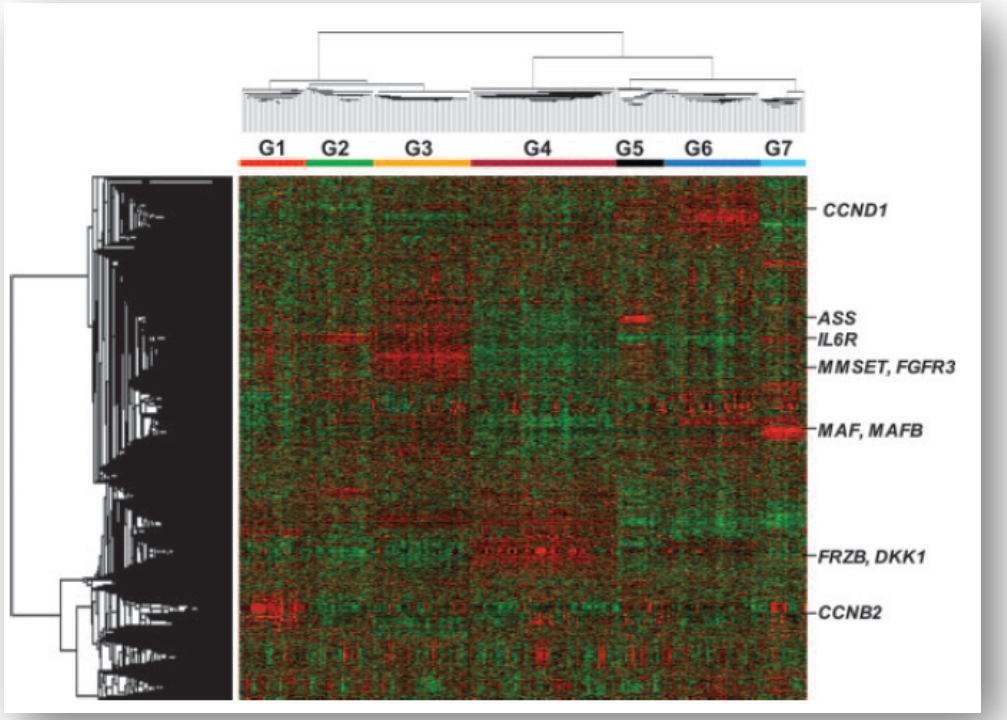
HOVON-65 / GMMG-HD4

VAD (Arm A) vs. PAD (Arm B)

Trial	Time point	EFS all patients	EFS/PFS t(4;14)	PFS del(17p)	OS % all patients	OS % t(4;14)	OS % del(17p)
VD vs VAD	4 years	36 mo	28 mo	14 mo	77	63	49
		NR	16 mo	NR	82	32	50
VTD vs TD	3 years	74%	69%	NR	86	NR	NR
		63%	37%	NR	84	NR	NR
PAD vs VAD	3 years	28 mo	25 mo	26 mo	85	66	69
		35 mo	21 mo	12 mo	80	44	17

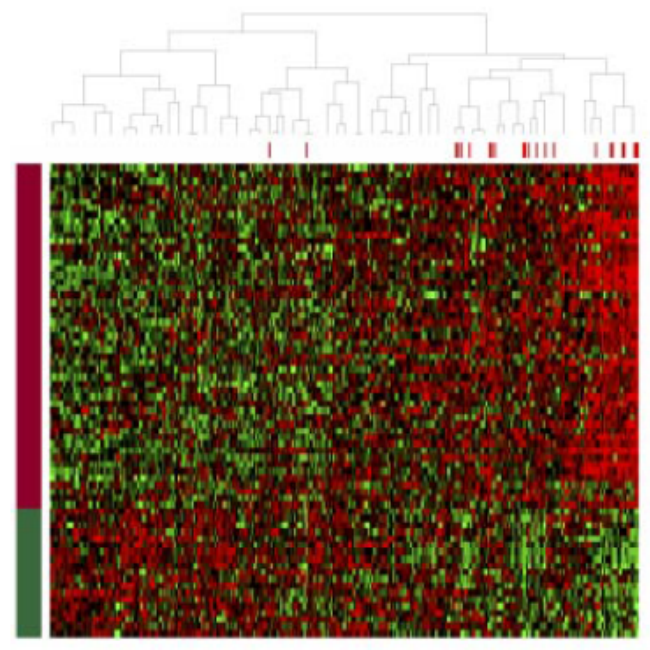
Harousseau JL, et al *J Clin Oncol* 2010;28:4621-9; Avet-Loiseau H, et al. *J Clin Oncol* 2010;28:4630-4; Cavo M, et al. *Lancet* 2010;376;2075-85; Sonneveld P, et al. *J Clin Oncol* 2012;30:2946-55.

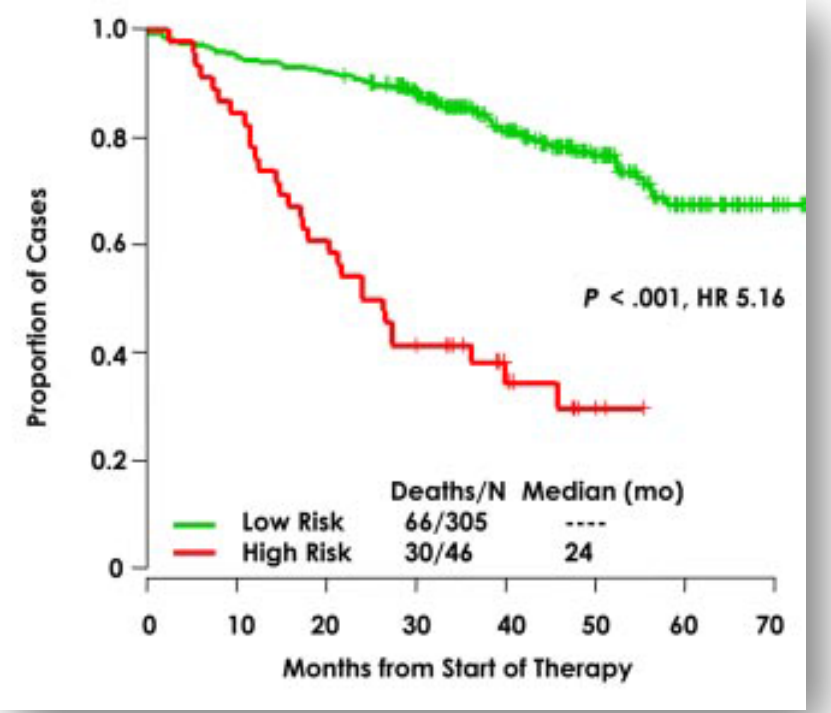
Molecular Classification: Gene Expression Profiling



Zhan F, et al. *Blood* 2006;108:2020-8.

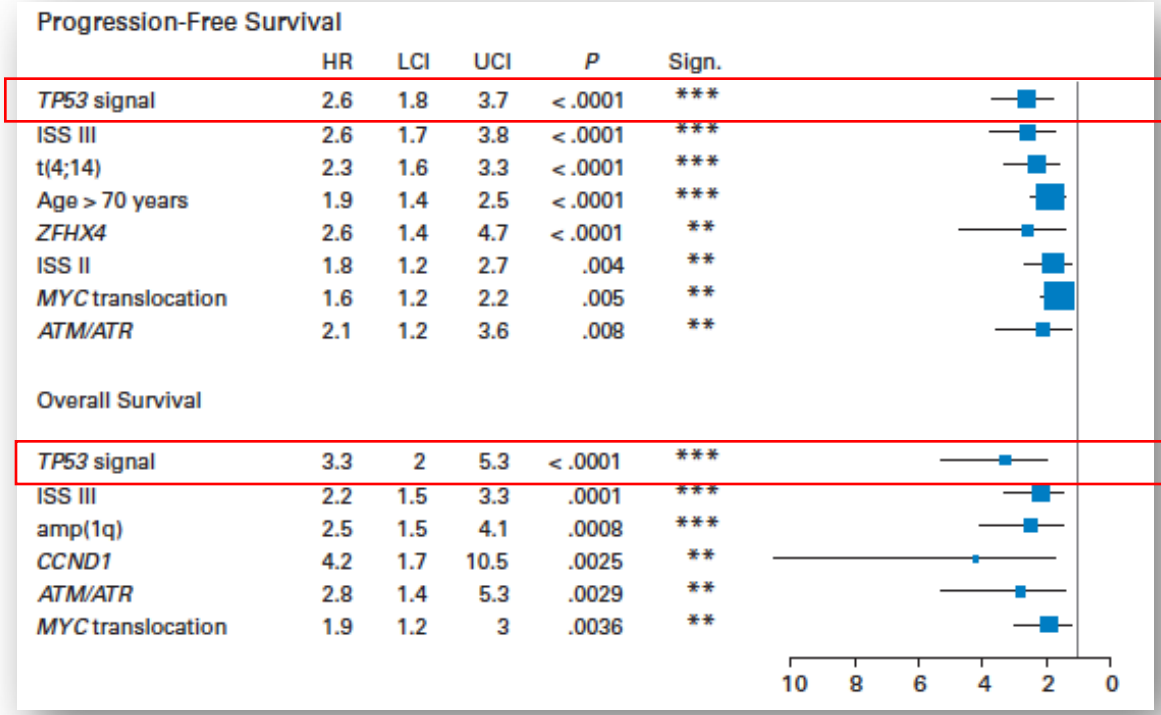
70-Gene GEP Predicts Adverse Outcomes





Shaughnessy JD Jr, et al. *Blood* 2007;109:2276-84.

Molecular Classification: Gene Sequencing (Emerging)



Progression-Free Survival

	HR	LCI	UCI	*P*	Sign.
TP53 signal	2.6	1.8	3.7	< .0001	***
ISS III	2.6	1.7	3.8	< .0001	***
t(4;14)	2.3	1.6	3.3	< .0001	***
Age > 70 years	1.9	1.4	2.5	< .0001	***
ZFHX4	2.6	1.4	4.7	< .0001	**
ISS II	1.8	1.2	2.7	.004	**
MYC translocation	1.6	1.2	2.2	.005	**
ATM/ATR	2.1	1.2	3.6	.008	**

Overall Survival

TP53 signal	3.3	2	5.3	< .0001	***
ISS III	2.2	1.5	3.3	.0001	***
amp(1q)	2.5	1.5	4.1	.0008	***
CCND1	4.2	1.7	10.5	.0025	**
ATM/ATR	2.8	1.4	5.3	.0029	**
MYC translocation	1.9	1.2	3	.0036	**

10 8 6 4 2 0

Walker BA, et al. *J Clin Oncol* 2015;33:3911-20.

Myeloma International Staging System

	Parameters	Median Overall Survival
Stage I	Albumin > 3.5 g/dL and β-2 microglobulin < 3.5 mg/L	62 months
Stage II	Neither stage I or stage III	44 months
Stage III	β-2 microglobulin > 5.5 mg/L	29 months

Greipp PR, et al. *J Clin Oncol* 2005;23:3412-20.

Revised ISS (R-ISS) – NEW 2015

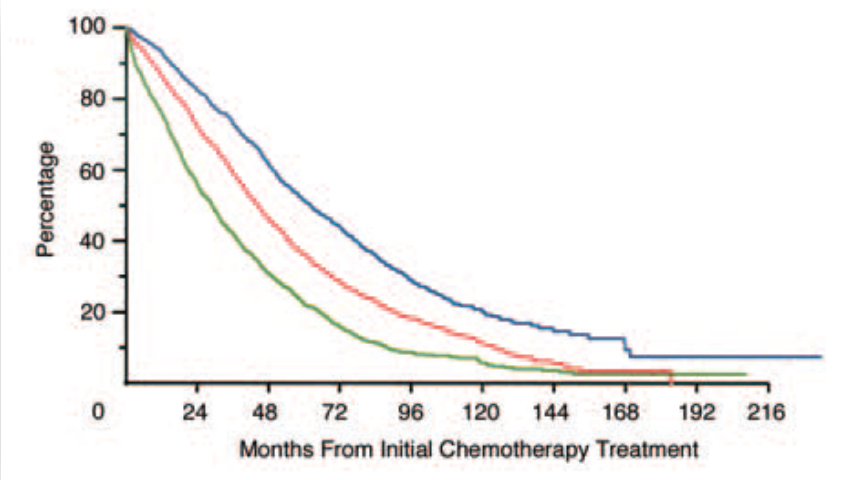
	Parameters	Median Overall Survival
R-ISS Stage I	ISS stage I AND 1) Standard risk cytogenetics AND 2) Normal LDH	Not reached
R-ISS Stage II	Not R-ISS stage I or III	83 months
R-ISS Stage III	ISS stage III AND 1) High-risk cytogenetics OR 2) Elevated LDH	43 months

High-risk cytogenetics = del 17p, t(4;14), and/or t(14;16); standard-risk cytogenetics = no high-risk cytogenetics
R-ISS = Revised International Staging System.

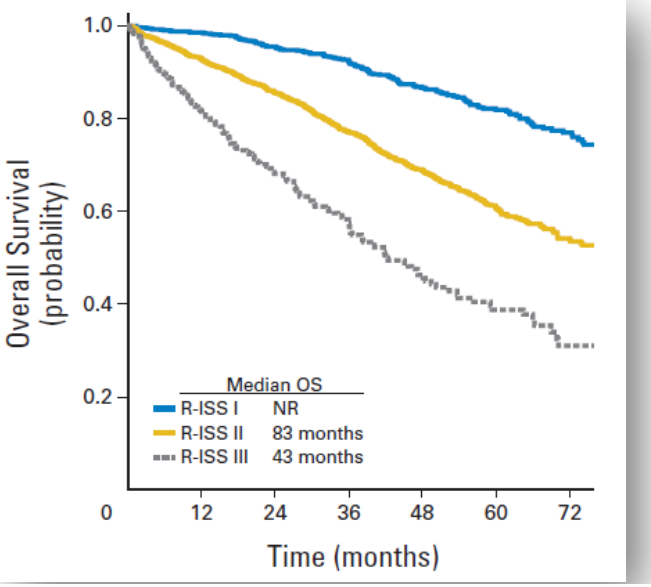
Palumbo A et al. *J Clin Oncol* 2015;33:2863-9.

ISS (2005) vs R-ISS (2015)

ISS



R-ISS



95% of patients received IMiDs or proteasome inhibitors

IMiDs = immunomodulatory drugs.

Greipp PR, et al. *J Clin Oncol* 2005;23:3412-20; Palumbo A et al. *J Clin Oncol* 2015;33:2863-9.

IMWG Myeloma Risk Stratification

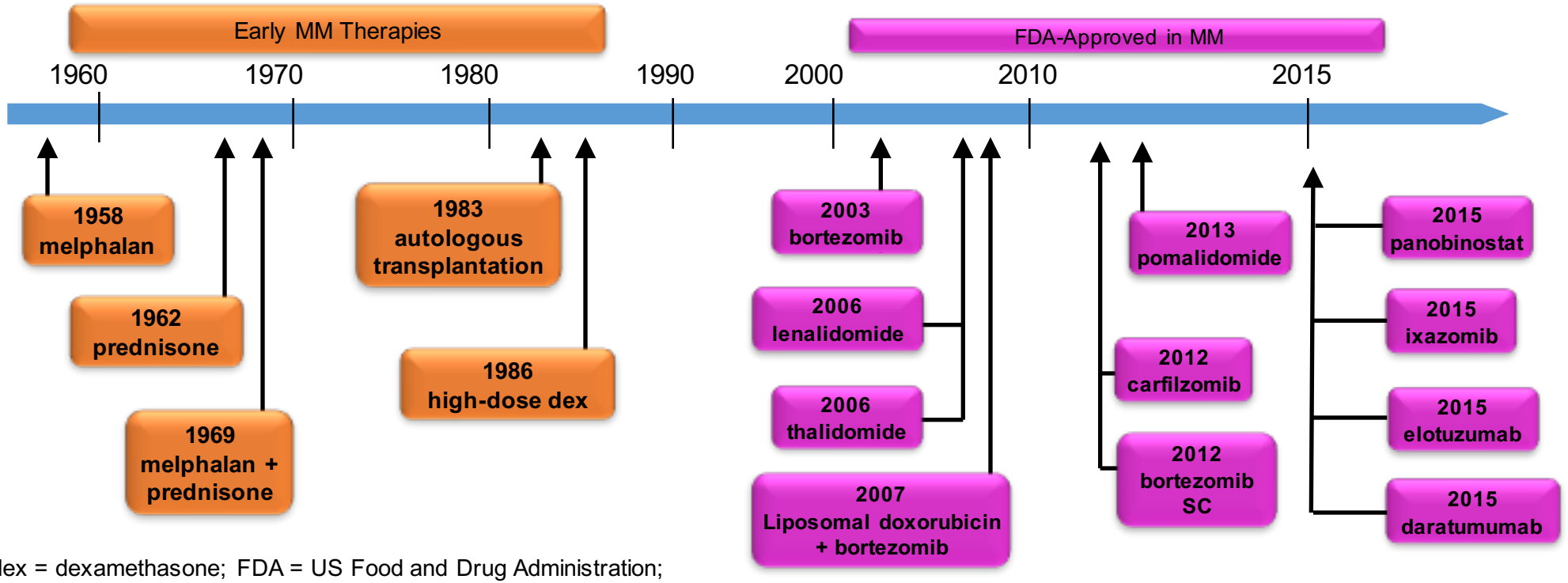
Standard Risk	High Risk	Ultra High Risk
• t(11;14) • t(6;14) • Hyperdiploid karyotype	• Del 17/17p • Amplification of 1q21 • t(14;20) • t(14;16) • t(4;14) • Del 13 (karyotype) • High-risk GEP profile • Hypodiploid karyotype • Plasma cell leukemia • Elevated plasma cell proliferation rate	≥ 3 adverse cytogenetic abnormalities

Sonneveld P, et al. *Blood* 2016;127:2955-62.

Case Study 1

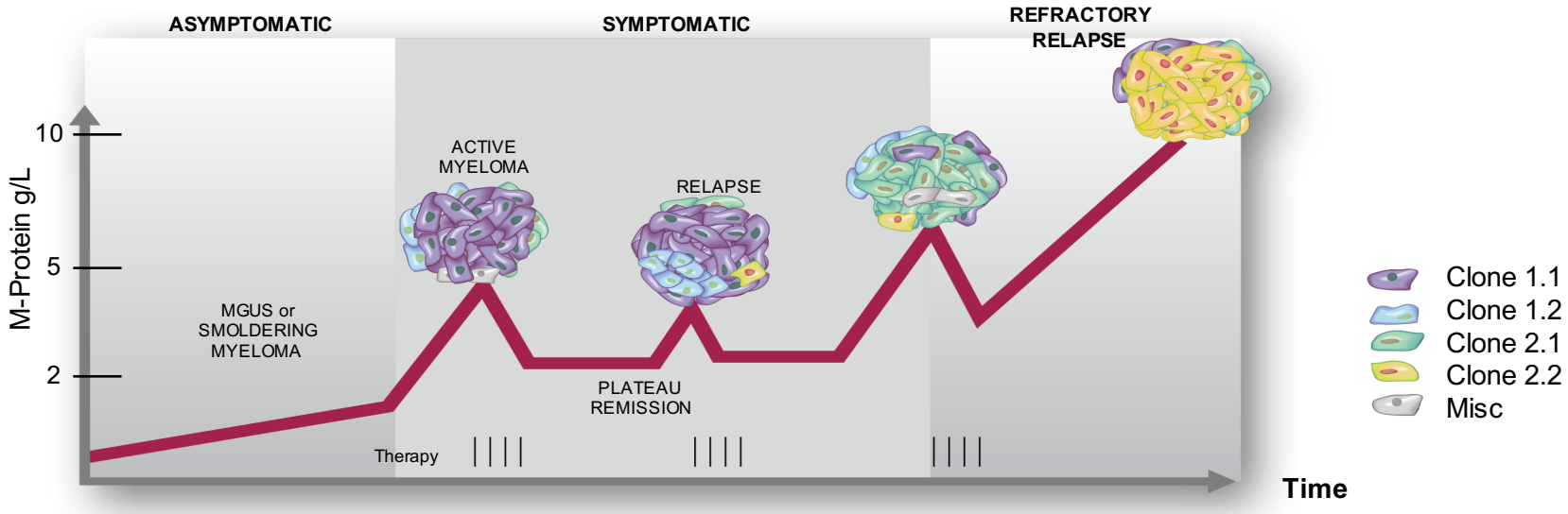
- Ms. D is diagnosed with symptomatic multiple myeloma warranting treatment
- High-risk FISH demonstrated by del 17p; t(4;14)
- R-ISS: III (ISS III + high risk cytogenetics)
- What are the treatment options for this patient?

Evolving Myeloma Treatment Landscape



dex = dexamethasone; FDA = US Food and Drug Administration; SC = subcutaneously.

Relapsing Nature of Multiple Myeloma



Adapted from Durie B, et al. *Blood* 2012;120:1067-76; courtesy of the IMF NLB.

Good news: Many treatment options for myeloma patients!

Challenge: How do we choose and sequence myeloma treatment regimens?

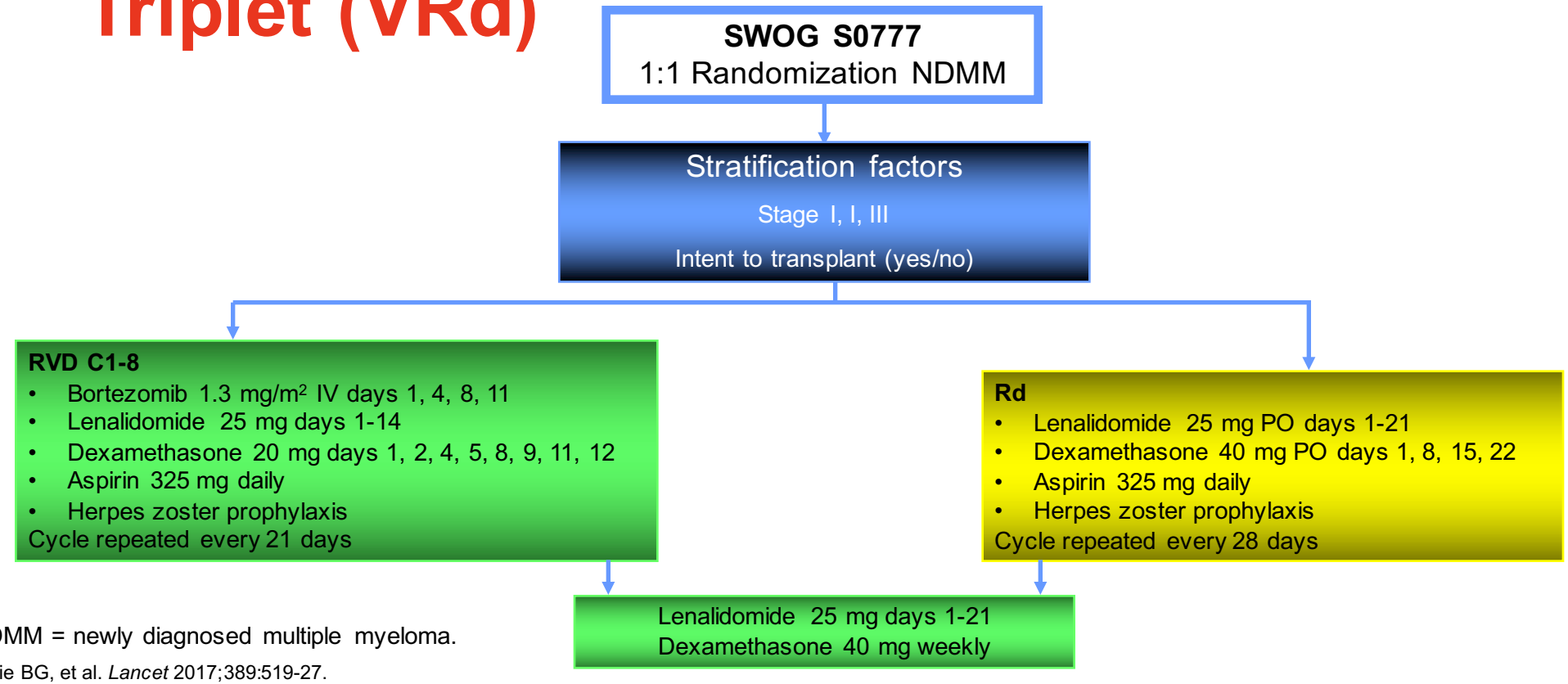
Important Considerations

Transplant Candidate

VERSUS

~~**Transplant Candidate**~~

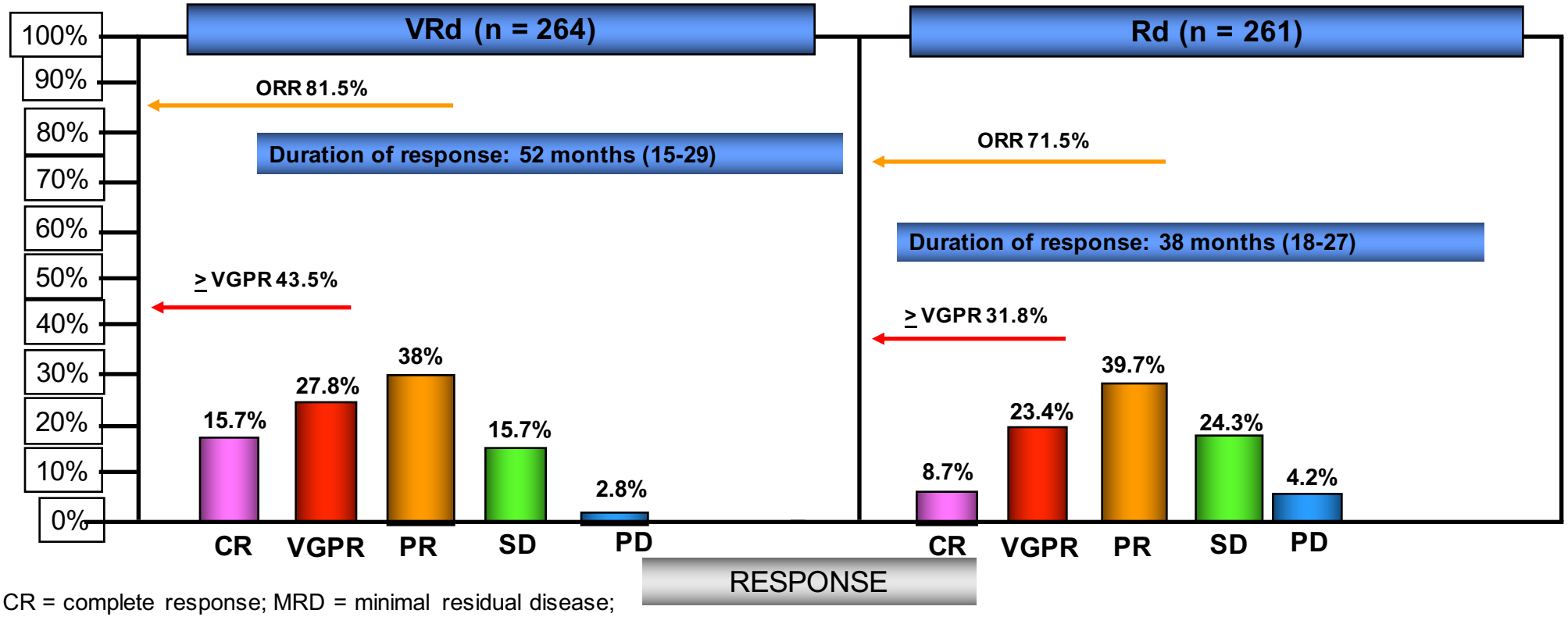
Frontline Therapy: Doublet (Rd) vs. Triplet (VRd)



NDMM = newly diagnosed multiple myeloma.

Durie BG, et al. *Lancet* 2017;389:519-27.

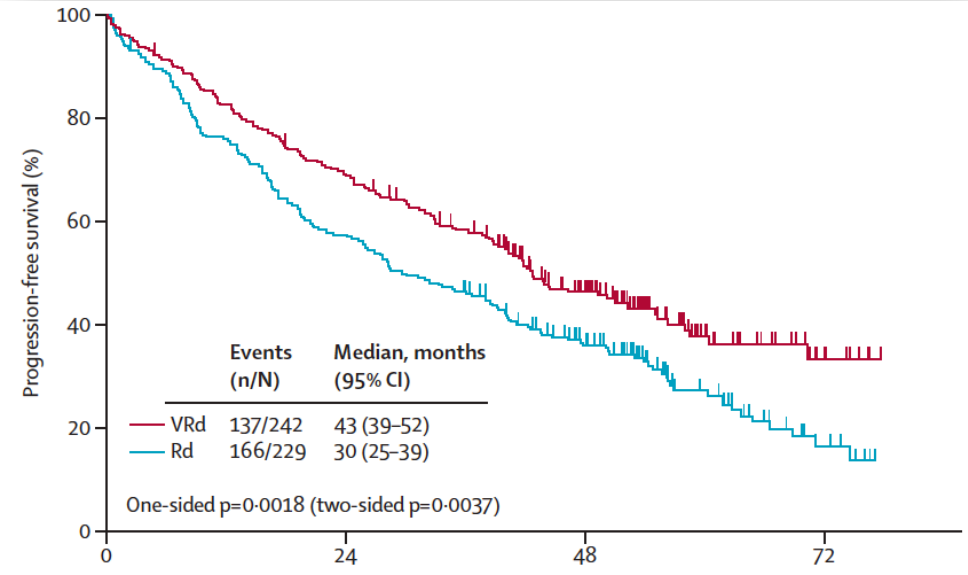
VRd vs. Rd: Overall Response Rate



CR = complete response; MRD = minimal residual disease;
ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease; VGPR = very good partial response.

Durie BG, et al. *Lancet* 2017;389:519-27.

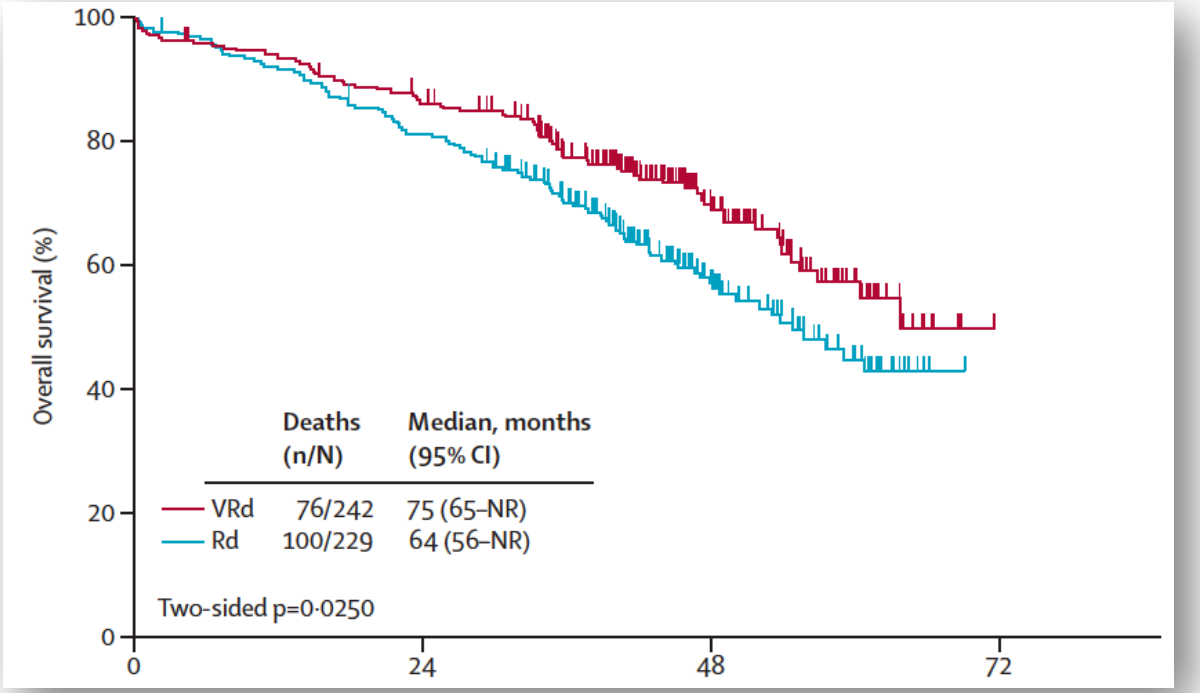
VRd vs. Rd: Progression-Free Survival



High-risk subgroup analysis PFS		
	VRd	**Rd**
High-risk FISH (n = 44)	38 months	16 months
t(4;14) (n = 17)	34 months	15 months

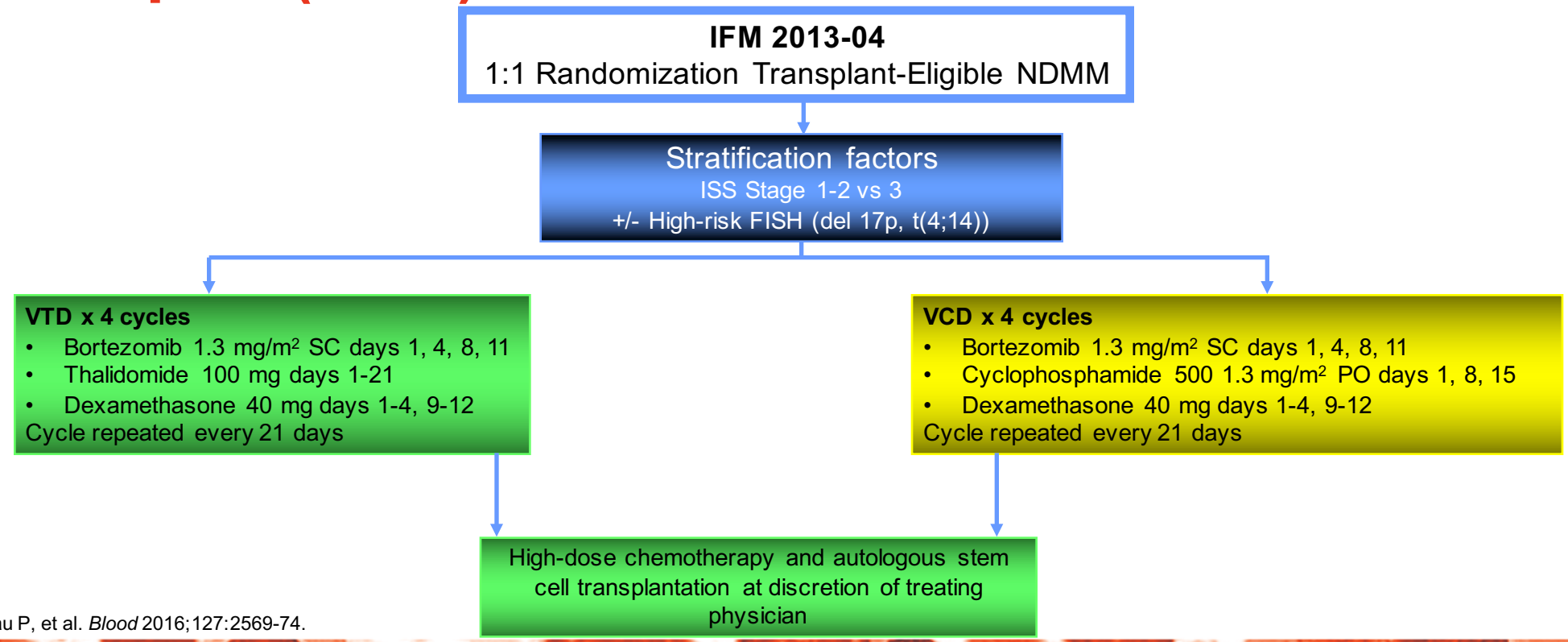
Durie BG, et al. *Lancet* 2017;389:519-27.

VRd vs. Rd: Overall Survival



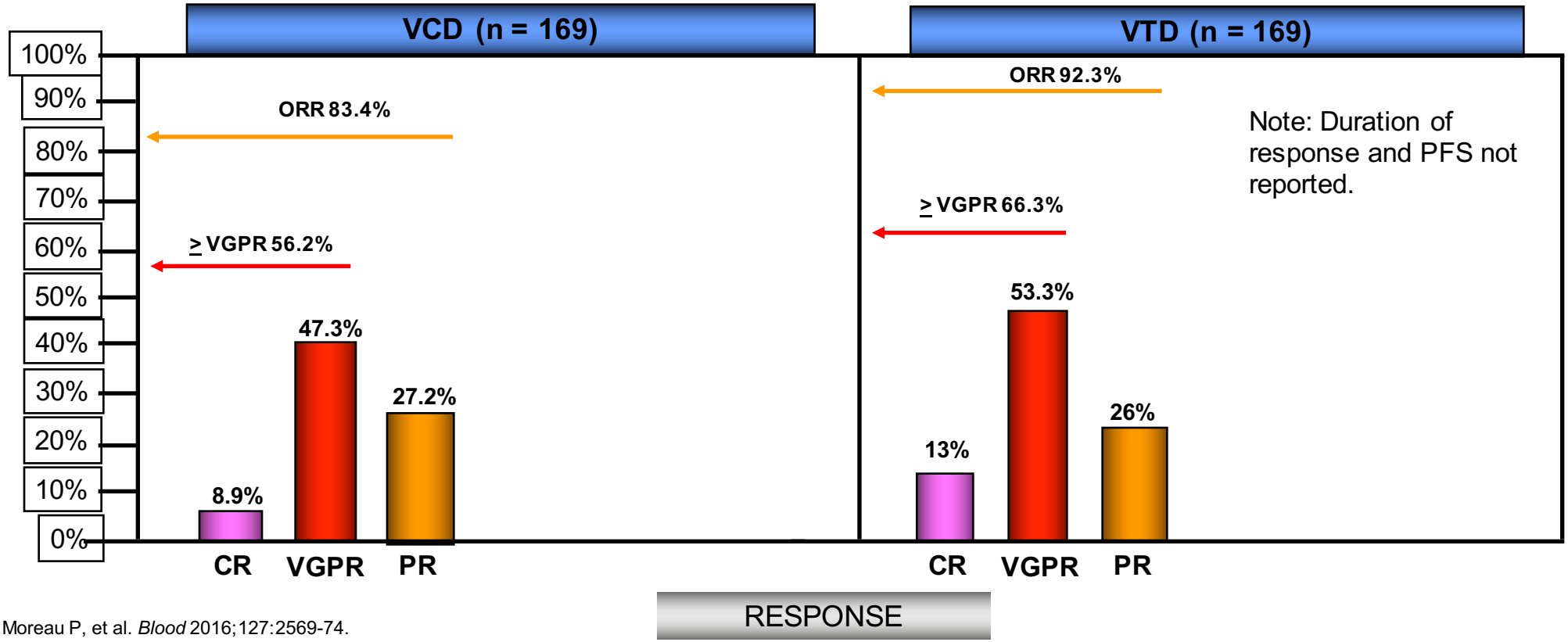
Durie BG, et al. *Lancet* 2017;389:519-27.

Frontline Therapy: Triplet (VTD) vs. Triplet (VCD)



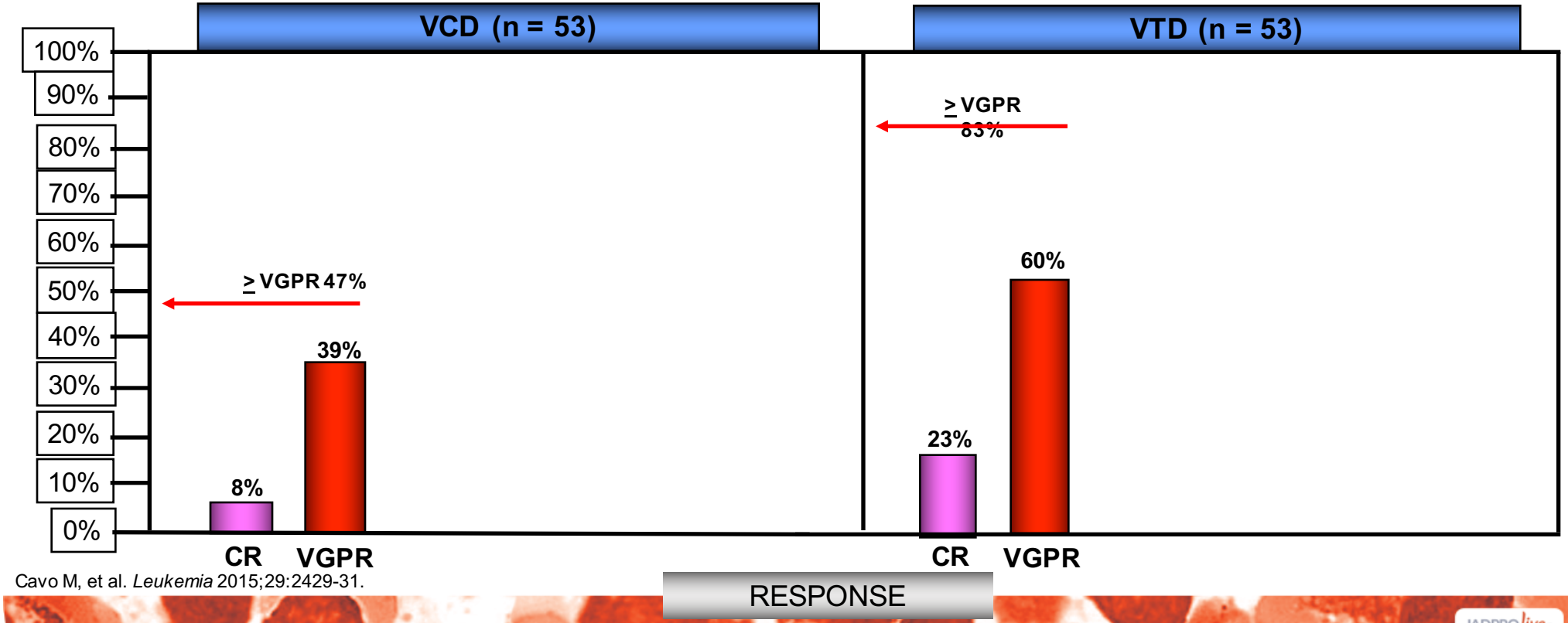
Moreau P, et al. *Blood* 2016;127:2569-74.

VCD vs. VTD: Overall Response



Moreau P, et al. *Blood* 2016;127:2569-74.

VCD vs. VTD Retrospective Review: Overall Response in High-Risk Disease



Cavo M, et al. *Leukemia* 2015;29:2429-31.

Survival in High-Risk Subgroups in Randomized Trials with Bortezomib in NDMM

FISH	N1/N2	End point	Arm 1	Arm 2	Arm 1 (%)	Arm 2 (%)	Comment
t(4;14)	26/24	3-y OS	PAD/ASCT/thalidomide*	VAD/ASCT/bortezomib*	44	66	HOVON65/GMMG- HD4
	98/106	4-y OS	VAD	VD	32	63*	IFM-2005
	21/23	2-y OS	Thalidomide*	Placebo*	67	87	TT2
	21/29	2-y OS	Thalidomide-TT2	Bortezomib TT3	67	97*	TT2 vs TT3
Del(17p)	21/16	3-y OS	VAD/ASCT/thalidomide	PAD/ASCT/bortezomib*	17	69*	HOVON65/GMMG-HD4
	119/54	4-y OS	VAD	V D	36	50	IFM-2005

Sonneveld P, et al. *Blood* 2016;127:2955-62.

Carfilzomib, Lenalidomide, and Dexamethasone in NDMM

	Jakubowiak et al (Phase I/II, n = 53)	Korde et al (Phase II, n = 45)
Combination therapy	CRd (phase II Cfz 20/36 mg/m^2) 8 cycles	CRd (Cfz 20/36 mg/m^2) 8 cycles
Extended dosing	CRd (Cfz every other week) 16 cycles, off-protocol Ln at last tolerated dose d1-21 after 16 cycles	Len 10 mg d1-21, 24 cycles
Transplant	≥ PR stem cell collection, HDM optional	Stem cell collection

Cfz = carfilzomib; HDM = high-dose melphalan; n = lenalidomide.

Jakubowiak AJ, et al *Blood* 2012;120:1801-9; Korde N, et al. *JAMA Oncol* 2015;1:746-54.

Carfilzomib, Lenalidomide, and Dexamethasone in NDMM

	Jakubowiak et al (Phase I/II, n = 53)	Korde et al (Phase II, n = 45)
ORR	62% nCR/CR, 81% VGPR, 98% PR after 12 cycles	56% CR/nCR (100% flow MRD **negative**– 67% **negative** by NGS), 62% nCR, 89% VGPR, 98% PR (without ASCT) after 8 cycles
PFS	92% (at 24 months)	92% (at 18 months)

ASCT = autologous stem cell transplant; nCR = near complete remission; NGS = next-generation sequencing; PFS = progression-free survival.

Jakubowiak AJ, et al *Blood* 2012;120:1801-9; Korde N, et al. *JAMA Oncol* 2015;1:746-54.

Carfilzomib, Lenalidomide, and Dexamethasone in NDMM

	Response			
	≥ PR	≥ VGPR	≥ nCR	sCR
ISS Stage				
I	100%	76%	57%	33%
II	100%	72%	55%	44%
III	93%	66%	79%	50%
Cytogenetics				
Standard	100%	76%	59%	38%
Unfavorable*	94%	76%	65%	53%

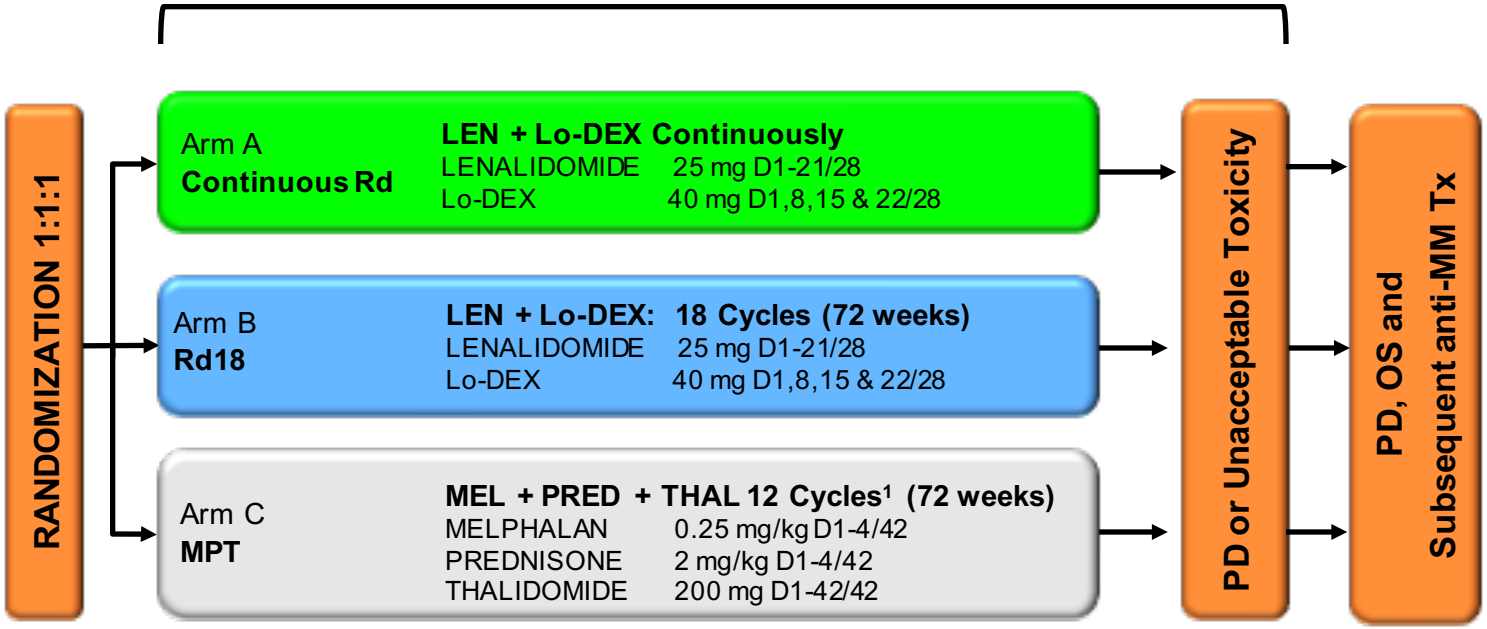
*Any of del 13 by metaphase or hypodiploidy or t(4;14) or t(14;16) or del 17p considered as unfavorable; all others considered normal/favorable.
sCR = stringent complete response.

Jakubowiak AJ, et al. *Blood* 2012;120:1801-9.

Ongoing Randomized Trials in NDMM

- Bortezomib, lenalidomide, dexamethasone with up-front or delayed autologous stem cell transplant (DFCI/IFM)
- Bortezomib, lenalidomide, dexamethasone vs. carfilzomib, lenalidomide, dexamethasone (ECOG-ACRIN)
- Bortezomib, lenalidomide, dexamethasone +/- elotuzumab for high risk myeloma patients (SWOG S1211)
- Bortezomib, lenalidomide, dexamethasone +/- daratumumab (NCT02874742)

Frontline Therapy Elderly Non-Transplant-Eligible: FIRST Study



Pts > 75 years: Lo-DEX 20 mg D1, 8, 15 & 22/28; THAL[2] (100 mg D1-42/42); MEL[2] 0.2 mg/kg D1–4

LT, long-term; PD, progressive disease; OS, overall survival

1. Facon T, et al. *Blood* 2013;122 2. Benboubker L. et al. *N Engl J Med* 2014;371:906-17.

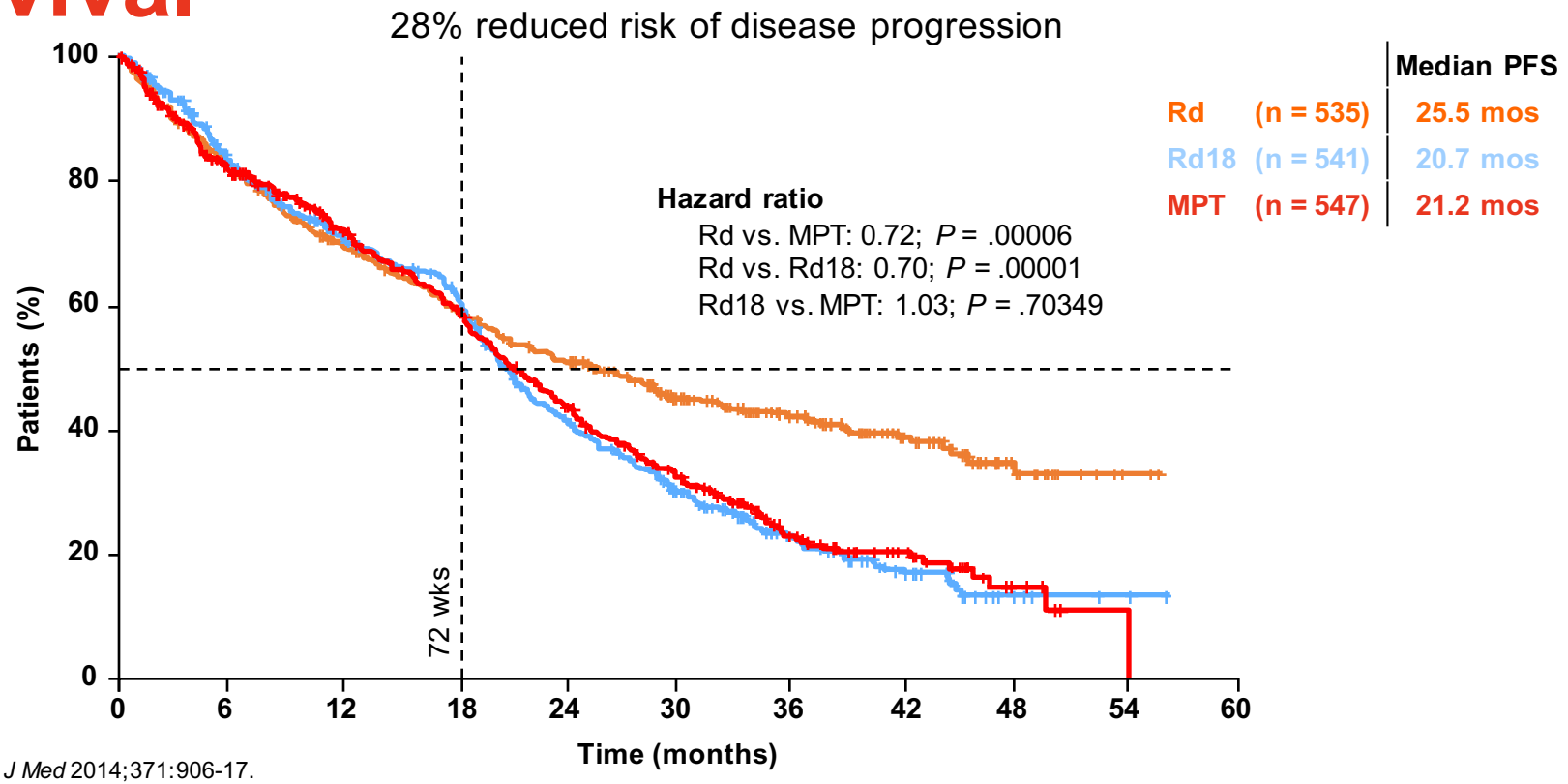
FIRST Study: Overall Response

Response[a] (%)	Continuous Rd (n = 535)	Rd18 (n = 541)	MPT (n = 547)
ORR (≥ PR)[b]	75	73	62
CR	15	14	9
VGPR	28	28	19
PR	32	31	34
SD	19	21	27
VGPR or better	43	42	28
Time to response (median, mos)	1.8	1.8	2.8
Duration of response (median, mos)	35.0	22.1	22.3

[a]IMWG Criteria; [b]Response assessment for Rd obtained every 4 weeks and for MPT every 6 weeks; Response and progression rate based on IRAC assessment.

Benboubker L. et al. *N Engl J Med* 2014;371:906-17.

FIRST Study: Progression-Free Survival



Benboubker L. et al. *N Engl J Med* 2014;371:906-17.

Frontline Therapy Summary

- Transplant-eligible patients
  - Triplet therapy preferred
    - Bortezomib, lenalidomide, and dexamethasone is standard of care
    - Consider carfilzomib, lenalidomide, and dexamethasone in high-risk patients
  - Do not give melphalan-based regimens
- Transplant-ineligible patients
  - Can consider doublet (e.g., lenalidomide/dexamethasone) or triplet therapy (e.g., VRd) depending on patients frailty and comorbidities
  - Recommend maintenance after initial therapy

Less Intense Therapy Recommended for Frail Individuals; Determining Frailty: Charlson Comorbidity Index

- Predicts 10-year mortality for patients by summing scores associated with comorbid conditions and age scores by assigning points to factors
  - 1 point each: myocardial infarct, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease, diabetes
  - 2 points each: hemiplegia, moderate or severe kidney disease, diabetes with end organ damage, tumor, leukemia, lymphoma
  - 3 points each: moderate or severe liver disease
  - 6 points each: malignant tumor, metastasis, AIDS
  - Age scores
    - < 50 years: 0 points
    - Age 50-59 years: 1 point
    - Age 60-69 years: 2 points
    - Age 70-70 years: 3 points

- Doublet instead of triplet therapy (e.g., Rd continuous therapy; FIRST trial)
- No ASCT
- Lower starting doses (e.g., Palumbo recommendations)

Charlson M, et al. *J Clin Epidemiol* 1994;47:1245-51; D'Hoore W, et al. *J Clin Epidemiol* 1996:49:1429-33; Palumbo A, et al. *Blood*. 2015;125:2068-74; courtesy of the IMF NLB.

Proposed Drug Dosing by Frailty/Risk Score

Agent	Dose Level 0 (No Risk Factors)	Dose Level -1 (≥ 1 Risk Factor)	Dose Level -2 (≥ 1 Risk Factor + Grade 3/4 Nonheme AE)
Thalidomide	100 mg/day	50 mg/day	50 mg QOD
Lenalidomide	25 mg/day Days 1-21/4 wks	15 mg/day on Days 1-21/4 wks	10 mg/day Days 1-21/4 wks
Pomalidomide	4 mg/day Days 1-21/4 wks	Reduce dose to 3 mg/day or further due to hematologic toxicity, reduce dose by 50% with strong CYP1A2 inhibitor	
Bortezomib	1.3 mg/m^2 2x/wk Days 1, 4, 8, 11/3 wks	1.3 mg/m^2 1x/wk Days 1, 8, 15, 22/5 wks	1.0 mg/m^2 1x/wk Days 1, 8, 15, 22/5 wks
Ixazomib	4 mg/day Days 1, 8, 15/4 wks	First reduction: 3 mg Hold treatment if low blood counts or PN (resume at lower dose)	Second reduction: 2.3 mg/day; discontinue if grade 4 PN
Dexamethasone	40 mg/day Days 1,8,15, 22/4 wks	20 mg/day Days 1, 8, 15, 22/4 wks	10 mg/day Days 1, 8, 15, 22/4 wks
Prednisone	60 mg/m^2 Days 1-4 or 50 mg QD	30 mg/m^2 Days 1-4 or 25 mg QD	15 mg/m^2 Days 1-4 or 12.5 mg QD
Cyclophosphamide	100 mg/day Days 1-21/4 wks or 300 mg/m^2/day Days 1, 8, 15/4 wks	50 mg/day Days 1-21/ 4 wks or 150 mg/m^2/day Days 1, 8, 15/4 wks	50 mg/day Days 1-21/4 wks or 75 mg/m^2/day Days 1, 8, 15/4 wks
Melphalan	0.25 mg/kg or 9 mg/m^2 Days 1-4/4-6 wks	0.18 mg/kg or 7.5 mg/m^2 Day 1-4/4-6 wks	0.13 mg/kg or 5 mg/m^2 Day 1-4/4-6 wks

AE = adverse event.

Palumbo A, et al. *Blood*. 2011;118:4519-29; Palumbo A, et al. *Blood*. 2015;125:2068-74; Ninlaro (Ixazomib) package insert. 2015. https://www.ninlaro.com/prescribing-information.pdf; Pomalyst (Pomalidomide) [package insert]. 2013. http://media.celgene.com/content/uploads/pomalyst-pi.pdf; courtesy of the IMF NLB.

Selected Common Side Effects with Proteasome Inhibitors

- **Asthenia**
  - Exercise program
  - Energy sparing activities
  - Assess depression
- **Gastrointestinal effects**
  - Diarrhea
  - Constipation
- **Thrombocytopenia**
  - Cyclical with lowest levels on day 11 of cycle with bortezomib (21 day schedule)
  - Hold therapy for platelets less than 25,000 or ANC <1
- **Cardiac events**
  - Baseline echo prior to carfilzomib
  - Instruct patient to report increased dyspnea
- **Peripheral neuropathy** (less with carfilzomib and ixazomib)
  - Monitor neuropathy at each patient encounter
  - Dose adjust per recommended guidelines
  - Educate patients on signs and symptoms of neuropathy
- **Herpes zoster**
  - Increased incidence
  - Recommend prophylaxis with proteasome inhibitors based regimens
- **Renal insufficiency**
  - IV fluids with carfilzomib
  - Dose reduce ixazomib
  - Monitor renal function with carfilzomib

Pomalidomide package insert. 2013. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204026lbl.pdf; Lenalidomide package insert. 2005. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021880s049lbl.pdf.

Thromboembolic Events

- Patients with cancer are at increased risk of thromboembolic events (4- to 5-fold)
- Risk of mortality from a TEE is 2-fold higher in patients with cancer
- Individuals with advanced disease are at higher risk of TEE
- Myeloma patients at highest risk at time of initial diagnosis

TEE = thromboembolic event.

Kristinsson S. *Hematology Am Soc Hematol Educ Program.* 2010;2010:437.

Risk Assessment Model for Management of VTE

Risk Factors	Recommendations
Myeloma Therapy	
High-dose dexamethasone, multiagent chemotherapy, or doxorubicin	LMWH or full-dose warfarin when combined with thalidomide or lenalidomide
Individual	
• Obesity • Previous venous thromboembolism • Central venous catheter or pacemaker • Comorbidity such as diabetes, cardiac disease, acute infection, immobilization, renal disease • Surgery • Medications (erythropoietin) • Blood clotting disorder	No risk factor or only 1 risk factor, aspirin 81–325 mg daily
Myeloma Related	
• Diagnosis • Hyperviscosity	If 2 or more risk factors are present, then full-dose warfarin or LMWH

LMWH = low molecular weight heparin; VTE = venous thromboembolism.

Kristinsson S. *Hematology Am Soc Hematol Educ Program.* 2010;2010:437; Palumbo A, et al. *Leukemia* 2008;22:414-23.

Patient Education: Venous Thromboembolism

- Educate patients on signs and symptoms of VTE
  - Unilateral swelling
  - Redness behind the calf
  - Pain in the extremity
  - Distention of superficial venous collateral circulation
  - Chest pain
  - Shortness of breath (acute onset)
  - Tachycardia

Rome S, et al. *Clin J Oncol Nurs* 2008;12(3 Suppl):21-8.

Nurse's Role in IV and Oral Adherence

- Essential in both IV and oral therapy adherence
- Reinforce the rationale for ongoing treatment plan
  - Myeloma is a chronic condition, ongoing therapy needed
  - Patients who receive therapy live longer
  - Pill in bottle or at pharmacy are not able kill myeloma cells
- Encourage shared decision-making and mutual treatment/quality-of-life goals
- Optimize treatment; prevent and/or reduce the severity of adverse events
- Provide tools, education for AE awareness, and management
- Engage caregivers in the treatment process and education
- Offer advice (consistent time, alarm clocks, pillboxes, smart phone "alerts")
- Engage members of the interdisciplinary team to identify solutions and resources
- Combat treatment fatigue

Faiman BM. *J Adv Pract Oncol* 2012;2:26-34; Miaskowski C, et al. *Clin J Oncol Nurs* 2008;12:213-21; Gleeson T, et al. *Osteoporos Int* 2009;20:2127-34; Accordino MK, et al. *Am Soc Clin Oncol Educ Book* 2013:271-276; Kurtin S, et al. *J Adv Pract Oncol* 2016; 7(suppl 1):71-77; courtesy of the IMF NLB.

Barriers to Adherence and Persistence

Personal

- Low health literacy
- Lifestyle: poor motivation, limited adaptation to healthy lifestyle
- Hopelessness
- History of nonadherence
- History of mental illness or substance abuse
- Cultural beliefs
- Competing comorbidities/polypharmacy
- Age
  - Peak at age 70 years, then gradual declines in some patients due to age-related processes
  - Impaired executive function

Socioeconomic

- Limited financial or social resources:
  - Homelessness
  - Unstable housing
  - Uninsured
  - Lack of coverage for oral therapies
  - Copayment > $90
- Lack of family/caregiver support
- Inconvenience

Krueger KP, et al. *Adv Ther* 2015;22:313-56; Mallick R, et al. *Curr Med Res Opin* 2013;29:1701-8; Accordino MK, et al. *Am Soc Clin Oncol Educ Book 2013;*271-6.

Tailoring Treatment to Patient-Specific Comorbidities

- Pre-existing neuropathy
  - Consider carfilzomib-based regimen (versus bortezomib) as incidence of peripheral neuropathy only ~5% with carfilzomib
- Pre-existing cardiomyopathy
  - Consider bortezomib-based regimen (versus carfilzomib) as carfilzomib can lead to congestive heart failure in ~5% of cases
- Renal failure
  - Consider bortezomib, cyclophosphamide, dexamethasone (CyBorD) initially for rapid initiation of treatment
- Diabetes
  - Consider endocrinology referral for patients with a history of pre-diabetes and diabetes while on steroids
- History of bleeding (e.g., gastrointestinal bleed)
  - Consider avoiding IMiD-dexamethasone combinations and consider proteasome inhibitor alkylator combinations instead to avoid need for thromboprophylaxis

Case Study

- Ms. D starts carfilzomib, lenalidomide, and dexamethasone as her frontline therapy and develops a pruritic, raised macular rash on her upper torso and face three days after she starts lenalidomide.

What would you advise the patient?

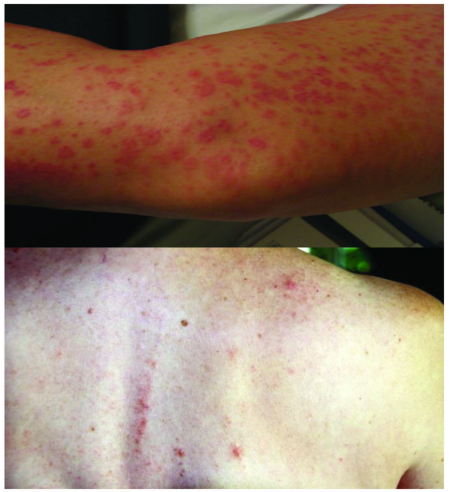


Image from Fowler NH, et al. *Haematologica* 2015;100:e454-7.

Selected Common Side Effects with IMiDs

- **Asthenia**
  - Exercise program
  - Energy sparing activities
  - Assess depression
- **GI effects**
  - Diarrhea
    - Colestyramine can be helpful in patients with lenalidomide induced diarrhea
  - Constipation (More common with thalidomide)
  - Instruct patient on bowel program
- **Thrombocytopenia**
  - Hold for platelets <25,000
- **Neutropenia**
  - Hold for ANC <1
- **Peripheral neuropathy** (more common with thalidomide)
  - Monitor neuropathy at each patient encounter
  - Dose adjust per recommended guidelines
  - Educate patients on signs and symptoms of neuropathy
- **Rash**
  - 10-20% incidence
  - Combination of cetirizine, ranitidine, and L-lysine can help mitigate IMiD-related rash
- **Thromboembolic Events**
  - Increased incidence
  - Prophylaxis with aspirin, warfarin, or low molecular weight heparin depending on risk
- **Renal**
  - Dose reduce lenalidomide and pomalidomide for creatinine clearance

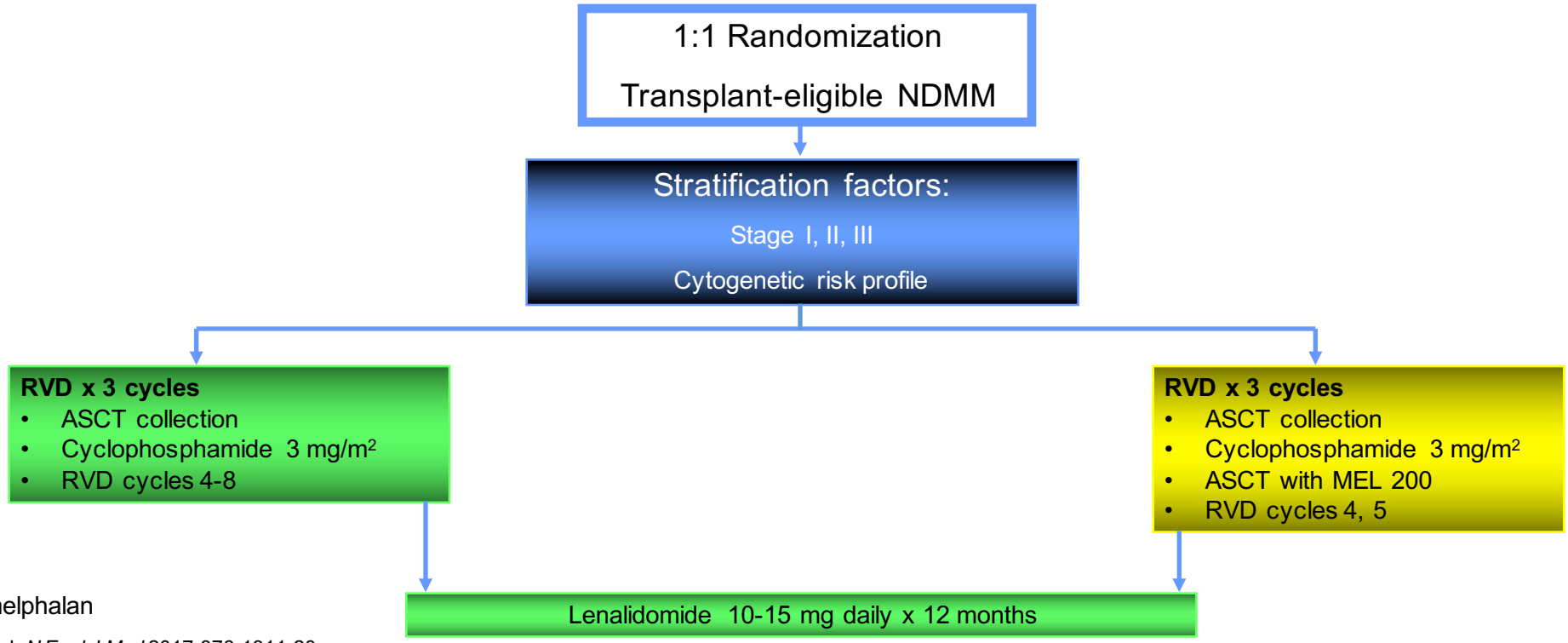
Pomalidomide package insert. 2013. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204026lbl.pdf; Lenalidomide package insert. 2005. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021880s049lbl.pdf.

Case Study

- Ms. D completes four cycles of carfilzomib/lenalidomide/dexamethasone and achieves a VGPR
- She is now ready to proceed to high-dose chemotherapy and autologous stem cell transplant

She asks, "What is the potential benefit of undergoing an autologous stem cell transplant?"

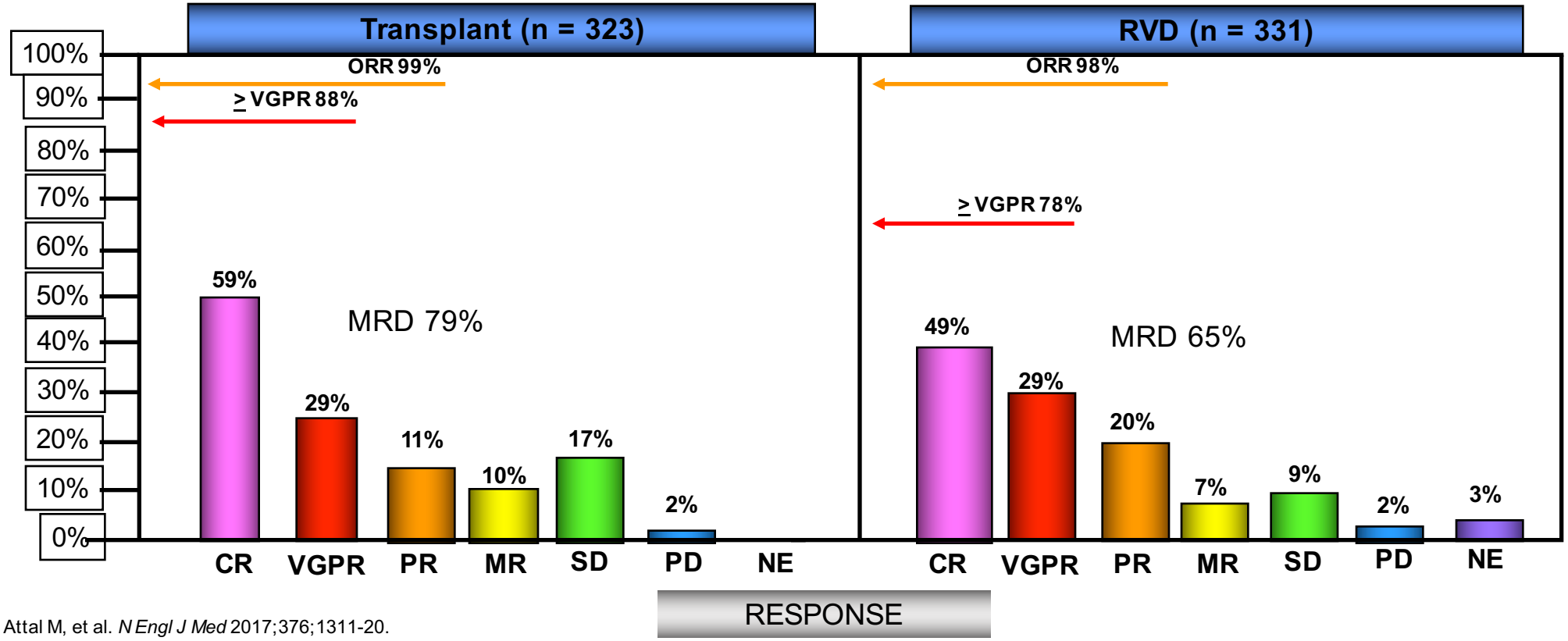
IFM 2009: RVD +/- ASCT



MEL = melphalan

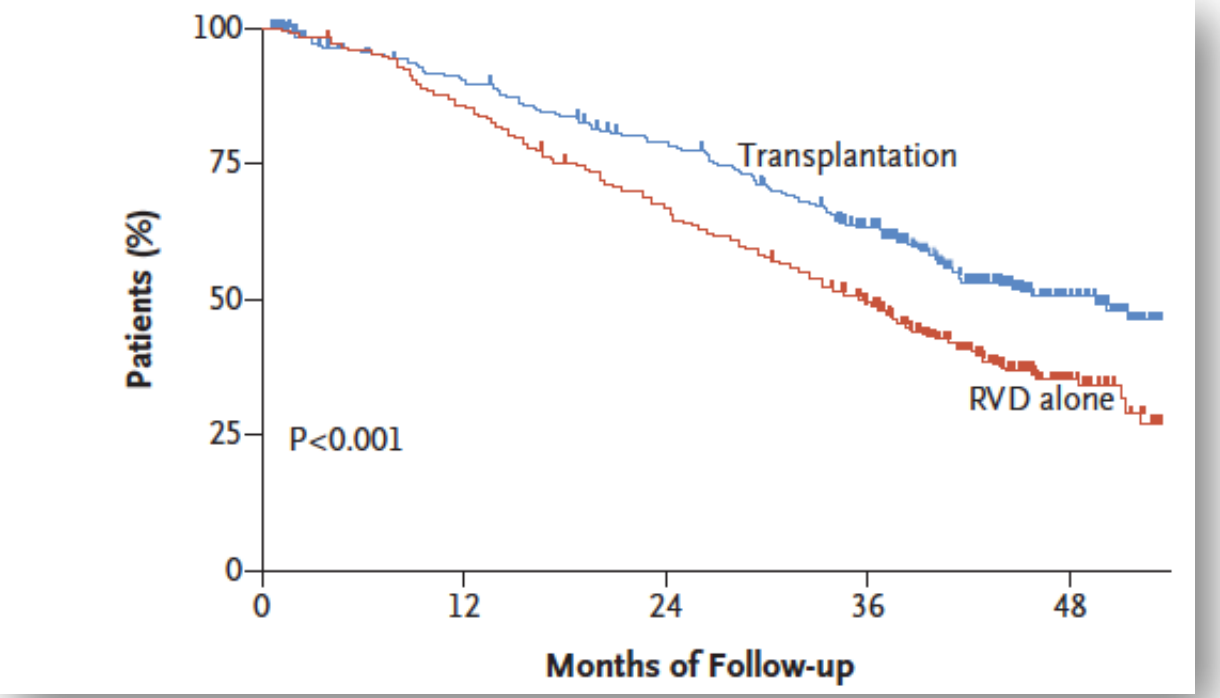
Attal M, et al. *N Engl J Med* 2017;376;1311-20.

RVD +/- ASCT: Overall Response



Attal M, et al. *N Engl J Med* 2017;376;1311-20.

RVD +/- ASCT: Progression-Free Survival



PFS

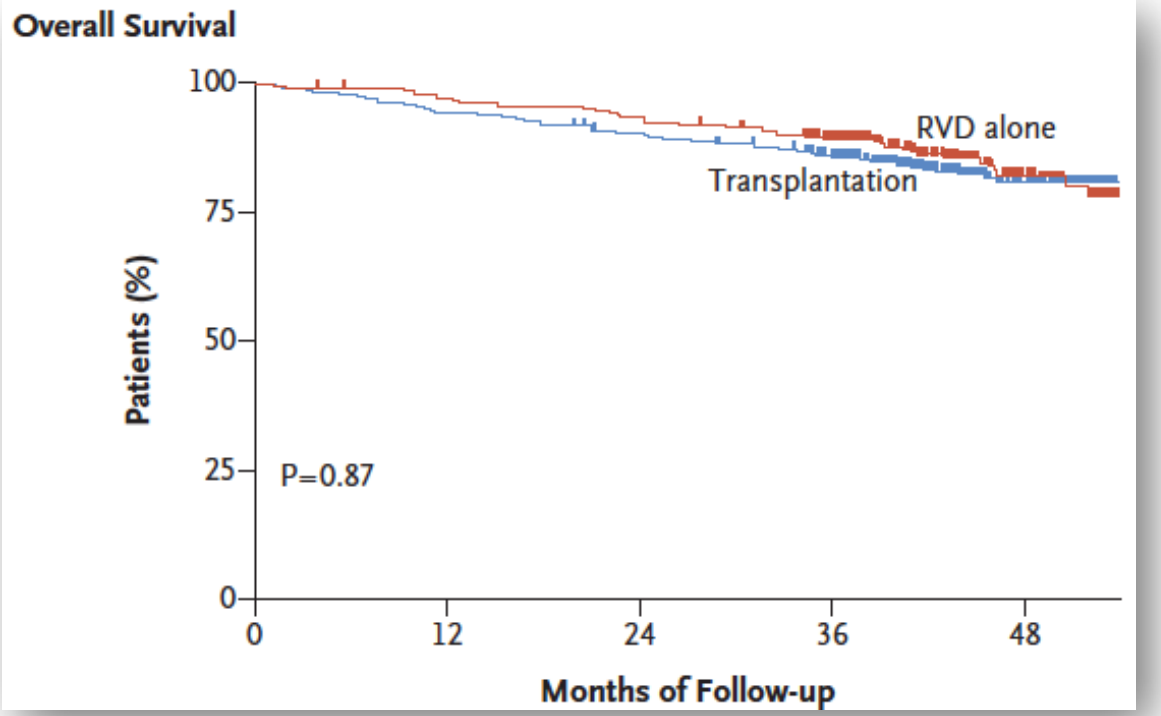
50 months (RVD + ASCT)

vs.

36 months (RVD)

Attal M, et al. *N Engl J Med* 2017;376;1311-20.

RVD +/- ASCT: Overall Survival



4-year OS

81% (RVD + ASCT)

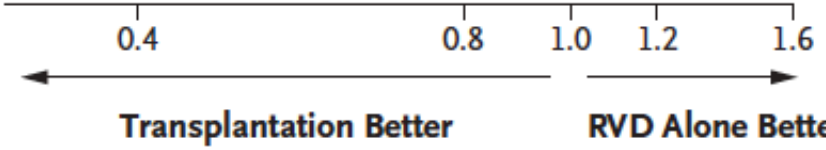
vs.

82% RVD)

Attal M, et al. *N Engl J Med* 2017;376;1311-20.

RVD +/- ASCT: High-Risk Subgroup

Subgroup	Transplantation	RVD Alone	Hazard Ratio (95% CI) for Progression or Death	P Value for Interaction
	no. of events/no. of patients			
International Staging System disease stage				0.98
I	60/115	44/118		
II	107/170	81/171		
III	44/65	32/61		
Cytogenetic risk at screening				0.51
Standard risk	122/212	83/213		
High risk	32/44	31/46		
Test failure	57/94	43/91		



Attal M, et al. *N Engl J Med* 2017;376;1311-20.

Up-Front Transplant vs Delayed Transplant: Evolving Questions

- Role of indefinite maintenance with lenalidomide on long-term outcomes (will be answered by DFCI cohort of trial)
- Role of MRD negativity as a clinically relevant endpoint in deciding on up-front versus delayed ASCT approach

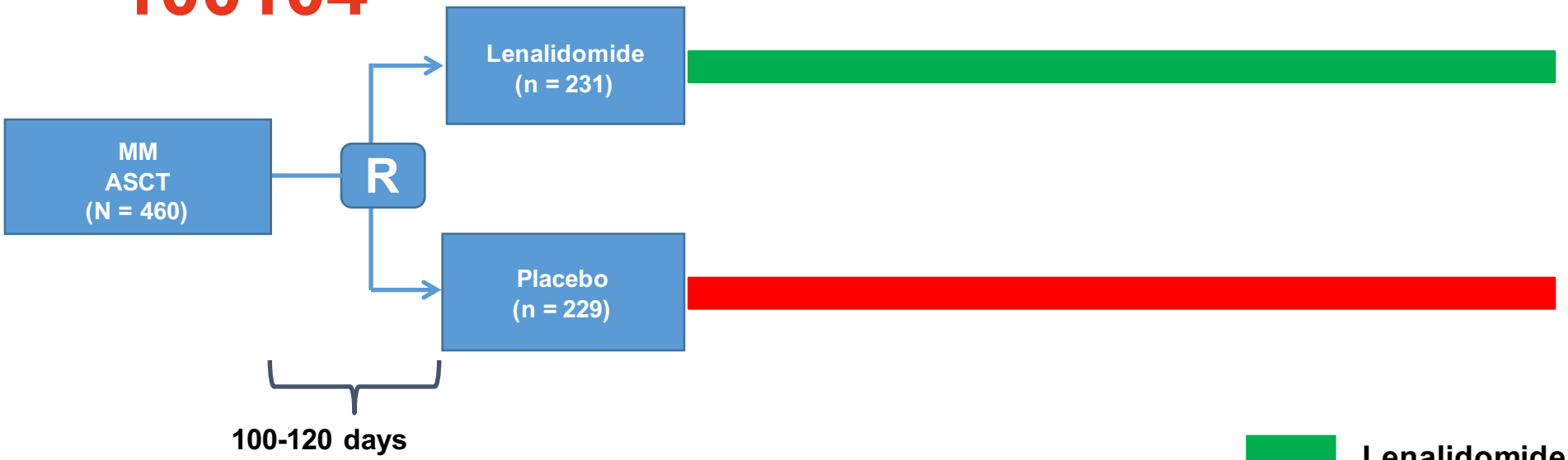
- **High dose chemotherapy and ASCT still considered standard of care in 2017 for the treatment of newly diagnosed transplant-eligible patients.**

Case Study

- Ms. D proceeds with high dose chemotherapy and autologous stem cell transplantation. She returns to clinic and is 2 ½ months post transplant and is in a near CR.

She is here to discuss maintenance therapy options with you.

Lenalidomide Maintenance: CALGB 100104



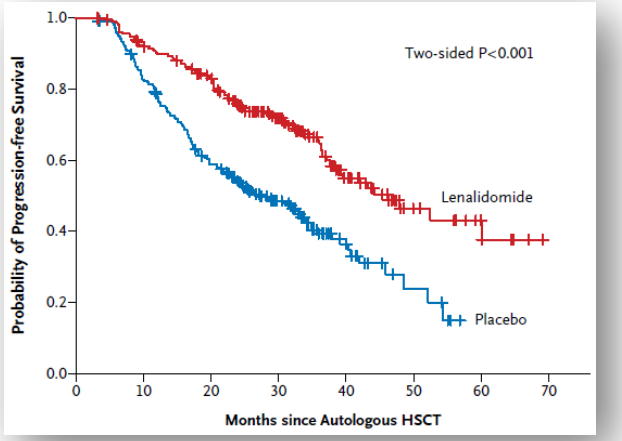
- Starting dose: lenalidomide 10 mg daily
- Dose escalation by 5 mg (max 15 mg) after 3 months if ANC > 1000, platelets > 75,000
- Drug held for 8 weeks if ANC < 500, platelets < 30,000, then restarted at 5 mg dose decrease
- Prophylactic ASA or LMWH mandated in high-risk patients for DVT/PE

ASA = acetylsalicylic acid; DVT = deep vein thrombosis; PE = pulmonary embolism.

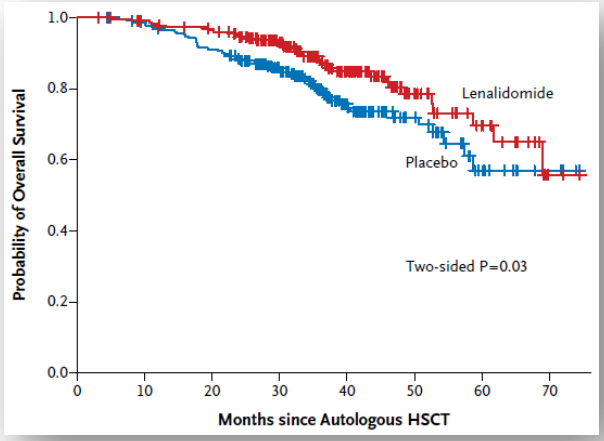
McCarthy PL, et al. *N Engl J Med* 2012;366:1770-81.

Lenalidomide Maintenance: CALGB 100104

Progression-Free Survival



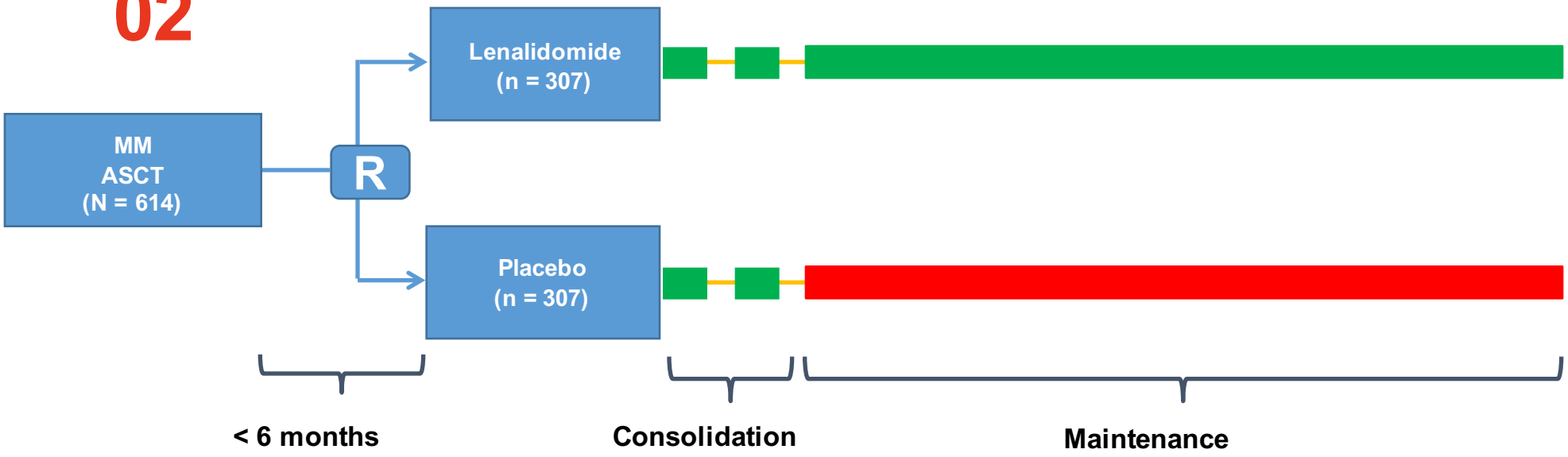
Overall Survival



Outcome	Lenalidomide	Placebo	P value or HR
PFS	46 months	27 months	*P* < .001
3-year OS rate	88%	80%	HR 0.62 95% CI 0.40-0.95

McCarthy PL, et al. *N Engl J Med* 2012;366:1770-81.

Lenalidomide Maintenance: IFM 2005-02



- Consolidation phase: lenalidomide 25 mg daily 21/28 days x 2 cycles
- Maintenance phase: starting dose lenalidomide 10 mg daily, increased to 15 mg daily after 3 months if well tolerated

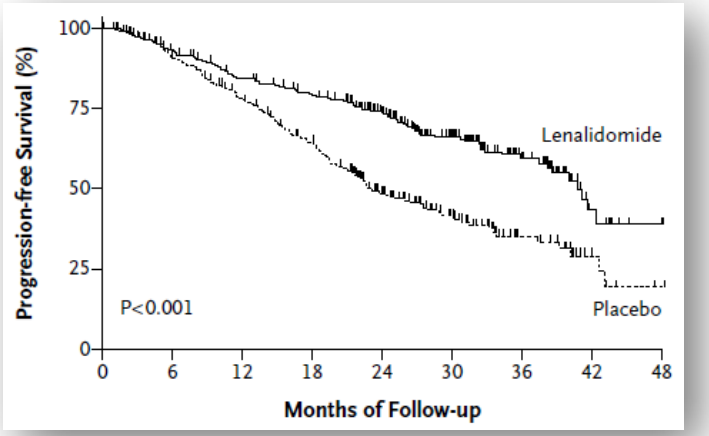
Lenalidomide

Placebo

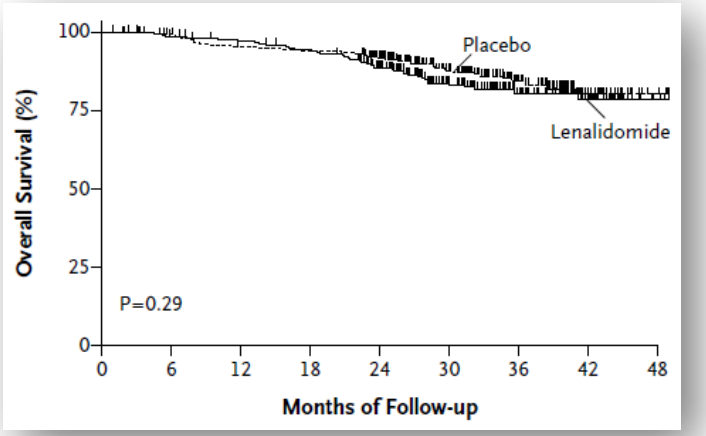
Attal M, et al. *N Engl J Med* 2012;336:1782-91.

Lenalidomide Maintenance: IFM 2005-02

Progression-Free Survival



Overall Survival



Outcome	Lenalidomide	Placebo	P value or HR
PFS	41 months	23 months	*P* < .001
4-year OS rate	73%	75%	*P* = .7

Attal M, et al. *N Engl J Med* 2012;336:1782-91.

Lenalidomide Maintenance: IFM 2005-02

Subgroup	Lenalidomide	Placebo	Hazard Ratio for Progression or Death	p-value for interaction
	no. of events / no. of patients			
Cytogenetic abnormalities				
13 q deletion	46 / 114	72 / 116		0.90
No 13 q deletion	44 / 161	74 / 167		
t(4;14) or 17 p deletion	21 / 52	17 / 29		0.39
Neither t(4;14) nor 17 p deletion	60 / 203	109 / 224		

Attal M, et al. *N Engl J Med* 2012;336:1782-91.

Lenalidomide Maintenance: Secondary Malignancies

CALGB 100104

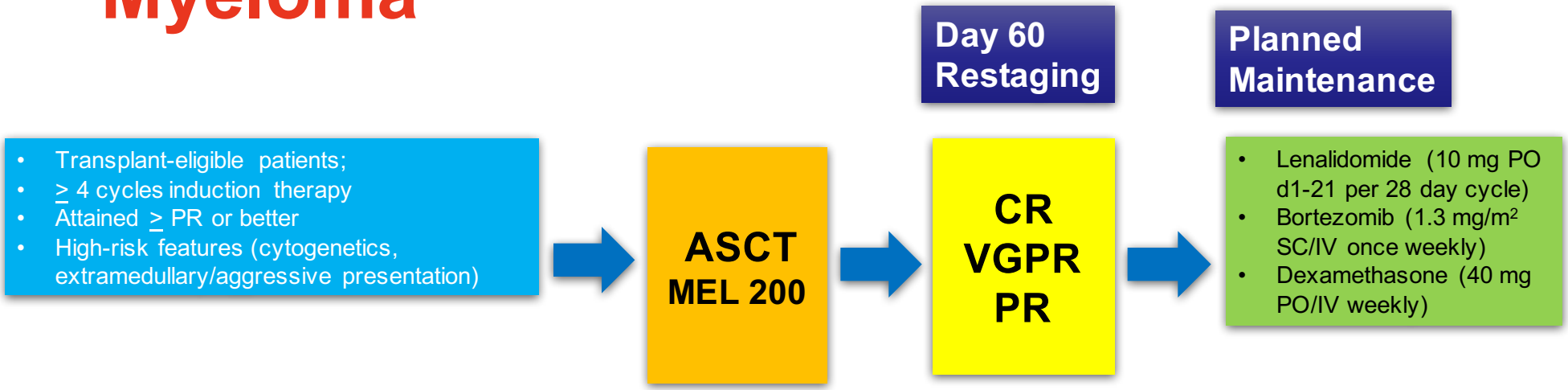
Second Cancer	Lenalidomide (N=231)	Placebo (N=229)
	number of patients	
Hematologic cancers*		
Acute lymphoblastic leukemia	1	0
Acute myeloid leukemia	5	0
Hodgkin's lymphoma	1	0
Myelodysplastic syndrome	1	0
Non-Hodgkin's lymphoma	0	1
Total	8	1
Solid-tumor cancers		
Breast cancer	3	0
Carcinoid tumor	0	1
Central nervous system cancer	1	0
Gastrointestinal cancer	2	1
Gynecologic cancer	1	1
Malignant melanoma	1	2
Prostate cancer	1	0
Thyroid cancer	1	0
Total	10	5
Basal-cell carcinoma	2	1
Squamous-cell carcinoma	2	2

IFM 2005-02

Type of Lesion	Lenalidomide Group (N=306)	Placebo Group (N=302)	Total (N=608)
	number of patients (percent)		
Hematologic cancers	13 (4)	5 (2)	18 (3)
AML or MDS	5	4	
ALL	3	0	
Hodgkin's lymphoma	4	0	
Non-Hodgkin's lymphoma	1	1	
Solid tumors	10 (3)	4 (1)	14 (2)
Esophageal	1	0	
Colon	3	0	
Prostate	2	1	
Breast	2	0	
Lung	0	1	
Sinus	1	0	
Kidney	1	1	
Melanoma	0	1	
Nonmelanoma skin cancers	5 (2)	3 (1)	8 (1)
Total	26 (8)	11 (4)	37 (6)

McCarthy PL, et al. *N Engl J Med* 2012;366:1770-81; Attal M, et al. *N Engl J Med* 2012;336:1782-91.

RVD Maintenance for High-Risk Myeloma



- Evaluation of efficacy and safety of RVD maintenance in patients with high-risk multiple myeloma
- Objectives
  - To determine the efficacy of RVD maintenance in prolonging PFS in high-risk patients following induction therapy with RVD x 4 cycles and ASCT
  - Secondary objective: to determine the safety of RVD regimen as maintenance therapy

Nooka AK, et al. *Leukemia* 2014;28:690-3.

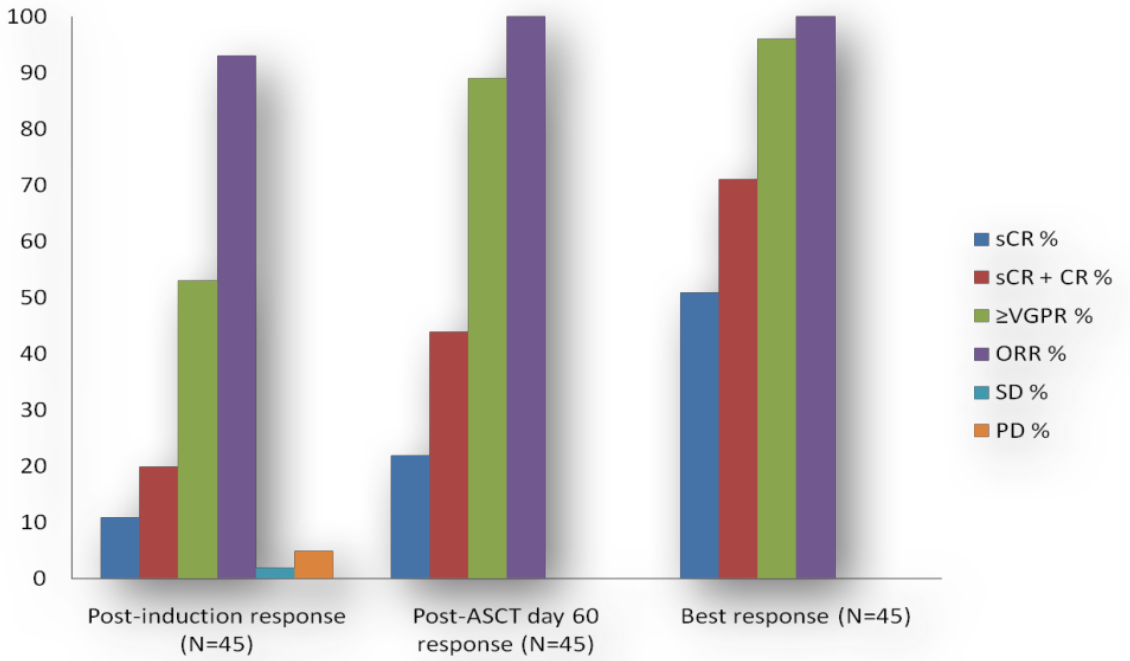
VRD Maintenance After ASCT in High-Risk Disease

- 45 patients received VRD maintenance after ASCT for 3 years
  - Bortezomib 1.3 mg/m^2 weekly
  - Lenalidomide 10 mg d1-21
  - Dexamethasone 40 mg weekly

High-Risk Features	n (%)
Del 17p	19 (42)
Del 1p	9 (20)
t (4;14)	2 (5)
t (14;16)	5 (11)
PCL	11 (24)
Others (aggressive presentation)	7 (16)
> 1 cytogenetic abnormalities	34 (75)

Nooka AK, et al. *Leukemia* 2014;28:690-3.

VRD Maintenance High-Risk MM: Response Rates

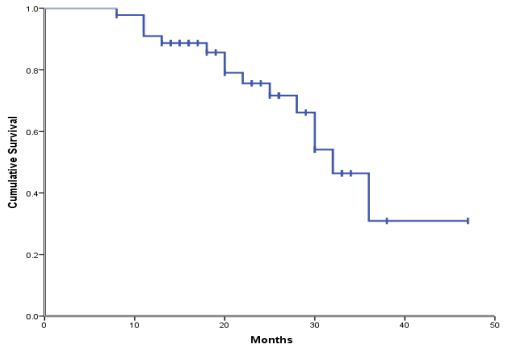


Nooka AK, et al. *Leukemia* 2014;28:690-3.

VRD Maintenance High-Risk MM: PFS and OS

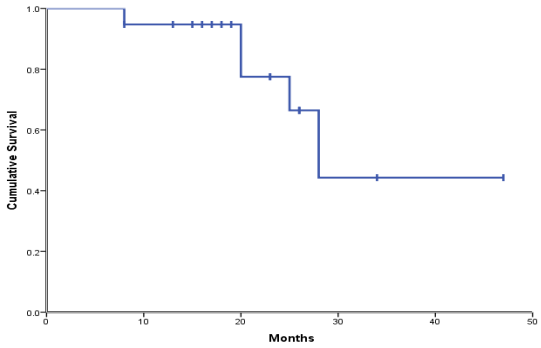
PFS in all patients: 32 months

A

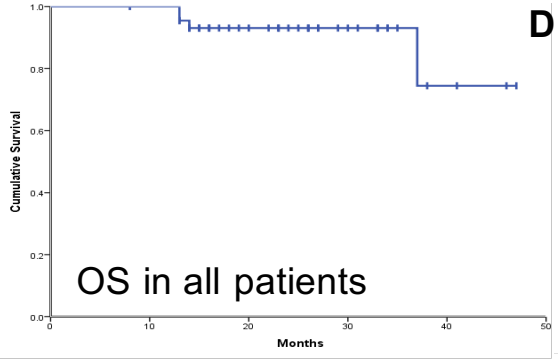


PFS in del 17p: 26 months

B

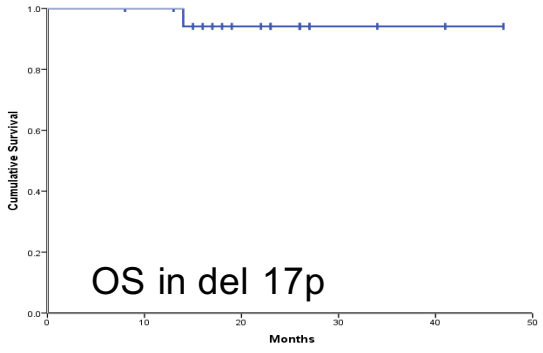


C



OS in all patients

D



OS in del 17p

Nooka AK, et al. *Leukemia* 2014;28:690-3.

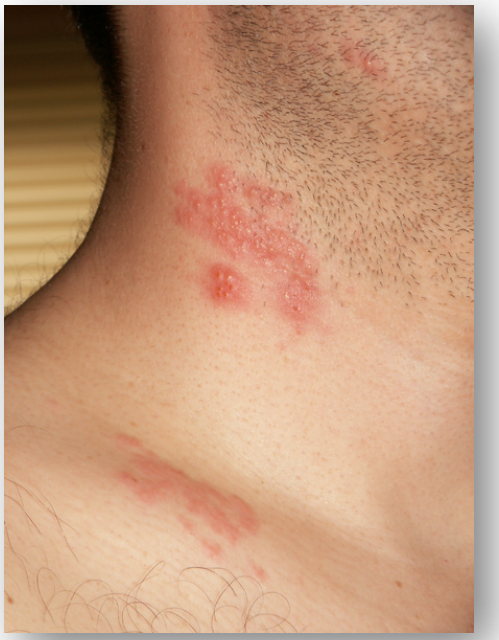
Case Study

Ms. D starts bortezomib, lenalidomide, and dexamethasone maintenance therapy given her high-risk disease. One year later, she develops a painful vesicular rash over her left T9 dermatome. A diagnosis of varicella zoster is confirmed. Upon further questioning, she had stopped taking her anti-viral prophylaxis 3 months ago.

Which myeloma drug likely contributed to her increased risk of varicella zoster?

Herpes Zoster

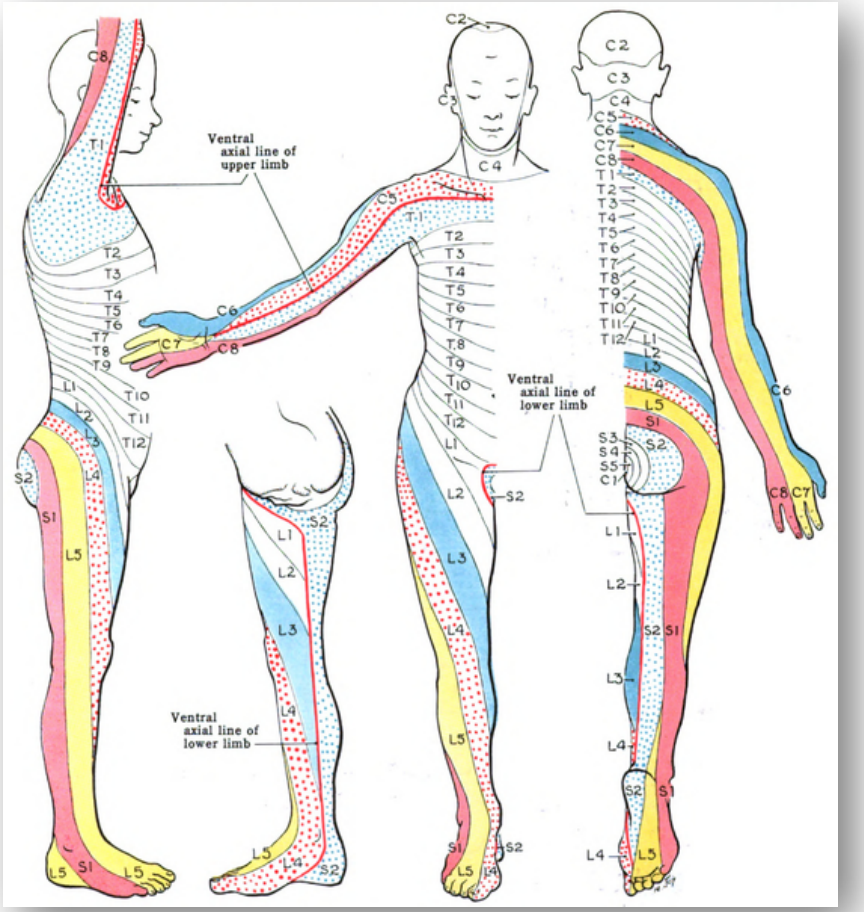
- Incidence of herpes zoster in patients receiving a bortezomib regimen ranges from 10% to 16%
- Prophylaxis recommended in individuals receiving proteasome inhibitors (e.g., bortezomib, carfilzomib, and ixazomib) with either acyclovir or valcyclovir
- Educate patients on signs and symptoms of zoster



Herpes zoster reactivation treated with acyclovir 800 mg 5× day

Nucci M, et al. *Clin Infect Dis* 2009;49:1211.

Dermatome Map of the Body



Case Study

Ms. D returns to clinic for follow-up. After 2 years on maintenance therapy, laboratory testing shows that she has had reappearance of her M-protein at 0.5 g/dL.

What would you recommend for treatment?

Definitions for Relapsed Disease: Clinical Relapse

- Clinical relapse requires one or more of
  - Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)
    - Calcium ↑ in serum (> 11.5 g/dL)
    - Renal insufficiency (SCr > 2 mg/dL)
    - Anemia (Hgb < 10 g/dL [Durie et al.] or decrease in Hbg ≥ g/dL [NCCN])
    - Bone lesions or osteoporosis
  - Development of new soft tissue plasmacytomas or bone lesions
  - Definite increase in the size of existing plasmacytomas or bone lesions (50%+ increase and at least 1 cm)

Hgb = hemoglobin; SCr = serum creatinine.

NCCN, 2013; Durie BG, et al. *Leukemia* 2006;20:1467-73.

Definitions for Relapsed Disease: Relapse from CR

- Clinical relapse requires one or more of the following
  - Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)
  - Reappearance of serum or urine M-protein by immunofixation or electrophoresis
  - Development of > 5% plasma cells in the bone marrow

NCCN, 2013; Durie BG, et al. *Leukemia* 2006;20:1467-73.

Definitions for Relapsed Disease: Progressive Disease

- Increase of > 25% from baseline (NCCN) or lowest value (Durie et al.) in any one or more of the following:
  - Serum M-component and/or (the absolute increase must be > 0.5 g/dL)
  - Urine M-component and/or (the absolute increase must be > 200 mg/24 hours)
  - Only in patients without measureable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels; the absolute increase must be > 10 mg/dL
  - Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
  - Development of hypercalcemia (correct serum calcium > 11.5 mg/dl) attributed solely to plasma cell proliferative disorder

FLC = free light chain.

NCCN, 2013; Durie BG, et al. *Leukemia* 2006;20:1467-73.

Which Treatment to Choose?

- What is the goal?
- Previous therapy
- Previous responses
- Toxicities
- Patient characteristics/other factors
- Standard-of-care versus clinical trials

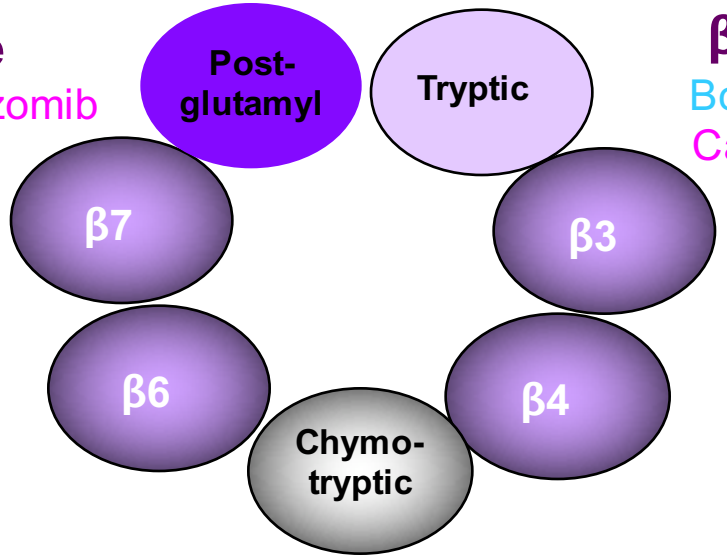
NCCN Preferred (Category 1) Regimens for First Relapse

- Carfilzomib, lenalidomide, dexamethasone
- Ixazomib, lenalidomide, dexamethasone
- Elotuzumab, lenalidomide, dexamethasone
- Daratumumab, lenalidomide, dexamethasone
- Daratumumab, bortezomib, dexamethasone
- Carfilzomib, dexamethasone

NCCN Guidelines v2.2018.

Proteasome Inhibitor Comparison

β1 Caspase-like
Bortezomib 74 nM Carfilzomib 2400nM



β2 Trypsin-like
Bortezomib 4200 nM
Carfilzomib 3600 nM

β5 Chymotrypsin-like
Bortezomib 7 nM
Carfilzomib 6 nM

Adapted from Stewart et al, 2007; slide courtesy of Dr. Donna Weber

Lenalidomide/Dexamethasone +/- Carfilzomib (ASPIRE)

INCLUSION
- ≥1 line prior therapy
- ≥ PR at least once
- Documented PD during/after last line treatment
- Secretory MM by IMWG criteria

1:1 Randomization

Stratification factors
B2M (<2.5 vs >2.5)
Prior lenalidomide (yes vs. no)
Prior Bortezomib (yes vs. no)

EXCLUSION
- ANC ≤ 1 x 10^9
- Hemoglobin ≤ 8.0 g/dL
- Platelets ≤ 50 x 10^9
- CrCl ≤ 50 mL/min
- >2 peripheral neuropathy
- NYHA class III or IV heart failure
- Refractory to lenalidomide or bortezomib
- Prior d/c lenalidomide due to AE

- Lenalidomide 25 mg D1-21 PO
- Dexamethasone 40 mg PO weekly

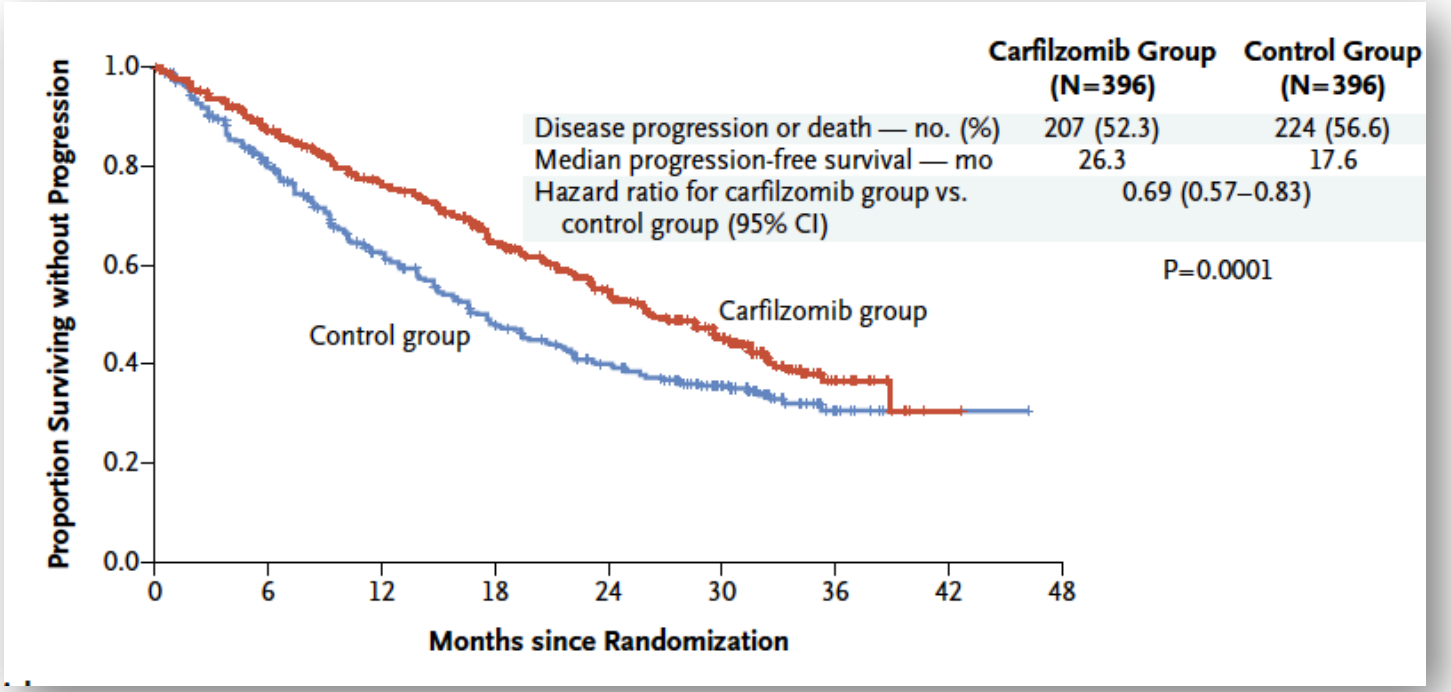
Repeat q 28 D

Cycles 1-2:
- Lenalidomide 25 mg D1-21 PO
- Dexamethasone 40 mg D1,8,15,22
- Carfilzomib 20 mg/m^2 Days 1,2 and 27 mg/m^2 IV on D8,9, 15,16

All cycles repeat q 28 D

Stewart AK, et al *N Engl J Med* 2015;372:142-52.

Lenalidomide/Dexamethasone +/- Carfilzomib



	Carfilzomib Group (N=396)	Control Group (N=396)
Disease progression or death — no. (%)	207 (52.3)	224 (56.6)
Median progression-free survival — mo	26.3	17.6
Hazard ratio for carfilzomib group vs. control group (95% CI)	0.69 (0.57–0.83)	

Stewart AK, et al *N Engl J Med* 2015;372:142-52.

KRd vs. Rd: High-Risk Subgroup Analysis

	Standard Risk PFS	Del 17p PFS	Del 17p ORR	t(4:14) PFS	t(4:14) ORR
KRd	29.6	24.5	76.9%	23.1	80%
Rd	19.5	16.7	46.2%	16.7	72%

KRd = carfilzomib, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone.

Avet-Loiseau H, et al. *Blood* 2016;128:1174-80.

Carfilzomib/Dexamethasone vs. Bortezomib/Dexamethasone (ENDEAVOR)

INCLUSION
- 1-3prior lines of therapy
- ≥ PR to bortezomib with a treatment free interval of 6 months
- PD during/after last line of treatment
Secretory MM by IMWG criteria

1:1 Randomization

Stratification factors
Stage I, I, III
Lines of prior therapy
Route of prior bortezomib therapy
Prior proteasome inhibitor (yes vs. no)

EXCLUSION
- ANC ≤ 1 x 10^9
- Hemoglobin ≤ 7.5 g/dL
- Platelets ≤ 75 x 10^9
- CrCl ≤ 30 mL/min
- ALT, AST > 2.5 x ULN
Bilirubin ≥ 1.5 x ULN
- Refractory to bortezomib
- Prior d/c lenalidomide due to AE

- Carfilzomib 20 mg/m^2 IV on days 1,2 of first cycle and then 56 mg/m^2 IV on days 8, 9, 15,16
- Dexamethasone 20 mg IV on days 1, 2, 8, 9, 15, 16

Repeat q 28 D

Cycles 1-2:
- Bortezomib 1.3 mg/m^2 SC on days 1, 4, 8, 11
- Dexamethasone 20 mg PO on days 1, 2, 4, 5, 8, 9, 11, 12

All cycles repeat q21D

Dimopoulos MA, et al *Lancet Oncol* 2016;17:27-38.

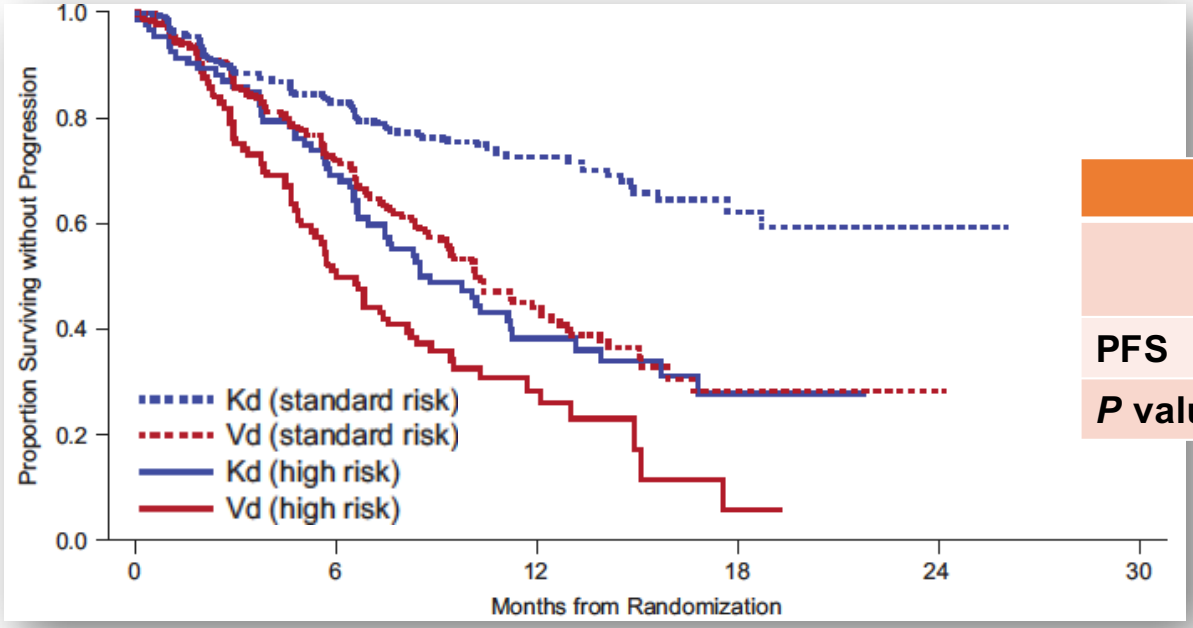
Kd vs. Vd: High-Risk Subgroup ORR

	Response			
	Standard Risk		High Risk	
	Kd	Vd	Kd	Vd
CR	13%	7.9%	15.5%	4.4%
VGPR	45.8%	21.6%	30.9%	25.7%
PR	20.1%	36.1%	25.8%	28.3%
MR	4.2%	12.4%	8.2%	9.7%
SD	7.4%	9.6%	9.3%	15%
PD	5.3%	5.5%	6.2%	5.3%
DOR	NE	11.7	10.2	8.3
PFS	NE	10.2	8.8	6

DOR = duration of response; Kd = carfilzomib/dexamethasone; Vd = bortezomib/dexamethasone.

Dimopoulos MA, et al *Lancet Oncol* 2016;17:27-38.

Kd vs. Vd: High-Risk Subgroup PFS



	Standard Risk		High Risk	
	Kd (n = 284)	**Vd (n = 291)**	**Kd (n = 97)**	**Vd (n = 113)**
PFS	NE	10.2 mo	8.8 mo	6.0 mo
***P* value**		< .0001		.0075

Chng WJ, et al *Leukemia* 2017;31:1368-74.

Lenalidomide/Dexamethasone +/- Ixazomib

INCLUSION

- 1-3 lines prior therapy
- ≥ PR at least once
- Documented PD after last line therapy
  Secretory MM by IMWG criteria

1:1 Randomization

Stratification factors

ISS (I, II or III)
Lines of prior therapy (1 vs. 2 or 3)
Prior bortezomib exposure

EXCLUSION

- ANC ≤ 1 x 10^9
- Hemoglobin ≤ 7.5 g/dL
- Platelets ≤ 75 x 10^9
- CrCl ≤ 30 mL/min
- ALT, AST ≥ 2.5 x ULN
- Bilirubin ≥ 1.5 x ULN
- Refractory to lenalidomide
- Prior d/c lenalidomide due to AE

- Ixazomib 4 mg PO days 1, 8, 15
- Lenalidomide 25 mg D1-21 PO (CrCl 30-60 mL/min 10 mg PO daily)
- Dexamethasone 40 mg PO weekly

Repeat every 28 days

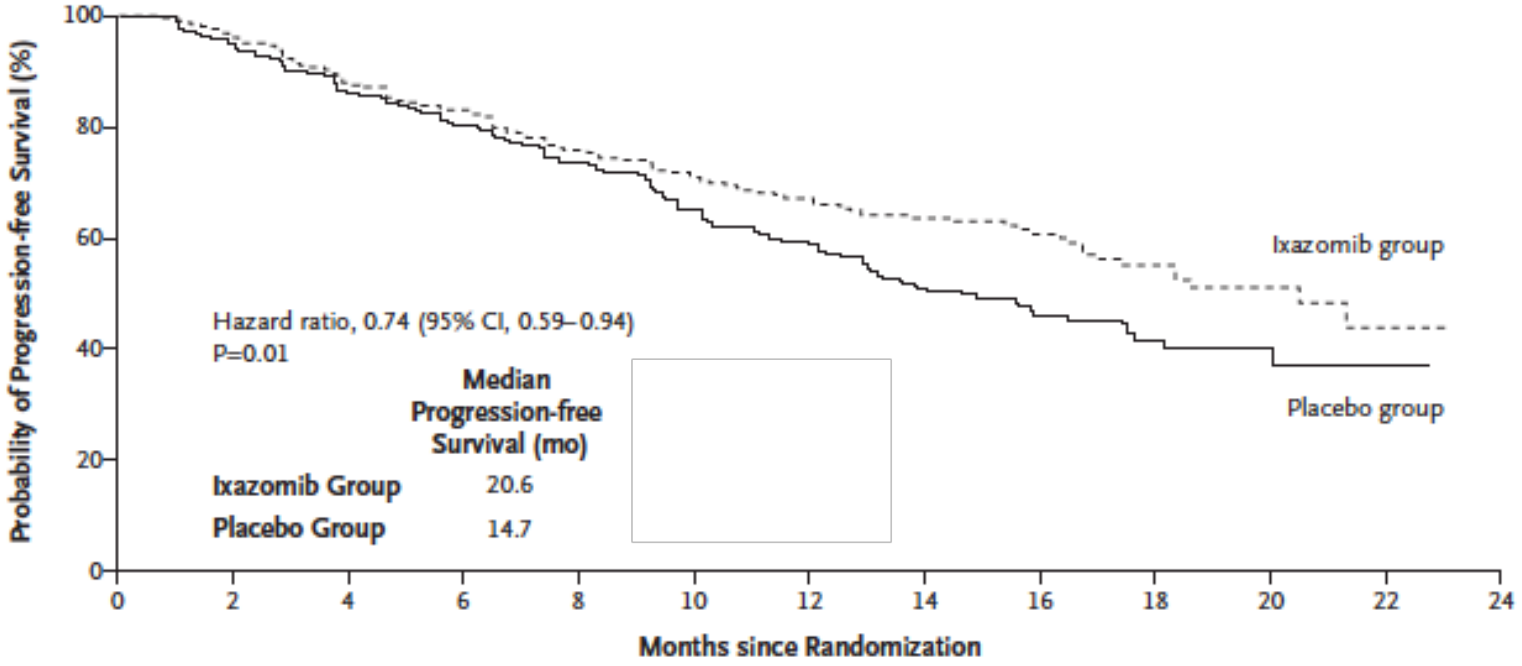
- Lenalidomide 25 mg D1-21 PO (CrCl 30-60 mL/min 10 mg PO daily)
- Dexamethasone 40 mg PO D1,8,15,22

Repeat every 28 days

d/c = discontinue.

Moreau P, et al. *N Engl J Med* 2016;374:1621-34.

Lenalidomide/Dexamethasone +/- Ixazomib: PFS



Moreau P, et al. *N Engl J Med* 2016;374:1621-34.

Lenalidomide/Dexamethasone +/- Ixazomib: High-Risk Subset Analysis

Patients, N (ixazomib vs placebo group)	Duration of response, median, months		Progression-free survival, median, months				Time to progression, median, months		
	IRd	Placebo-Rd	IRd	Placebo-Rd	HR	95% CI	IRd	Placebo-Rd	HR
All (360 vs 362)	20.5 (n=282)	15.0 (n=259)	20.6	14.7	0.742	0.587–0.939	21.4	15.7	0.712
Standard-risk (199 vs 216)	NR (n=160)	15.0 (n=158)	20.6	15.6	0.640	0.462–0.888	20.6	15.9	0.626
High-risk* (75 vs 62)	20.5 (n=59)	11.3 (n=37)	21.4	9.7	0.543	0.321–0.918	21.4	12.0	0.534
del(17p)† (36 vs 33)	20.5 (n=26)	12.0 (n=16)	21.4	9.7	0.596	0.286–1.243	21.4	12.9	0.590
t(4;14) alone (36 vs 25)	17.5 (n=32)	7.2 (n=19)	18.5	12.0	0.645	0.250–1.663	18.5	12.0	0.645
Amp 1q21 alone (80 vs 92)	16.6 (n=56)	11.3 (n=63)	15.4	11.3	0.781	0.492–1.240	16.4	12.3	0.787
Expanded high-risk‡ (155 vs 154)	20.5 (n=115)	11.3 (n=100)	17.5	11.1	0.664	0.474–0.928	18.5	12.1	0.672

*t(4;14) and/or t(14;16) and/or del(17p). †Alone or in combination with t(4;14) or t(14;16). ‡t(4;14) and/or t(14;16) and/or del(17p) and/or amp 1q21.

Avet-Loiseau H, et al. *Blood* 2017 [Epub ahead of print].

Lenalidomide/Dexamethasone +/- Ixazomib: Peripheral Neuropathy

	Ixa-Len-Dex (n = 361)			Placebo-Len-Dex (n = 359)		
	Any Grade N (%)	Grade 3 N (%)	Grade 4 N (%)	Any Grade N (%)	Grade 3 N (%)	Grade 4 N (%)
Peripheral neuropathy	97(27)	9 (2)	0	78 (22)	6 (2)	0

Moreau P, et al. *N Engl J Med* 2016;374:1621-34.

Peripheral Neuropathy

- Peripheral neuropathy is common in myeloma
- Neuropathy may be present in approximately 75% of previously treated patients
- Possibly due to a combination of factors
  - Direct damage to nerve cell
  - Toxicity to dorsal root ganglion
  - Decreased nerve blood flow
- Baseline assessment, monitoring at each visit promotes early detection, dose modification

Faiman B, et al. *Clin J Oncol Nurse* 2017;21:19-36.

Assessment of Neuropathy

- History
  - Numbness, tingling, burning sensation
  - Ability to perform ADLs
  - Sensation
- Physical Exam
  - Sensation
  - Heel to toe
  - Gait
  - Fine motor movements
  - Reflexes
  - Muscle strength

ADLs = activities of daily living.

Tariman JD, et al. *Clin J Oncol Nurs* 2008;12:29-36.

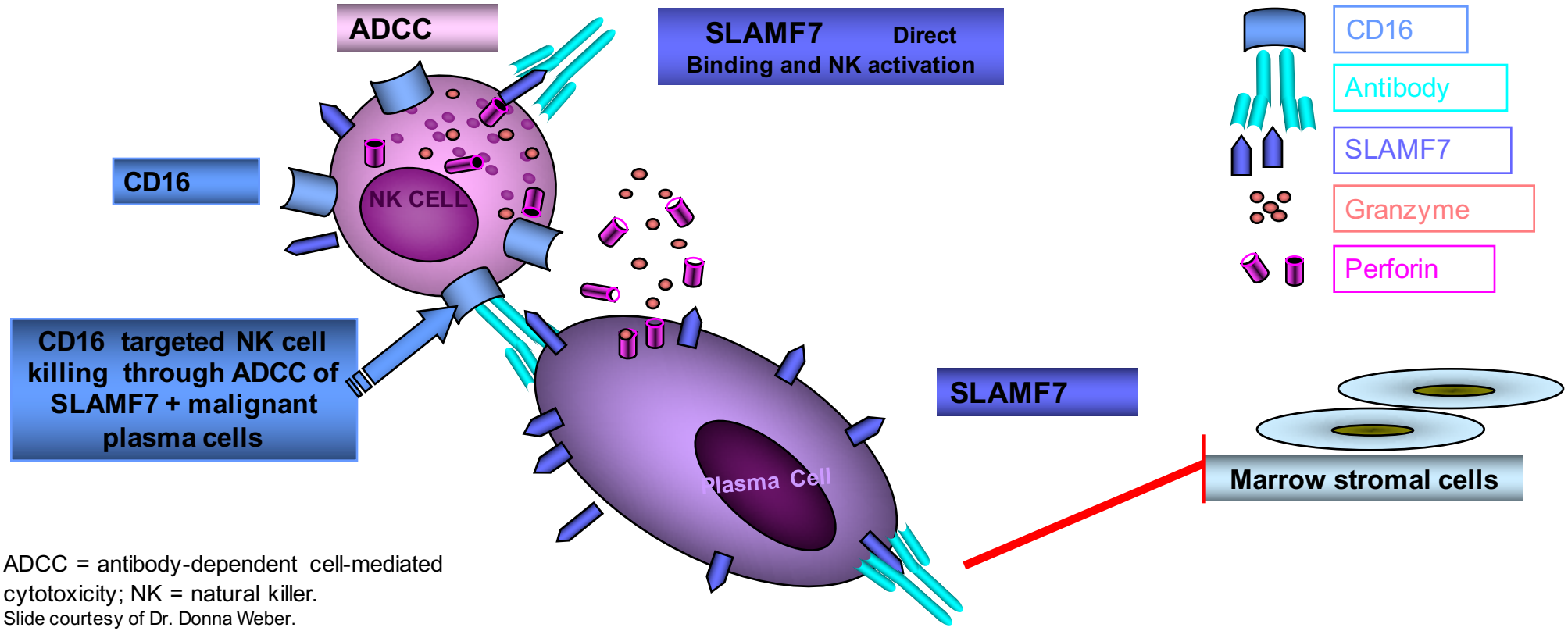
Treatment of Neuropathy

- Educate patients on prompt reporting of symptoms
- Intervene early and dose reduce causative agent
- Use SC bortezomib rather than IV
- Consider use of glutamine in patients receiving bortezomib
- Check for Vitamin B12, B6, and folate deficiency and replete accordingly
- Depending on severity initiate gabapentin, pregabalin, or duloxetine; may consider lidocaine patch
- Acupuncture
- Refer to a pain management specialist and/or physical therapist
- Educate patients on neuropathy precautions

ADLs = activities of daily living.

Faiman et al 2017; CJON Suppl 21(5); Berlotti et al (2017), seminars in oncology nursing.

Mechanisms of Action of Elotuzumab



ADCC = antibody-dependent cell-mediated cytotoxicity; NK = natural killer.

Slide courtesy of Dr. Donna Weber.

Lenalidomide/Dexamethasone +/- Elotuzumab

INCLUSION
- 1-3 lines prior therapy
- ≥ PR at least once
- Documented PD after last line therapy
  Secretory MM by IMWG criteria

1:1 Randomization

Stratification factors
ß2M (3.5 mg/L vs. ≥ 3.5 mg/L)
Lines of prior therapy (1 vs. 2 or 3)
Prior IMiD (none vs. Thal only or other)

EXCLUSION
- ANC ≤ 1 x 10^9
- Hemoglobin ≤ 7.5 g/dL
- Platelets ≤ 75 x 10^9
- CrCl ≤ 30 mL/min
- ALT, AST ≥ 2.5 x ULN
- Bilirubin ≥ 1.5 x ULN
- Refractory to lenalidomide
- Prior d/c lenalidomide due to AE

- Lenalidomide 25mg D1-21 PO (CrCl 30-60 mL/min 10 mg PO daily)
- Dexamethasone 40 mg PO weekly

Repeat q28 D

Cycles 1-2:
- Lenalidomide 25mg D1-21 PO (CrCl 30-60 mL/min 10 mg PO daily)
- Dexamethasone 28 mg PO D1,8,15,22 (3-24 hrs prior to elo) and 8 mg IV 45–90 minutes prior to
- Elotuzumab 10 mg/kg IV D1,8,15,22

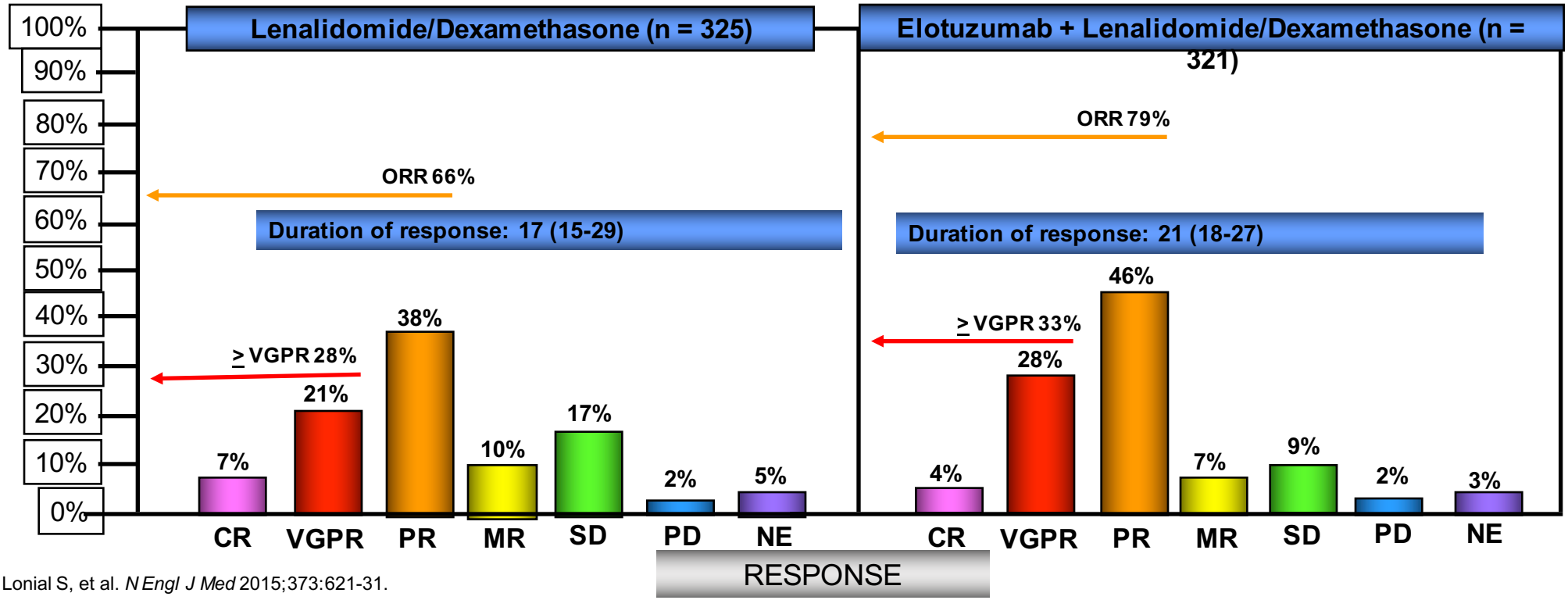
Cycle >3:
- Lenalidomide as in C 1-2
- Dexamethasone Day 1, 15 as per cycle 1-2
- Dexamethasone Day 8, 22: 40 mg PO
- Elotuzumab 10 mg/kg IV D1,15

All cycles repeat q28 D

Thal = thalidomide.

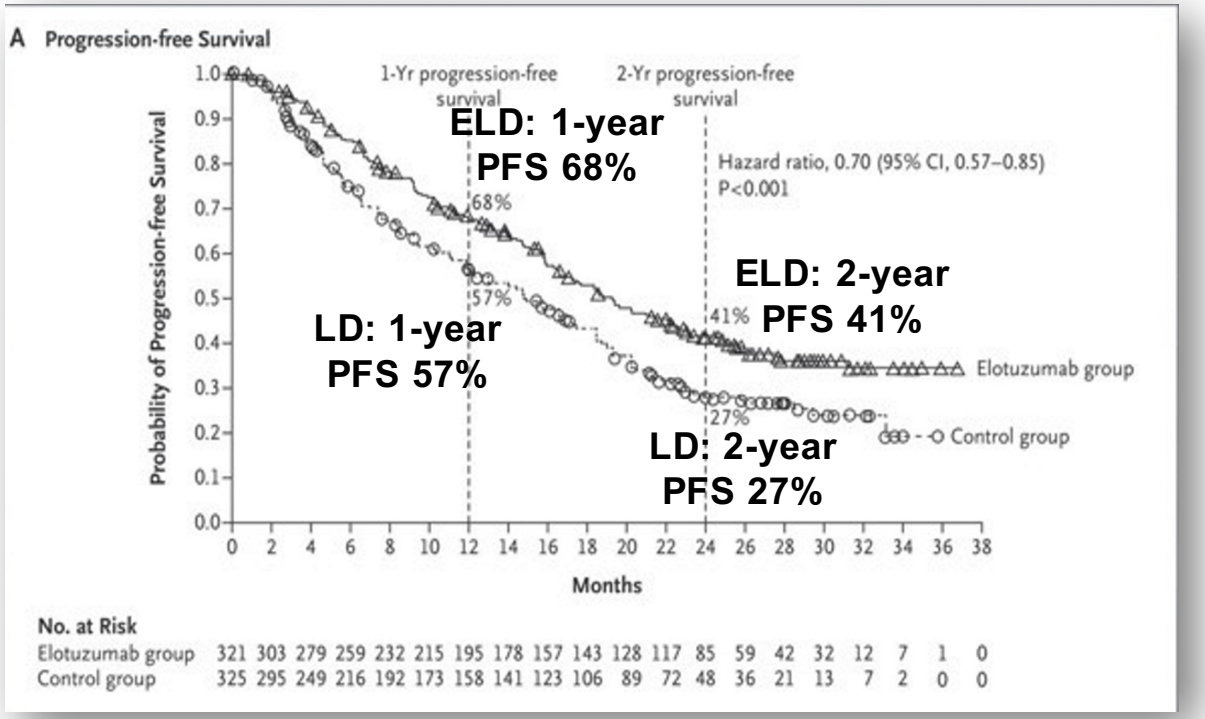
Lonial S, et al. *N Engl J Med* 2015;373:621-31.

Eloquent 2: Elotuzumab/LD vs. LD: Efficacy



Lonial S, et al. *N Engl J Med* 2015;373:621-31.

Eloquent 2: Elotuzumab/LD vs. LD



PFS
Elotuzumab/LD: 19.4 months
LD: 14.9 months

ELD = elotuzumab; LD = lenalidomide.

Lonial S, et al. *N Engl J Med* 2015;373:621-31.

Eloquent 2: Elotuzumab/LD vs. LD

	Elo + LD	LD	*P*
Overall response	79	66	.0002
PFS			
Overall (median, months)	19.4	14.9	.0004
Del 17p (median, months)	21.2	14.9	
t(4;14)	15.8	5.5	
1 year (%)	68	41	
2 year (%)	57	27	
Time to next therapy (median, months)	33	21	
OS (median, months)	43.7	39.6	.0257

Lonial S, et al. *N Engl J Med* 2015;373:621-31; Dimopoulos MA, et al. *Blood* 2015;126:28.

IRR: Elotuzumab

- Most common symptoms
  - Fever, chills, flushing
  - Nausea/vomiting
  - Dyspnea
  - Hypertension
  - Headache
  - Dizziness
  - Rash

IRR = infusion-related reaction.

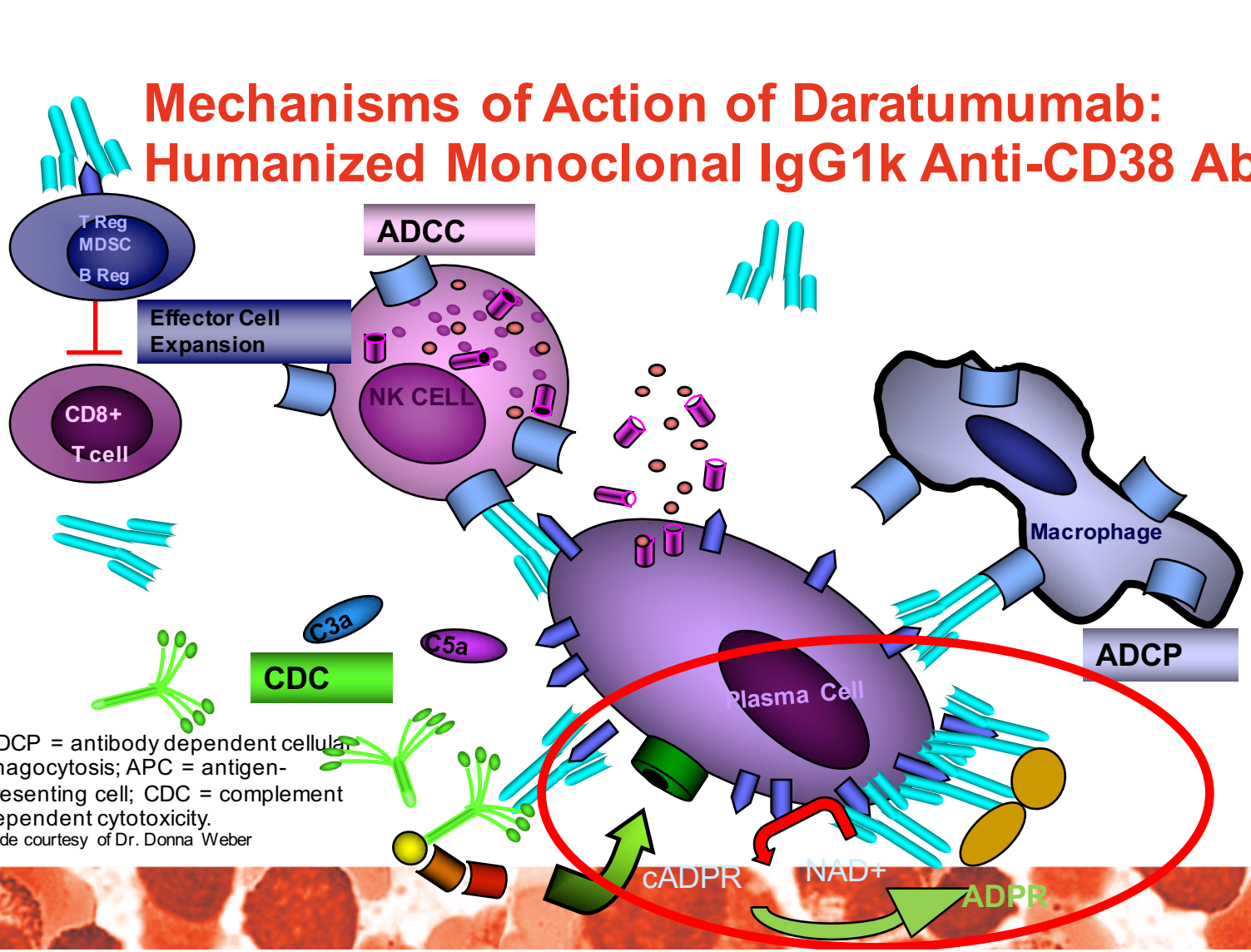
van de Donk NW, et al. *Blood* 2015;127:681-95.

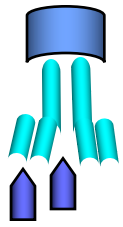
IRR: Elotuzumab

- Occurs in 7% to 10% of patients who receive premedications
- Premedications given 30-60 minutes prior to infusion
  - Diphenhydramine 25 mg IV
  - Acetaminophen 650 mg
  - Dexamethasone 12 mg
  - Pepcid 20 mg IV
- Dexamethasone 28 mg PO 3-24 hours before infusion

van de Donk NW, et al. *Blood* 2015;127:681-95.

Mechanisms of Action of Daratumumab: Humanized Monoclonal IgG1k Anti-CD38 Ab





FC receptor

Antibody

CD38

Granzyme

Perforin

C1q

Complement components

Membrane attack complex

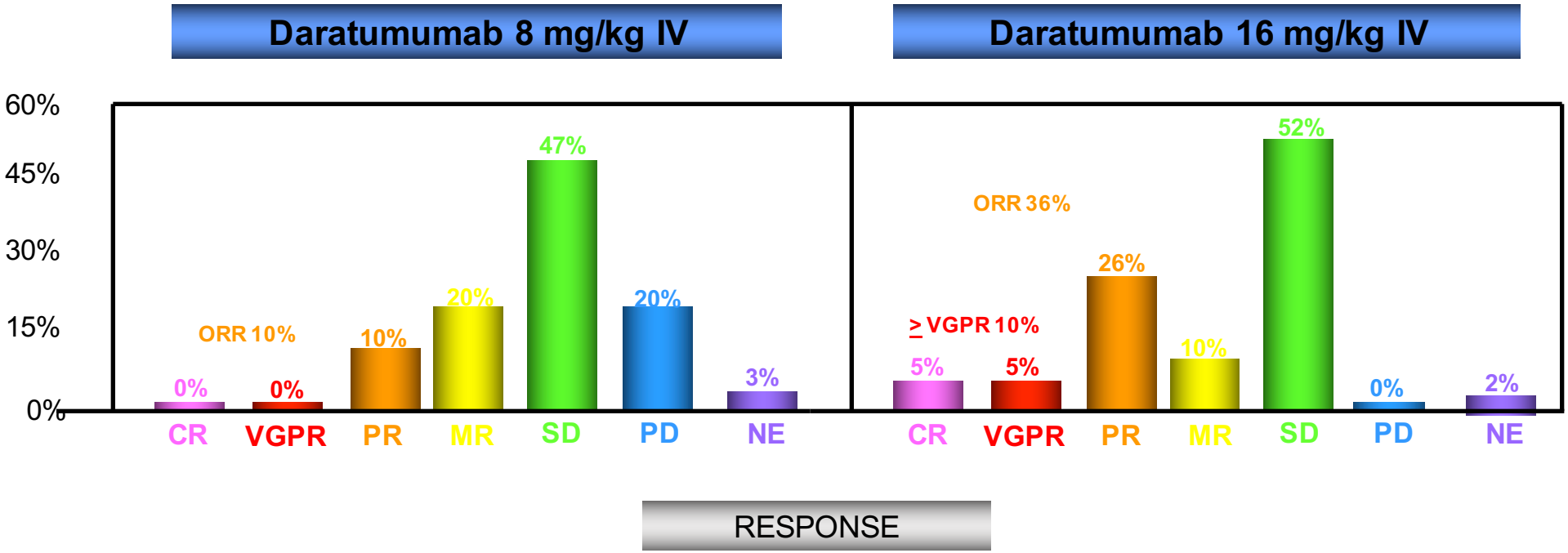
Direct Effects on Targeted Ag

- Signaling and modulation target
- Function growth factors, cellular adhesion, etc.
- APC interactions + T cell response enhanced

ADCP = antibody dependent cellular phagocytosis; APC = antigen-presenting cell; CDC = complement dependent cytotoxicity.

Slide courtesy of Dr. Donna Weber

Daratumumab: Monotherapy Trial



Lokhorst HM, et al. *N Engl J Med* 2015;373:1207-19.

Bortezomib/Dexamethasone +/- Daratumumab (CASTOR)

INCLUSION
- 1 line prior therapy
- ≥ PR at least once
- Documented PD
- Secretory by IMWG criteria

Randomization

Stratification factors

Stage I, I, III
Lines of prior therapy (1 vs. 2; 3 vs. >3)
Prior bortezomib (yes vs. no)

EXCLUSION
- ANC ≤ 1 x 10^9
- Hemoglobin ≤ 7.5 g/dL
- Platelets ≤ 75 x 10^9
- CrCl ≤ 20 mL/min per 1.73 mm^2
- ALT, AST ≥ 2 x ULN
- Bilirubin ≥ 1.5 x ULN
- Refractory to another proteasome inhibitor
- ≥ grade 2 peripheral neuropathy

- Bortezomib 1.3 mg/m^2 D1,4,8,11 SC
- Dexamethasone 20 mg PO on D1,2,4,5,8,9,11,12

Repeat q 21 D x 8 cycles

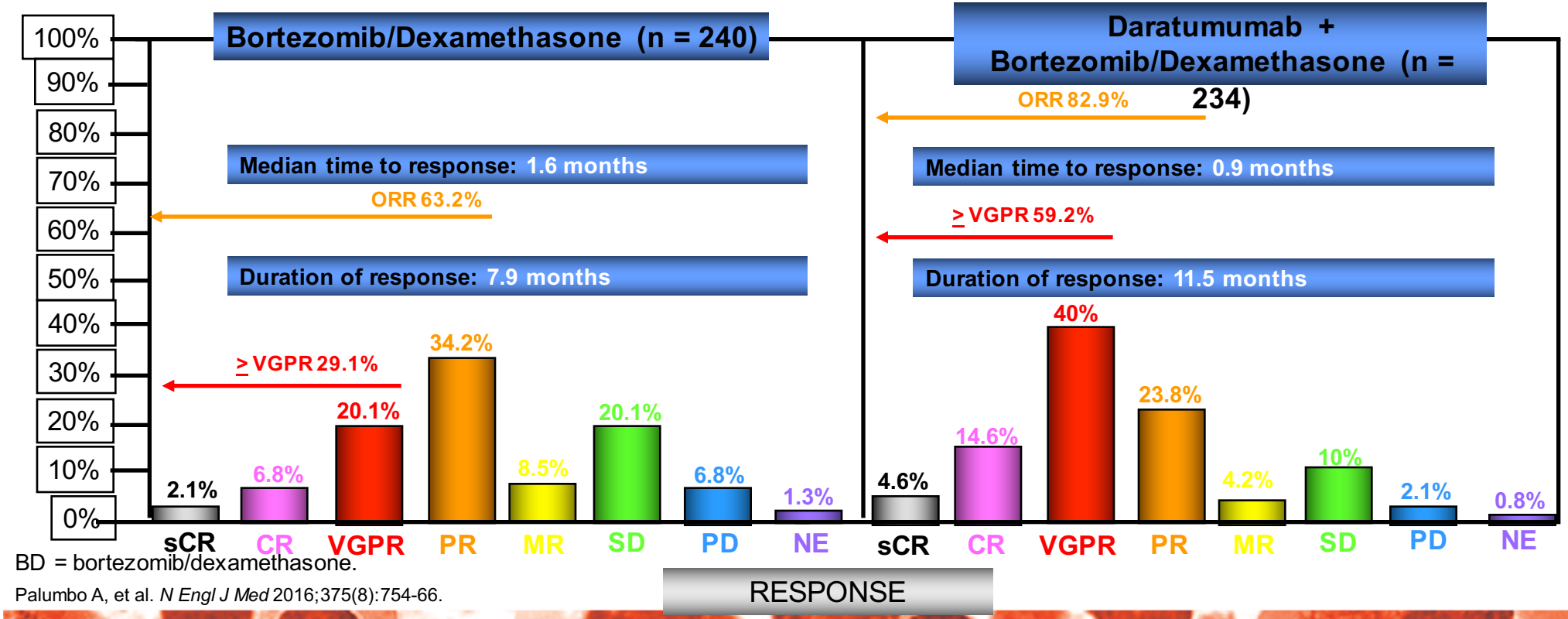
Cycles 1-3:
- Bortezomib 1.3 mg/m^2 D1,4,8,11 SC
- Dexamethasone 20 mg PO on D1,2,4,5,8,9,11,12
- Daratumumab 16 mg/kg IV D1,8,15

Cycle 4:
- Bortezomib/dexamethasone as C 1-3
- Daratumumab 16 mg/kg IV D1

Repeat q21D x 8 cycles

Palumbo A, et al. *N Engl J Med* 2016;375(8):754-66.

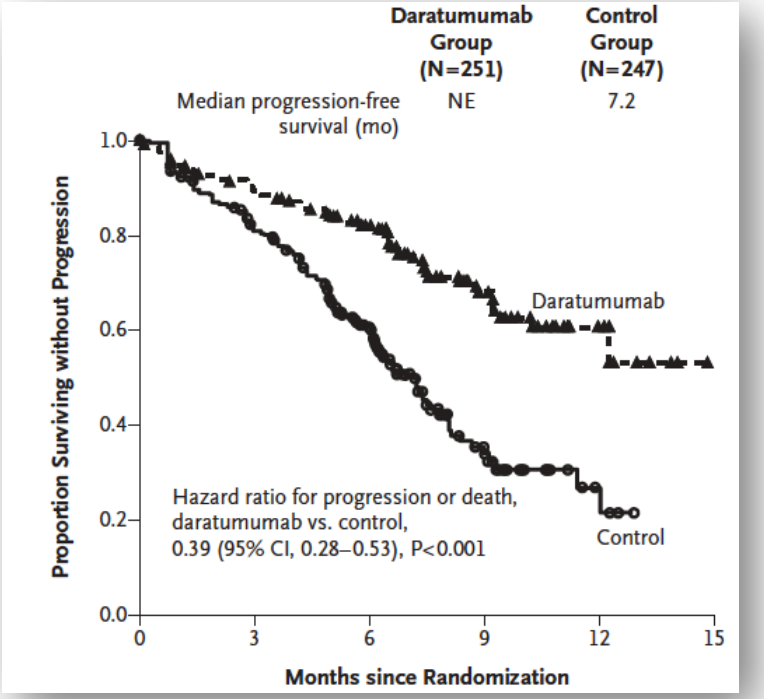
Daratumumab/BD vs. BD: Response



BD = bortezomib/dexamethasone.

Palumbo A, et al. *N Engl J Med* 2016;375(8):754-66.

Daratumumab/BD vs. BD: PFS



PFS
Daratumumab/BD: Not evaluable
BD: 7.2 months

HR for progression or death with daratumumab vs. control: 0.39; 95% CI, 0.28-0.53; *P* < .001

Palumbo A, et al. *N Engl J Med* 2016;375(8):754-66.

Lenalidomide/Dexamethasone +/- Daratumumab (POLLUX)

INCLUSION
- >1 line prior therapy
- > PR at least once
- Documented PD during/after last line of treatment
  Secretory MM by IMWG criteria

1:1 Randomization

Stratification factors

Stage I, I, III
Lines of prior therapy (1 vs. 2; 3 vs. >3)
Prior lenalidomide (yes vs. no)

EXCLUSION
- ANC $\leq 1 \times 10^9$
- Hemoglobin ≤ 7.5 g/dL
- Platelets $\leq 75 \times 10^9$
- CrCl ≤ 30 mL/min
- ALT, AST $\geq 2.5 \times$ ULN
- Bilirubin $\geq 1.5 \times$ ULN
- Refractory to lenalidomide
- Prior d/c lenalidomide due to AE

- Lenalidomide 25 mg D1-21 PO (CrCl 30-60 mL/min 10 mg PO daily)
- Dexamethasone 40 mg PO weekly

Repeat q28D

Cycles 1-2:
- Lenalidomide 25 mg D1-21 PO (CrCl 30-60 mL/min 10 mg PO daily)
- Dexamethasone 20 mg D1,8,15,22 prior to daratumumab and 20 mg PO on D2,9,16,23
- Daratumumab 16 mg/kg IV D1,8,15,22

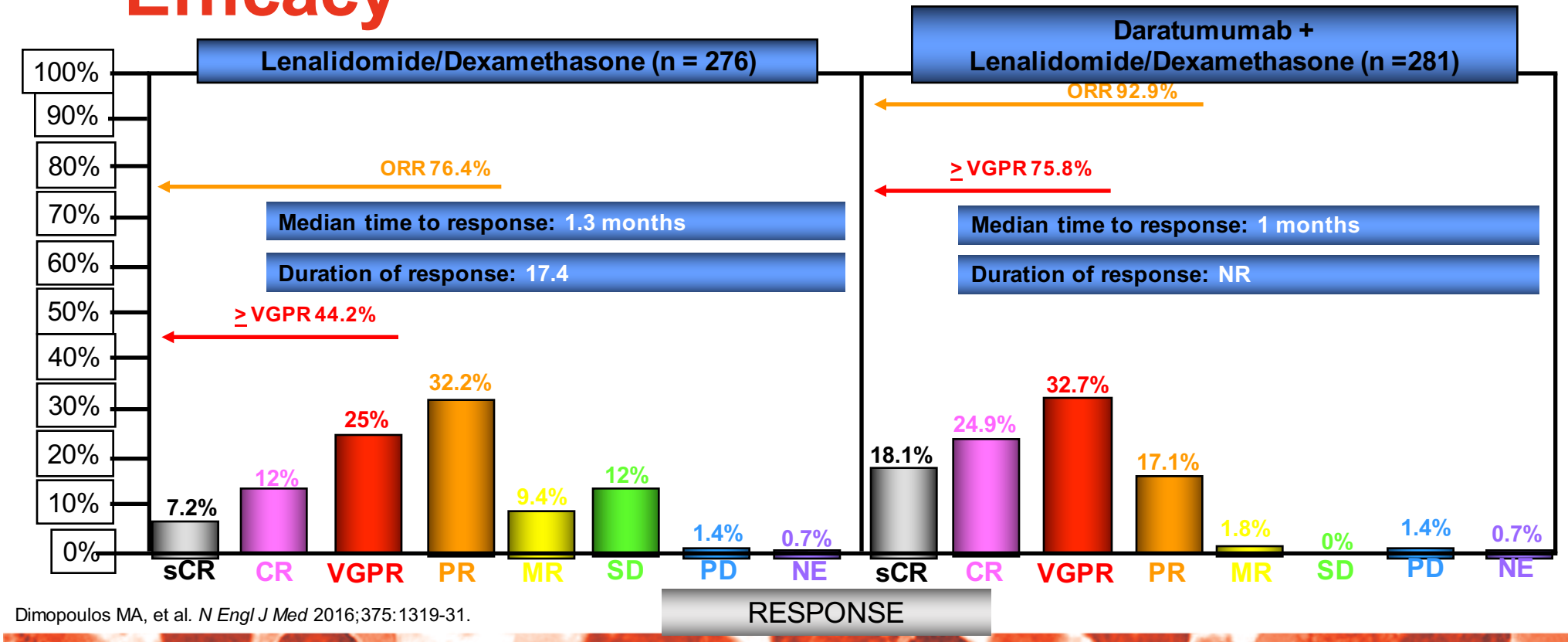
Cycle 3-6:
- Lenalidomide/dexamethasone as C 1-2
- Daratumumab 16 mg/kg IV D1,15

Cycles > 7:
- Lenalidomide/dexamethasone as C 1-2
- Daratumumab 16 mg/kg IV D1

All cycles repeat q28D

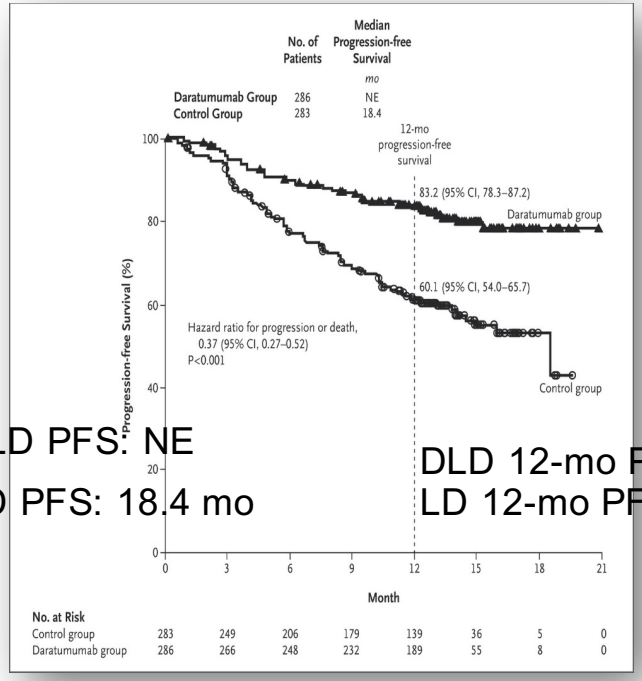
Dimopoulos MA, et al. *N Engl J Med* 2016;375:1319-31.

Pollux: Daratumumab/LD vs. LD: Efficacy



Dimopoulos MA, et al. *N Engl J Med* 2016;375:1319-31.

Lenalidomide/Dexamethasone +/- Daratumumab



DLD PFS: NE

LD PFS: 18.4 mo

DLD 12-mo PFS 83.2%

LD 12-mo PFS 60.1%

	DLD	LD
≥ VGPR 12-month PFS	91.7%	85.8%
≥ PR 12-months PFS	87.8%	73.6%
Deaths at interim analysis	30	45
OS at 12 months	92.1%	86.8%
SAEs	48.8%	42%
Pneumonia	8.1%	8.5%
AEs leading to d/c therapy	6.7%	7.8%
AEs leading to death	3.9%	5.3%
Acute kidney injury	0.4%	1.1%
Septic shock	1.1%	0.4%
Pneumonia	0.7%	0.7%
Second primary cancers	2.8%	3.6%
DVT	1.8%	3.9%
IRR (92% during infusion 1)	47%	

DLD = daratumumab, lenalidomide, dexamethasone; LD = lenalidomide and dexamethasone.

Dimopoulos MA, et al. *N Engl J Med* 2016;375:1319-31.

POLLUX: Daratumumab/ LD vs. LD

Table 3. Most Common Adverse Events during Treatment in the Safety Population.*

Event	Daratumumab Group (N=283)		Control Group (N=281)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Hematologic adverse event				
Neutropenia	168 (59.4)	147 (51.9)	121 (43.1)	104 (37.0)
Anemia	88 (31.1)	35 (12.4)	98 (34.9)	55 (19.6)
Thrombocytopenia	76 (26.9)	36 (12.7)	77 (27.4)	38 (13.5)
Febrile neutropenia	16 (5.7)	16 (5.7)	7 (2.5)	7 (2.5)
Lymphopenia	17 (6.0)	15 (5.3)	15 (5.3)	10 (3.6)
Nonhematologic adverse event				
Diarrhea	121 (42.8)	15 (5.3)	69 (24.6)	9 (3.2)
Fatigue	100 (35.3)	18 (6.4)	78 (27.8)	7 (2.5)
Upper respiratory tract infection	90 (31.8)	3 (1.1)	58 (20.6)	3 (1.1)
Constipation	83 (29.3)	3 (1.1)	71 (25.3)	2 (0.7)
Cough	82 (29.0)	0	35 (12.5)	0
Muscle spasms	73 (25.8)	2 (0.7)	52 (18.5)	5 (1.8)
Nasopharyngitis	68 (24.0)	0	43 (15.3)	0
Nausea	68 (24.0)	4 (1.4)	40 (14.2)	0
Pyrexia	57 (20.1)	5 (1.8)	31 (11.0)	4 (1.4)
Insomnia	55 (19.4)	1 (0.4)	55 (19.6)	2 (0.7)
Dyspnea	52 (18.4)	9 (3.2)	32 (11.4)	2 (0.7)
Back pain	50 (17.7)	4 (1.4)	48 (17.1)	4 (1.4)
Vomiting	47 (16.6)	3 (1.1)	15 (5.3)	2 (0.7)
Asthenia	45 (15.9)	8 (2.8)	36 (12.8)	7 (2.5)
Peripheral edema	43 (15.2)	2 (0.7)	37 (13.2)	3 (1.1)
Pneumonia	40 (14.1)	22 (7.8)	37 (13.2)	23 (8.2)

* The safety population included all patients who received at least one dose of trial treatment. Adverse events of any grade that are listed are those that occurred in more than 15% of the patients in either group. Adverse events of grade 3 or 4 that are listed are those that occurred in more than 5% of the patients in either group.

Dimopoulos MA, et al. *N Engl J Med* 2016;375:1319-31.

Practical Points for Daratumumab IRR

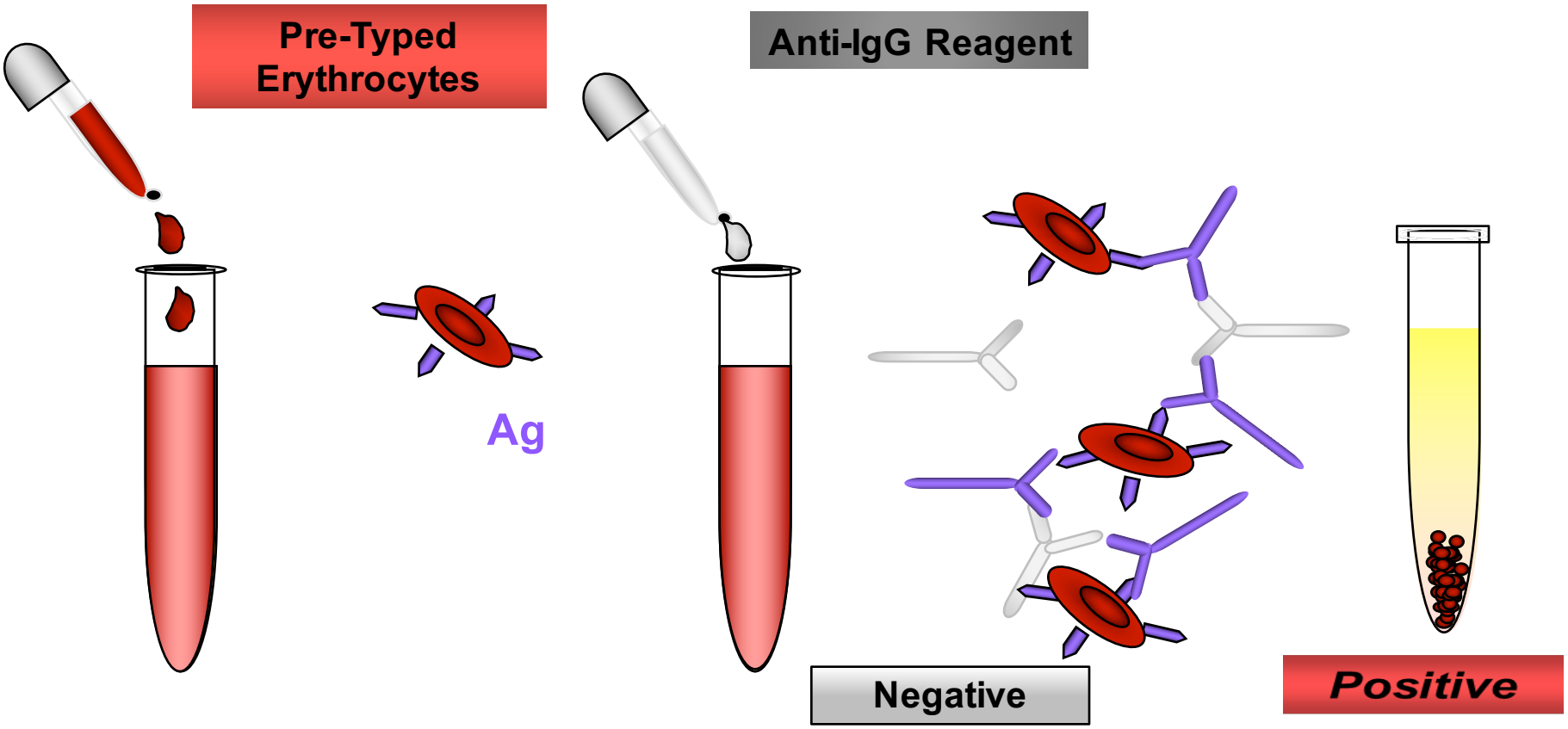
- Pre-medications
  - Antipyretic: acetaminophen 1 g PO 1-2 hours prior
  - H1 antihistamine (diphenhydramine 25-50 mg)
  - H2 antihistamine (famotidine 20 mg PO)
  - Methylprednisolone 100 mg 4 hours prior IV (reduce to 60 mg after doses 1,2) or equivalent
  - Oral leukotriene receptor antagonist (e.g. montelukast)
  - FEV-1 $\leq$ 80%, β2-adrenergic agonist inhaler
- Post-meds: methylprednisolone 40 mg PO on days 2, 3, or equivalent

Practical Guidelines for RBC Compatibility Testing

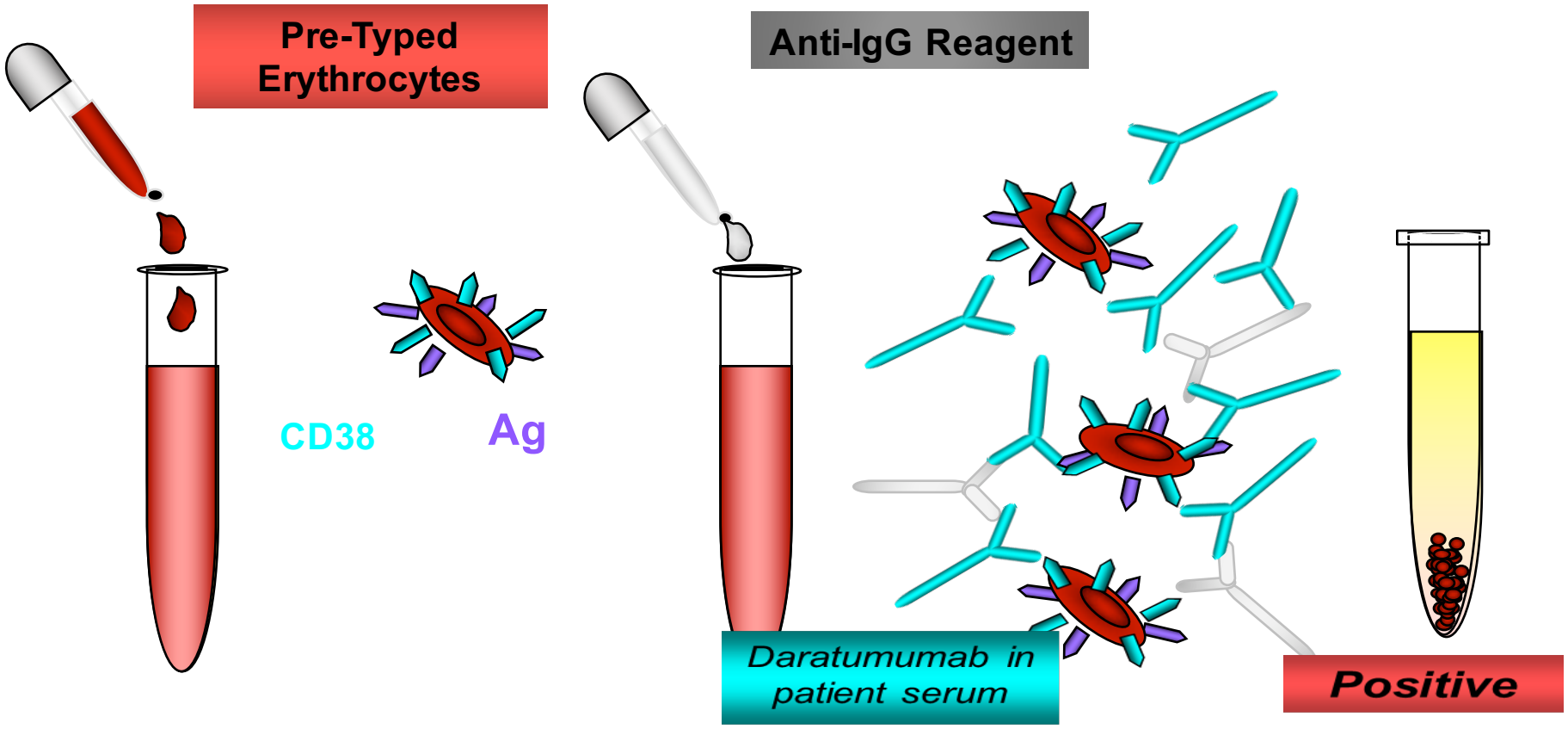
- Notify local bank of anti-CD38 directed therapy; may persist months after discontinuation
- ABO–Rh typing not affected
- Perform RBC phenotyping (or genotyping if transfusion past 3 months) prior to C1D1
- Provide wallet card to inform blood banks of potential interference with testing and results of phenotype or genotype
- Transfuse with Kell negative blood (O RhD compatible or negative blood) in emergency
- Close monitoring for reactions

RBC = red blood cell.

van de Donk NW, et al. *Blood* 2016;127:681-95.



Based on van de Donk NW, et al. *Blood* 2016;127:681-95; slide copyright by Donna M. Weber, MD; used with permission.



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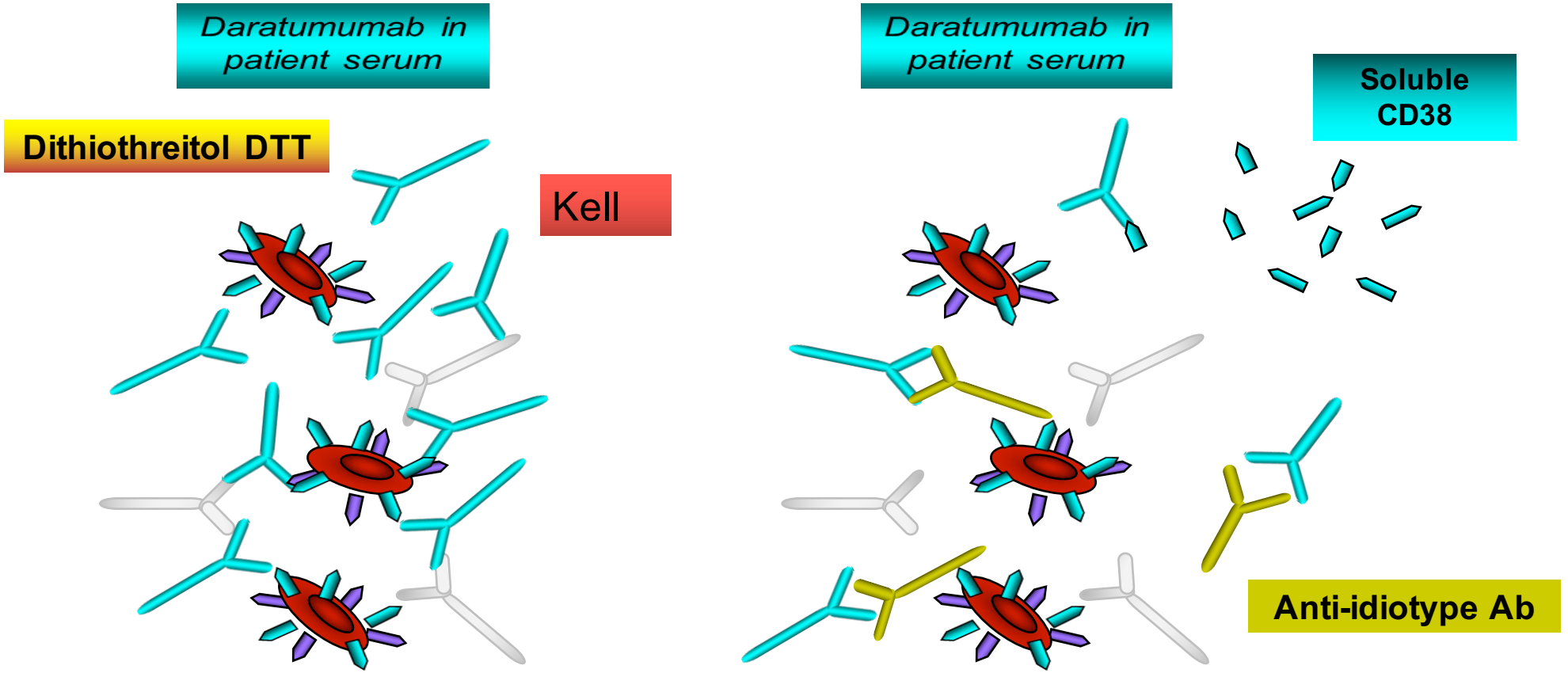

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Special Considerations with MoABs: Laboratory Tests

- SPEP and Immunofixation
  - MoABs can be detected in the gamma region
  - 50% of IgG Kappa M bands comigrate with daratumumab and elotuzumab
  - May lead to overestimation of M protein
  - Reduced CR rates
  - Interference reduces after completion of therapy

MoABs = monoclonal antibodies; SPEP = serum protein electrophoresis.

van de Donk NW, et al. *Blood* 2015;127:681-95.

Special Considerations with MoABs: Laboratory Tests

- SPEP and immunofixation solutions
  - Development of daratumumab interference reflex assay (DIRA assay)
  - Shifts migration of daratumumab
  - Performed when IgG K < 0.2 g/dL
  - New assays in development for elotuzumab, isatuximab

van de Donk NW, et al. *Blood* 2015;127:681-95.

Special Considerations with MoABs: Laboratory Tests

- Flow cytometry
  - CD38 expression on plasma cells is reduced
  - After daratumumab CD38 is unreliable plasma cell identifier
  - Persists for 6 months post-daratumumab
- Solution
  - Development of new ways to perform flow cytometry in patients who have received monoclonal antibodies to CD38

van de Donk NW, et al. *Blood* 2015;127:681-95.

Selected Common Side Effects with Monoclonal Antibodies

- **Infusion-Related Reactions**
  - Premedication
  - Monitor for IRR (nasal congestion, nausea, temperature, chills, tachycardia, dyspnea)
  - Check PFTs prior to starting daratumumab
- **Asthenia**
  - Exercise program
  - Energy sparing activities
  - Assess depression
- **GI effects**
  - Diarrhea
    - Ensure no other causes of diarrhea
    - If given in combination with lenalidomide, recommend starting colestyramine
  - Nausea/vomiting
    - Generally mild
    - Consider anti emetic
    - Monitor electrolytes
- **Thrombocytopenia**
  - Hold for platelets < 25,000
- **Neutropenia**
  - Hold for ANC < 1
- **Peripheral neuropathy** (when given in combination with bortezomib)
  - Monitor neuropathy at each patient encounter
  - Dose adjust per recommended guidelines
  - Educate patients on signs and symptoms of neuropathy
- **Thromboembolic events** (when given in combination with lenalidomide or pomalidomide)
  - Increased incidence
  - Prophylaxis with aspirin, warfarin, or low molecular weight heparin depending on risk
- **Renal**
  - Dose reduce lenalidomide and pomalidomide for creatinine clearance
- **Infection**
  - Monitor for signs/symptoms of infection
  - Place on antiviral prophylaxis

PFTs = pulmonary function tests.

Pomalidomide package insert. 2013. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204026lbl.pdf; Lenalidomide package insert. 2005. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021880s049lbl.pdf; Thalidomide prescribing information, 2006. https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021430lbl.pdf.

Pomalidomide/Dexamethasone: MM-003

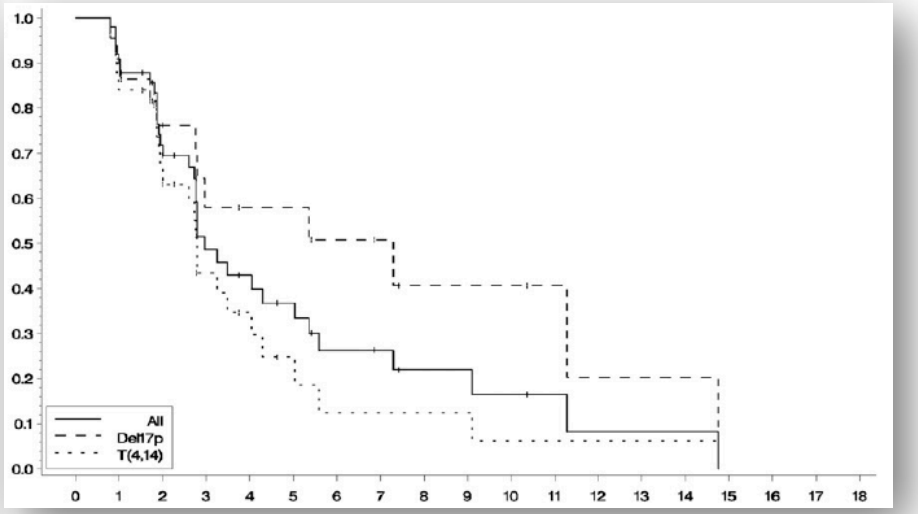
		PFS del 17p	PFS t(4:14)	PFS Standard Risk	OS del 17p	OS t(4:14)	OS Standard Risk
Dimopoulos	Pd	4.6	2.8	4.2	12.6	7.5	14
	High-dose Dex	1.1	1.9	2.3	7.7	4.9	9

- Dimopoulos MA, et al. *Haematologica* 2015;100:1327-33.

Pomalidomide/Dexamethasone in High-Risk Disease

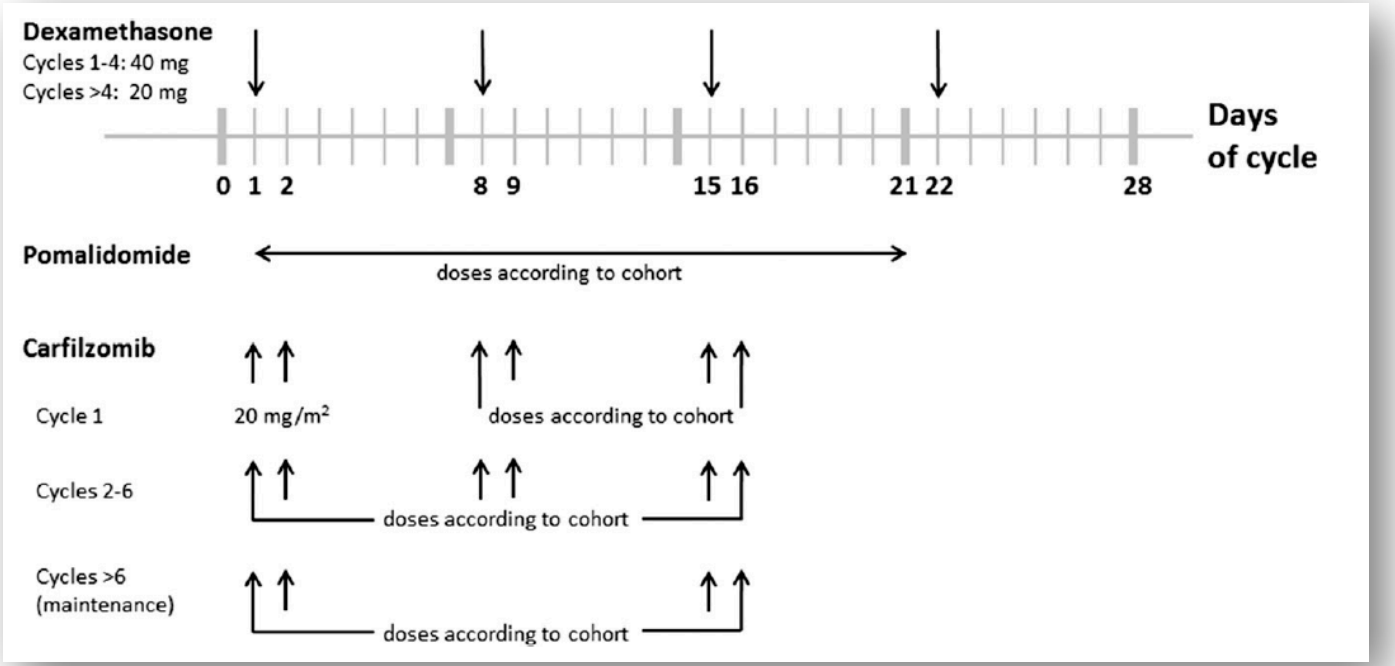
	Total	del(17p)	t(4;14)
Response rate, ITT (n = 50), n (%)			
ORR (≥PR)	11 (22)	7 (32)	5 (15)
≥VGPR	3 (6)	2 (9)	1 (3)
PR	8 (16)	5 (23)	4 (12)
Stable disease	30 (60)	9 (41)	22 (69)
CBR (≥MR)	17 (34)	7 (32)	11 (34)
Progressive disease	7 (14)	4 (18)	5 (15)
Not evaluable	2 (4)	2 (9)	0
Time to first response, mo			
Median (95% CI)	4.1 (4;8)	—	—
Range	3-28	—	—
Duration of response, mo			
Median (95% CI)	5.5 (0.95;–)	8.3 (1.9;–)	2.4 (0.95;8.3)
One-year free, %	44	67	25
Response rate, EE (n = 47), n (%)			
ORR	11 (23)	—	—
CBR	17 (36)	—	—

Progression-Free Survival



Leleu X, et al. *Blood* 2015;125:1411-7.

Carfilzomib, Pomalidomide, Dexamethasone



Shah JJ, et al. *Blood* 2015;126:2284-90.

Carfilzomib, Pomalidomide, Dexamethasone High-Risk MM Subset

Response category, n (%)	All evaluable patients, N = 32	Hyperdiploid, n = 10	Del(13), n = 9	Del(17p), n = 5
ORR	16 (50)	5 (50)	1(11)	4 (80)
VGPR	5 (16)	1 (10)	1(11)	1 (20)
PR	11 (34)	4 (40)	0	3 (60)
MR	5 (16)	3 (30)	3 (33)	0
SD	8 (25)	2 (20)	5 (56)	1 (20)
PD	3 (9)	0	0	0

Shah JJ, et al. *Blood* 2015;126:2284-90.

Infections

- 45% of early deaths in myeloma was attributed to infections
- 7-fold increase in bacterial infection and 10-fold increase in viral infections risk
- Infection risk due to
  - Immune deficiency: hypogammaglobulinemia, lymphocyte dysfunction, neutropenia
  - Older age
  - Steroids (hyperglycemia)
  - Kyphosis due to compression fractures
  - Comorbidities (COPD, renal failure, diabetes)
  - Antimyeloma therapy (grade 3 infections 6-21%)
  - Diminished response to vaccinations

COPD = chronic obstructive pulmonary disorder.

Bilmark C, et al. *Haematologica* 2015;100(1):107-13; Bilotti E, et al. *CJON* 2011;15(4):5-8; Nucci M, et al. *Clin Infect Disease* 2009;49(8):1211-25; Teh BW, et al. *Blood* 2014;28(2):75-86.

Infections: Recommendations

- Consider IVIG in patients with repeat infections
- Antibiotic prophylaxis
- Antiviral prophylaxis with proteasome inhibitors and monoclonal antibodies
- Vaccines (NO LIVE VACCINES: shingles, yellow fever, intranasal influenza)
  - Post-stem cell vaccines
  - Influenza
  - Pneumococcal (PPSV and PCV)
- Patient education
  - Good hand washing
  - Prompt reporting of symptoms
  - Avoid drinking contaminated water
  - Avoid being around people who have signs/symptoms of illness
  - If traveling outside the country, they should meet with an ID specialist

IVIG = intravenous immunoglobulin; PPSV = pneumococcal polysaccharide vaccine; PSV = pneumococcal conjugate vaccine.

Bilotti E, et al. *Clin J Oncol Nurse* 2011;15(4):5-8; Nucci M, et al. *Clin Infect Disease* 2009;49(8):1211-25; Teh BW, et al. *Blood* 2014;28(2):75-86.

Summary: Treatment for Relapsed/Refractory Myeloma

- Many different treatment options for relapsed/refractory myeloma
- Asymptomatic biochemical relapse
  - Consider waiting to intervene in standard-risk patients based on M-protein trend; intervene early in high-risk MM relapse
  - Offers more flexibility to consider doublet and/or oral regimens (e.g., IRd)
- Aggressive clinical relapse
  - Consider daratumumab- or carfilzomib-based regimen
- Carefully consider common side effects of different drugs to individually tailor treatment to patient in balancing therapeutic efficacy vs. quality of life

Summary (Continued)

- Landscape of myeloma therapy rapidly evolving.
- Risk-stratify patients at diagnosis, which informs prognosis.; novel treatment approaches needed in high-risk myeloma patients
- Frontline therapy
  - Determine transplant eligibility
  - Triplet therapy (e.g., VRd) preferred over doublet therapy for transplant-eligible patients
- Role of up-front stem cell transplant will continue to evolve in the era of novel agents but still considered standard of care today

Summary (Continued)

- Maintenance therapy
  - Lenalidomide maintenance in standard-risk patients
  - Consider proteasome inhibitor + lenalidomide combination maintenance therapy for high-risk myeloma patients
- Relapsed and refractory myeloma
  - Type of relapse (indolent/asymptomatic relapse vs. florid clinical relapse) may help guide choice of next treatment regimen
  - Always intervene early in relapsed high-risk myeloma
- Must carefully consider common side effects of different drugs to individually tailor treatment to patient in balancing therapeutic efficacy vs. quality of life

Question #1

Ms. D is a 59-year-old patient with newly diagnosed multiple myeloma. A myeloma FISH panel at diagnosis revealed high-risk disease with deletion 17p and t(4;14). Which therapy would be the preferred treatment option in a newly diagnosed myeloma patient with high-risk cytogenetics?

1. Lenalidomide/dexamethasone
2. Bortezomib/pomalidomide
3. Thalidomide/dexamethasone
4. Bortezomib/lenalidomide/dexamethasone
5. Unsure

Question #2

Ms. D starts carfilzomib, lenalidomide, and dexamethasone as her frontline therapy and develops a pruritic, raised macular rash on her upper torso and face three days after she starts the lenalidomide. What would you advise the patient?

1. Hold lenalidomide and refer to dermatology for skin biopsy
2. Hold lenalidomide, and once rash resolves, restart lenalidomide concurrently with cetirizine, ranitidine, and L-lysine
3. Discontinue lenalidomide permanently and continue carfilzomib and dexamethasone alone
4. Hold lenalidomide, and once rash resolves, restart lenalidomide concurrently with hydrocortisone topical cream
5. Unsure

Question #3

Ms. D completes four cycles of carfilzomib/lenalidomide/dexamethasone, achieving a very good partial response to therapy, followed by high-dose chemotherapy and autologous stem cell transplantation. She returns to clinic and is 2 ½ months post-transplant and is in a near complete remission. She is here to discuss maintenance therapy options with you.

Which therapy would you recommend?

1. Lenalidomide maintenance
2. Bortezomib/lenalidomide/dexamethasone consolidation/maintenance
3. Melphalan/prednisone maintenance
4. Observation
5. Unsure

Question #4

Ms. D starts bortezomib, lenalidomide, and dexamethasone maintenance therapy given her high-risk disease. One year later, she develops a painful vesicular rash on over her left T9 dermatome. A diagnosis of varicella zoster is confirmed. Upon further questioning, she had stopped taking her anti-viral prophylaxis 3 months ago. Which of the following myeloma drugs is varicella zoster prophylaxis mandatory?

1. Daratumumab and bortezomib
2. Lenalidomide
3. Dexamethasone
4. Pomalidomide
5. Unsure