ASSOCIATION OF COMMUNITY CANCER CENTERS

MULTIPLE MYELOMA LECTURE SERIES

Managing Toxicities of Myeloma Therapy

Tomer M. Mark, MD, MSc

Thursday, November 1, 2018
Denver, Colorado
6:30 – 9:00 PM (MDT)

ROCKY MOUNTAIN ONCOLOGY SOCIETY

Association of Community Cancer Centers

Managing Toxicities of Myeloma Therapy

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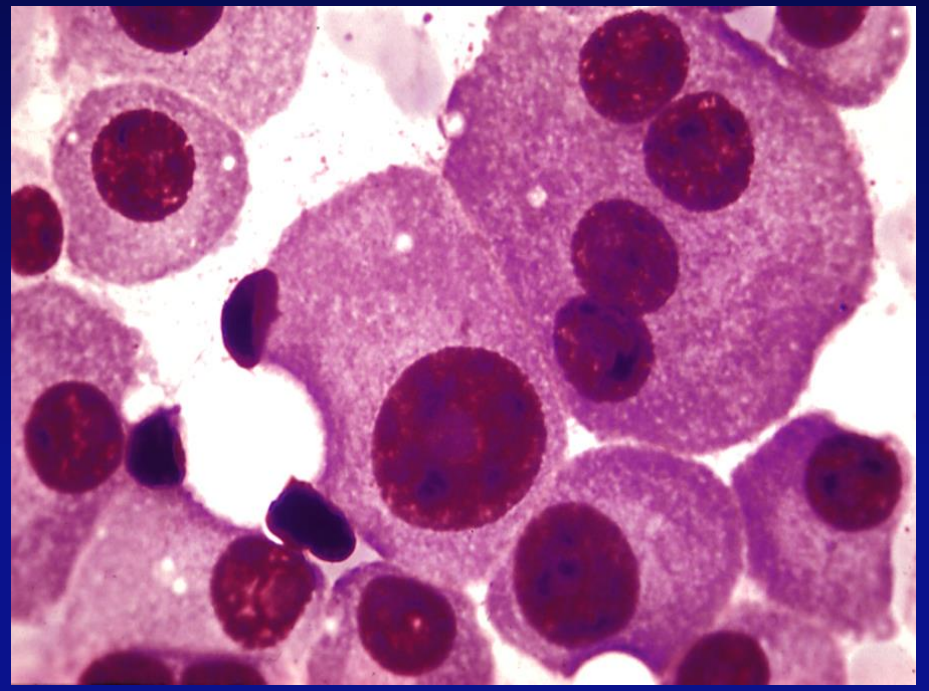


School of Medicine
UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

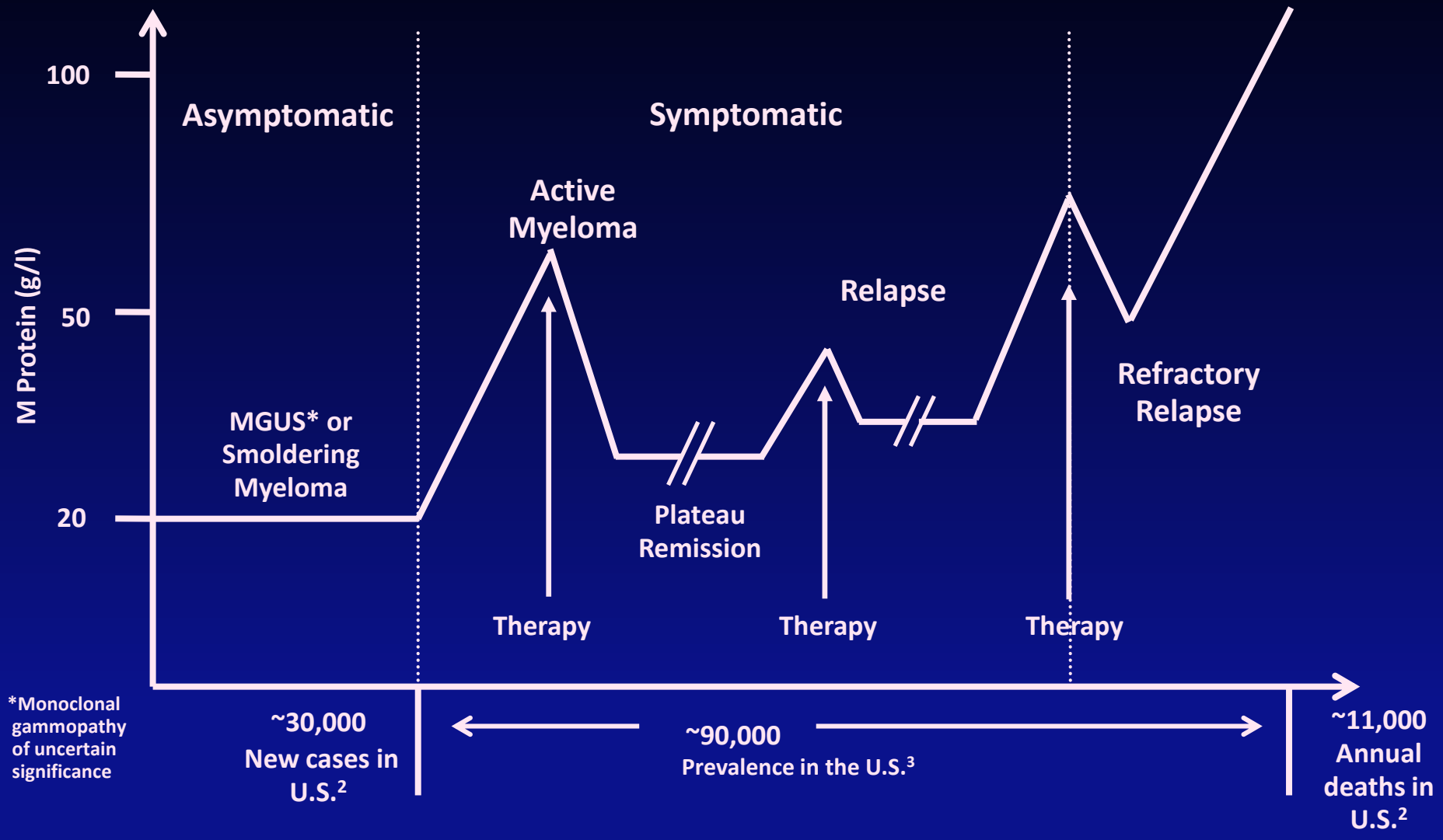
Outline

- Quick review of important updates and implication for practice:
  - Definition of myeloma
  - Staging system
  - Guiding principles of MM therapy - preventing relapse

- Toxicities of currently used agents in MM
  - IMiDs: Thalidomide, Lenalidomide, Pomalidomide
  - PIs: Bortezomib, Carfilzomib, Ixazomib
  - Monoclonal Antibodies: Elotuzumab, Daratumumab
  - Adjuncts: Dexamethasone, Zoledronic acid

- Toxicities from autologous stem cell harvest and transplantation
- Common patient and caregiver questions
- Last-minute pearls

Natural History of MM



Outcomes in Relapsed and Refractory Multiple Myeloma

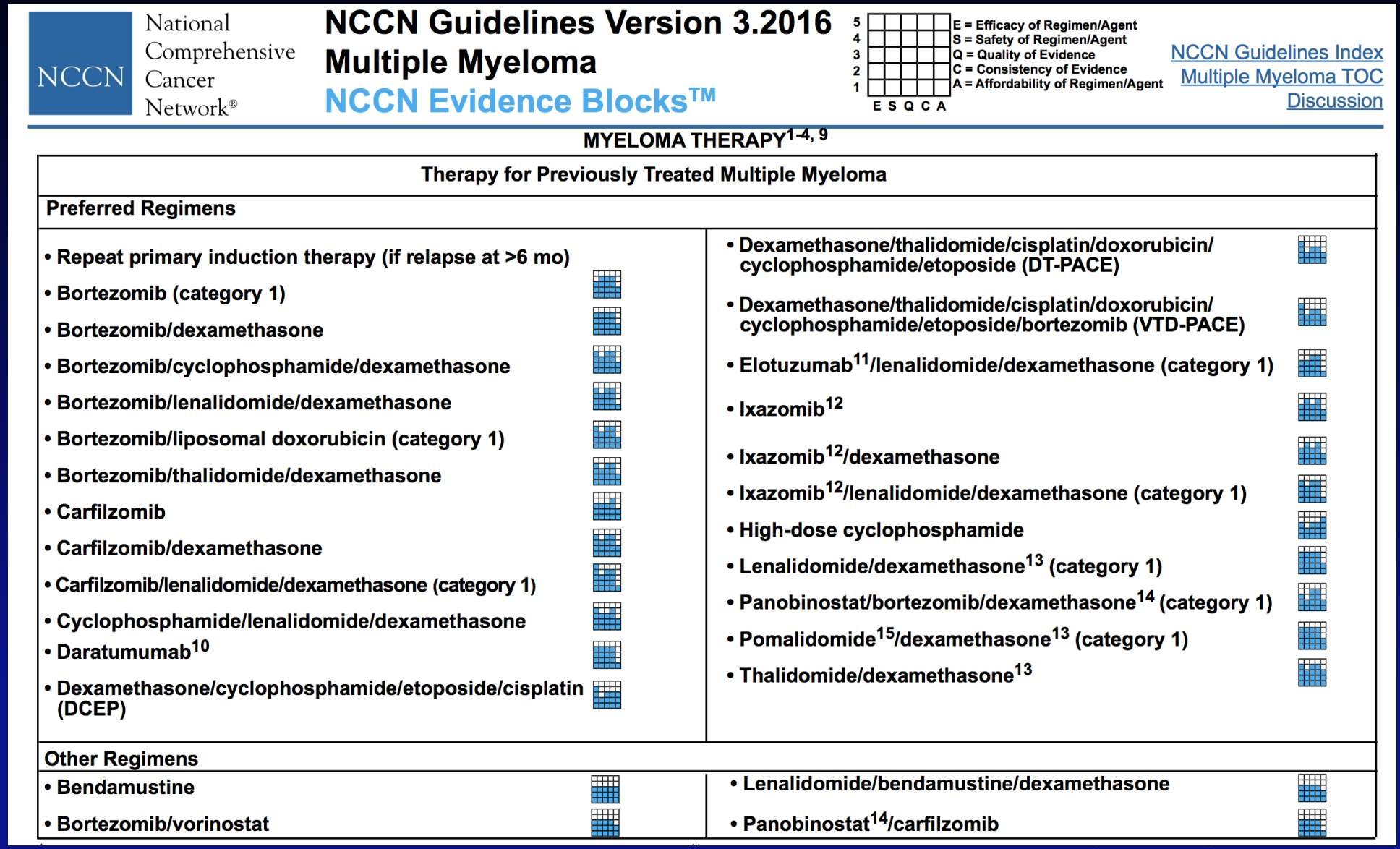
	Frontline Treatment	Relapsed	Relapsed /Refractory
Expected survival (months)	**20-50**	**14-16**	**6-10**
Sensitivity to therapy	Sensitive	Less Sensitive/Resistant	Resistant
Treatment limitations/ comorbidities	Peripheral neuropathy (~15% at diagnosis)	>80% incidence of peripheral neuropathy Compromised marrow reserve Cytopenia	Intolerant to or ineligible for available therapy

Elderly population (↑ risk for heart, lung, renal, liver dysfunction, diabetes)

Adapted from: Durie BGM. Multiple Myeloma. International Myeloma Foundation. 2011/2012 edition. Jagannath S. *Clin Lymphoma Myeloma*. 2008;8 Suppl 4:S149-S156.

Drugs for MM: Many Choices for Your Patient

Here's a List of Options from NCCN:



National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2016
Multiple Myeloma
NCCN Evidence Blocks™

5 4 3 2 1 — E S Q C A
E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

NCCN Guidelines Index
Multiple Myeloma TOC
Discussion

MYELOMA THERAPY[1-4, 9]

Therapy for Previously Treated Multiple Myeloma

Preferred Regimens

- Repeat primary induction therapy (if relapse at >6 mo)
- Bortezomib (category 1)
- Bortezomib/dexamethasone
- Bortezomib/cyclophosphamide/dexamethasone
- Bortezomib/lenalidomide/dexamethasone
- Bortezomib/liposomal doxorubicin (category 1)
- Bortezomib/thalidomide/dexamethasone
- Carfilzomib
- Carfilzomib/dexamethasone
- Carfilzomib/lenalidomide/dexamethasone (category 1)
- Cyclophosphamide/lenalidomide/dexamethasone
- Daratumumab[10]
- Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib (VTD-PACE)
- Elotuzumab[11]/lenalidomide/dexamethasone (category 1)
- Ixazomib[12]
- Ixazomib[12]/dexamethasone
- Ixazomib[12]/lenalidomide/dexamethasone (category 1)
- High-dose cyclophosphamide
- Lenalidomide/dexamethasone[13] (category 1)
- Panobinostat/bortezomib/dexamethasone[14] (category 1)
- Pomalidomide[15]/dexamethasone[13] (category 1)
- Thalidomide/dexamethasone[13]

Other Regimens

- Bendamustine
- Bortezomib/vorinostat
- Lenalidomide/bendamustine/dexamethasone
- Panobinostat[14]/carfilzomib

MYELOMA DIAGNOSTIC CRITERIA

“Old” Diagnostic Criteria for MM

- Presence of M protein in serum or urine
- Identification of >10% monoclonal plasma cells in bone marrow and/or plasmacytoma
- Evidence of end-organ damage: CRAB(I) criteria
  - **C**alcium Elevation: $Ca^{++} \geq 11$ mg/dL
  - **R**enal Failure: SCr ≥ 2 mg/dL
  - **A**nemia: Hb < 12 g/dL
  - **B**one: Lytic lesions, pathologic fracture
  - **I**nfections: Recurrent, due to hypogammaglobulinemia

Image Source: wikimedia commons

Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia 2009; 23: 3–9.

Revised International Myeloma Working Group Myeloma Diagnostic Criteria

DEFINITION OF MM

Clonal bone marrow plasma cells ≥10% OR biopsy-proven bony or extramedullary plasmacytoma

The above, plus any 1 or more of the following myeloma-defining events

Biomarkers of malignancy

- Clonal bone marrow plasma cell percentage ≥60%
- Involved:uninvolved serum free light chain ratio ≥100
- >1 focal lesion on MRI studies

Evidence of end organ damage

- Calcium elevation (>1 mg/dL higher than the upper limit of normal or >11 mg/dL)
- Renal insufficiency (creatinine clearance <40 mL/min or serum creatinine >2 mg/dL)
- Anemia (Hb <10 g/dL or >2 g/dL below the lower limit of normal)
- Bone lesions (1 or more osteolytic lesions on skeletal radiography, CT, or PET-CT)

The presence or absence of monoclonal protein is used to divide MM into secretory and nonsecretory types

Rajkumar SV et al. *Lancet Oncol.* 2014;15(12):e538-e548.

MYELOMA STAGING

Durie-Salmon Staging for MM

Stage	Criteria	Myeloma cell mass ($\times 10^{12}$ cells/m^2)	Median OS
I	All of the following: Hemoglobin >10 g/dL Serum calcium level ≤12 mg/dL (normal) Normal bone or solitary plasmacytoma on x-ray Low M component production rate: IgG <5 g/dL; IgA <3 g/dL Bence Jones protein <4 g/24 hr	<0.6 (low)	1a: 191 m 1b: N/A
II	Not fitting stage I or III	0.6–12 (intermediate)	2a: 54 m 2b: 11m
III	One or more of the following: Hemoglobin <8.5 g/dL Serum calcium level >12 mg/dL Multiple lytic bone lesions on x-ray High M-component production rate: IgG >7 g/dL; IgA >5 g/dL Bence Jones protein >12 g/24 hr	>1.2 (high)	3a: 34m 3b: 5m

Subclassification	Criteria
A	Normal renal function (serum creatinine level <2.0 mg/dL)
B	Abnormal renal function (serum creatinine level ≥2.0 mg/dL)

Durie B, Salmon S. *Cancer*. 1975;36:842; Multiple Myeloma Research Foundation. Available at: www.multiplemyeloma.org

International Staging System (ISS) for MM

Stage 1	ALB > 3.5 and β2M < 3.5	62m
Stage 2	ALB < 3.5 and β2M < 3.5 OR β2M 3.5 – 5.5	44m
Stage 3	β2M > 5.5	29m

β_2M=serum β_2 microglobulin in mg/dL; ALB=serum albumin in g/dL

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

Revised International Staging System (ISS) for MM

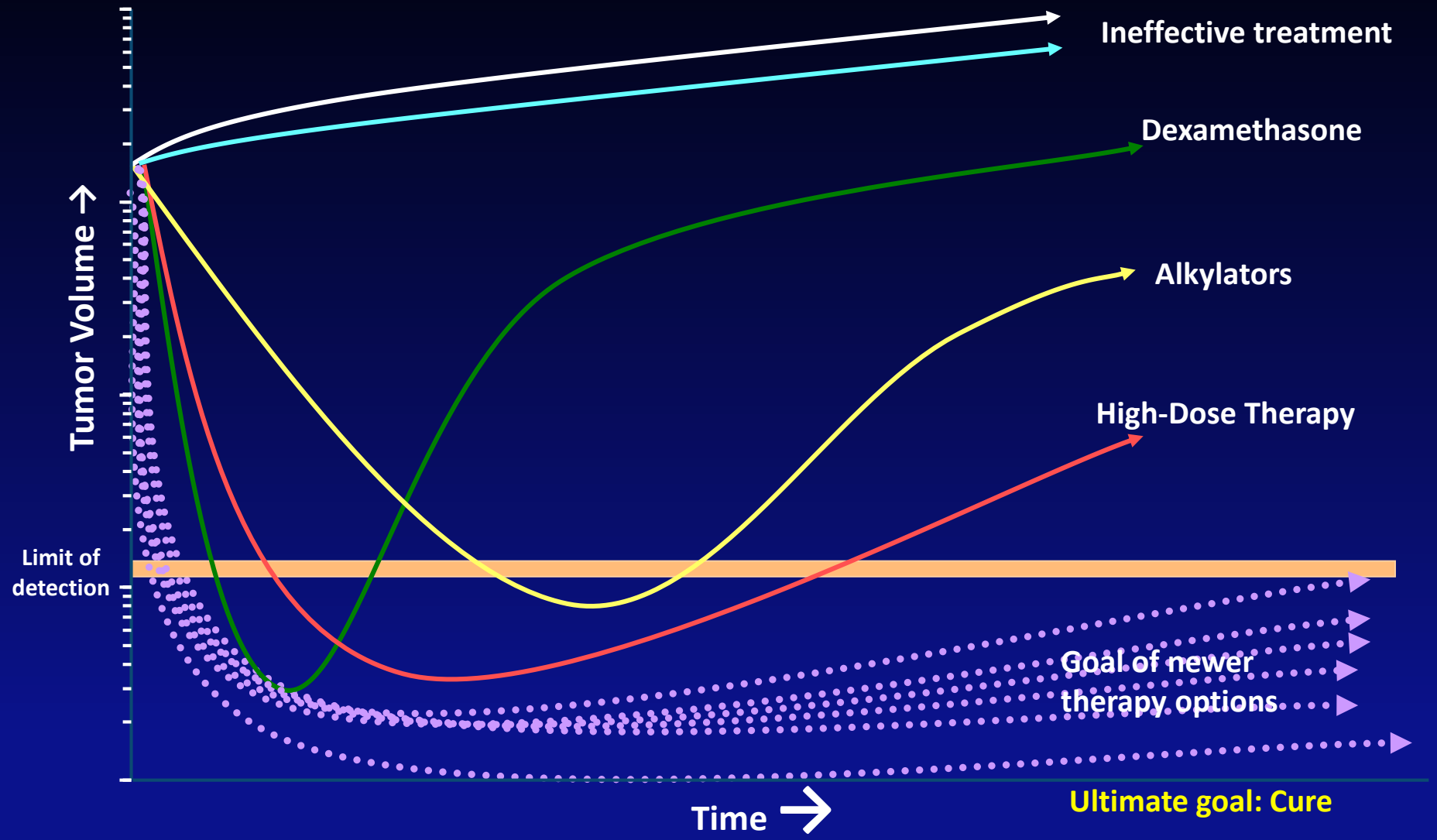
Stage 1	ALB > 3.5 and β2M < 3.5 + Absence of high risk CA AND LDH wnl	NR
Stage 2	Neither stage 1 or 3	83m
Stage 3	β2M > 5.5 + High risk CA OR LDH > ULN	43m

β_2M=serum β_2 microglobulin in mg/dL; ALB=serum albumin in g/dL,
CA = cytogenetic abnormalities (del 17p, t(4;14),t(14;16)

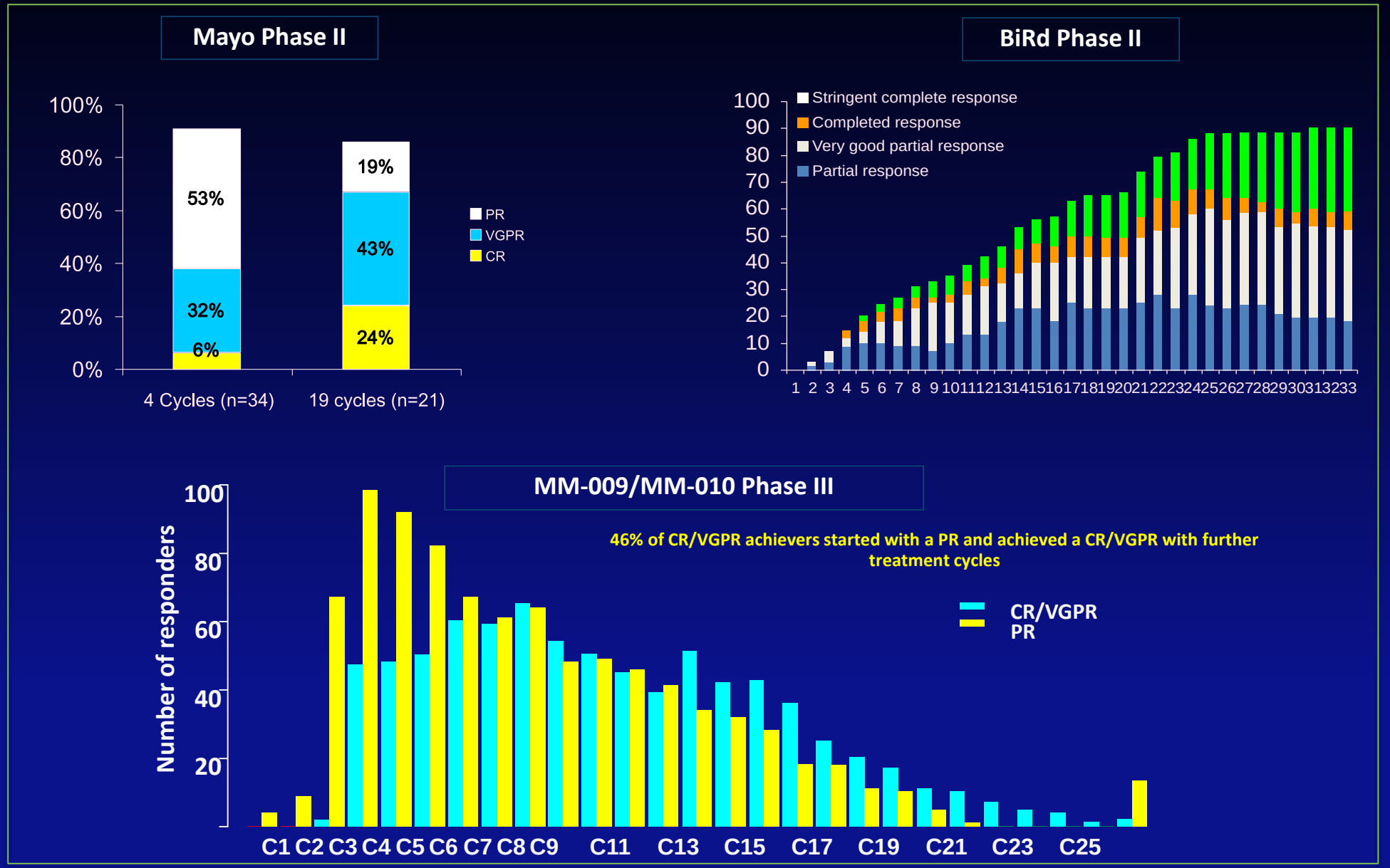
Palumbo A. et al. J Clin Oncol. 2015;33(26), 2863-9.

LENGTH OF THERAPY

What Is the Goal of Maintenance?

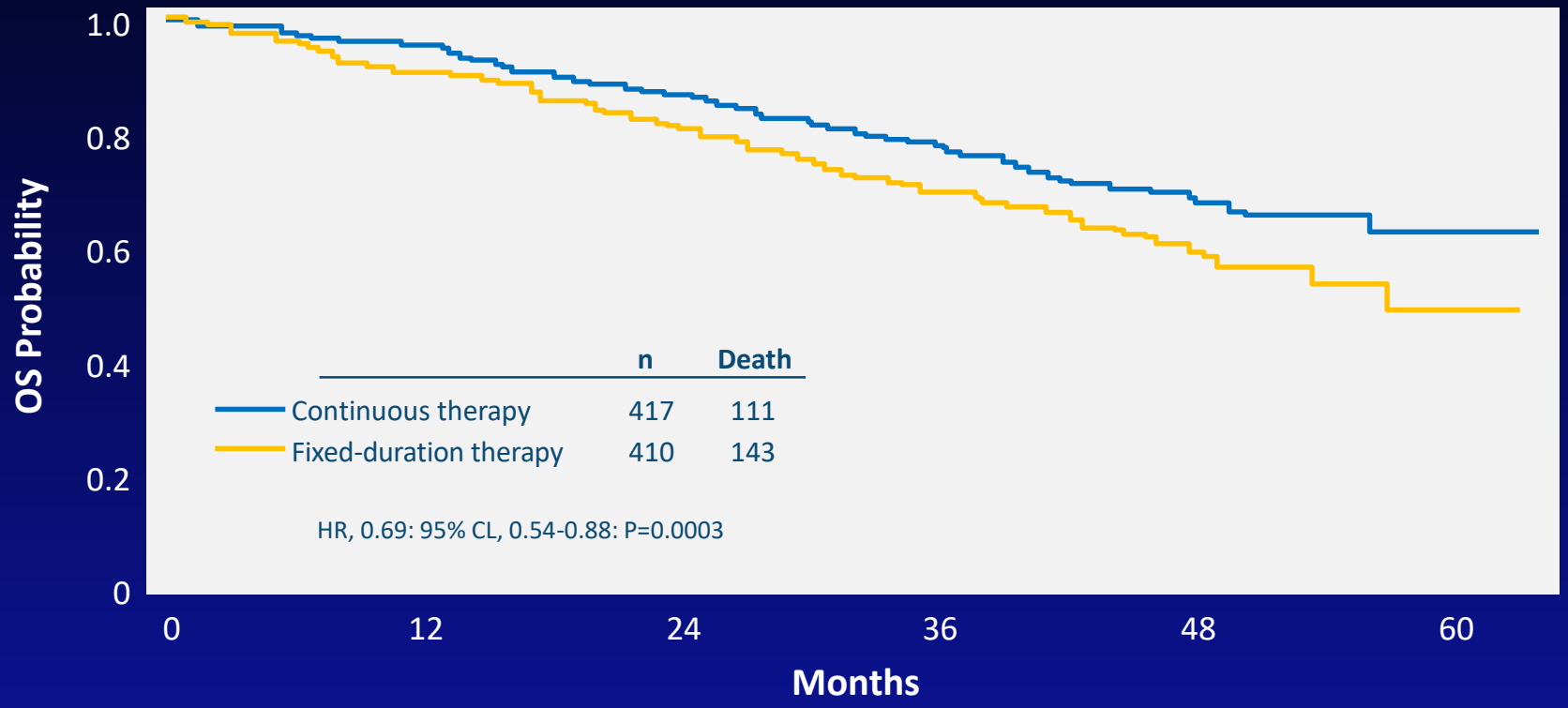


Responses Deepen with Length of Therapy



The Importance of Continuous Therapy[1]

Continuous therapy may be associated with significant improvement in patient outcomes[1]

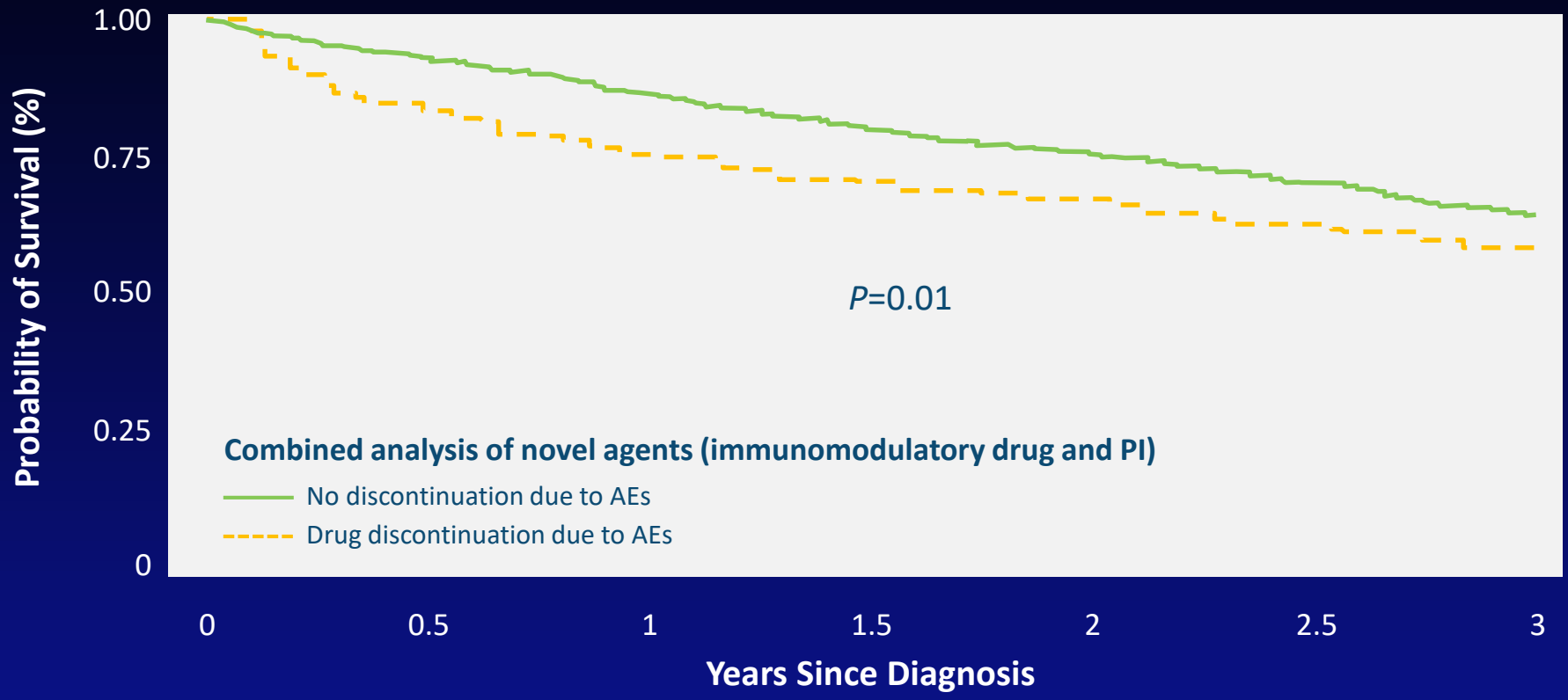


Pooled analysis of 3 phase 3 trials analyzing continuous therapy vs fixed-duration therapy in 1218 patients with newly diagnosed multiple myeloma. Primary endpoints were PFS1, PFS2, and OS. Median follow-up was 52 months.

OS=overall survival.

Reference: 1. Palumbo, A. et al. *J Clin Oncol.* 2015; 33:3459-3466.

Treatment Discontinuation Can Adversely Impact Outcomes[1]



- Drug discontinuation due to AEs was correlated with increased risk of death within the first 6 months (HR: 1.67; 95% CI, 1.12-2.51; *P*=0.01)

AE = adverse event; CI = confidence interval; HR = hazard ratio.

Reference: 1. Bringhen S et al. *Haematologica.* 2013;98(6):980-987.

Treatments Are Discontinued in the Real World for Many Different Reasons[1]

- Stable disease/ remission
- Toxicity
- As planned
- Progression
- Poor PS
- Patient refusal

Reference: 1. Yong K et al. Br J Haematol. 2016;175(2):252-264.

Guiding Principles:

- Patients who are now asymptomatic may have active myeloma and require treatment
- Continuous combination therapy provides best outcomes
  - Stopping treatment for ANY reason leads to relapse and potentially inferior survival
  - We have to learn how to safely treat through AEs

Treatment Decision in Older Patients

Patients

- ADL
- Comorbidities
- Hospitalization
- Medications
- Social Support

Multiple Myeloma

- Cytogenetics
- Stage
- Tumor Burden
- Optimal Chemo
- Supportive Meds

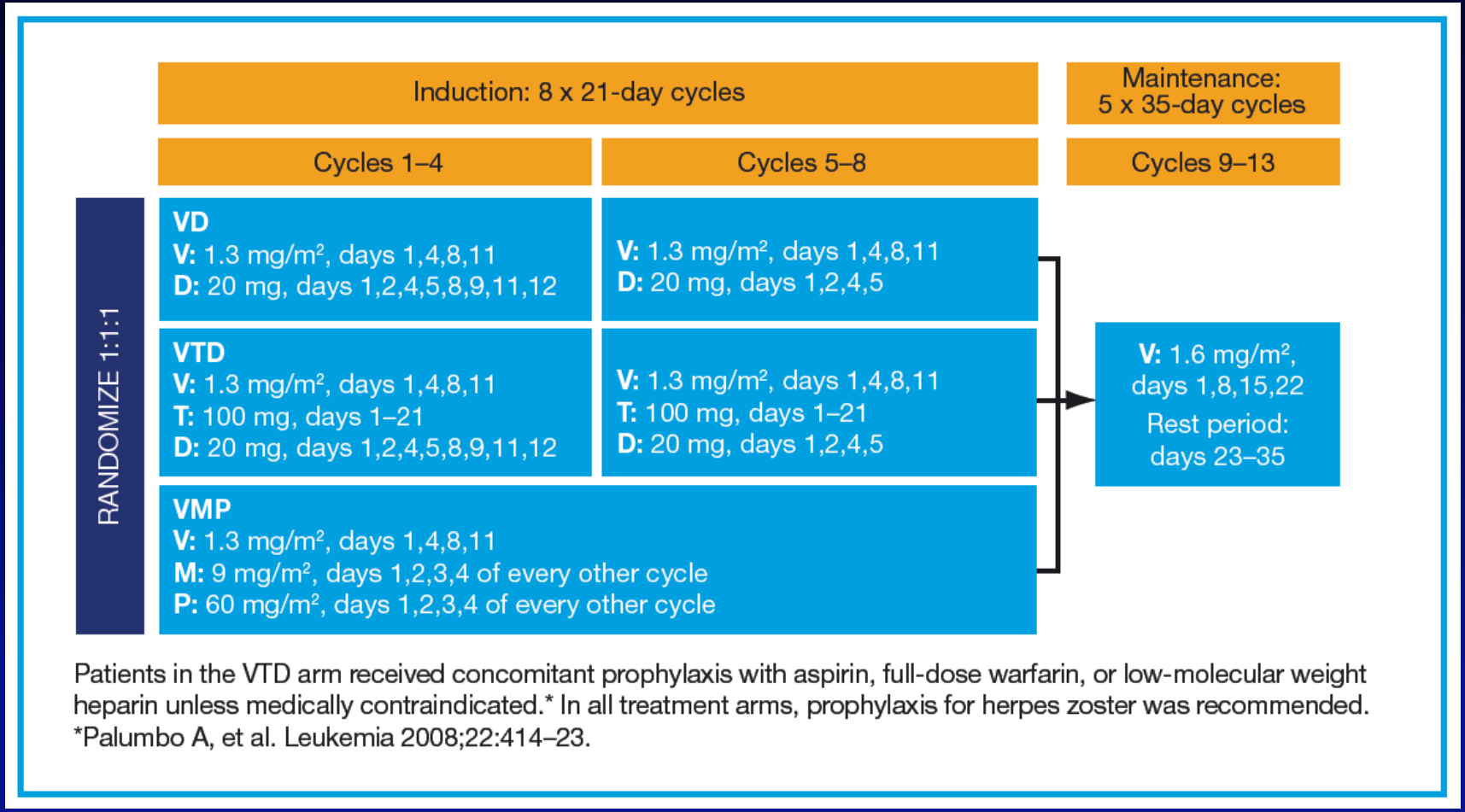
Goals of Care (CR vs. Disease Control?)

Expectations

Understanding

Life Expectancy

Efficacy and Safety of Three Bortezomib-Based Induction and Maintenance Regimens in Previously Untreated, Transplant-Ineligible Multiple Myeloma Patients: Final Results from the Randomized, Phase 3b, US Community-Based UPFRONT Study



Patients in the VTD arm received concomitant prophylaxis with aspirin, full-dose warfarin, or low-molecular weight heparin unless medically contraindicated.* In all treatment arms, prophylaxis for herpes zoster was recommended.
*Palumbo A, et al. Leukemia 2008;22:414–23.

Slide Courtesy Niesvizky, R; ASH 2013

RESULTS

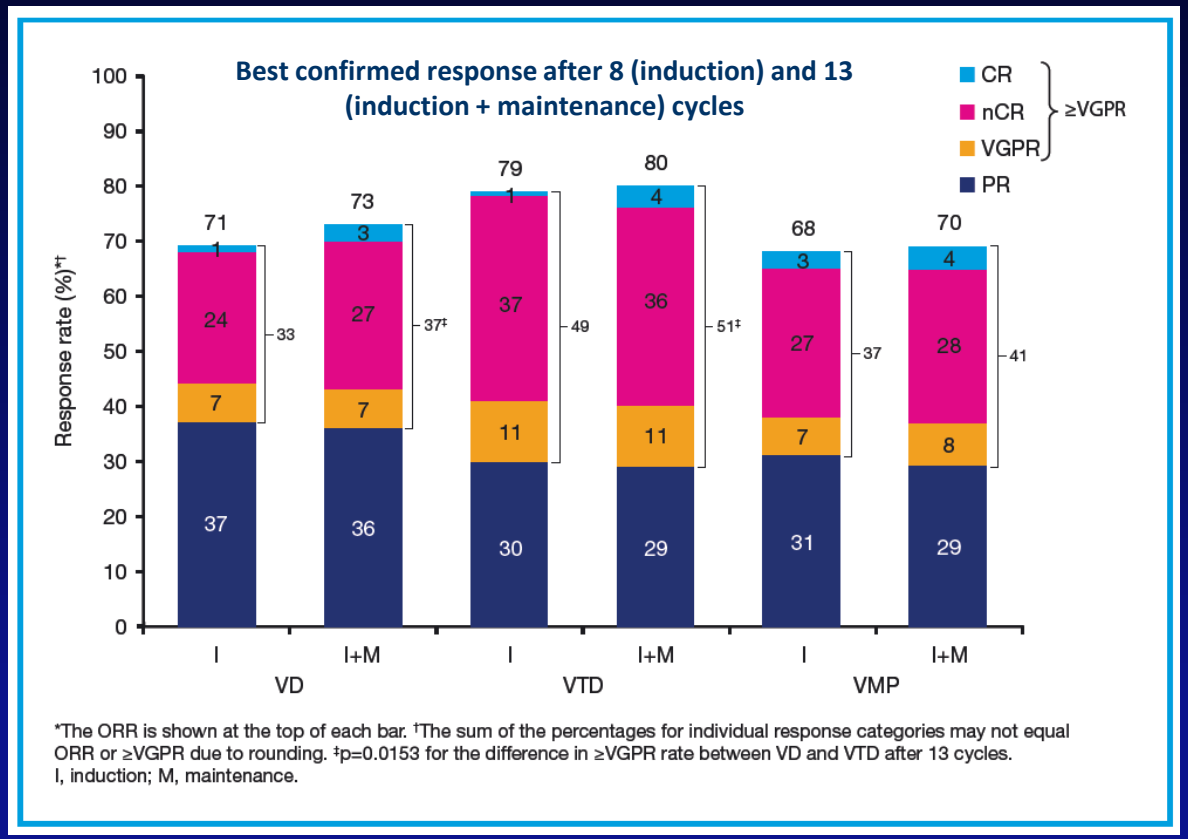
- 502 patients were randomized to
  - VD (n=168)
  - VTD (n=167)
  - VMP (n=167)

- Baseline characteristics were well-balanced across the treatment arms
  - Median age was 73 years (range 38-91)
  - 48% of patients had comorbidities at baseline
    - The most common were diabetes mellitus (21%), renal disease (15%), and chronic pulmonary disease (8%)

Slide Courtesy Niesvizky, R; ASH 2013

Response*

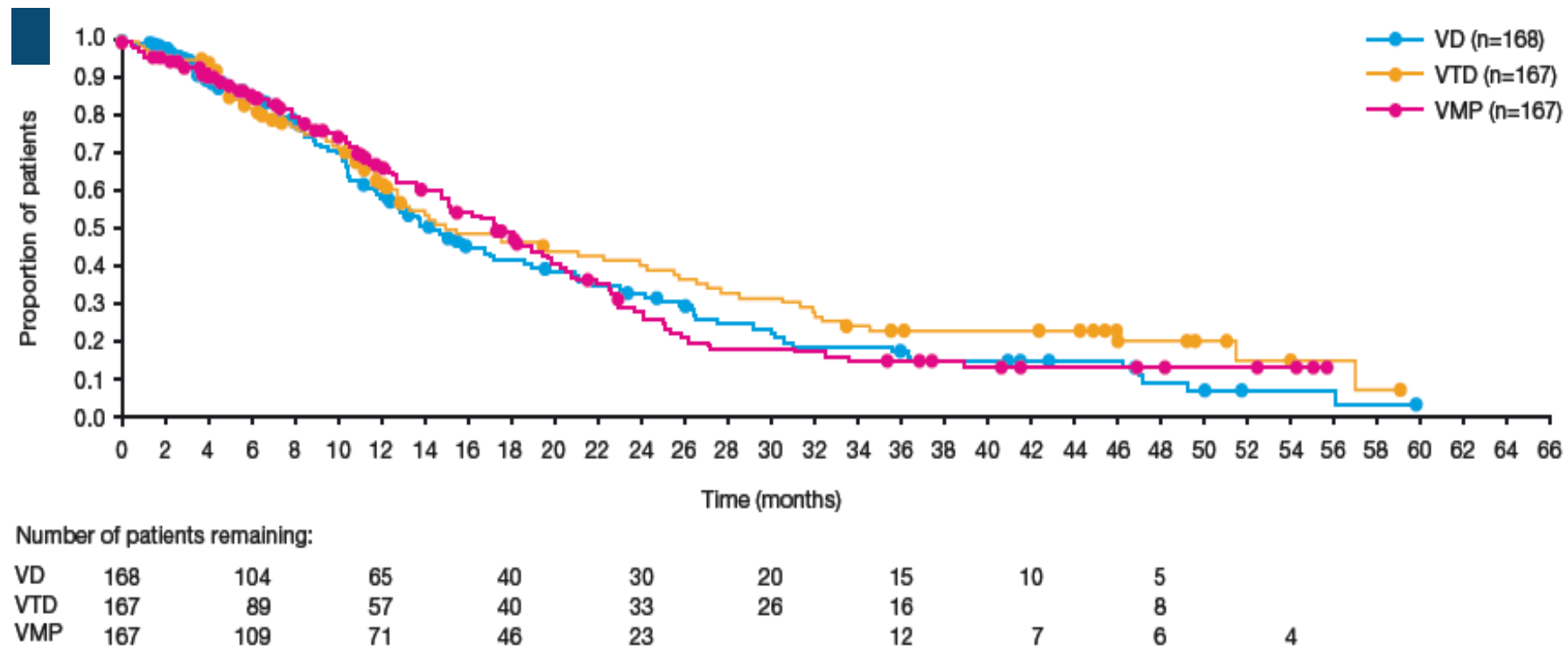
- ORRs after 13 cycles were 73% (VD), 80% (VTD), and 70% (VMP) including:
  - 30%, 40%, and 32% CR/nCR, respectively
  - 37%, 51%, and 41% ≥VGPR, respectively



*Response-evaluable population (n=425 patients who received at least one dose of study drug, had measurable disease at baseline, and had at least one post-baseline M-protein measurement)

Slide Courtesy Niesvizky, R; ASH 2013

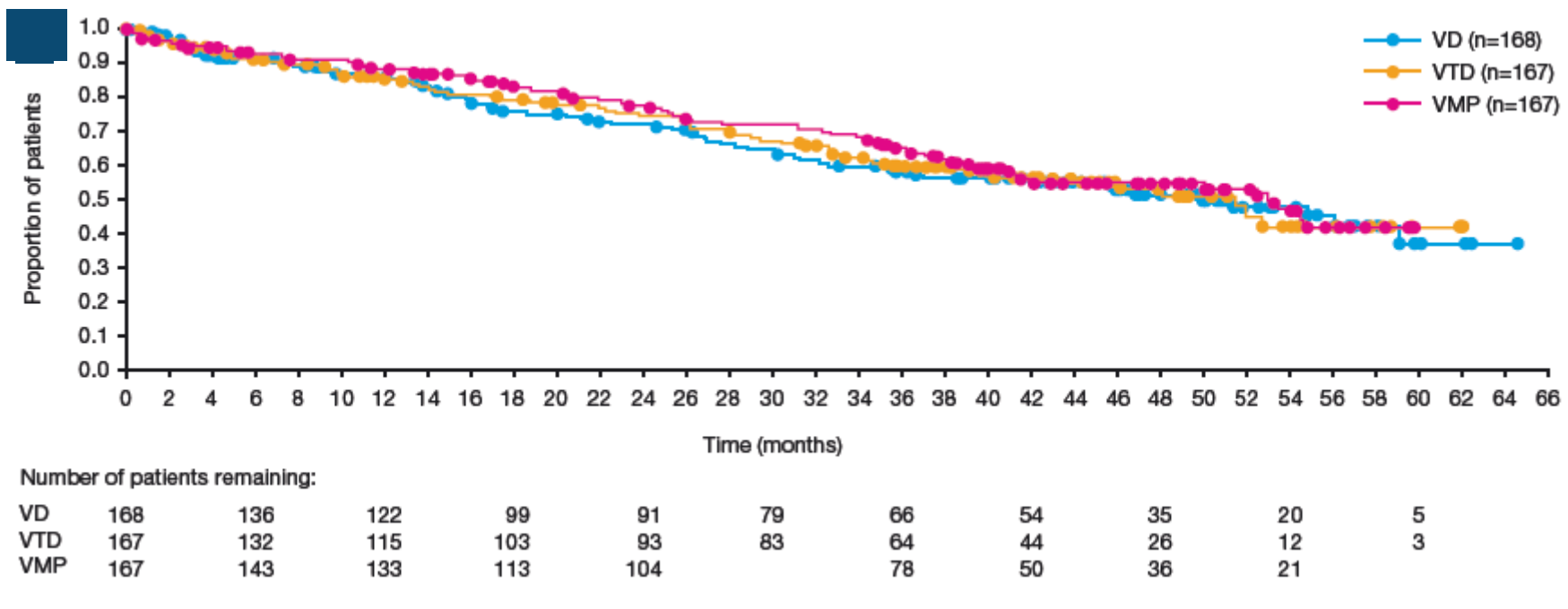
PFS (Intent-to-Treat Population)



- After a median follow-up of 42.7 months, 265 (53%) patients had progressed and/or died
- Median PFS (95% CI) was 14.7 months (12.0, 18.6), 15.4 months (12.6, 24.2), and 17.3 months (14.8, 20.3), for VD, VTD, and VMP, respectively, with no global difference among arms **(p=0.458)**

Slide Courtesy Niesvizky, R; ASH 2013

OS (Intent-to-Treat Population)

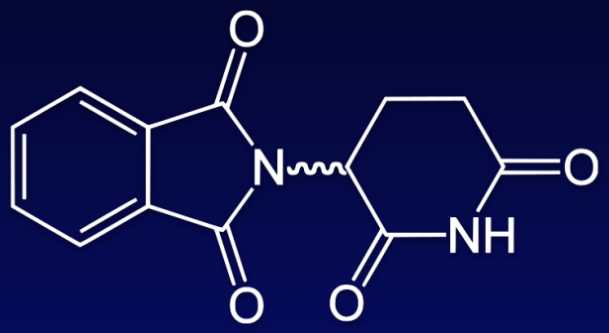


- Median OS (95% CI) was 49.8 months (35.7, not estimable [NE]), 51.5 months (38.5, NE), and 53.1 months (41.1, NE) for VD, VTD, and VMP, respectively, with no global difference among arms **(p=0.789)**

Slide Courtesy Niesvizky, R; ASH 2013

MANAGING SIDE EFFECTS WITH COMMONLY USED ANTI-MM AGENTS

Immunomodulatory Agents

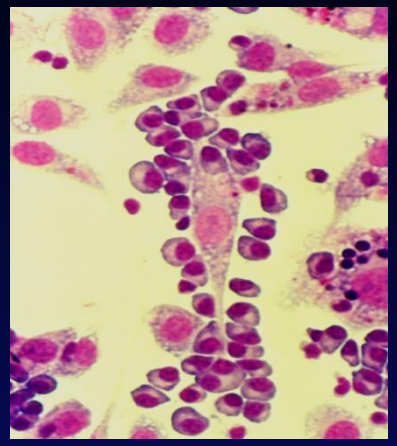


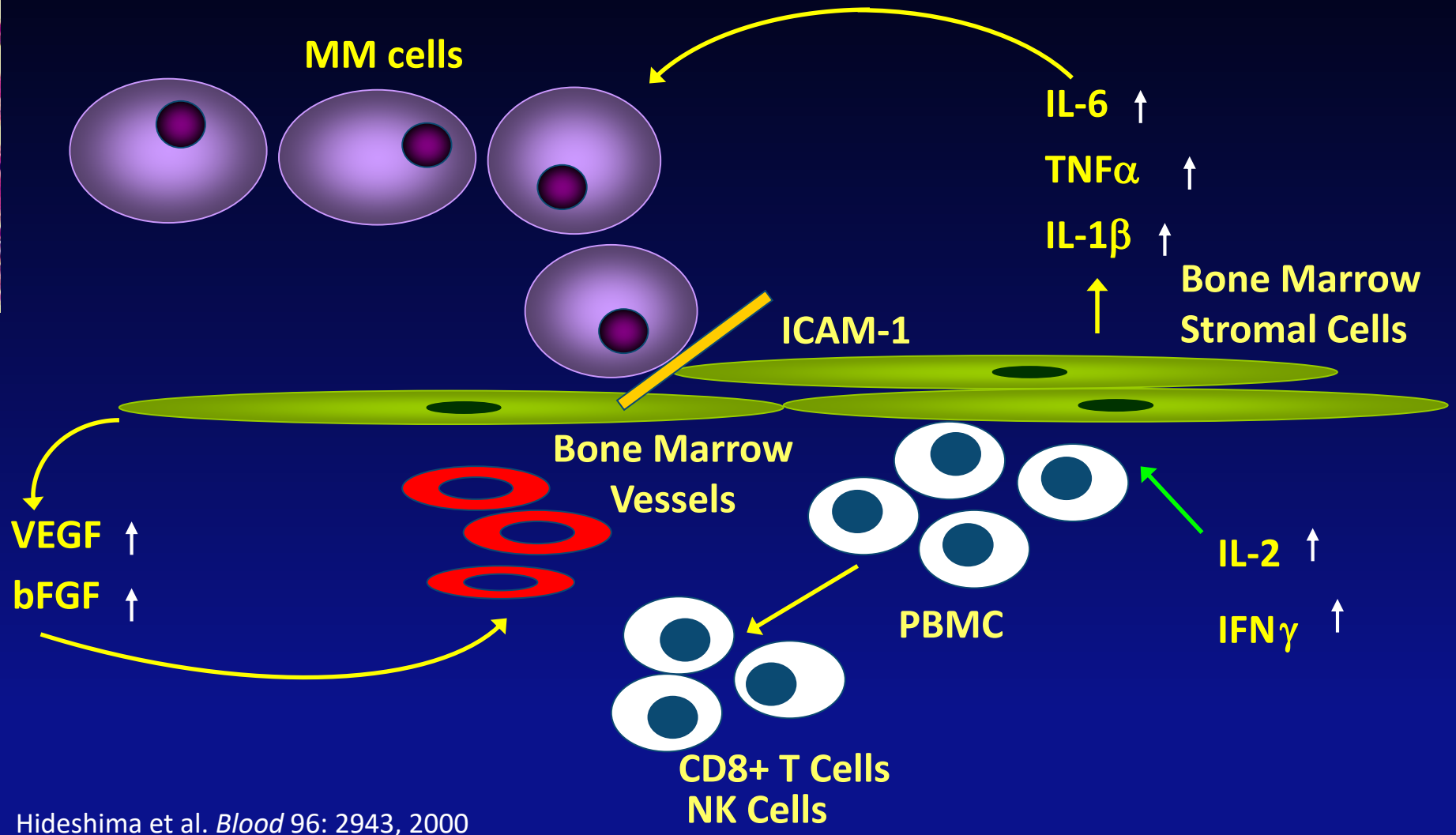
Thalidomide

Lenalidomide

Pomalidomide

IMiDs Alter the Bone Marrow Microenvironment





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

Mitsiades et al. *Blood* 99: 4525, 2002
Lentzsch et al *Cancer Res* 62: 2300, 2002

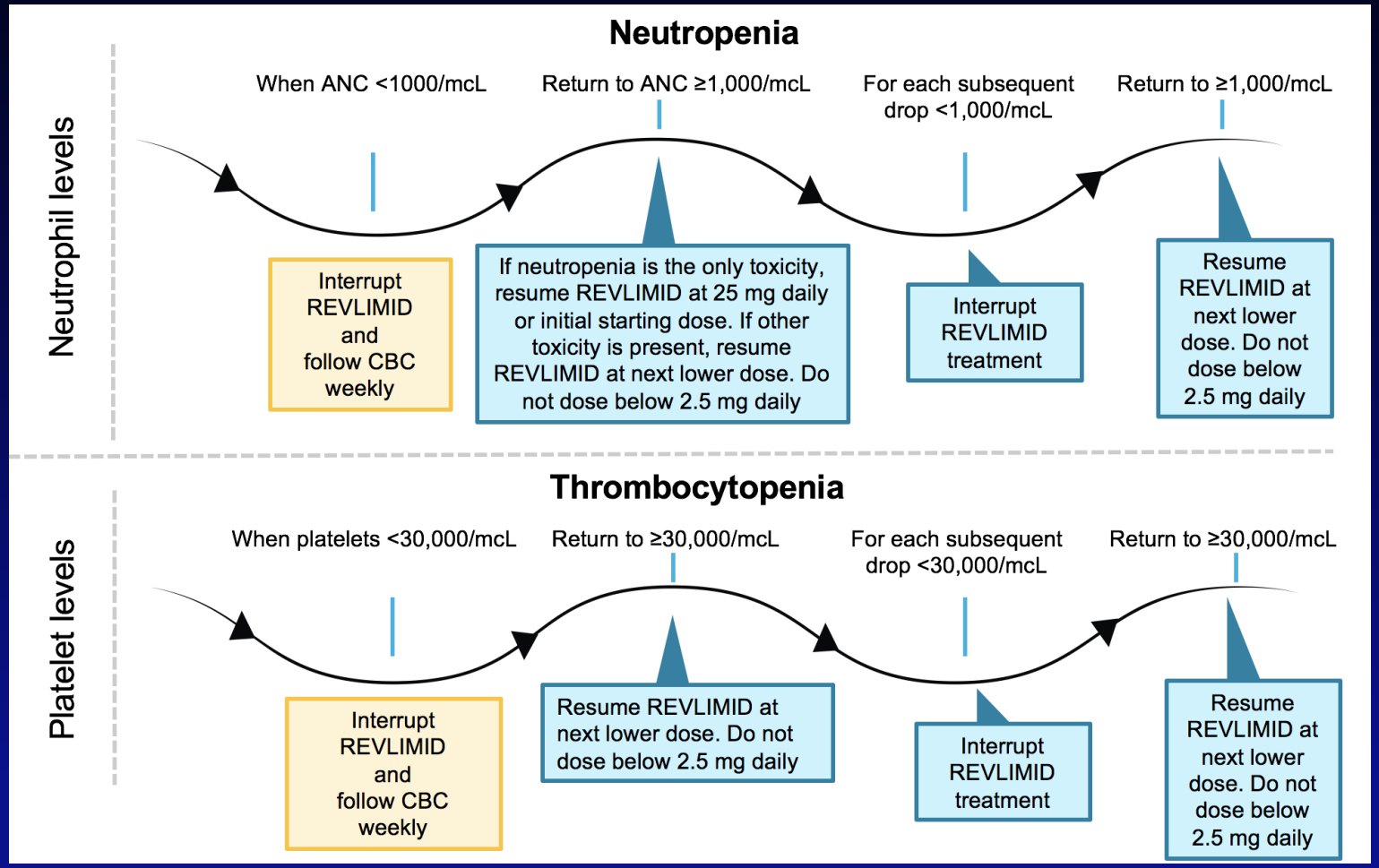
Thalidomide (Thalomid): Immunomodulatory Agent

Side Effect	Rate	Management
Increased risk of blood clot	23%	Aspirin; if higher risk, need heparin or other anticoagulation
Fatigue	80%	Exercise, limit carbohydrates, coffee, other stimulants, taking thalidomide at night; dose reduction
Constipation	55%	Stool softeners, laxatives
Rash	30%	Common at beginning of therapy; treat through. Can apply topical hydrocortisone if itchy
Brain fog	28%	Exercise, dose reduction
Peripheral neuropathy	55%	*** CAN BE PERMANENT *** Dose effect threshold: ~60 grams = 100% neuropathy rate (approx. 1 year of thal treatment)

Lenalidomide (Revlimid): Immunomodulatory Agent

Side Effect	Rate	Management
Low blood counts, esp. neutropenia	40%	Transfusions, G-CSF (neupogen, neulasta), erythropoietin (procrit/aranesp); **OK to give G-CSF and lenalidomide at the same time**
Increased risk of blood clot	22%	Aspirin; if higher risk, need heparin or other anticoagulation
Fatigue	32%	Exercise, limit carbohydrates, coffee, other stimulants
Muscle cramping	21%	Pickle juice, apple cider vinegar
Diarrhea	46%	Cholestyramine, colestipol; **there is lactose in the LEN cap
Rash	28%	Common at beginning of therapy; treat through. Can apply topical hydrocortisone if itchy
Atrial fibrillation	7%	**high index of suspicion; treat as per standard of care; be wary of amyloidosis

Managing Cytopenias with Lenalidomide



- Prior PI had G-CSF and lenalidomide concomitantly
- PI changed to reflect practice of clinical trials, no scientific basis
- JUST LIKE MDS: blood counts get worse before better on lenalidomide – TREAT THROUGH CYTOPENIAS!!!

Perfectly safe to give lenalidomide to patients with renal insufficiency, even with ESRD!

The recommendations for initial starting doses for patients with MM are as follows:

Category	Renal Function (Cockcroft-Gault)	Dose in Multiple Myeloma
Normal / mild renal impairment	CLcr >50 mL/min	**25 mg every 24 hours**
Moderate renal impairment	CLcr 30-50 mL/min	**10 mg every 24 hours**
Severe renal impairment	CLcr <30 mL/min (not requiring dialysis)	**15 mg every 48 hours**
End-stage renal disease	CLcr <30 mL/min (requiring dialysis)	**5 mg once daily; on dialysis days, administer the dose following dialysis**

- Lenalidomide is NOT nephrotoxic, it is cleared by the kidney
- No excess harm to patients if started at correct dose, just as effective as standard dose LEN[1]

1) Niesvizky R, Naib T, Christos P, et al: Lenalidomide-induced myelosuppression is associated with renal dysfunction: adverse events evaluation of treatment-naive patients undergoing front-line lenalidomide and dexamethasone therapy. Br J Haematol 138:640-3, 2007

Pomalidomide (Pomalyst): Immunomodulatory Agent

Side Effect	Rate	Management
Low blood counts, esp neutropenia	50%	Transfusions, G-CSF (neupogen, neulasta), erythropoietin (procrit/aranesp); **OK to give G-CSF and pomalyst at the same time**
Increased risk of blood clot	8%	Aspirin; if higher risk, need heparin or other anticoagulation
Fatigue and asthenia	55%	Exercise, limit carbohydrates, coffee, other stimulants

Pomalidomide (Pomalyst): Immunomodulatory Agent

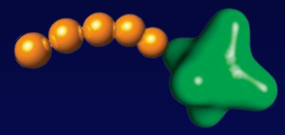
Side Effect	Rate	Management
Dyspnea	35%	Often subjective and passes with time. R/o PE, infection
URI/Pneumonia	23%	* Similar to rates of URI in other late-line MM txs
Dizziness/Confusion	20%	** Be careful about co-metabolism of narcotics and other CYP inhibitors/inducers
Fever	20%	Rule out infection; antipyretics

Pomalidomide (Pomalyst): Special Considerations

- Pomalyst is metabolized hepatically via CYP3A4 and CYP1A2
- This means:
  - Do not give with strong CYP inducers/inhibitors (i.e., narcotics)
  - Cigarette smoking can induce CYP1A2. Tell your patients to stop smoking
  - Teas (with exception of black tea) should be avoided
  - Take on EMPTY stomach (Cmax is 30% lower when taken with food)
  - Older patients tolerate pomalyst well! No dose reduction needed except for HD patients

Bortezomib (Velcade): Proteasome Inhibitor

Side Effect	Rate	Management
Low platelet count	50%	Transfusions, dose reduction
Peripheral neuropathy	46%	Lower the velcade dose, *happens early, risk reduced with subcutaneous administration
Fatigue	25%	Exercise, limit carbohydrates, coffee, other stimulants
Increased risk for shingles	11%	Acyclovir/Valacyclovir
Diarrhea	35%	Imodium, lomotil, kaopectate
Boron allergy	???	
Interstitial pneumonitis	reported	

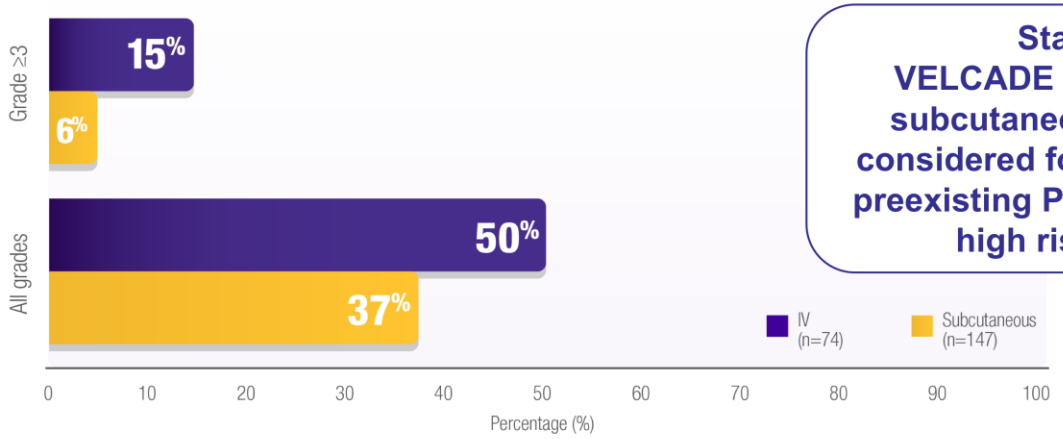


bortezomib

Proteasome

Give Bortezomib Subcutaneously!

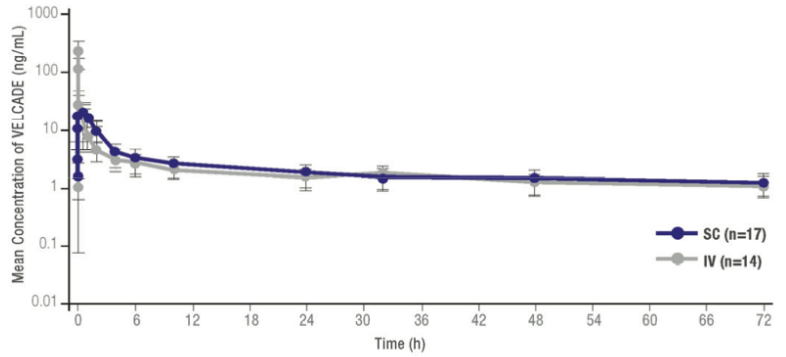
INCIDENCE OF PN IN RELAPSED MULTIPLE MYELOMA: SUBCUTANEOUS AND IV



Starting VELCADE (bortezomib) subcutaneously may be considered for patients with preexisting PN or patients at high risk for PN

- In a study of patients with relapsed MM, ORR* at 12 weeks; 43% with subcutaneous VELCADE and 42% with IV VELCADE
  - — The study met its primary non-inferiority objective that single-agent subcutaneous VELCADE retained at least 60% of the ORR after 4 cycles relative to single-agent IV VELCADE

Plasma Concentration–Time Profiles Following Subcutaneous and IV Administrations of VELCADE® (bortezomib)

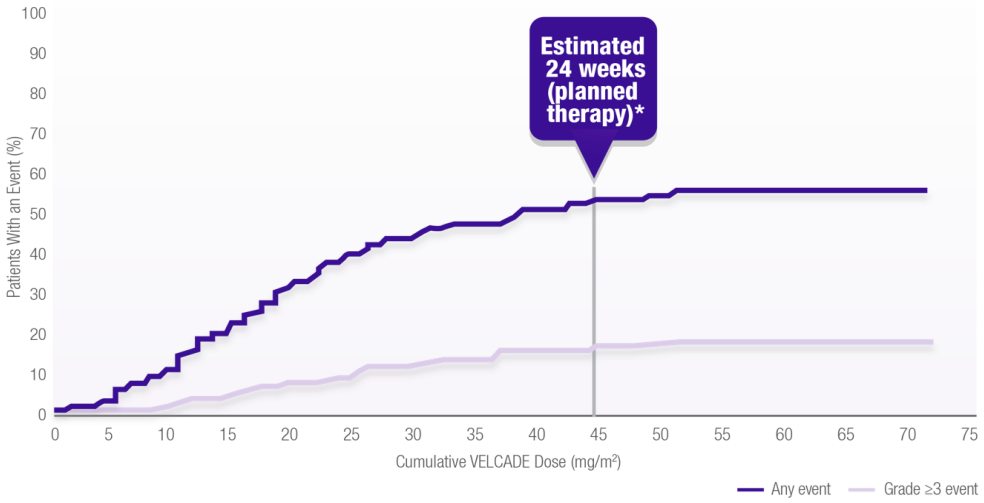


- The total systemic exposure after repeat dose administration (AUC_{last}) was equivalent for subcutaneous and IV administration

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

The peripheral neuropathy from bortezomib happens EARLY

CUMULATIVE DOSE OF IV VELCADE TO FIRST ONSET OF PN[1]



*A cumulative VELCADE dose of approximately 45 mg/m² is equivalent to approximately four 6-week cycles of VELCADE+MP.[1]

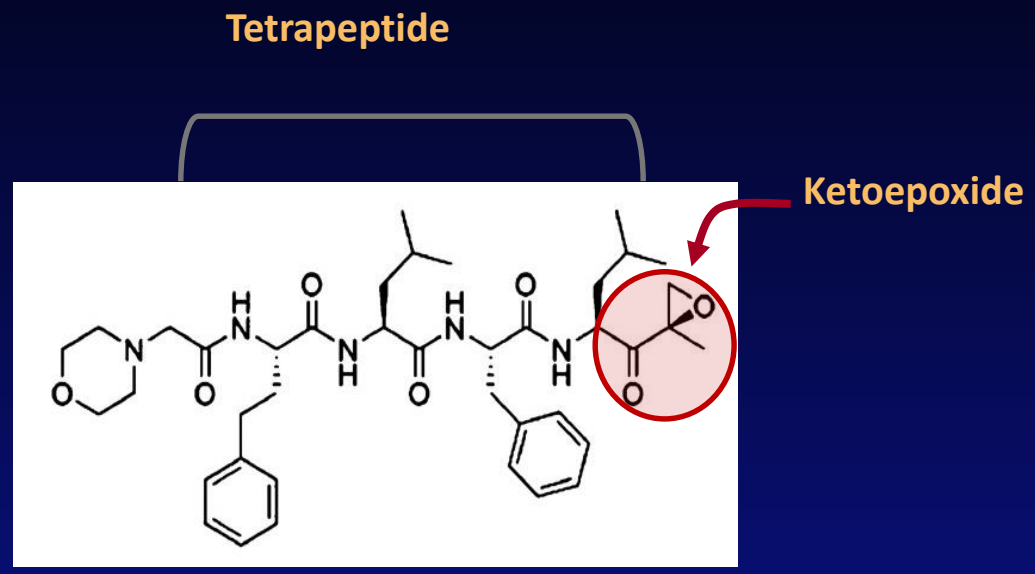
- In patients treated with VELCADE (bortezomib)+MP, 47% experienced treatment-emergent PN, including 13% with grade ≥3[1]
- 11% of patients discontinued treatment with VELCADE due to PN and continued MP; 3% of patients discontinued treatment with VELCADE+MP due to PN[1]
- Patients with preexisting severe neuropathy should be treated with VELCADE only after careful risk-benefit assessment

- Treatment with VELCADE may cause PN that is predominantly sensory. However, cases of severe sensory and motor PN have been reported. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain, or weakness

Reference: 1. Dimopoulos MA et al. *Eur J Haematol*. 2011;86(1):23-31.

Carfilzomib (Kyprolis): Proteasome Inhibitor

- Irreversible inhibitor of the 26S proteasome
- Has been shown to overcome bortezomib resistance
- ORR in phase 2 trial of CRD: 100%, >VGPR: 100% (in patients treated with >11 cycles)



Jakubowiak et. al. ASH 2011

Carfilzomib (Kyprolis): Toxicities

Side Effect	Rate	Management
Anemia	47%	Transfusions, dose reduction
Dyspnea	35%	Tends to be transient, like pomalidomide
Fatigue	56%	Exercise, limit carbohydrates, coffee, other stimulants
URI	28%	Also very similar to pomalidomide
Diarrhea	33%	Imodium, lomotil, kaopectate
Increased creatinine	24%	1 of 3 patterns emerges
Fever	30%	Antipyretics, rule out infection
Tumor lysis syndrome	reported	Premedicate with allopurinol and IVF**
Pulmonary hypertension	2%	Monitor carefully for emergence of sx, hold dosing
Thrombotic microangiopathy	reported	Monitor carefully

Carfilzomib (Kyprolis): Cardiac Toxicities

Side Effect	Rate	Management
Hypertension	18-30%	antihypertensives
Congestive Heart Failure	12%	Early identification; stop carfilzomib, reversible; biggest risk factor is prior cardiac disease

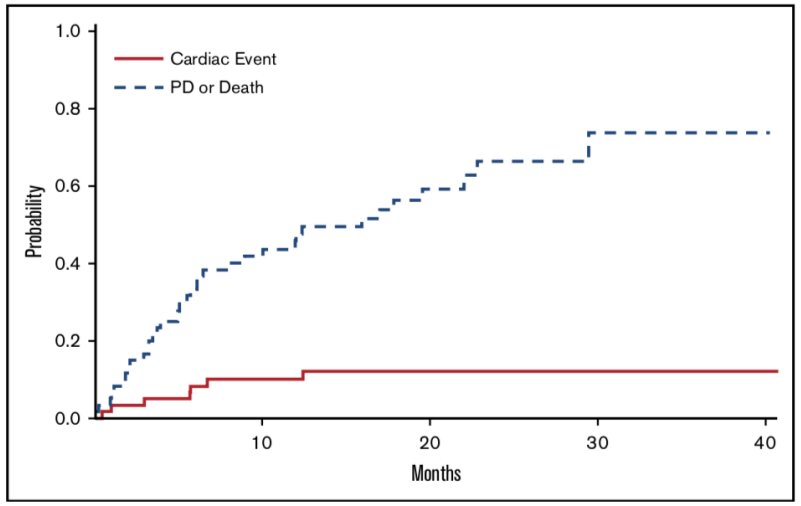


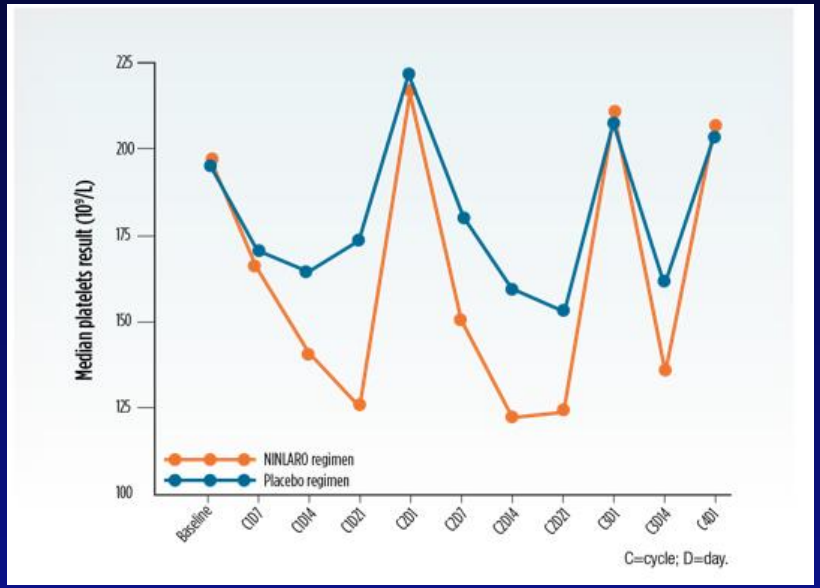
Figure 1. Incidence of cardiac events in patients treated with carfilzomib. Cumulative incidence function estimates of cardiac events and discontinuation because of progressive disease or for other (nontoxicity) reasons.

60 consecutive myeloma patients treated with carfilzomib-based regimens who were thoroughly evaluated for cardiovascular risk factors, 12% experienced a reversible reduction of left ventricular ejection fraction (LVEF) by ≥20%. The incidence of LVEF reduction was 5% at 3m, 8% at 6m, 10% at 12m, and 12% at 15m

Dimopoulos MA, Roussou M, Gavriatopoulou M, et al: Cardiac and renal complications of carfilzomib in patients with multiple myeloma. Blood Advances 1:449-454, 2017

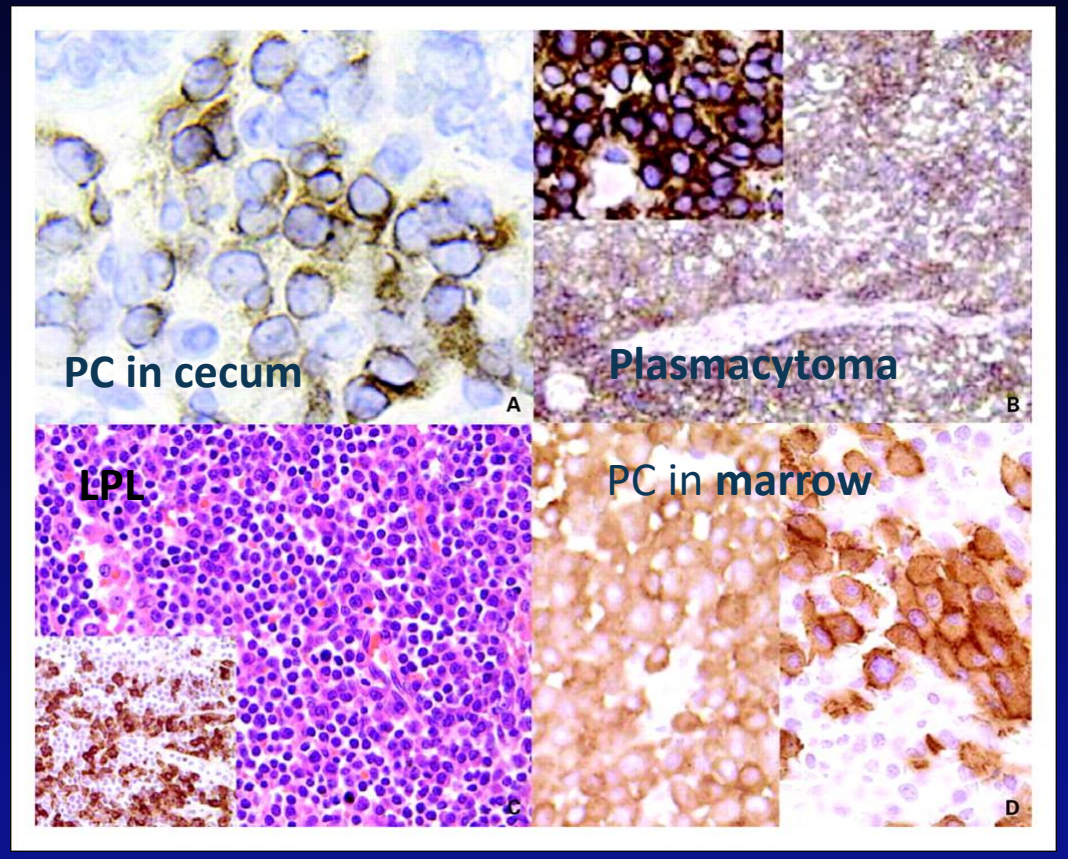
Ixazomib (Ninlaro): Oral Proteasome Inhibitor

Side Effect	Rate	Management
Thrombocytopenia	78%	Similar pattern to bortezomib
URI	19%	Similar to other agents in relapsed setting
Diarrhea	42%	Imodium, lomotil, kaopectate
Constipation	34%	Laxatives
Nausea and vomiting	22%	Consider premedication
Rash	19%	Treat through if not severe
Peripheral neuropathy	19%	Placebo + Rd comparator was 14%



Elotuzumab: CS1, SLAMF7m CRACC, CD319

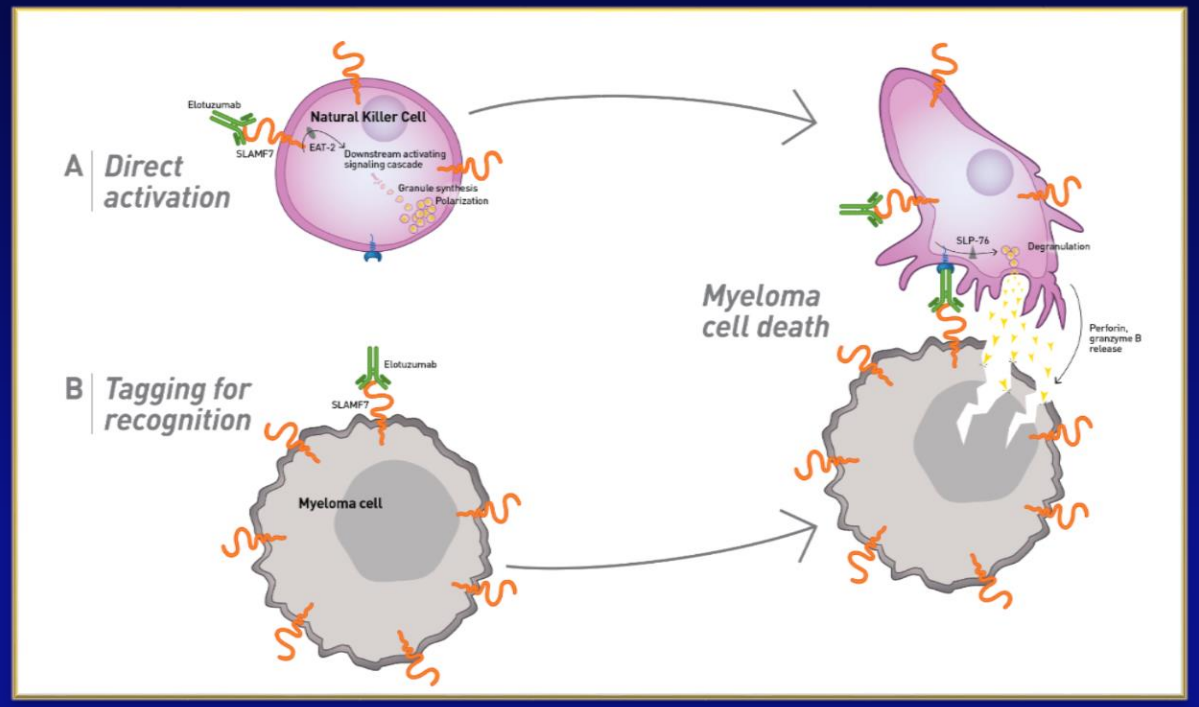
- Elotuzumab (HuLuc63) is a humanized monoclonal IgG1 antibody targeting human CS1, a cell surface glycoprotein
- CS1 is highly and uniformly expressed on >95% of primary MM cells
  - Restricted expression on NK cells
  - Little to no expression on normal tissues
  - May promote adhesion to bone marrow stroma
- Acts primarily through NK cell-mediated ADCC



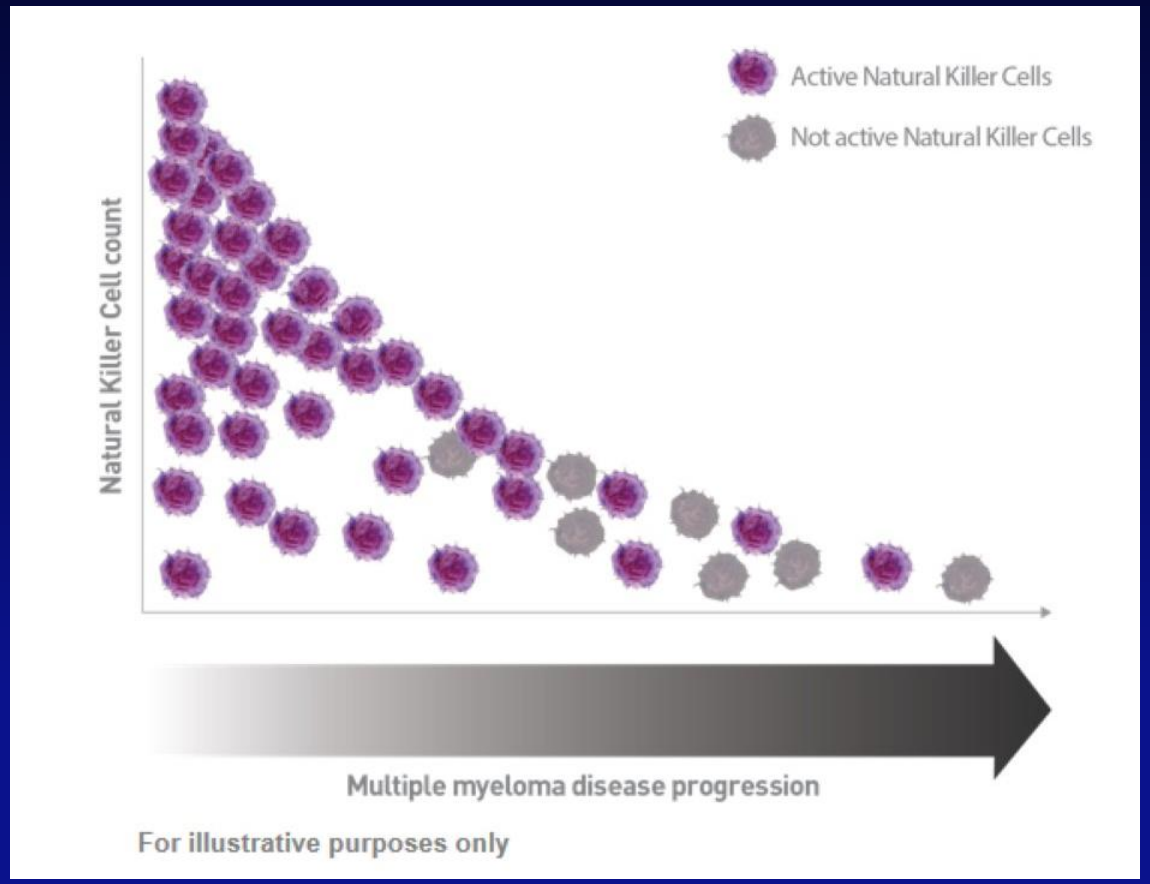
Hsi et al, 2008; Tai et al, 2008;

Elotuzumab Mechanism of Action

- Elotuzumab works via a dual mechanism of action
  - By directly activating natural killer cells
  - And through antibody-dependent cell-mediated cytotoxicity (ADCC) to cause targeted myeloma cell death



Collins et al, 2013.

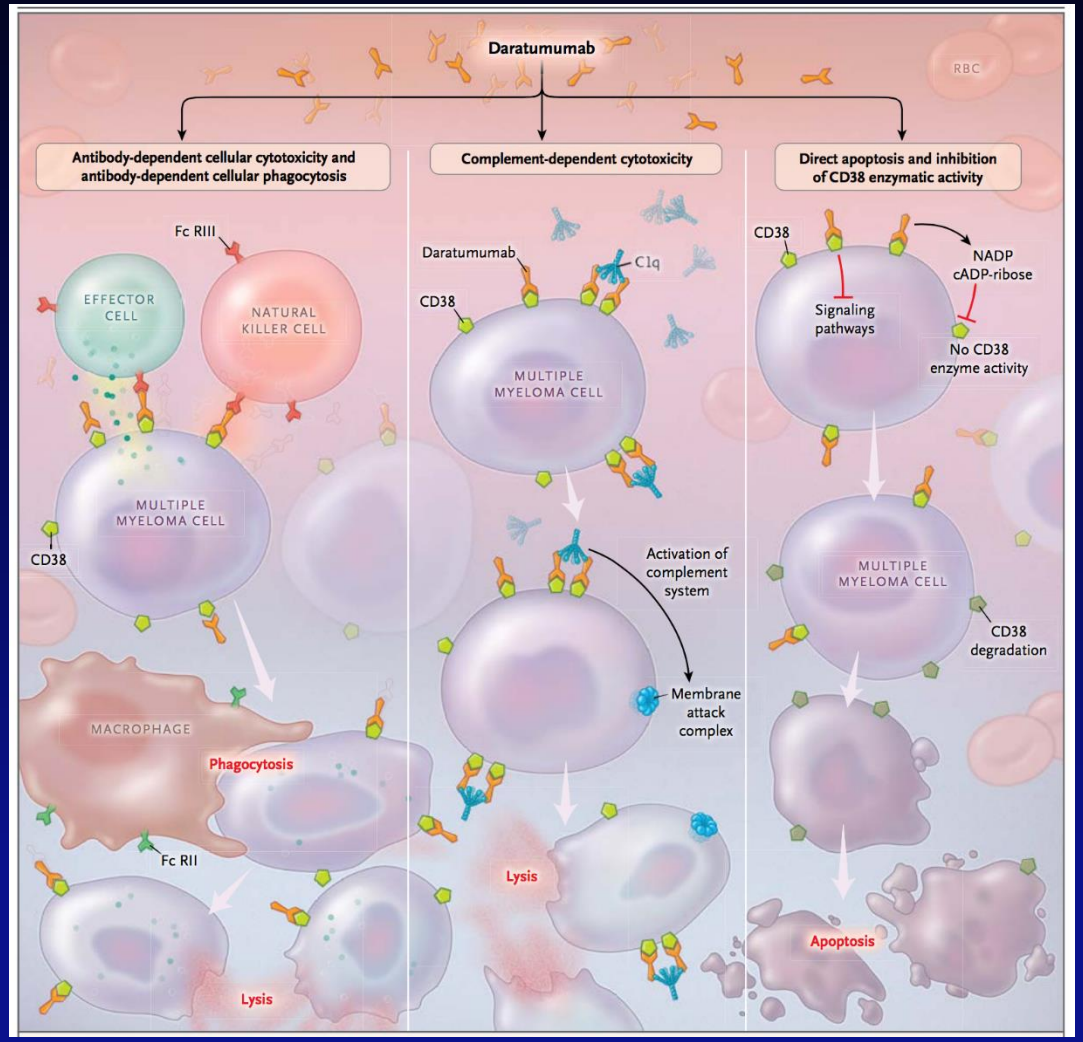


Elotuzumab (Empliciti): Toxicities

Side Effect	Rate	Management
Nasopharyngitis	27%	Slow infusion, antihistamines, APAP, and steroid, premedication
Cough	34%	Rule out URI, slow rate, antitussives, 1g magnesium, pretreatment montelukast
Fatigue	62%	Exercise, limit carbohydrates, coffee, other stimulants
URI	23%	Also very similar to pomalidomide and carfilzomib
Diarrhea	47%	Imodium, lomotil, kaopectate
Constipation	36%	Laxatives
Fever	37%	Antipyretics, rule out infection
Lymphopenia	13.2%	Anti-VZV prophylaxis

Daratumumab (Darzalex): Monoclonal Antibody Anti-CD38

- Binds to CD38 and elicits signaling cascade and immune effector function engagement, leading to
  - Complement-dependent cytotoxicity (CDC)
  - Antibody-dependent cell-mediated cytotoxicity (ADCC)
  - Antibody-dependent cell-mediated phagocytosis (ADCP)
  - Induction of apoptosis
  - Modulation of cellular enzymatic activities associated with calcium mobilization and signaling
  - Combination of these activities leads to elimination of plasma cells from bone marrow in MM patients
- CD38 is ALSO found on rbcs, HPSCs, smooth muscle (bronchioles)



Daratumumab (Darzalex): Monoclonal Antibody Against CD38

Side Effect	Rate	Management
Nasopharyngitis	17%	Slow infusion, antihistamines, APAP, and steroid, premedication
Cough	20%	Rule out URI, slow rate, antitussives, 1g magnesium, pretreatment montelukast
Fatigue	39%	Exercise, limit carbohydrates, coffee, other stimulants
URI	23%	Also very similar to pomalidomide, carfilzomib, elotuzumab
Diarrhea	16%	Imodium, lomotil, kaopectate
Constipation	15%	Laxatives
Fever	21%	Antipyretics, rule out infection
Lymphopenia	72%	Anti-VZV prophylaxis, suspect CMV

MoAb-Related Adverse Events

Infusion-Related Reactions (IRRs)

STUDY	Grade 1-2	Grade 3-4	Discontinuation
Elotuzumab + Rd[1]	9%	1%	<1%
Elotuzumab + Vd[2]	5%	0	0
Daratumumab + Rd[3]	43%	5%	<1%
Daratumumab + Vd[4]	36%	9%	<1%

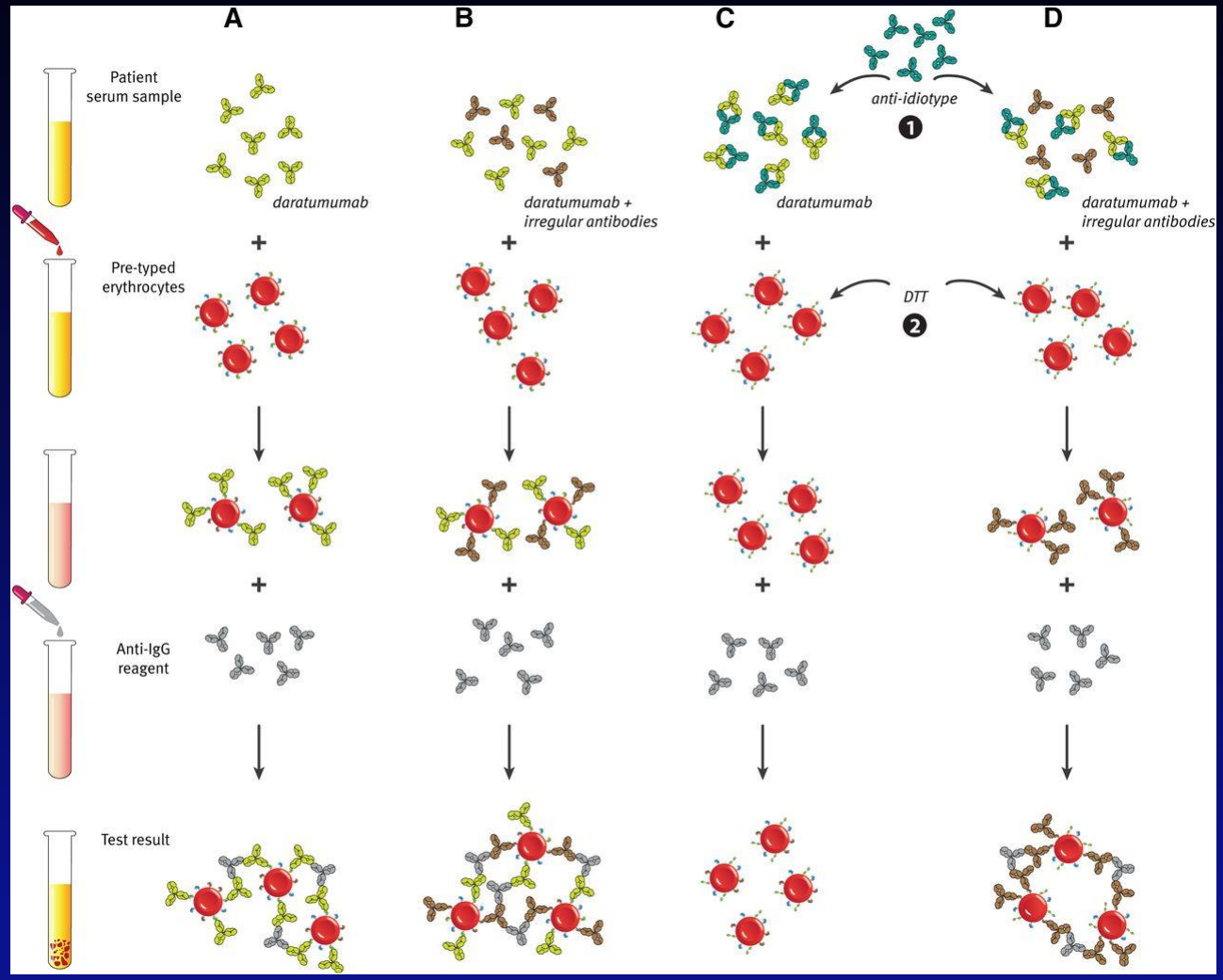
MoAb, monoclonal antibody; Rd, lenalidomide-dexamethasone; Vd, bortezomib-dexamethasone

1 Lonial S, et al. NEJM 2015
2 Jakubowiak A, et al. Blood 2016
3 Dimopoulos MA, et al. NEJM 2016
4 Palumbo A, et al. NEJM 2016

Challenges with MoAbs

- Interference RBC compatibility testing
- Interference CD38 detection by flow cytometry
- Interference IFX and SPEP testing

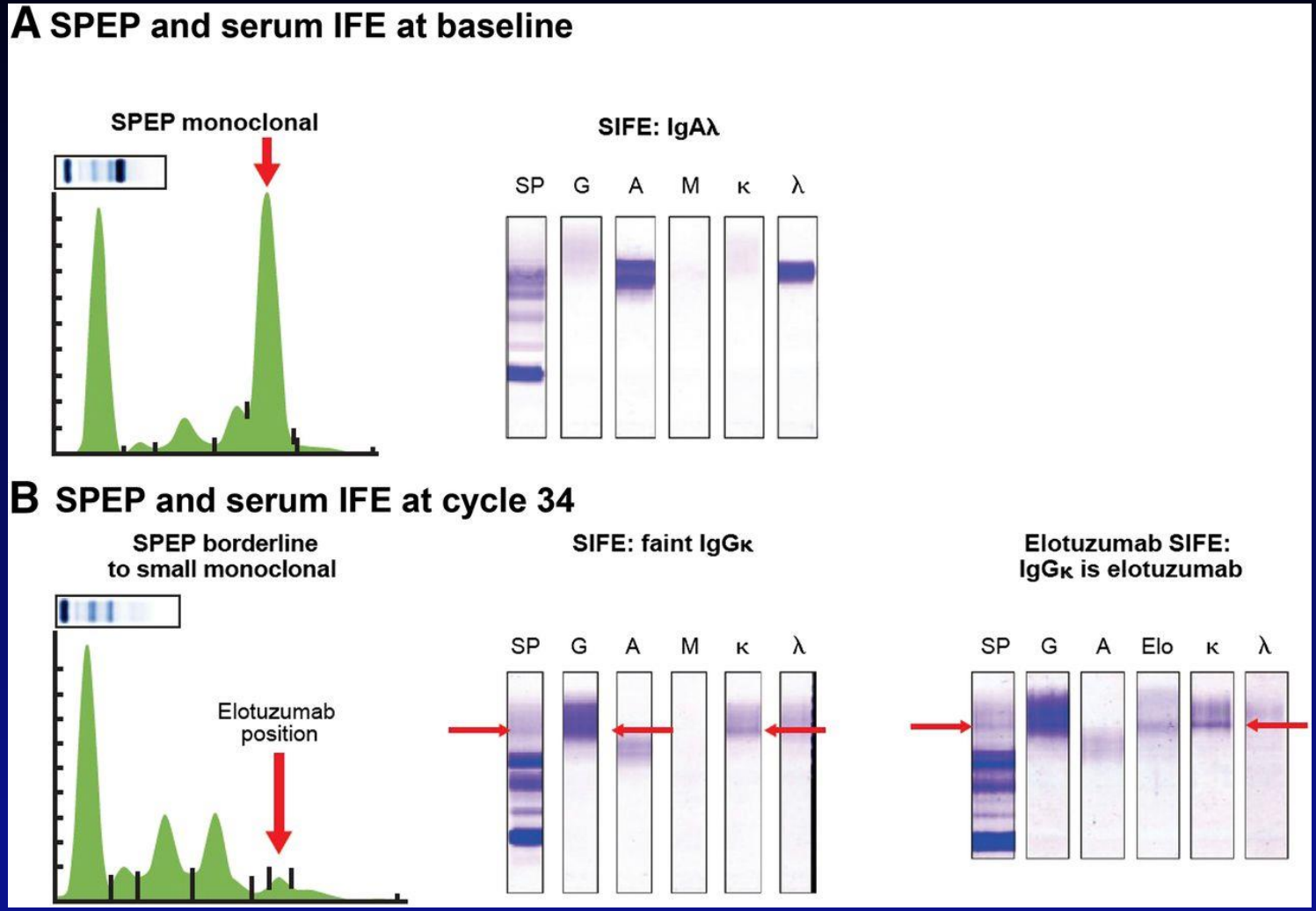
Daratumumab Interferes with Blood Compatibility Testing



Niels W. C. J. van de Donk et al. Blood 2016;127:681-695

blood

Elotuzumab can be detected in SPEP and IFE in samples from patients treated with elotuzumab



Niels W. C. J. van de Donk et al. Blood 2016;127:681-695

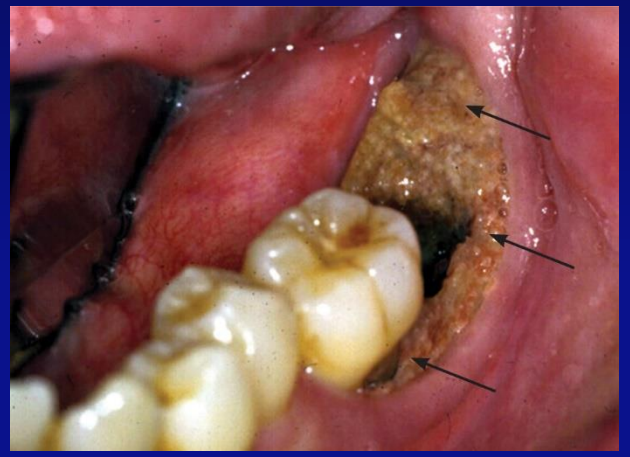
blood

Dexamethasone

Side Effect	Management
Hyperactivity/Insomnia	Benzodiazepines (valium, ativan, etc.), ambien, Tylenol-PM; split dexamethasone dosing; switch to IV form; can try prednisone
Fluid retention (ankle/face swelling)	Diuretics, limit salt intake on dexamethasone days
Hyperglycemia	Limit carbohydrates on dexamethasone days
Increased risk for infection	Prophylactic antibiotics (bactrim, dapsone, etc.)
Proximal muscle loss	Exercise
Cataracts	*** Incidence ~ 10% after 2 years

Zoledronic Acid (Zometa): Bisphosphonate

Side Effect	Management
Bone ache, low grade fever	1st infusion only, acetaminophen (Tylenol)
Kidney toxicity	Ensure infusion is given over 30 minutes (package insert says 15).
Osteonecrosis of the jaw	Keep teeth in good repair; follow up with dentist before and during zometa therapy; DO NOT ALLOW DENTAL EXTRACATIONS OR IMPLANTS.



Autologous Stem Cell Transplant Toxicities

Side Effect	Rate	Management
Fatigue	100%	Patients recover at a rate of 1%/day
Dry Mouth	100%	Lemon drops, tart food, time
Migratory myalgias/arthralgias	50%	Acetaminophen, loratadine
Decreased appetite	75%	Time; encourage fluid intake, grazing
Loose bowel movements	50%	Imodium, lomotil, kaopectate
Dyspnea	75%	Time
Failure to recover counts	1%	Consider stem cell boost
Hypogammaglobulinemia	100%	Time, IVIG

It’s mostly hand-holding.

COMMON PATIENT AND CAREGIVER QUESTIONS (WITH ANSWERS)

Should I take any supplements?

- OK to take calcium 500-1500mg/day + vitamin D 1000-2000 i.u./ day
- OK to take a centrum silver (or similar multivitamin) daily
- AVOID:
  - Antioxidants: Green tea, acai berries, etc.
  - Excess vitamin C (extra supplements; vit C in food is ok)
- Best supplement is water:
  - Adequate hydration flushes chemotherapy and excess light chains through the kidneys

Are there any medications to avoid?

- Never take NSAIDS:
  - Ibuprofen, Aleve, Motrin, Advil, naproxen, etc.→ can lead to kidney damage
- Never get IV contrast (iodine) for CT scan:
  - Can also cause kidney damage
  - Includes CT angiograms
  - MRI/PET-CT generally ok
- Ask your myeloma doctor about safety before starting IV antibiotics:
  - Certain antibiotics that are IV (like gentamycin) can also lead to renal failure in multiple myeloma

Are there any lifestyle changes that I should make?

- Try to get 20 minutes of cardiovascular exercise most days of the week
  - Reduces inflammation in the body
  - Better control of blood sugar
  - Get rid of excess weight
  - Tolerate chemo better
- Take care of your teeth!
  - See the dentist regularly to avoid osteonecrosis of the jaw

Last-Minute Pearls and Reminders

- Thalidomide is the only agent that is NOT myelosuppressive
- Only three drugs have been shown to mitigate del17p: pomalidomide, ixazomib, daratumumab
- Neuropathy with bortezomib occurs within first 4 cycles. If PN develops later in course, suspect MM relapse
- Diarrhea from IMiDs is due to bile acid salt malabsorption: use sequestrants
- PN from bortezomib is reversible; thalidomide generally is not
- Cardiac and renal toxicity from carfilzomib is reversible
- Do not stop treatment, even for patients in CR

You can contact me at: tomer.mark@ucdenver.edu

THANK YOU!

ASSOCIATION OF COMMUNITY CANCER CENTERS

MULTIDISCIPLINARY MULTIPLE MYELOMA CARE

Education Project

ACCC
Association of Community Cancer Centers

Project Goals and Objectives

Greatly enhance the education of community providers and adoption of effective practices, including incorporation of the latest and best treatment options for patients diagnosed with multiple myeloma.

I. Raise awareness about education needs of healthcare providers in the community setting related to the management of multiple myeloma patients.

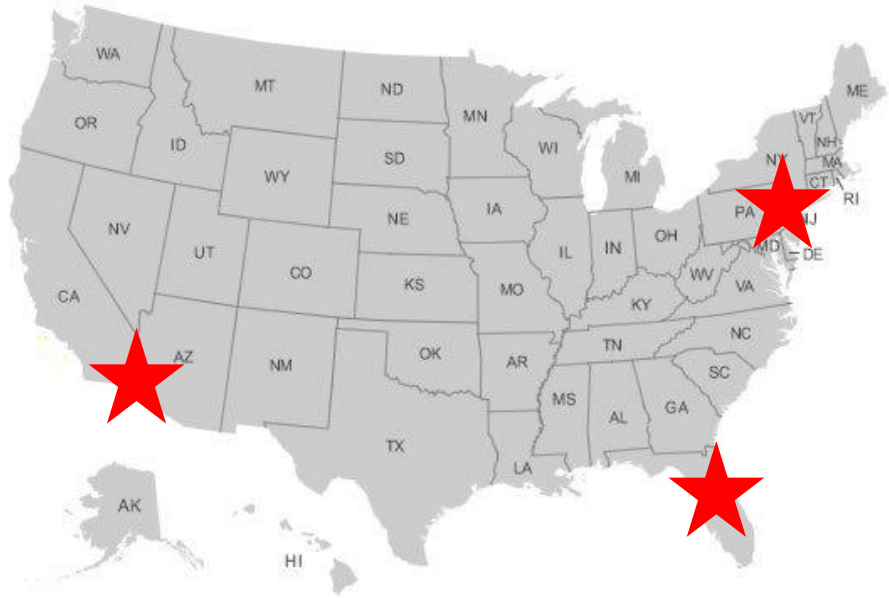
II. Educate the multidisciplinary healthcare team on how to implement effective practices in the treatment of multiple myeloma in community-based programs.

III. Establish vetted and designated resources for multiple myeloma that will be an enduring source of information for providers.

IV. Convene a strong network of advocacy and professional partners to increase peer-to-peer learning and adoption of effective practices.

Site Visits

- **Yuma Regional Medical Center Cancer Center**
  - Yuma, Arizona
  - *Comprehensive Community Cancer Program*
- **John Theurer Cancer Center at Hackensack University Medical Center**
  - Hackensack, New Jersey
  - *Academic Comprehensive Cancer Program*
- **Moffitt Cancer Center**
  - Tampa, Florida
  - *NCI-Designated Comprehensive Cancer Program*



International Myeloma Working Group (IMWG)

- Incorporating the latest guidance from the International Myeloma Working Group (IMWG) to improve diagnosis, assess prognosis, and develop tailored treatment plans

  - Diagnostic workup that includes flow cytometry, immunohistochemistry, cytogenetics, and molecular diagnostics
  - Revised International Staging System (R-ISS)
  - Assess risk profiles and engage in shared decision-making conversations with each patient
  - Refer patients who are eligible candidates for transplant evaluation

Skeletal-Related Events (SREs)

- Many patients with multiple myeloma have bony lesions and are often treated with either zoledronic acid (infusion) or denosumab (injection)
  - Monitor for side effects such as osteonecrosis of the jaw (ONJ)
  - Assess patient preferences
- Incorporating the 2018 ASCO Clinical Practice Guideline Update: Role of Bone-Modifying Agents in Multiple Myeloma
  - Key clinical question: “What is the role of bone-modifying agents in patients with multiple myeloma?”
- Severe SREs such as spinal cord compression or vertebral compression fractures may occur
  - Often requires surgical management to prevent permanent paralysis

Advancing Research to Improve Care

- John Theurer Cancer Center has been involved with the Multiple Myeloma Research Foundation (MMRF) CoMMpass (Relating Clinical Outcomes in MM to Personal Assessment of Genetic Profile) Study
  - Discovery of 12 different molecular types of multiple myeloma, each with its own level of risk

- Moffitt Cancer Center is a founding member of Oncology Research Information Exchange Network (ORIEN), a cross-institutional research partnership
  - Includes a longitudinal study called Total Cancer Care, which examines the effects of different cancers, treatment choices, and lifestyle so that physicians can have a better understanding of patient outcomes and treatment options

Project Webpage

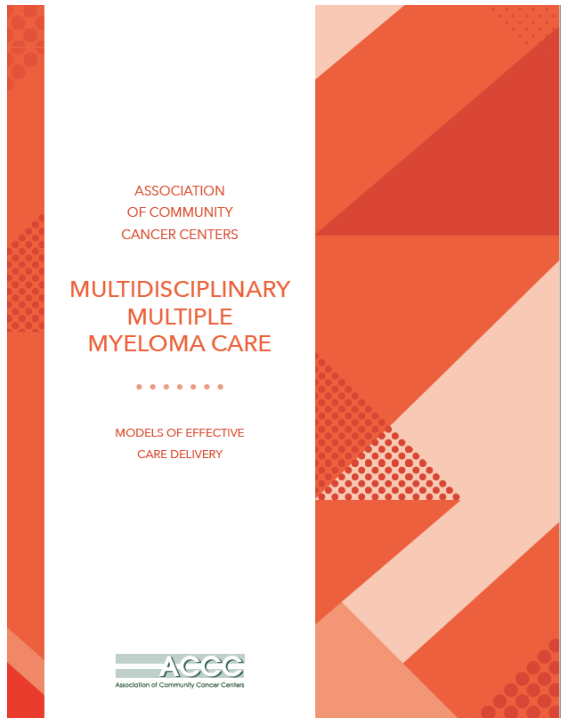
- Advisory Committee
- Educational Resources
  - Regional lecture series
  - Resource Portal for HCPs
- Journal Supplement -
  - *Released October 2018 – *Print* and Web**

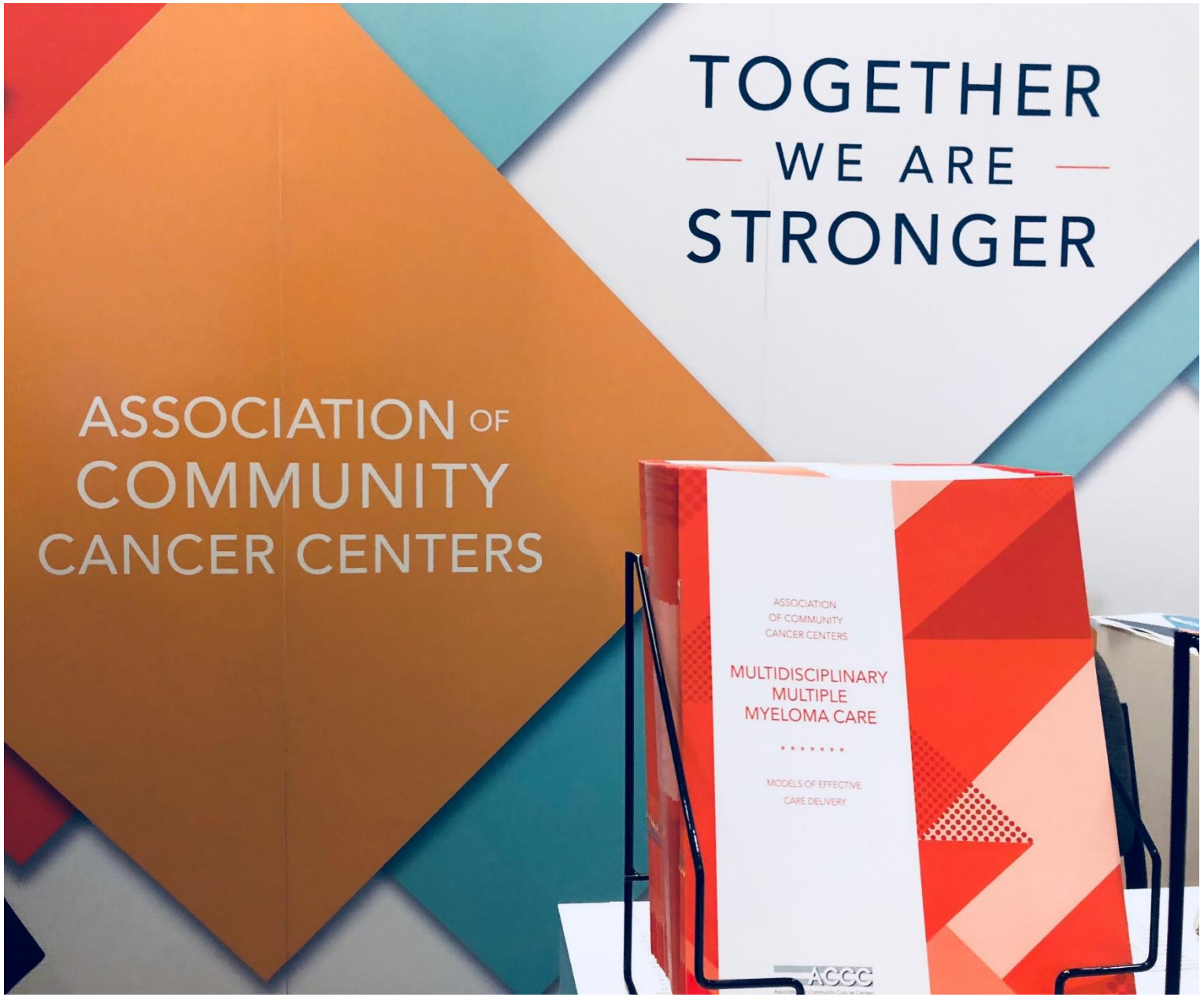
accc-cancer.org/multiple-myeloma-care

Models of Effective Care Delivery

- *Multidisciplinary Multiple Myeloma Care: Models of Effective Care Delivery* offers a convenient summary of recent updates in the management of this heterogeneous disease, including information on:
  - ✓ Diagnostic Criteria by the International Myeloma Working Group
  - ✓ Revised International Staging System
  - ✓ ASCO Clinical Practice Guideline Update: Role of Bone Modifying Agents in Multiple Myeloma
- Plus, read how three cancer programs—a community-based comprehensive program, an academic medical center, and an NCI-designed program—are delivering multidisciplinary care to this patient population.

Download Online





Models of Effective Care Delivery -

- Yuma Regional Medical Center Cancer Center
- John Theurer Cancer Center at Hackensack University Medical Center
- Moffitt Cancer Center

Questions?

University of Colorado
Denver | Anschutz Medical Center

Thank You!


ACCC
Association of Community Cancer Centers


RMOS
ROCKY MOUNTAIN
ONCOLOGY SOCIETY


University of Colorado
Denver | Anschutz Medical Center