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Risk Stratification in Multiple Myeloma: Putting the Pieces Together

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- Dr. Reeder has received research funding from Celgene, Millennium, and Novartis.
- Ms. Mayo has received honoraria from Celgene, Millennium, and Novartis and has served on the Advanced Practice Provider Steering Committee for Celgene.

Learning Objectives

1. Discuss agents for treatment of multiple myeloma (MM) and their side effects/management
2. Understand and discuss the heterogeneous genetic nature of MM
3. Learn the basic prognostic factors and how they impact treatment choices and outcomes
4. Understand the role of stem cell transplantation
5. Implement effective clinical strategies for minimizing toxicity
6. Utilize practical strategies for enhancing patients' adherence to treatment

Multiple Myeloma Statistics at a Glance

Estimated new
cases (2015):
26,850

Estimated deaths
(2015): 11,240

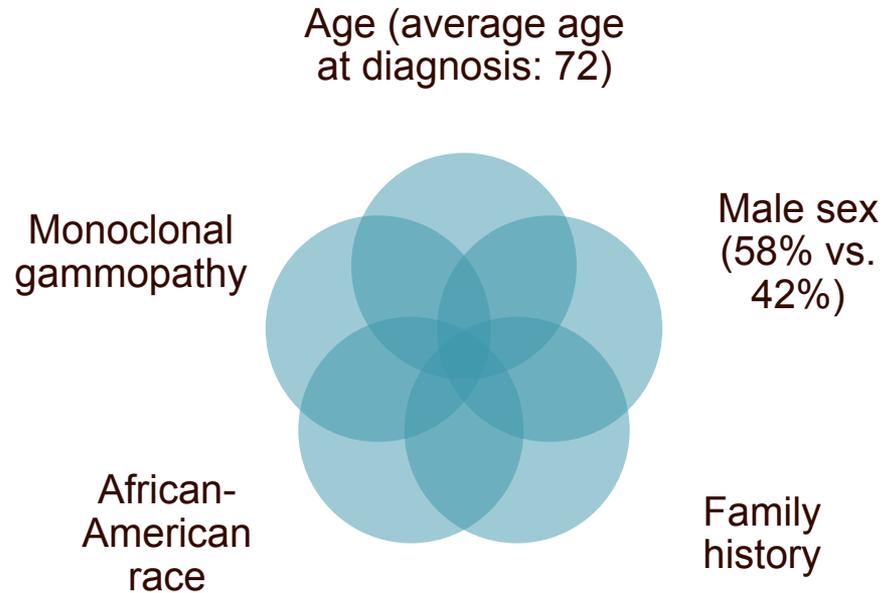
Percentage of
patients surviving
5 years: 46.6%
(2005–2011)

Estimated number
of people living
with myeloma in
US: 89,658

Percentage of all
cancer diagnoses:
1.6%

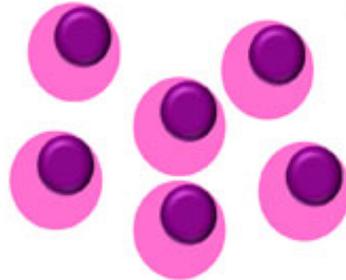
Percentage of all
cancer deaths:
1.9%

Risk Factors for Multiple Myeloma



Most patients who are diagnosed have NO known risk factors!

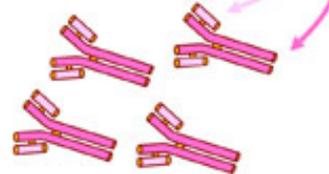
Bone marrow



**Myeloma cells
(plasma cells)**

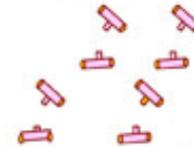
Blood stream (and urine)

**Intact
immunoglobulins**
heavy chains +
light chains



+

**Immunoglobulin
free light chains**



Presenting Signs and Symptoms

Patient-reported symptoms

- Fatigue
- Back/bone pain
- Weight loss
- Frequent infections
- Bruising/bleeding
- Foam in urine

Objective findings

- Anemia
- Lytic lesions on imaging
- Compression fractures
- Unexplained osteoporosis
- Pancytopenia
- Renal failure
- Hypercalcemia

However, many patients are asymptomatic!

Making a Diagnosis

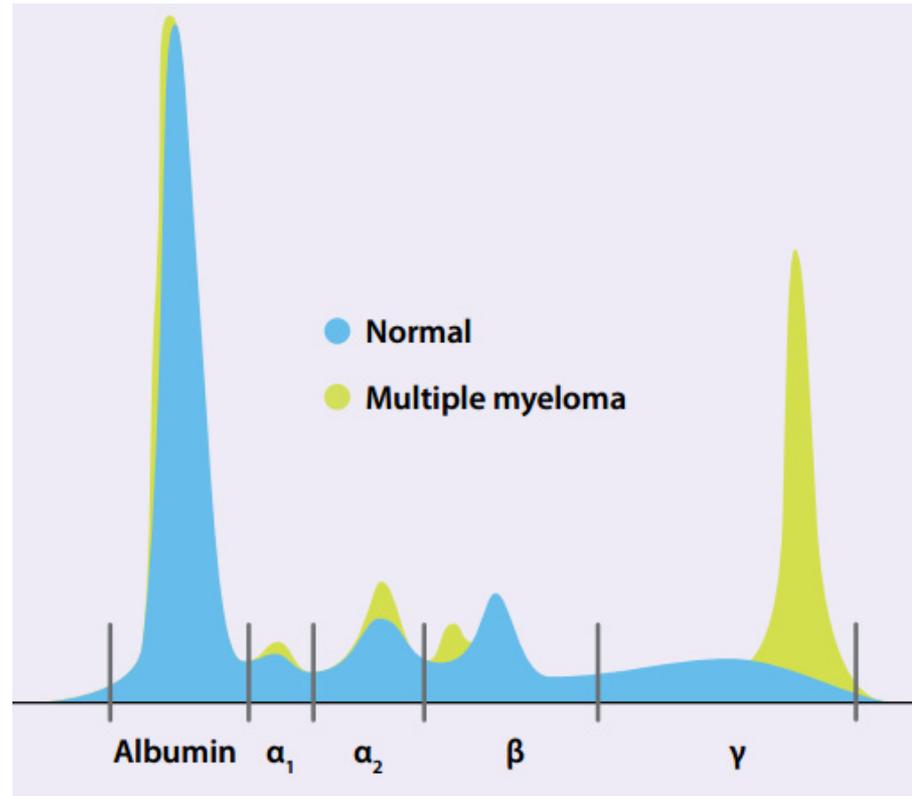
Blood tests

- CBC with differential
- CMP
- Serum protein electrophoresis
- Serum immunoglobulins (IgA, IgG, IgM)
- Serum free light chains (kappa FLC, lambda FLC)
- Beta-2 microglobulin (β_2 M)

Urine tests

- 24-hr urine for protein electrophoresis

Serum Protein Electrophoresis



Imaging

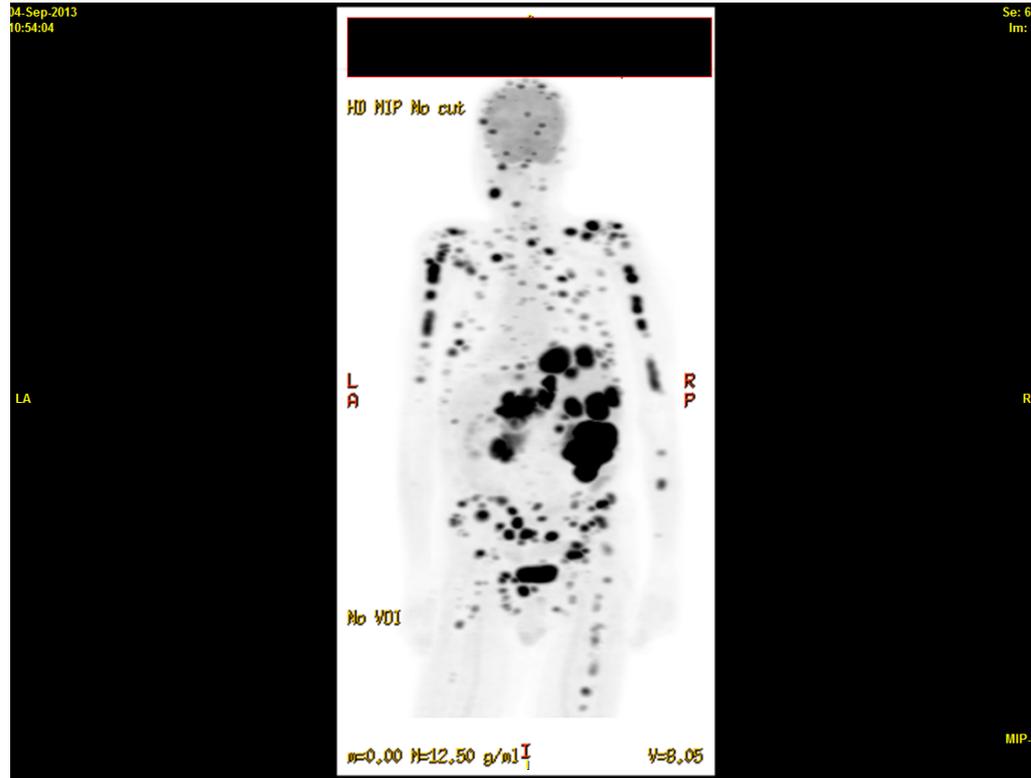
- **Skeletal survey:** Standard at diagnosis, x-rays of entire skeleton looking for lytic lesions
- **PET/CT:** Radioactive glucose is given, then CT scan is performed. Cells that are dividing rapidly (active cancer) show up bright on PET/CT. Can help to distinguish between active disease and old bone damage
- **MRI:** Generally performed on areas of concern to take closer look at bone where it is painful

Skeletal Survey



This image of a patient's skull shows lytic ("punched out") lesions due to multiple myeloma.

PET/CT



This patient has extensive, avid disease from multiple myeloma.

Image courtesy of Dr. Craig Reeder.

Bone Marrow Biopsy and Aspirate

Monoclonal gammopathy of unknown significance (MGUS)

- Less than 10% monoclonal plasma cells
- Precursor to myeloma
- However, NOT all MGUS progresses to myeloma; rate of about 1% to 2% per year, varies depending upon risk

Multiple myeloma

- Greater than 10% monoclonal plasma cells
- Not all multiple myeloma requires therapy! “Smoldering” vs. active disease
- “Active” (end organ damage) vs. “smoldering” (no end organ damage, no treatment)

Diagnostic Criteria for Symptomatic MM

C	Calcium elevation Serum calcium ≥ 11 mg/dL
R	Renal insufficiency CrCl < 40 mL/min ^a or serum creatinine > 2 mg/dL
A	Anemia Hemoglobin < 10 g/dL or > 2 g/dL below lower limit of normal
B	Bone ≥ 1 osteolytic lesion ^b

^aMeasured or estimated by validated equations.

^bAs determined by skeletal radiography, CT, or PET-CT. If bone marrow has $< 10\%$ clonal plasma cells, more than 1 bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

2014 Update

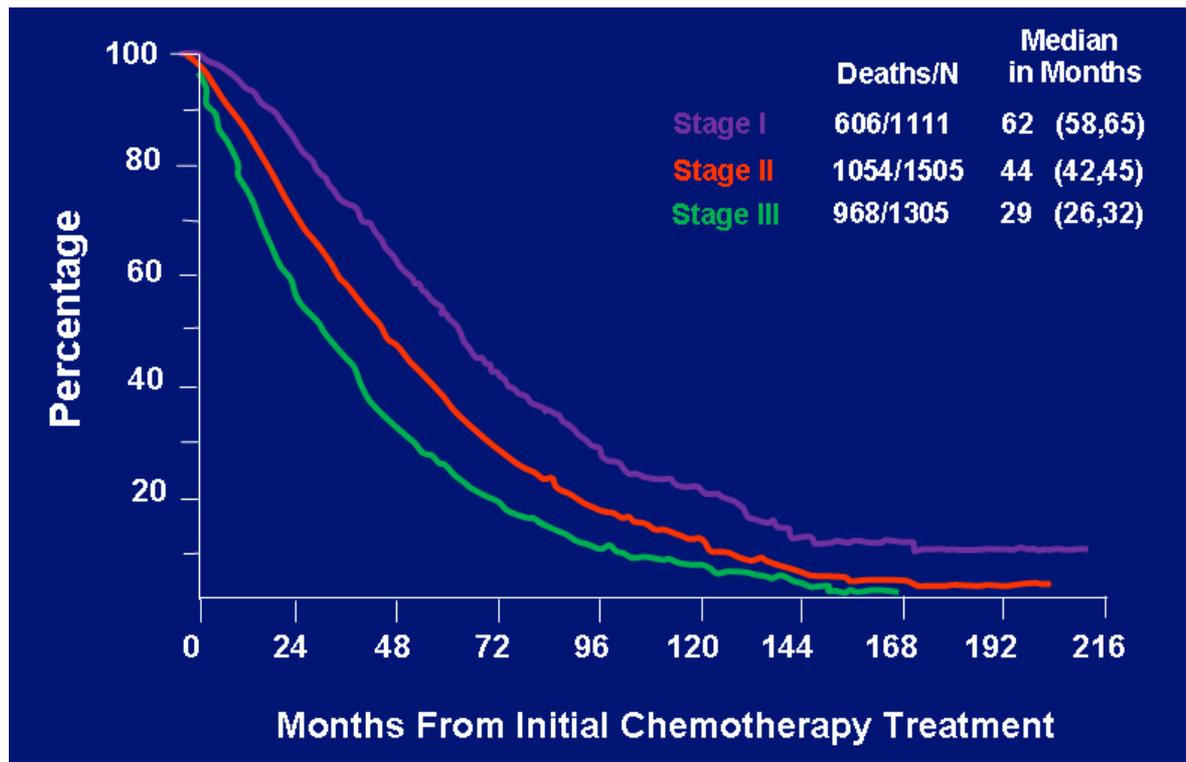
- “High-risk” smoldering myeloma is now classified as active
- Nearly all patients with these features progress to active disease within 1 year
- Sixty percent or more plasma cells on bone marrow biopsy
- Light chain ratio > 100
- MRI evidence of lesions

International Staging System (ISS) for Multiple Myeloma

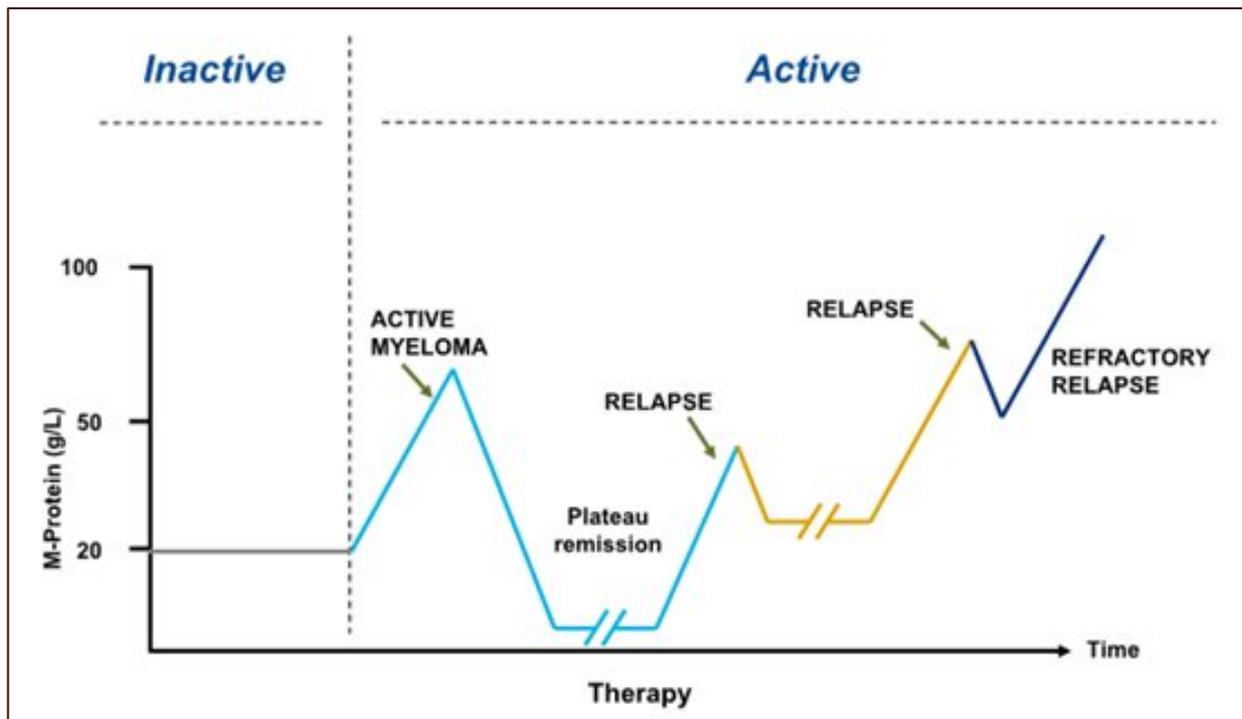
Stage	Criteria	Median survival
I	Serum β_2 M < 3.5 mg/L Serum albumin \geq 3.5 g/dL	62 mo
II	Serum β_2 M < 3.5 mg/L Serum albumin < 3.5 g/dL OR Serum β_2 M 3.5 to < 5.5 mg/L*	44 mo
III	Serum β_2 M \geq 5.5 mg/L	29 mo

*Irrespective of serum albumin level.

ISS: Survival



MM Characterized by Periods of Relapse and Remission



Goals of Myeloma Therapy

- Immediate goals
 - Gain rapid control of disease
 - Reverse toxicities disease has caused (bone pain, renal dysfunction, cytopenias)
 - Allow for stem cell collection if transplant candidate
- Long-term goals
 - Help patient to live longer
 - Prevent further organ damage by disease
 - Delay relapse
 - MULTIPLE MYELOMA IS STILL NOT CONSIDERED “CURABLE”

Phases of Therapy

- Induction
- Transplant for appropriate patients after induction has been successful (greater than 50% reduction in myeloma)
- Maintenance
- Relapse treatment

Long-Term Survival With CyBorD Induction Therapy in Newly Diagnosed Multiple Myeloma

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³Mayo Cancer Center Statistics

CyBorD: Introduction

- Triplet therapy commonly used in both standard- and high-risk multiple myeloma
- Cyclophosphamide, bortezomib, and dexamethasone (CyBorD) produces rapid and deep responses in newly diagnosed multiple myeloma
- CyBorD is one of the most active induction regimens and is cost-effective

CyBorD: Details

Agent	Dose	Schedule
Cyclophosphamide	300 mg/m ² po or 500 mg po	Days 1, 8, 15, 22
Bortezomib	1.5 mg/m ² SC or IV	Days 1, 8, 15, 22
Dexamethasone	40 mg po	Days 1, 8, 15, 22

CyBorD Results

	Progression-free survival	Overall survival
ALL (n = 63)	42% (95% CI, 31%–57%)	70% (95% CI, 59%–82%)
Standard risk (n = 39)	48% (95% CI, 33%–69%)	81% (95% CI, 69%–95%)
High risk (n = 24)	33% (95% CI, 19%–59%)	54% (95% CI, 37%–78%)

CI = confidence interval.

Other Induction Regimens

- Combination such as VRD (bortezomib, lenalidomide, dexamethasone)
- Combinations with carfilzomib are promising; FDA guidelines have not yet moved this drug into routine front-line therapy, but research is underway
- Lenalidomide/dexamethasone may be used (all oral regimen)
- Clinical trials to examine other effective combinations

The Role of Transplant in Myeloma

AUTOLOGOUS stem cell transplant

- Performance status
- Age is one factor, but there is not a strict cutoff, and we consider “physiologic” age
- Comorbidities (physical, psychiatric)
- Response to induction therapy
- Social/financial support

No transplant

- Often age/performance status related but may also be related to social situation, finances, or simply patient’s desire not to have the transplant
- Many other effective therapies that can be used, even when transplant is not possible

Maintenance Therapy

- Once patients have maximized response to induction therapy, they may or may not go on to transplant
- Those who do not go on to transplant will likely be maintained on same drug combination that worked for them, perhaps less often/lower dosage
- Following transplant, it is now increasingly common to use maintenance regimens to increase amount of time in remission

Major Classes of Myeloma Therapy

Proteasome inhibitors

- Bortezomib
- Carfilzomib
- Oral proteasome inhibitors in clinical trial

IMiDs (immune-modulating drugs)

- Thalidomide
- Lenalidomide
- Pomalidomide

Bortezomib

- Initial FDA approval 2003
- Revolutionized treatment of myeloma; prior to its approval, we had only a few, rather toxic drugs with limited efficacy
- Data after the mid-2000s showed a large increase in survival for patients with multiple myeloma because of this and other “novel” agents

Bortezomib Side Effects

- Sensory neuropathy: Lessened by subcutaneous administration, weekly administration
- Nausea/vomiting
- Diarrhea
- Fatigue

How Does Neuropathy Present?

- Numbness and/or tingling, starts distally and moves proximally as it progresses
- May or may not be associated with pain
- Interferes with function as it progresses (fine-motor skills, balance)
- May also be described as cold sensation in extremities, burning

Alternative Presentations of Neuropathy

- Intermittent sharp or shooting pains
- Autonomic dysfunction/hypotension
- Predominantly sensory but may contain a motor component for some patients (muscle weakness, generalized lack of coordination)
- Allodynia

Risk Factors for Neuropathy

- Older age
- Diabetes
- Prior chemotherapy exposure
- Amyloidosis and/or paraprotein-related neuropathy prior to therapy
- Spinal stenosis

Treatment of Peripheral Neuropathy

- Duloxetine is the only medication with American Society of Clinical Oncology (ASCO) recommendations, and those are moderate
- Other agents with potential beneficial effects
 - Gabapentin/pregabalin
 - Venlafaxine
 - Desipramine
 - Topiramate
 - Baclofen
 - Lidocaine dermal patch
 - Narcotic pain medications

Nonprescription Medications/Treatments

Potentially useful interventions

- Alpha-lipoic acid
- Omega-3 fatty acids
- Vitamin B₆
- Acupuncture
- Physical therapy
- Modification of environment

Carfilzomib

- FDA approved 2012
- Clinical trial for approval (PX-171-003), 22.9% overall response rate
- Initial approval for patients with relapsed/refractory disease who had previously received bortezomib and an IMiD (lenalidomide/thalidomide)
- Now also approved in combination with lenalidomide and dexamethasone in any relapsed setting

Carfilzomib Side Effects

- Fatigue (54%)
- Anemia (47%)
- Nausea (45%)
- Thrombocytopenia (36%)
- **Dyspnea (35%)**
- **Pyrexia (30%)**

Carfilzomib Warnings

- Cardiac events: Worsening congestive heart failure, ischemia
- Tumor lysis syndrome

Thalidomide

- Used for morning sickness for pregnant women in 1960s and caused severe birth defects (limb deformities); later found to work against myeloma
- Approved on limited basis in 1998, with special risk management program; FDA approval for myeloma in 2006
- Oral, effective, great improvement over other therapies available at the time!

Thalidomide (cont)

- Benefits: Oral therapy, effective, tolerable even in older patients, little effect on blood counts
- Black box warning: Fetal toxicity, thrombosis, cytopenias
- Other side effects: Neuropathy, dizziness, fatigue, constipation...
COST!
- Often a useful adjunct to other therapies

Lenalidomide

- Analog of thalidomide, FDA approved in 2005 for relapsed/refractory disease, initial therapy in 2015
- Oral, often well tolerated, may maintain patients for years with good quality of life!
- Often induction therapy of choice in older patients, younger alone, or in combination
- Same black box warning as thalidomide (fetal toxicity, thromboembolism, cytopenias)

Lenalidomide (cont)

- Common side effects: Cytopenias (especially neutropenia), diarrhea, muscle cramps, fatigue
- Can impair ability to collect stem cells, so want to collect after limited therapy rather than years if you may want to transplant
- Question about increased risk of secondary malignancies, especially hematologic (myelodysplastic syndrome, acute leukemias) in patients who also had high-dose melphalan (transplant)

Pomalidomide

- Third-generation “IMiD” drug
- Still effective in people who failed other IMiDs
- FDA approved for relapsed/refractory, post lenalidomide, post bortezomib in 2013, given with dexamethasone
- Appears promising in combination with proteasome inhibitors as well

Pomalidomide (cont)

- Same black box warning as all IMiDs and REMS program (fetal toxicity, thromboembolism, cytopenias)
- Side effects seem to be a cross between those with thalidomide and lenalidomide

REMS = Risk Evaluation and Mitigation Strategy.

Celgene 2013. Pomalyst (pomalidomide) package insert.

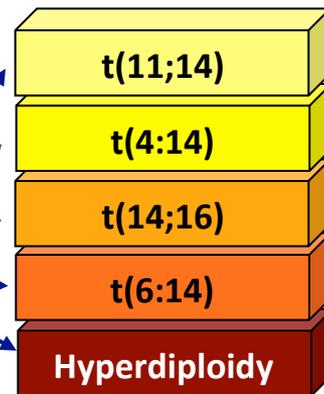
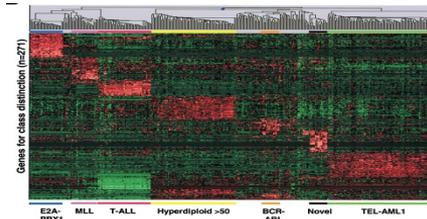
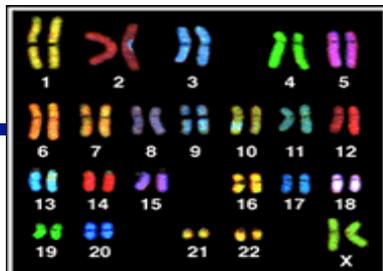
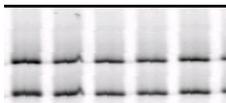
Other Myeloma Drugs in Use

- Cyclophosphamide, melphalan
- STEROIDS! (dexamethasone, prednisone)
- Liposomal doxorubicin
- Panobinostat (approved March 2015)

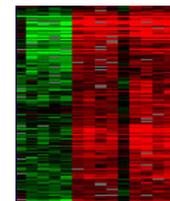
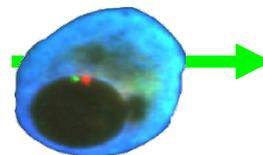
Clinical Trials

- Monoclonal antibodies (anti-CD38)
- Immune system
- Oral forms of proteasome inhibition
- Novel agents
- Genetic sequencing
- Right now, there are 13 open trials for myeloma at Mayo Clinic Arizona and 7 pending

Acute Leukemia

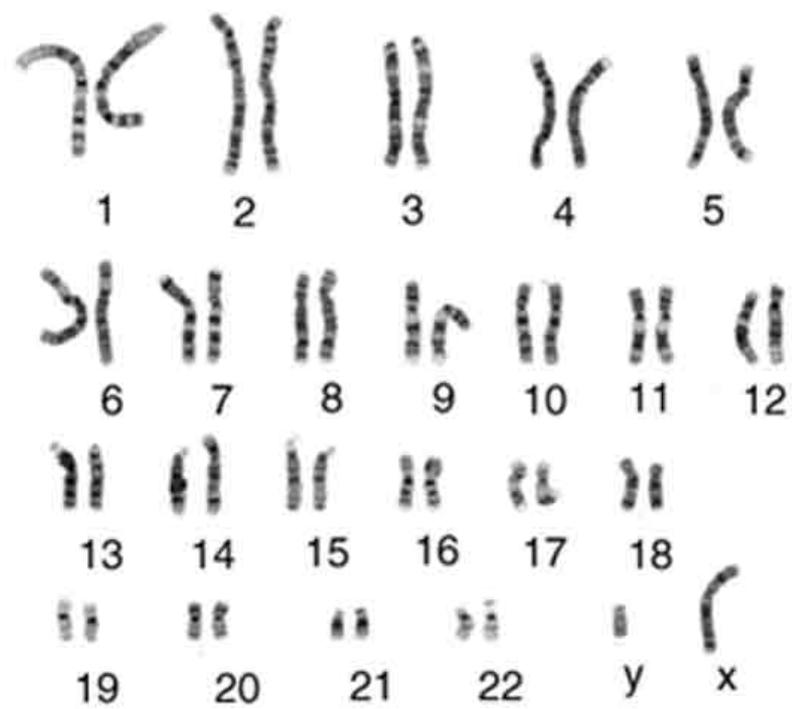


Myeloma

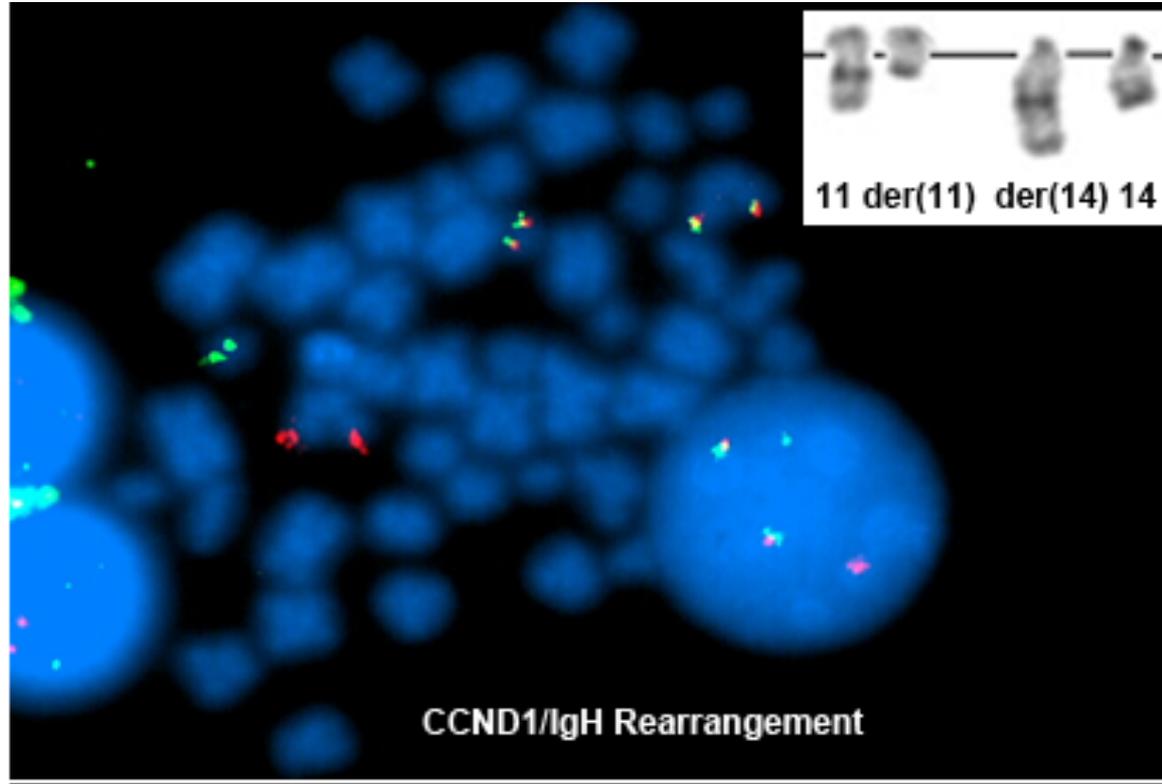


3 decades

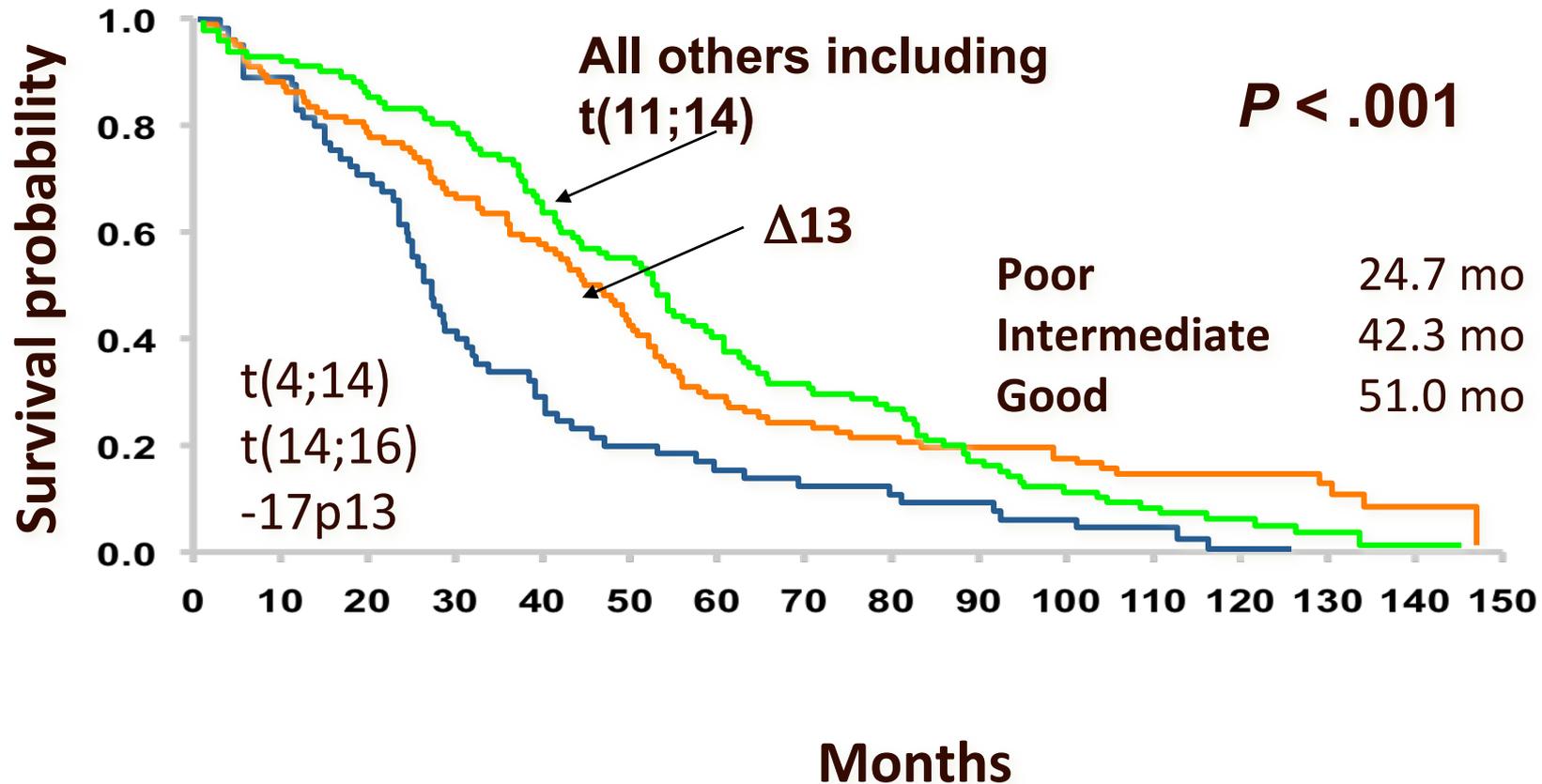
Multiple Myeloma Cytogenetics



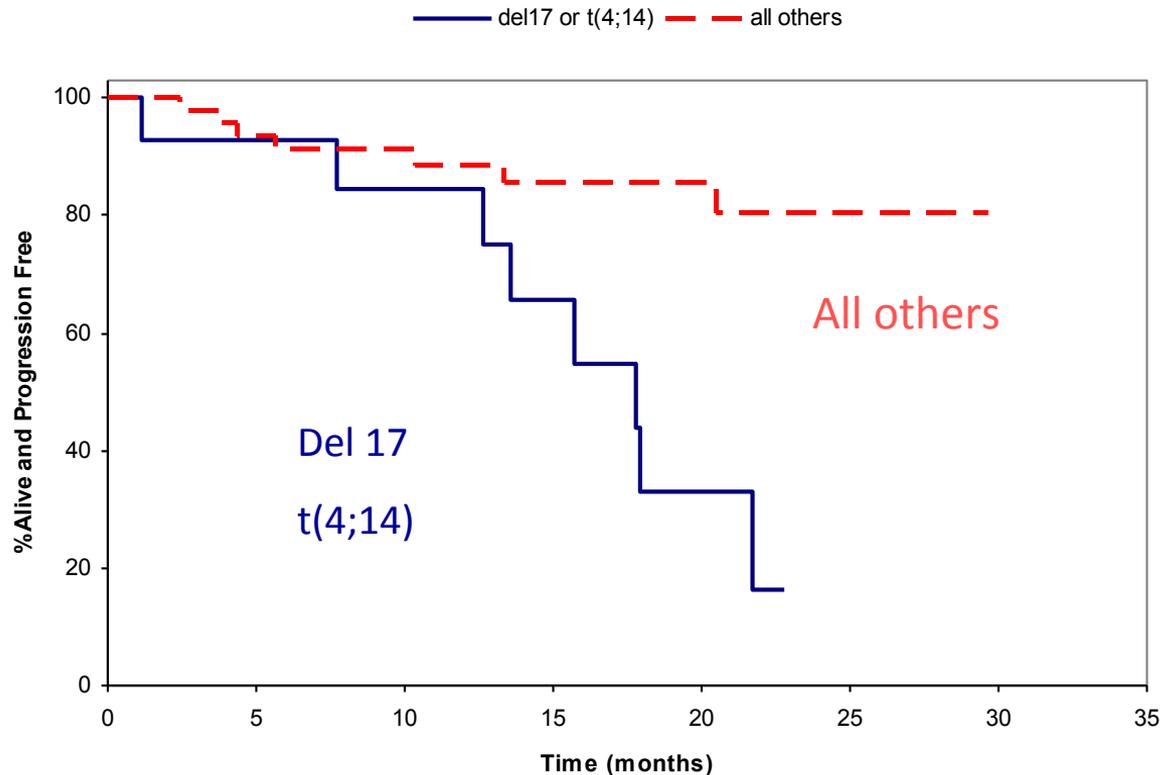
FISH



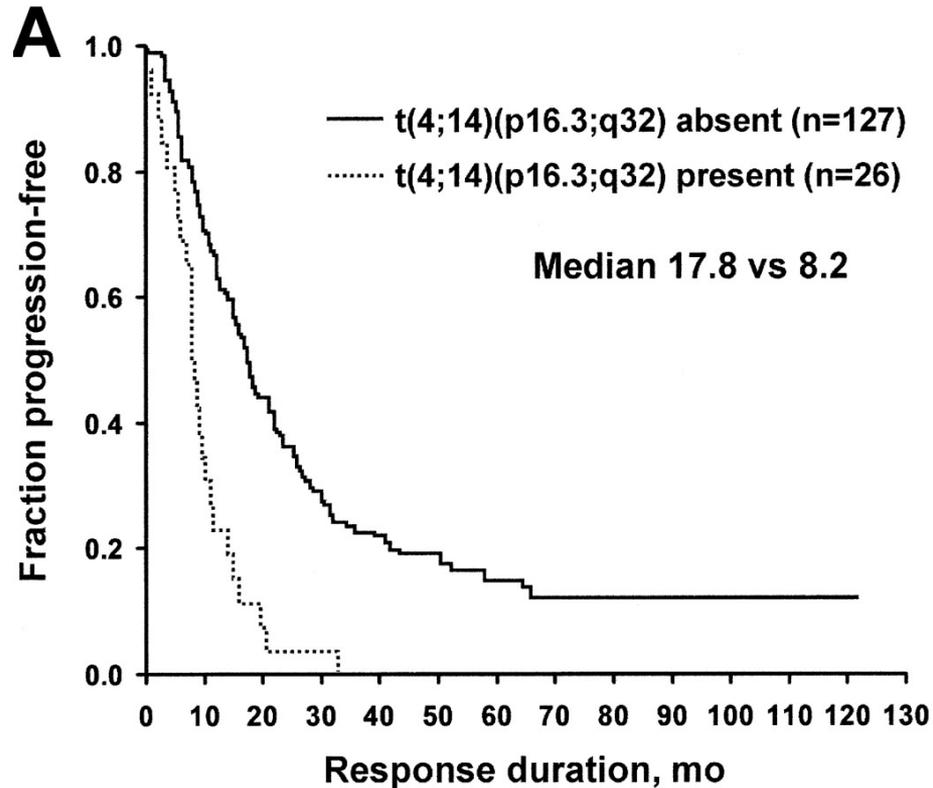
Molecular Prognostic Model



Progression-Free Survival: High Risk



SCT and PFS in Patients With t(4;14)



Genetic Classification

Hyperdiploid (h) MM

- 45% of all MM
- Numerous chromosome trisomies
- More favorable outcome
- Slightly more common in males
- More common in elderly

Nonhyperdiploid (nh) MM

- 40% of all MM
- Highly enriched for IgH translocations
- Overall less-favorable outcome
- Examples include t(11;14), t(4;14), t(14;16), del(17p)

Remaining 15% of MM is either with overlap or unclassified in the two major genetic categories

Multiple Myeloma: Nonhyperdiploid

- $t(11;14)(q13;q32)$: 15%–20%
 - “Good” prognosis with HDT/SCT (but, no enrichment in long-term survivors)
 - Associated with
 - IgM myeloma (90%)
 - AL amyloidosis (50%)
 - Light chain multiple myeloma
 - CD20+
 - Lymphoplasmacytic morphology
 - PC leukemia
- $t(4;14)(p16;q32)$: 14%
 - Poor prognosis
 - FGFR3 overexpression
- $t(14;16)(q32;q23)$: 5%
 - Poor prognosis

Nonhyperdiploid

- t(14;20): Uncommon
 - Poor prognosis, MAFB expression
- Del 17p (p53): 11%
 - Very poor prognosis
- Del 13, 13q: 50%
 - Surrogate for nonhyperdiploid myeloma
- Other mutations
 - *RAS*-activating mutations: 30%–50% multiple myeloma
 - p53 (17p13)
 - 5% at diagnosis, 30% in advanced disease
 - c-myc, late event
 - PTEN, leads to PI-3K, AKT activation
 - Tumor suppressors p16, p18
 - 1q21, overexpression/gains

Myeloma Prognosis

- Host factors: Age, performance status, comorbidities
- Stage: Durie-Salmon, ISS
- Disease aggressiveness: FISH, LDH, circulating PCs
- Response to therapy

Disease characteristics help in counseling and in choosing therapy.

ISS = International Staging System; FISH = fluorescence in situ hybridization;
LDH = lactate dehydrogenase; PC = plasma cell.

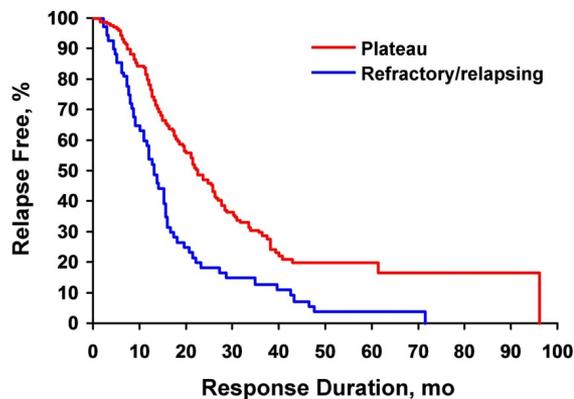
Defining High Risk

- FISH
- Metaphase cytogenetics abnormality
- PCLI > 3%
- PC leukemia
- High LDH, β_2 M, and low albumin
- Failure to respond to novel agent
- Early relapse after HDT
- Gene-expression profile (GEP) signature

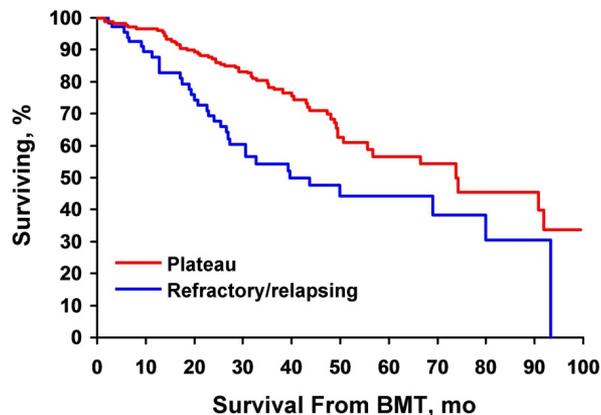
PC = plasma cell; PCLI = plasma cell-labeling index; HDT = high-dose therapy.

Failure to Respond to Induction With Novel Agent

PFS post SCT



OS post SCT



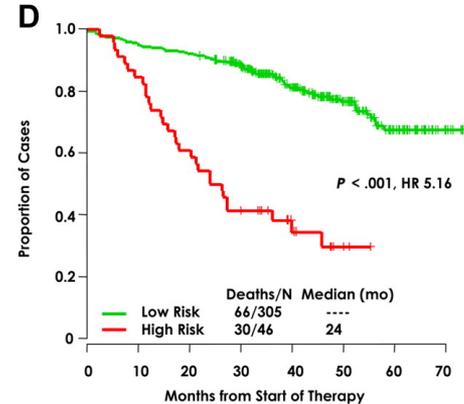
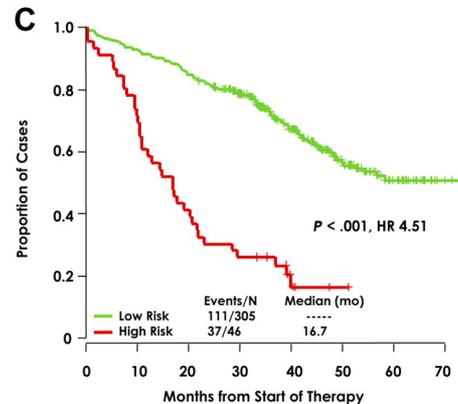
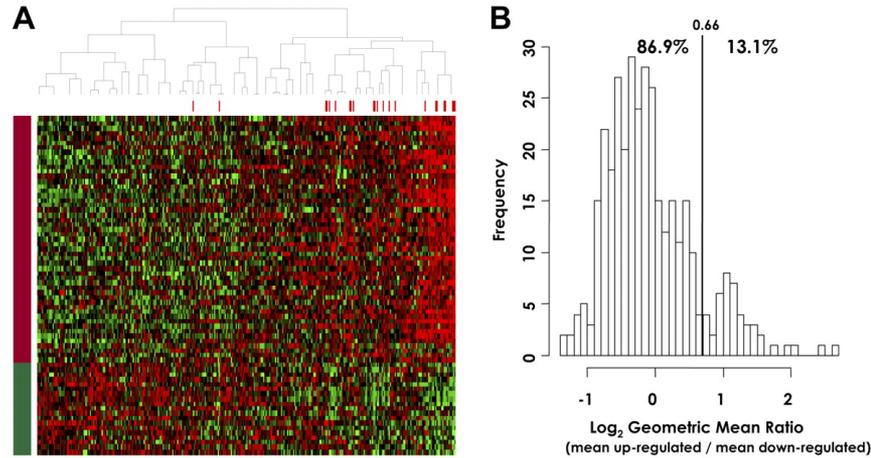
PFS = progression-free survival; OS = overall survival.

Gertz MA, et al. *Blood*. 2009;114 (abstract 1878).

Gene-Expression Profiling

- University of Arkansas and IFM (Intergroupe Francophone du Myélome) have identified gene signatures that can provide prognostic discrimination
- There is minimal overlap between these two signatures, and both will need validation
- It is conceivable that gene signatures may become predictive markers in the future

Gene-Expression Profile Signatures





mSMART

***Mayo Stratification for Myeloma
and Risk-Adapted Therapy***

Newly Diagnosed Myeloma

mSMART

- Multiple myeloma is increasingly recognized as more than one disease, characterized by marked cytogenetic, molecular, and proliferative heterogeneity.
- The result is a widely varied outcome, ranging from low to very high risk.
- Treatment is evolving rapidly as more effective agents and combinations become available.
- mSMART (Mayo Stratification for Myeloma and Risk-Adapted Therapy) is a consensus opinion that takes into account genetically determined risk status and the various treatment strategies currently available.
- Risk stratification and individualizing treatment options are complex and based not just on the cytogenetic classification presented here, but also on various host factors, disease stage, and a variety of other prognostic factors.
- Therefore, we recommend all patients with newly diagnosed myeloma be seen at least once at a referral center with expertise in the disease.

mSMART (cont)

- The general approach is presented here (mSMART: off study). However, clinical trials must be considered and are preferred at every level (mSMART: on study).
- Management decisions are also varied depending on renal function and the presence or absence of coexisting amyloidosis.

mSMART 2.0: Classification of Active MM

High risk

- FISH^c
 - Del 17p
 - t(14;16)
 - t(14;20)
- GEP
 - High-risk signature

Intermediate risk^a

- FISH
 - t(4;14)^d
 - 1q gain
- Complex karyotype
- Metaphase Deletion 13 or hypodiploidy
- High PC S-phase^f

Standard risk^{a,b}

- All others, including:
- Trisomies
 - t(11;14)^e
 - t(6;14)

^aNote that a subset of patients with these factors will be classified as high risk by GEP.

^bLDH > ULN and β_2 M > 5.5 may indicate worse prognosis.

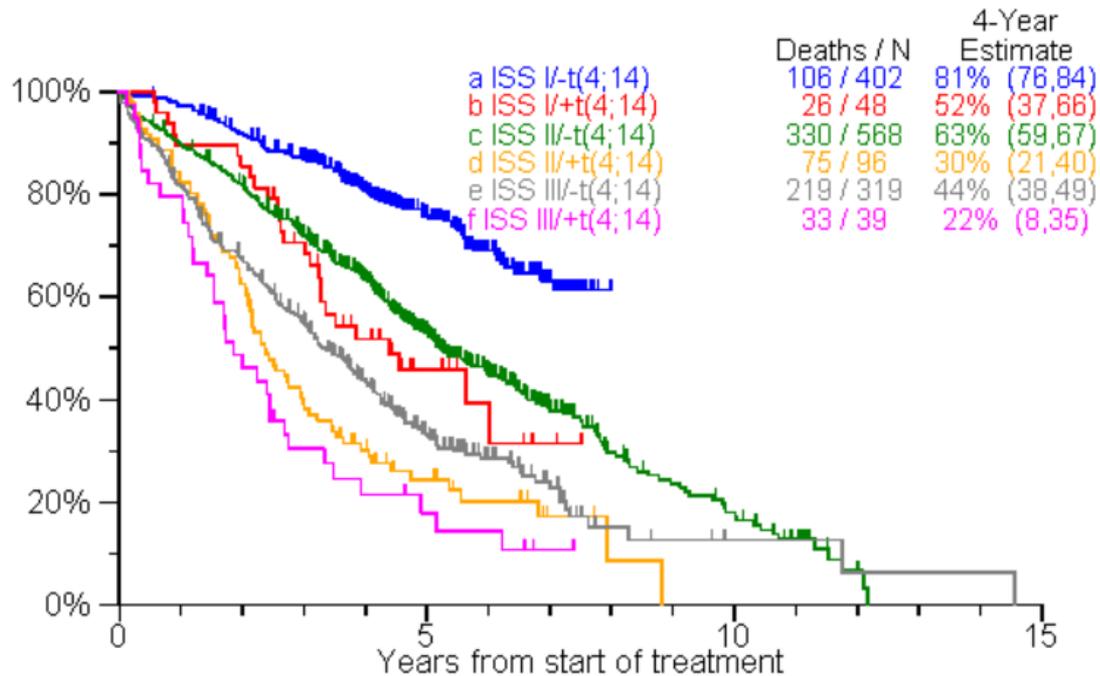
^cTrisomies may ameliorate.

^dPrognosis is worse when associated with high β_2 M and anemia.

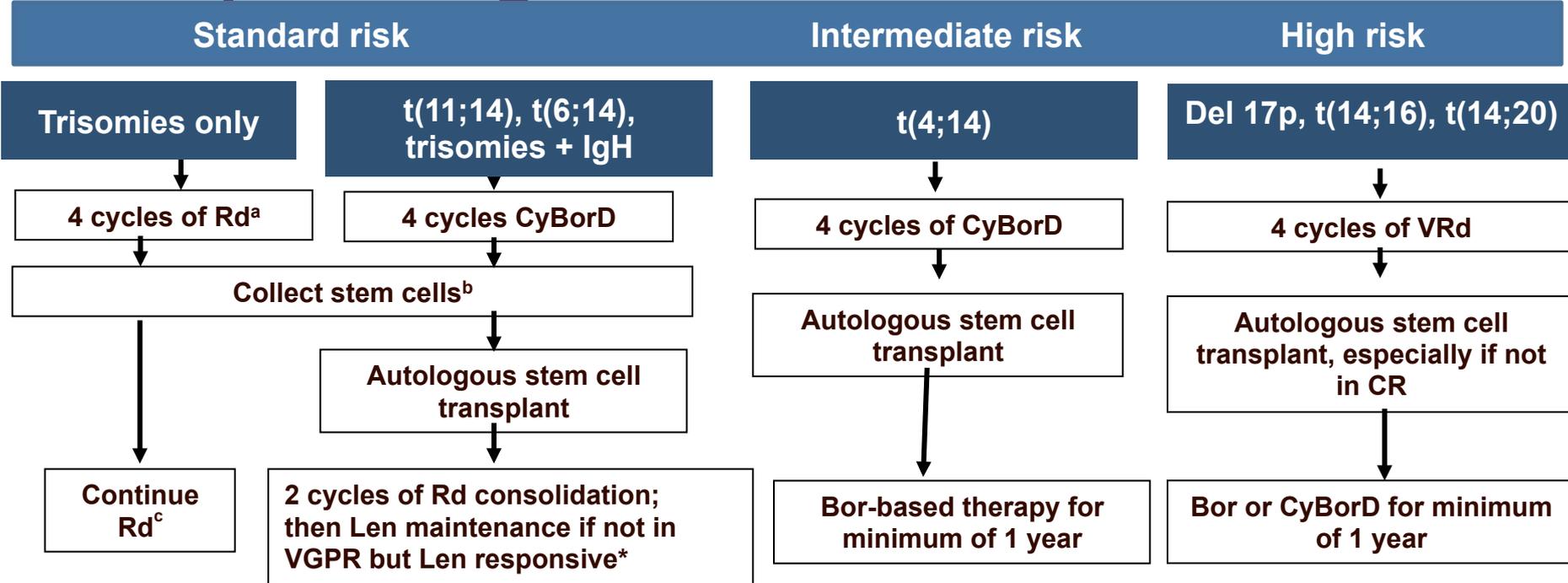
^et(11;14) may be associated with plasma cell leukemia.

^fCutoffs vary.

Impact of 4;14 and ISS Staging on Survival Outcomes in MM



mSMART: Off-Study Transplant Eligible



^aBortezomib-containing regimens preferred in renal failure or if rapid response needed.

^bIf age > 65 or > 4 cycles of Rd, consider G-CSF plus cyclophosphamide or plerixafor.

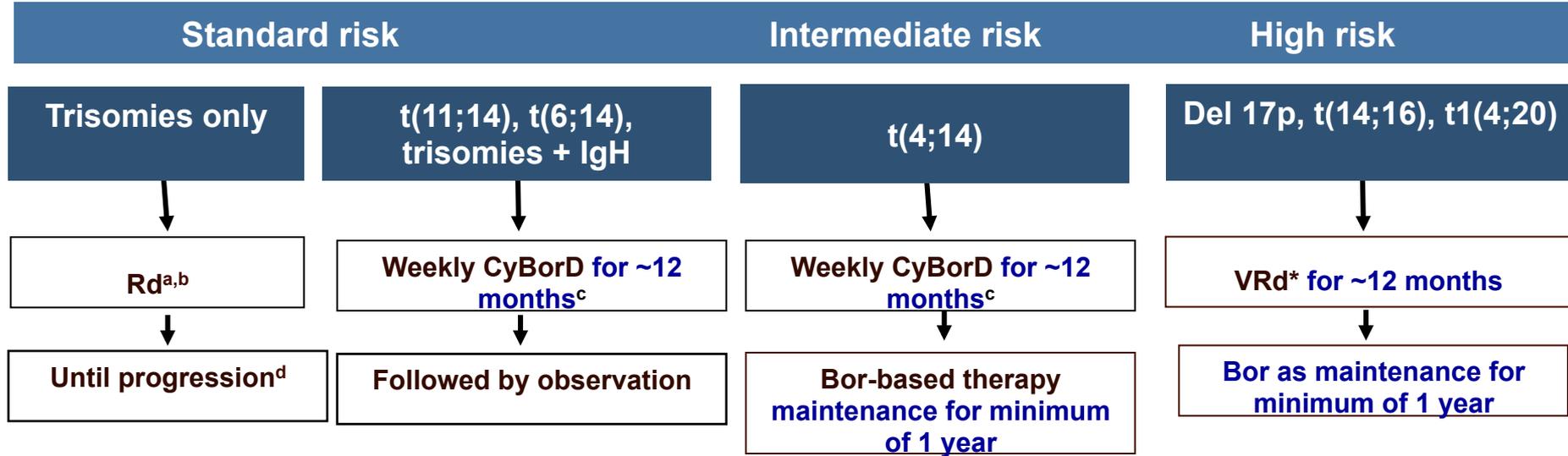
^cContinuing Rd for patients responding to Rd and with low toxicities; dex is usually discontinued after 1st year.

*Consider risks and benefits; if used, consider limited duration 12–24 months.

Dispenzieri A, et al. *Mayo Clin Proc.* 2007;82:323-341; Kumar SK, et al. *Mayo Clin Proc.* 2009;84:1095-1110;

Mikhael JR, et al. *Mayo Clin Proc.* 2013;88:360-376.

mSMART: Off-Study Transplant Ineligible



^aIn patients treated with Rd, continuing treatment is an option for patients responding well with low toxicities; dex is usually discontinued after 1st year.

^bBortezomib containing regimens preferred in renal failure or if rapid response needed.

^cCyBorD is considered a less toxic variation of VMP; VMP can be used as alternative.

^dContinuing Rd for patients responding to Rd and with low toxicities; dex is usually discontinued after 1st year.

*Clinical trials strongly recommended as the first option.

High-Risk Myeloma

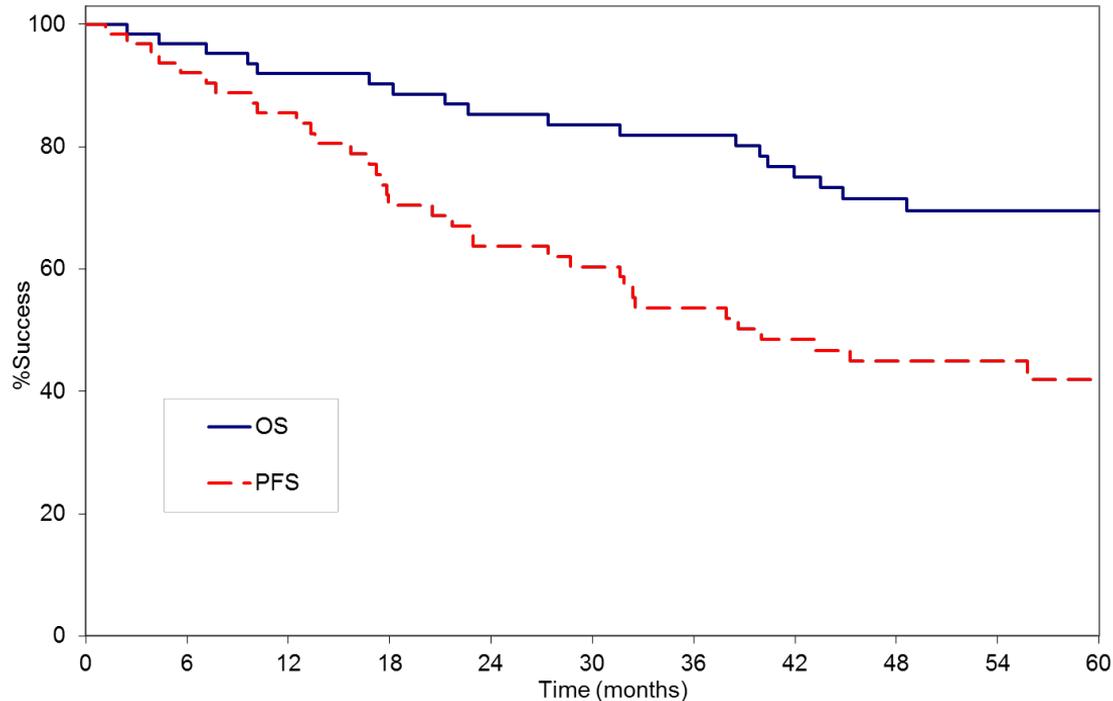
- Need complete response for long-term disease control (overall survival)
 - Aggressive therapy: All drugs up front
 - Triplet regimens
 - **VRD, VTD** (PI + IMiD + steroid)
 - **KRD?** (ENDURANCE trial underway)
- Intermediate risk: Need proteasome inhibitor
 - **CyBorD (VCD)** (alkylator + proteasome inhibitor + steroid), **VRD**

Standard-Risk Myeloma

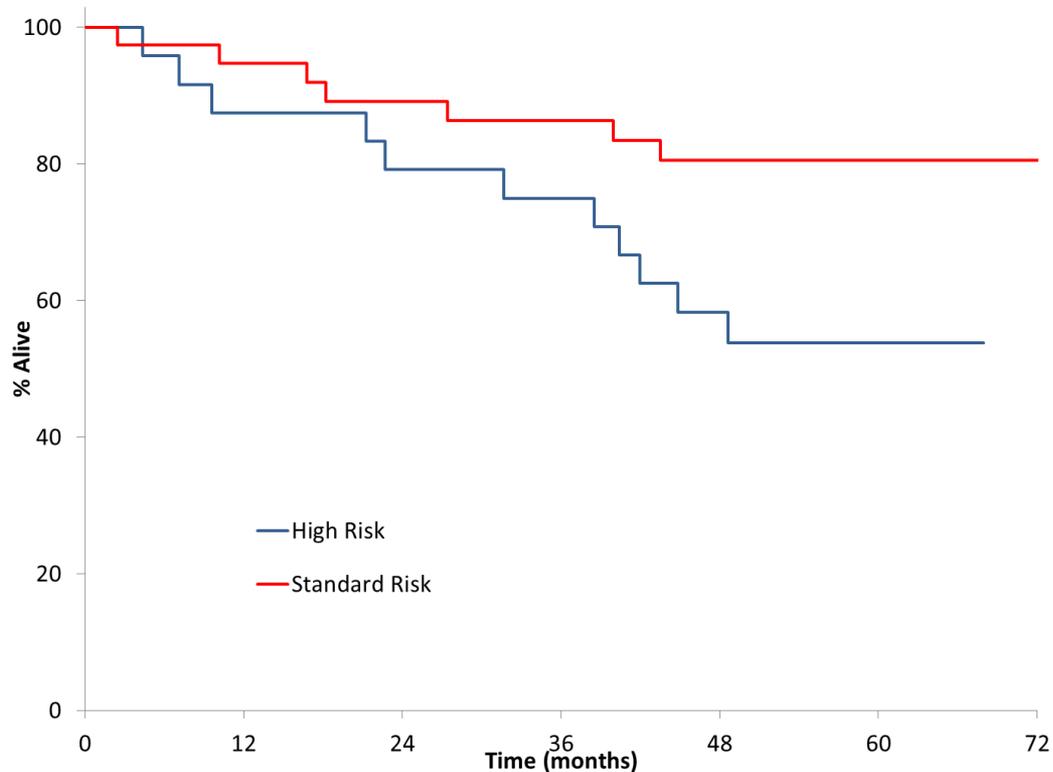
- Overall survival similar whether or not complete response is achieved
 - Option for less-aggressive therapy
 - **Sequential** agents vs. all up front
 - **Control** vs. cure approach

 - **CyBorD**
 - **Rd**
 - **MPT**

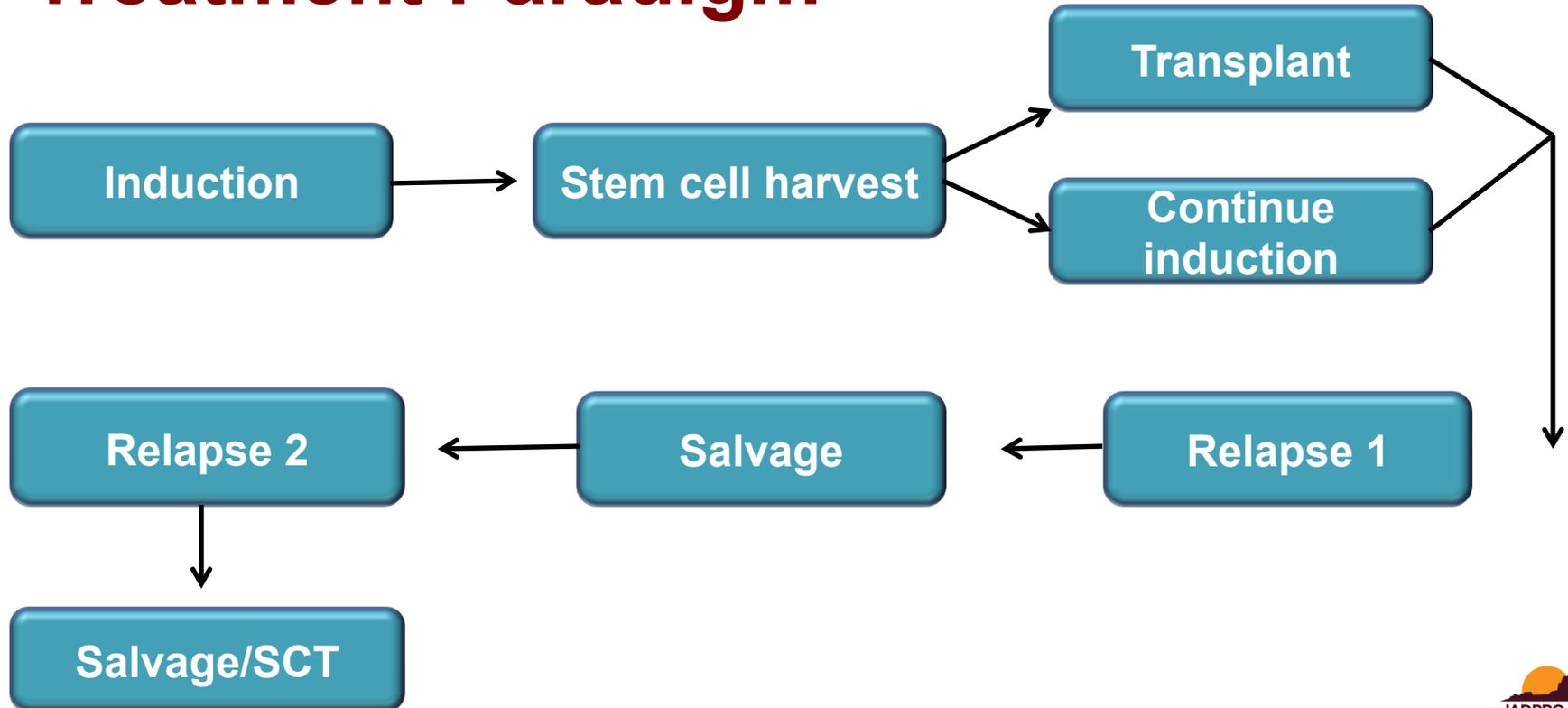
Kaplan-Meier Survival Curves for All Patients



Kaplan-Meier Survival Curves by mSMART Risk



Multiple Myeloma Treatment Paradigm



Autologous Stem Cell Transplant

- Most studies show improved progression-free survival and some overall survival compared with standard therapy
- Low mortality in young patients
- High-dose therapy increases depth of response
 - Depth correlates with survival
- Second stem cell transplant
 - Beneficial if $<$ VGPR after SCT #1
 - Rarely needed in era of novel agents
 - May not be needed if maintenance utilized
 - Can be used as salvage if first SCT remission $>$ 2 years
- Stem cell harvest, after 4–6 cycles of therapy

Stem Cell Transplant: Process

- Precollection evaluation
- Stem cell mobilization
- Stem cell harvest
- Cryopreservation
- Conditioning (high-dose melphalan)
- Stem cell infusion
- Supportive measures
- Engraftment

Stem Cell Harvesting After Novel Agents

- Thalidomide
 - Probably no impact (or minimal) on yield or engraftment
- Lenalidomide
 - Reduces stem cell yield
 - Duration of therapy > 4–6 cycles
 - Age of patient
 - Mobilization techniques: G-CSF vs. chemotherapy + G-CSF
 - No effect on engraftment
- Bortezomib
 - Probably no impact on yield or engraftment
- Chemotherapy
 - Melphalan: Significant impact (stem cell toxic)
 - Cyclophosphamide: No impact

Stem Cell Collection Guidelines

- Harvest early, after 3–4 cycles of induction
 - G-CSF alone usually adequate
 - If > 4 cycles of lenalidomide-based therapy
 - G-CSF + cyclophosphamide, or
 - G-CSF + plerixafor
 - If > 65 years old
 - G-CSF + reduced dose cyclophosphamide
 - Add plerixafor day 2 if needed

Maintenance Therapy

- Thalidomide
 - All maintenance studies show improvement in event-free survival
 - Three show improvement in overall survival
 - The benefits seem to be for those having less-than-maximal response from primary therapy
 - Toxicity and intolerance limit usefulness
- Lenalidomide
 - Less toxic than thalidomide
 - Two trials now show prolonged event-free survival/progression-free survival compared with placebo; one shows overall survival benefit
 - Second primary cancers a concern
- Bortezomib
 - Early data are promising, but optimal dose/schedule unclear



mSMART

*Mayo Stratification for Myeloma and
Risk-Adapted Therapy*

Relapsed Myeloma

mSMART 2.0: Classification of Relapsed Multiple Myeloma

High risk

- Relapse <12 mo from transplant or progression within 1st year of diagnosis
- FISH
 - Del 17p
 - t(14;16)
 - t(14;20)
- High-risk GEP

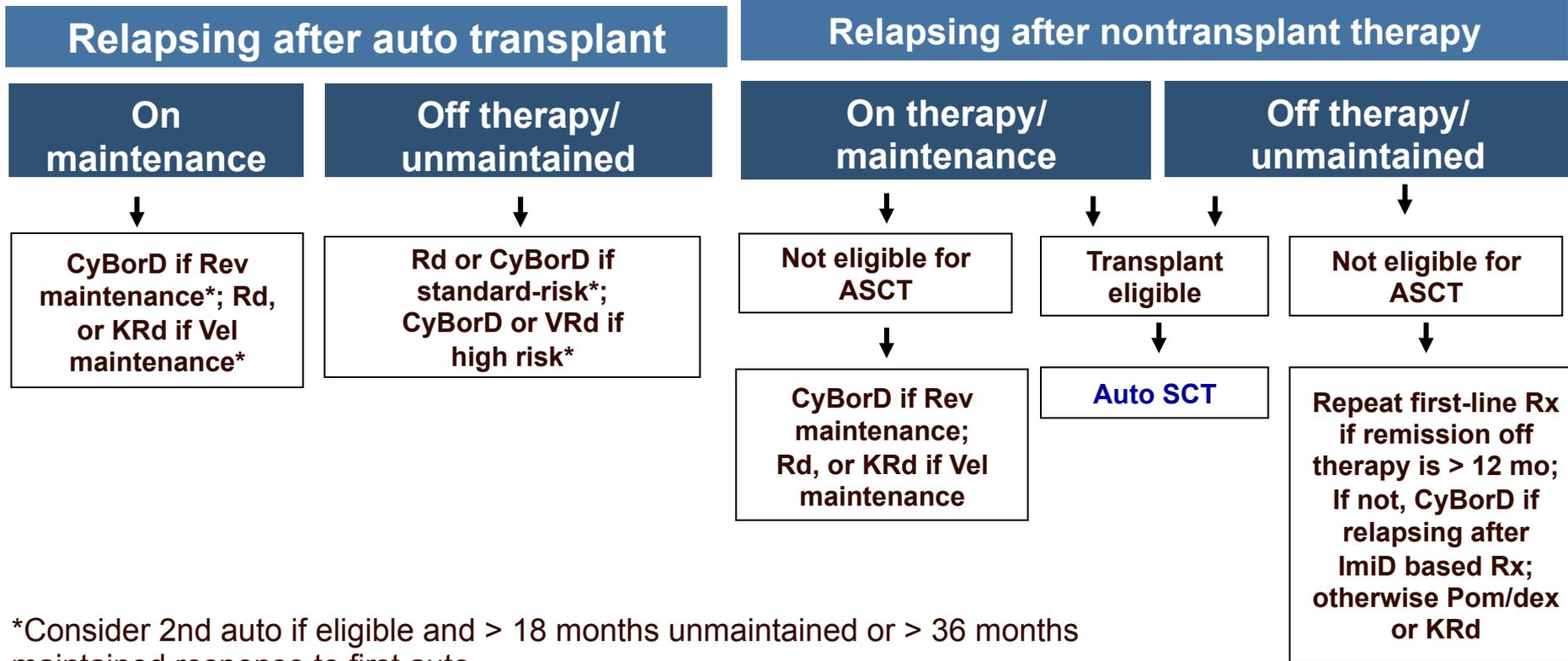
Intermediate risk

- FISH
 - t(4;14)
 - 1q gain
- Complex karyotype
- Metaphase Deletion 13 or hypodiploidy
- High PC S-phase

Standard risk

- All others, including:
- Trisomies
 - t(11;14)
 - t(6;14)

First Relapse: Off Study



*Consider 2nd auto if eligible and > 18 months unmaintained or > 36 months maintained response to first auto.

Dispenzieri A, et al. *Mayo Clin Proc.* 2007;82:323-341; Kumar SK, et al. *Mayo Clin Proc.* 2009;84:1095-1110; Mikhael JR, et al. *Mayo Clin Proc.* 2013;88:360-376.

Second or Later Relapse* Off Study

Not plasma cell leukemia (PCL) or similar extramedullary disease (EMD)

Dual-refractory
(bortezomib and
lenalidomide)**

KRd or Pom/dex to
maximum response or
18 months, then Rd

Triple-refractory
(bortezomib, lenalidomide,
and carfilzomib)**

PCD, PVD, or Car-Pom-Dex
to maximum response or
18 months, then Pom/dex

Triple-refractory
(bortezomib,
lenalidomide, and
pomalidomide)**

KRd or Car-Pom-Dex
to maximum response
or 18 months,
then Rd or Pom/dex

* If single refractory, refer to first-relapse algorithm.

**Auto transplant is an option if transplant candidate and feasible;

doublings such as Cyclo-Pred, Pd or Kd could be considered in patients with indolent disease.

Second or Higher Relapse: Off Study

**Secondary PCL
or
extensive EMD**



VDT-PACE x 2 cycles*
Auto transplant if transplant candidate;
if not, maintain with one of the regimens listed
that the patient is not known to be refractory
to (VRd, VCd, KRd, PVD, or Car-Pom-Dex)

**Quadruple-refractory
(lenalidomide, pomalidomide,
bortezomib, and carfilzomib)**



VDT-PACE* x 2 cycles if possible.*
Auto transplant if transplant candidate;
if not, consider alkylator-containing combination
if not alkylator refractory or treat with
anthracyclin-containing regimen such as
RAD, VDD, PAD, or CHOP**

*CVAD or similar regimen can be used in place of VDT-PACE in older patients or patients with poor functional status.

**Other options to consider in fit patients: bendamustine- or panobinostat-containing regimens.

Dispenzieri A, et al. *Mayo Clin Proc.* 2007;82:323-341; Kumar SK, et al. *Mayo Clin Proc.* 2009;84:1095-1110; Mikhael JR, et al. *Mayo Clin Proc.* 2013;88:360-376.

Risk Status and Relapse

- Recall the importance of risk stratification in myeloma and its varied presentation
- Relapse occurs more quickly and aggressively in high-risk patients
- Close monitoring and rapid institution of therapy are critical
- Risk factors can change since time of first diagnosis; reevaluate at time of relapse
- More likely require longer-term (if not indefinite) therapy
- Standard-risk patients may not need rapid intervention; fewer drugs at once, more likely sequential

Second Transplants

Three requirements should be met:

1. Did the patient benefit from the first ASCT? (i.e., response deepened)
2. Did the patient tolerate the first ASCT well?
3. Did the patient have a minimum 2-year progression-free survival after the first ASCT?^{1,2}

Expect 50%–70% of progression-free survival with second ASCT

1. Jimenez-Zepeda VH, et al. *Biol Blood Marrow Transplant.* 2012;18:773-779;
2. Michaelis LC, et al. *Biol Blood Marrow Transplant.* 2013;19:760-766.

Re-treatment in Combination

- Even if a patient has become resistant to a certain agent, may become sensitive
 - Due to clonal evolution
 - When combined with another agent (e.g., VRD 30% response in V- and D-resistant disease)¹
- Other combinations include:
 - VDT-PACE,² DCEP, melphalan + ... tend to be a bridge to more definitive therapy

1. Richardson PG, et al. *Blood*. 2014;123:1461-1469;
2. Gerrie AS, et al. *Br J Haematol*. 2013;161:802-810.

Future Therapies

Classes of Agents in Development for Myeloma

- Oral proteasome inhibitors: Ixazomib (MLN 9708), oprozomib
- Monoclonal antibodies
 - SLAMF7 (signaling lymphocytic activation molecule F7): elotuzumab (formerly CS-1)
 - Anti-CD38: Daratumumab, SAR650984
 - Anti-CD138: Indatuximab, ravatansine
- KSP inhibitors: Filanesib
- Histone deacetylase inhibitors: Panobinostat, ACY-1215
- Akt inhibitors: Afuresertib
- BCL family inhibitors: ABT-199

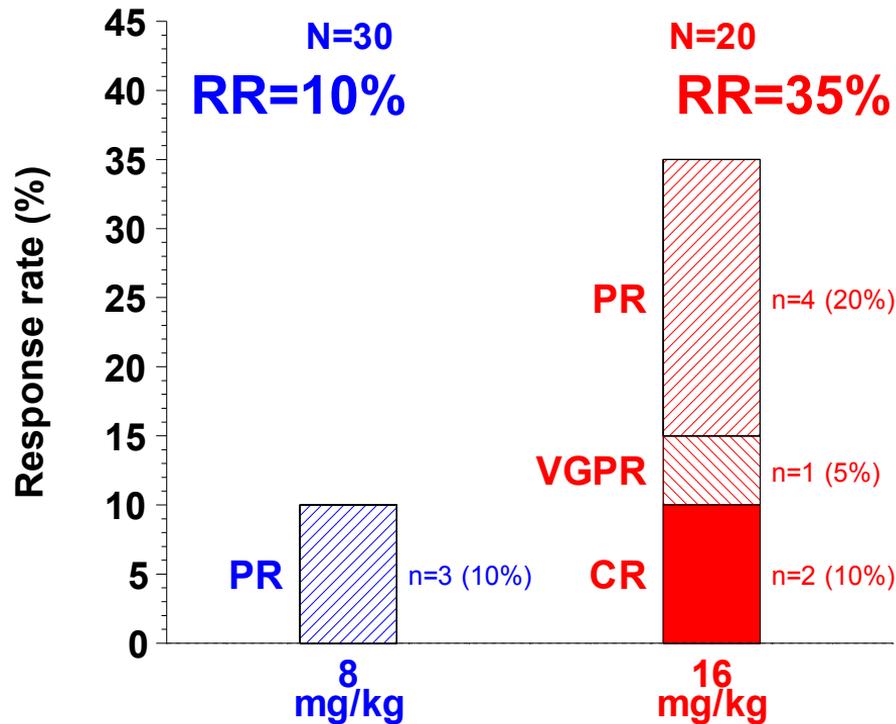
Future Therapies (cont)

- CDK inhibitors: Dinaciclib
- Nuclear transport: CRM/XPO1, selinexor
- IAP antagonists: LCL161
- PIM kinase inhibitors: LGH447
- Bromodomain and extraterminal (BET) inhibitors: GSK525762
- Immune therapies: Programmed cell death protein 1 (PD-1), programmed cell death-ligand 1 (PD-L1)

Anti-CD38 Monoclonal Antibodies

- Most promising agents for myeloma (according to 80% vote at International Myeloma Working Group)
- Two currently in later development: Daratumumab and SAR650984
- Both have significant single-agent activity and can be combined
- Will this be the “rituximab” of myeloma?

Daratumumab: Response



IMWG Criteria

Summary and Recommendations

- Baseline genetic information should be obtained in all cases of multiple myeloma.
- Minimal testing required for prognostication should include FISH, LDH, β_2 M, albumin.
- Gene-expression signatures should be incorporated in all clinical trials.
- Multiple tools are available for risk stratification.
- Risk determination can help guide therapy and counseling.

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