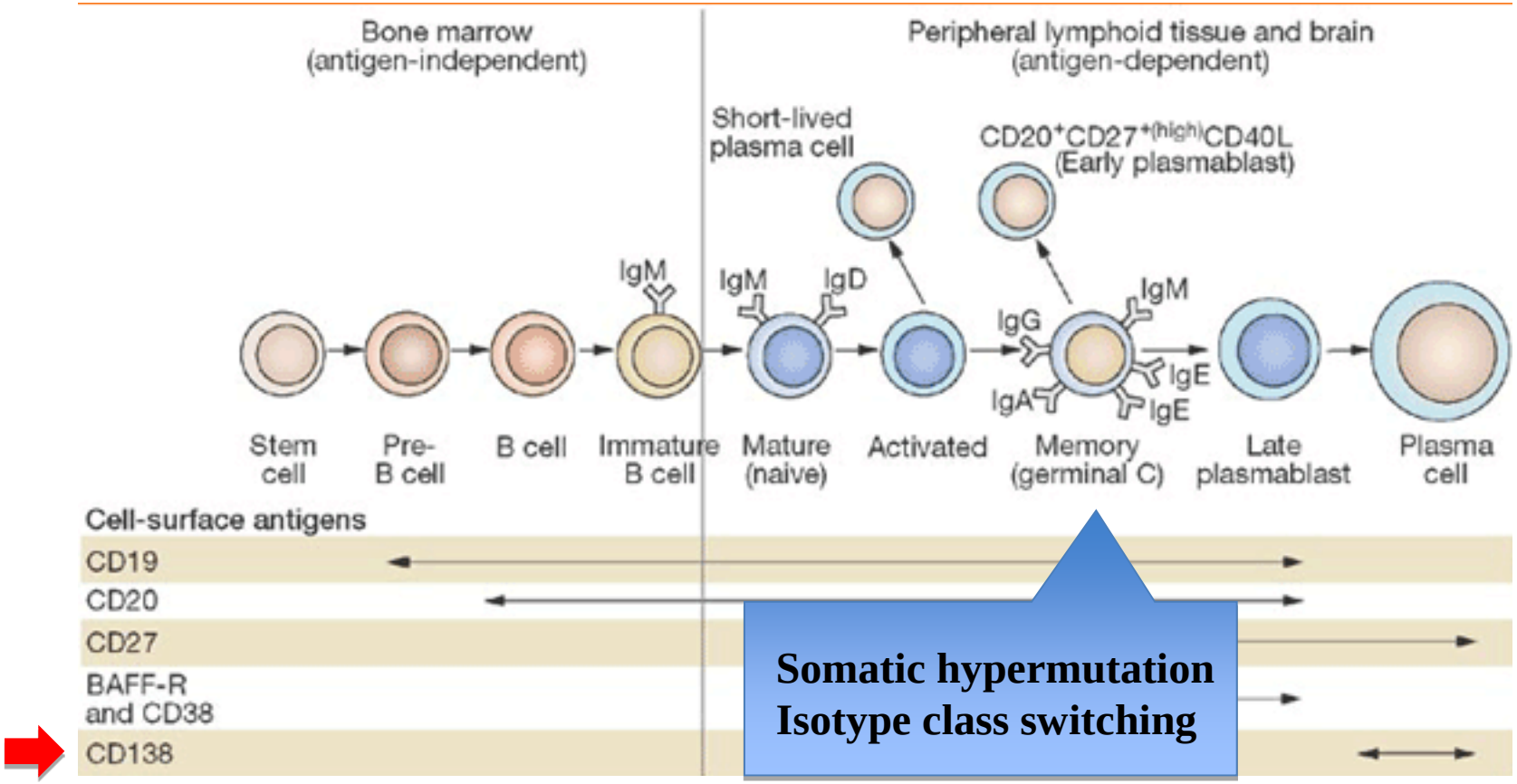
Current Concepts in Initial Diagnosis & Management of Multiple Myeloma

Abraham S Kanate, M.D.
Assistant Professor of Medicine
Osborn Hematopoietic Malignancy & Transplantation Program
WVU

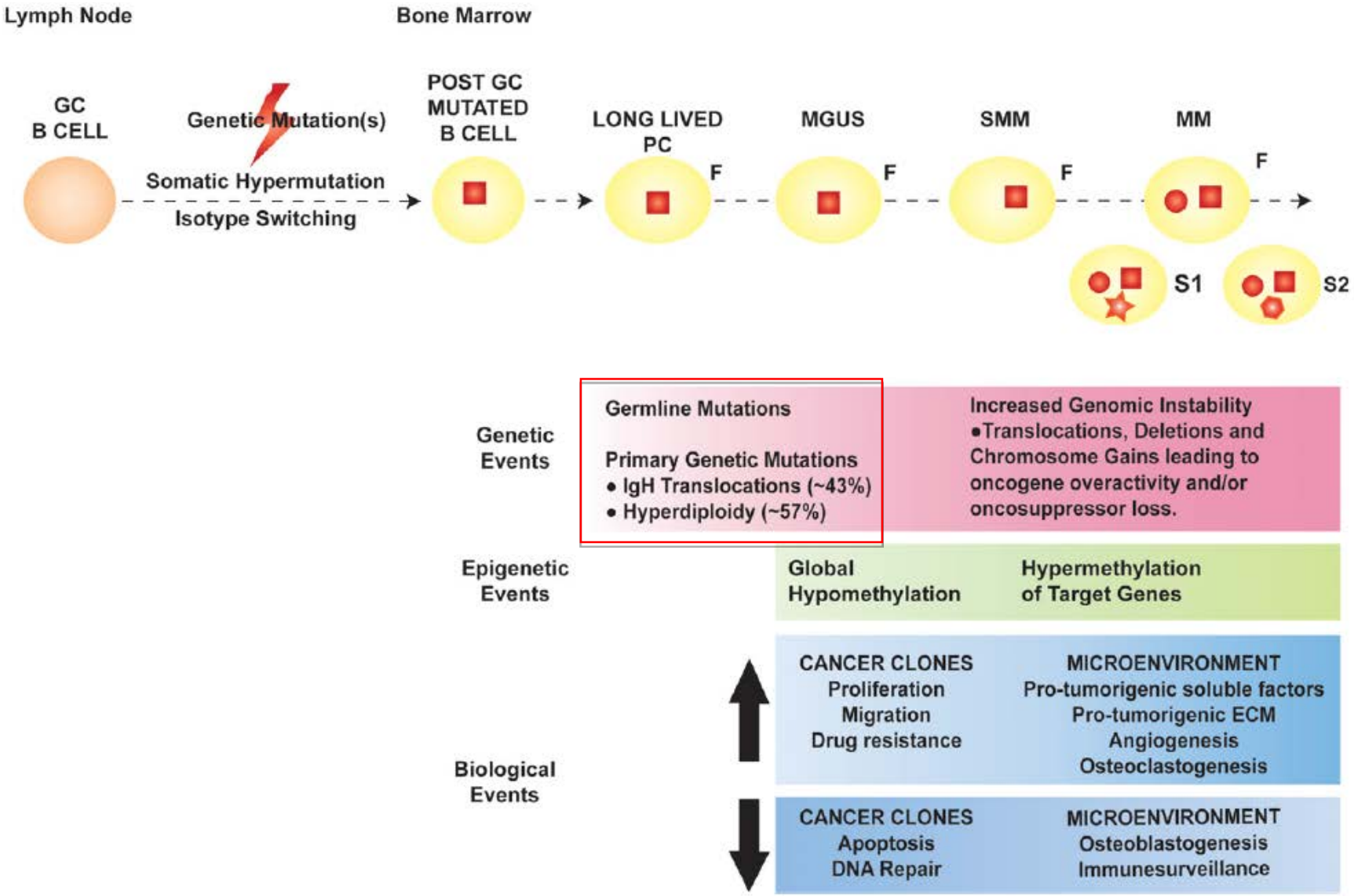
Presentation Aims

- Diagnosis
- Prognostic markers and Management
- Treatment/Management of Multiple Myeloma
  - Transplant ineligible
  - Transplant eligible

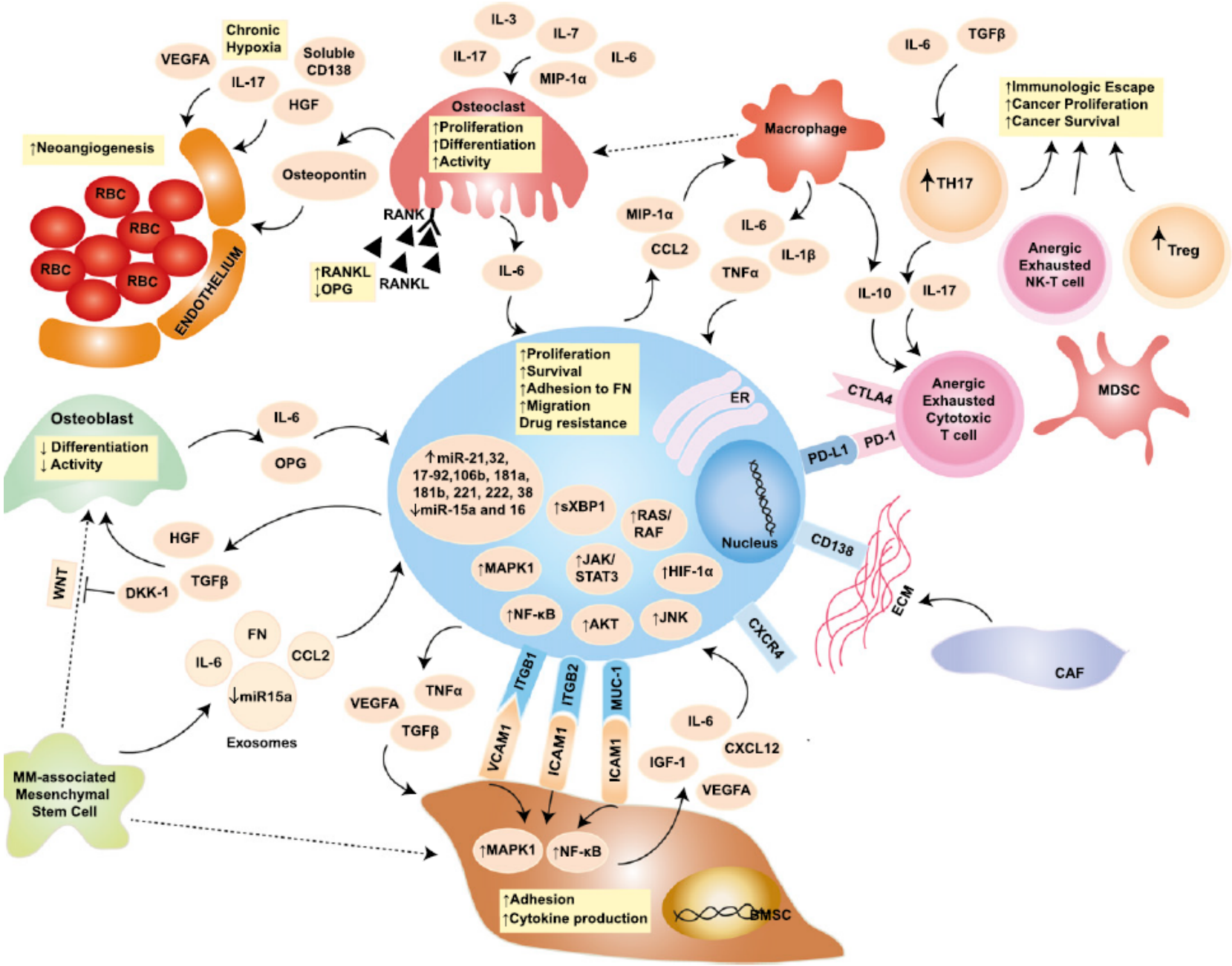
Plasma Cell Maturation



Pathogeneis

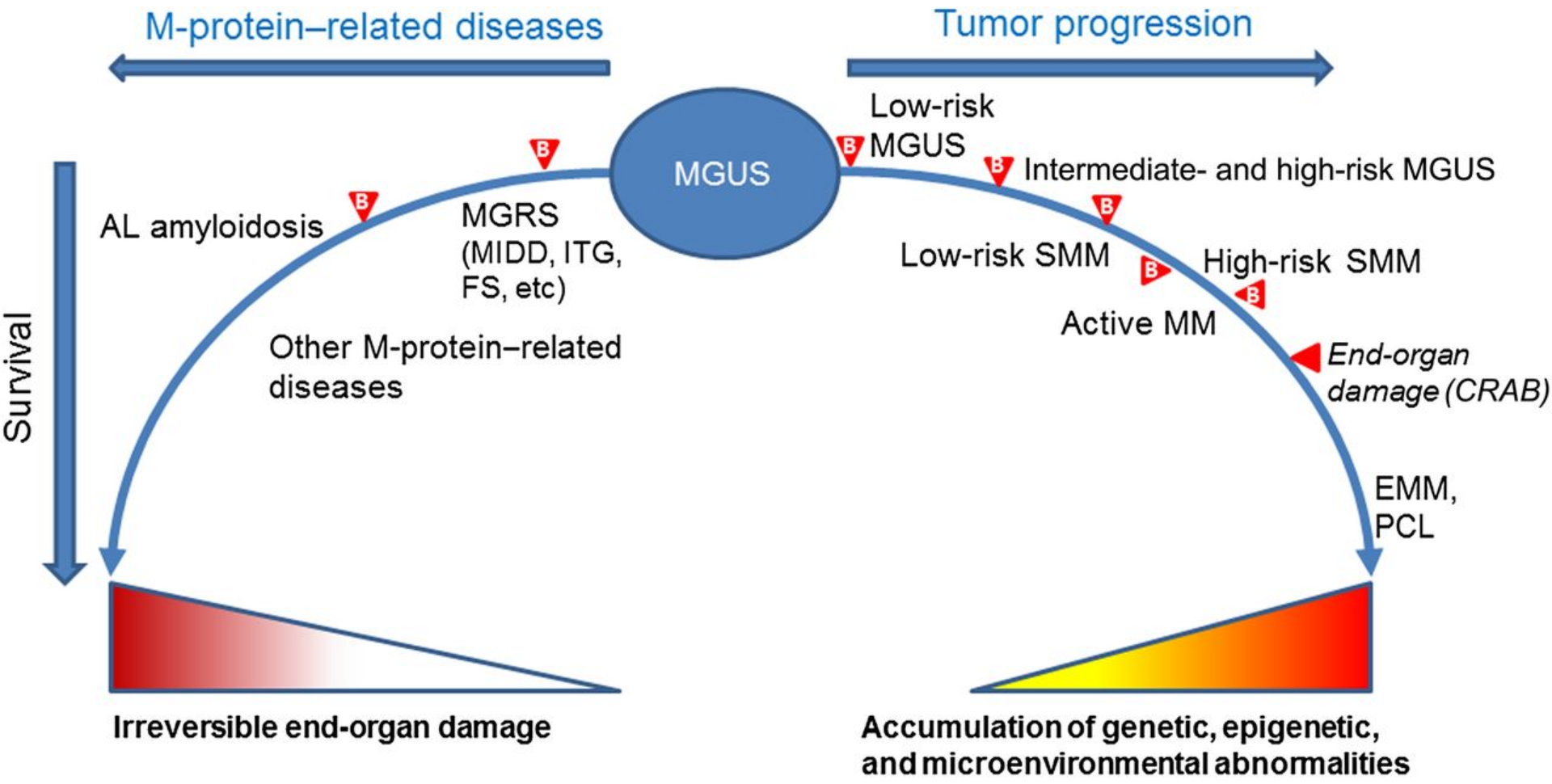


Bianchi. Blood 2015



Interactions between MMC with cellular and acellular components of BM

Bianchi. Blood 2015



- MGUS → SMM (AMM) → Multiple Myeloma
- Solitary Plasmacytoma
- AL Amyloidosis
- POEMS
- Waldenstroms Macroglobulinemeia

Merlini G Blood 2014;123:305-307

Diagnosis

	IMWG criteria, 2010 version[6]
MGUS	Serum M-protein $<$ 3g/dL Light-chain restricted BM plasma cells $<$ 10% No end-organ damage*
SMM	Serum M-protein $\geq$ 3 g/dL and/or light-chain restricted BM plasma cells $\geq$ 10% No end-organ damage*
Multiple myeloma	Serum M-protein (any level) Light-chain restricted BM plasma cells (any level) End-organ damage*

Based on expert discussions at the IMWG meeting in Stockholm in June 2013, it is anticipated that updated consensus criteria will be defined in the near future. Recent studies suggest that additional features such as BM plasmacytosis $\geq$ 60%,[48] an abnormal sFLC ratio $\geq$ 100 (involved kappa) or $<$ 0.01 (involved lambda),[39] and/or focal BM lesions detected by functional imaging including PET-CT and/or MRI[47,49] in asymptomatic individuals may warrant a clinical diagnosis of multiple myeloma.

*One or many of the following features: hypercalcemia with calcium level $>$ 11.5 mg/dL, renal insufficiency with serum creatinine $>$ 2.0 mg/dL, or estimated creatinine clearance $<$ 40 mL/minute, normochromic normocytic anemia with a hemoglobin value $<$ 10 g/dL (or a hemoglobin value $<$ 2 g/dL below the lower limit of normal), and bone lesions (lytic lesions, severe osteopenia, or pathological fractures).[6]

MGUS Progression

- 1% per year progression. Relative risk 25x (MM), 46x (WM), 8.4x (AL amyloidosis), 2.4x (lymphoma), 8.5x (plasmacytoma)
- Risk stratification model: Serum M protein level ≥1.5 g/dL, non-IgG MGUS, and an abnormal serum FLC ratio predict progression over 20 years
  - ✓ 3 risk factors — 58%
  - ✓ 2 risk factors — 37%
  - ✓ 1 risk factor — 21%
  - ✓ no risk factors — 5%

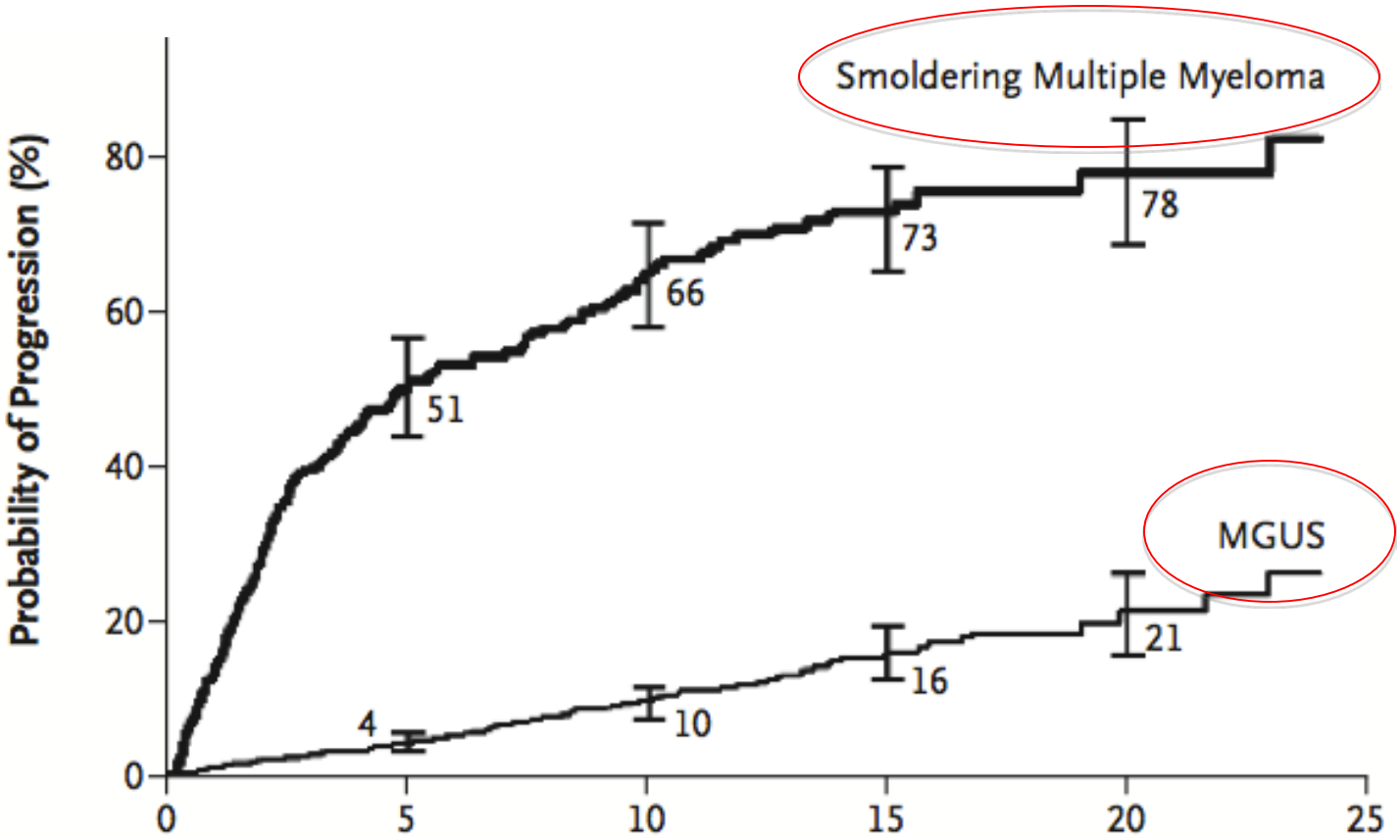
Free light chain only MGUS – less risk of progression

Check B-J proteinuria

Serial monitoring important

Kyle RA. NEJM 2002;346:564-9.
Rajkumar SV. Blood 2005;106(3):812-7.

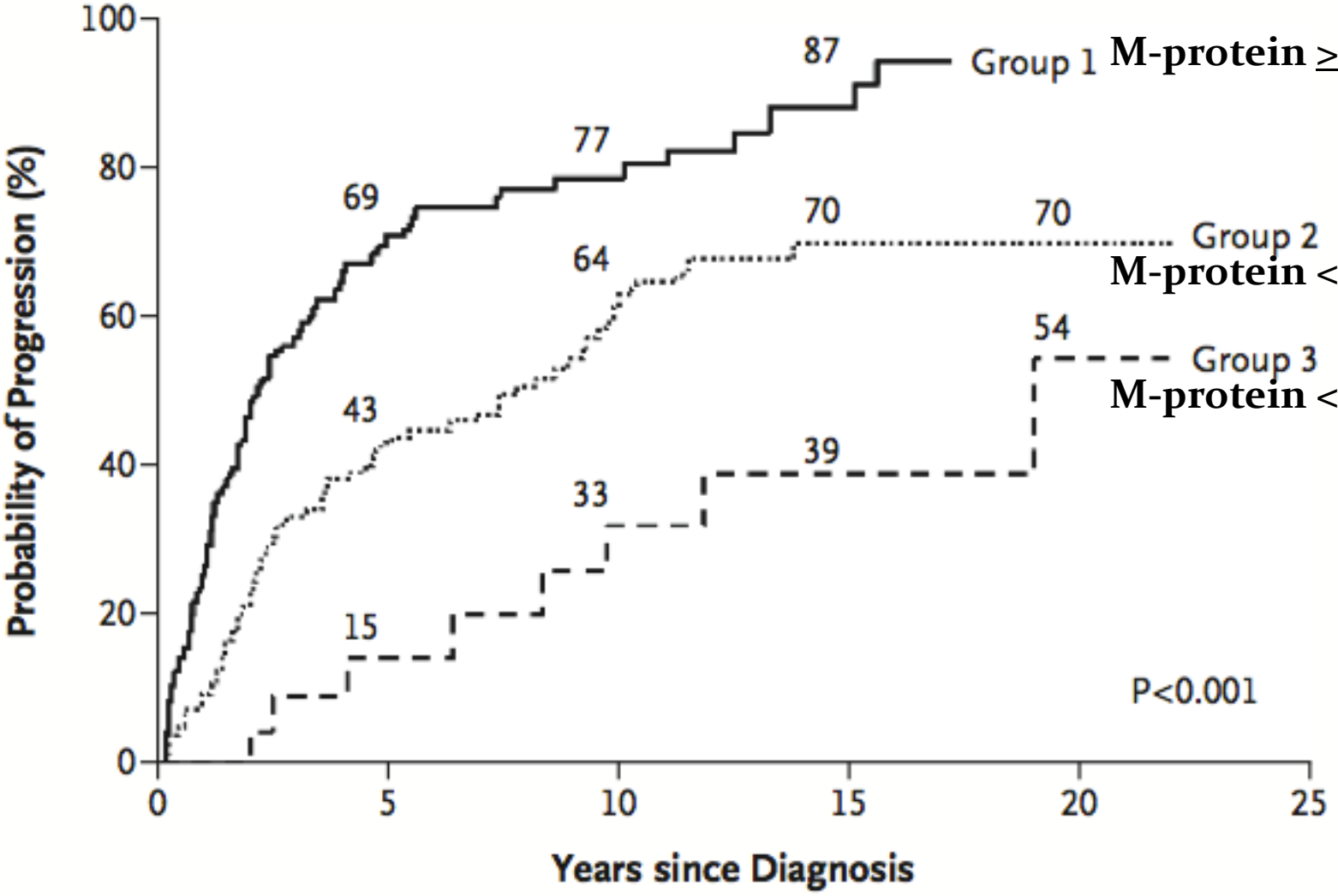
Clinical Course



Probability of Progression to Active Multiple Myeloma or Primary Amyloidosis in Patients with Smoldering Multiple Myeloma or Monoclonal Gammopathy of Undetermined Significance

N Engl J Med 2007;356:2582-90

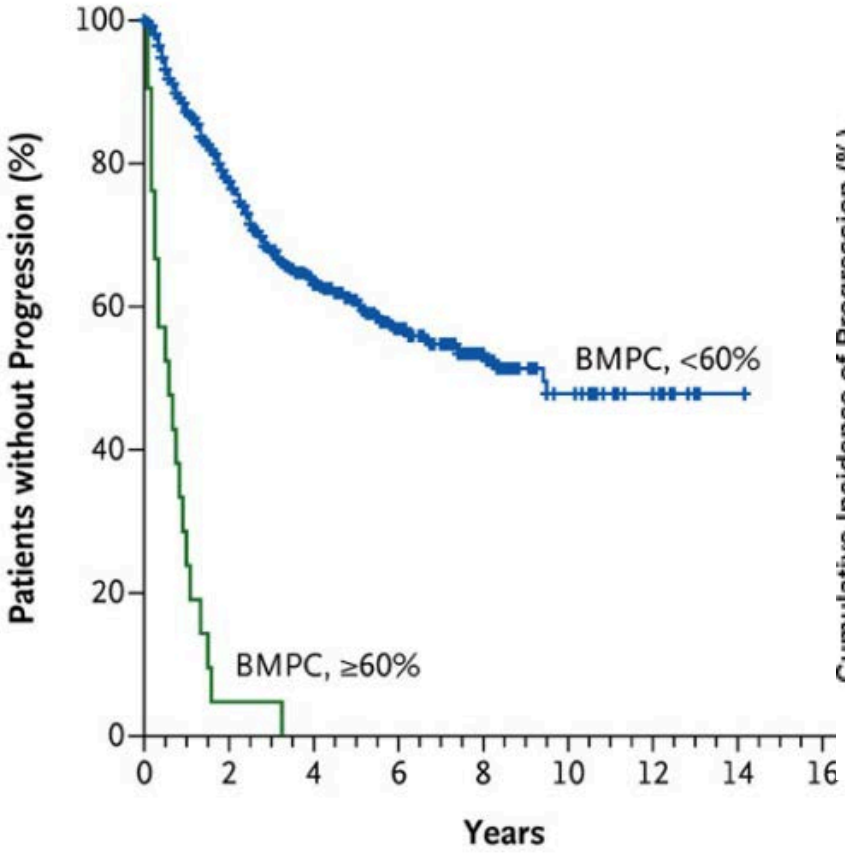
SMM/AMM Progression

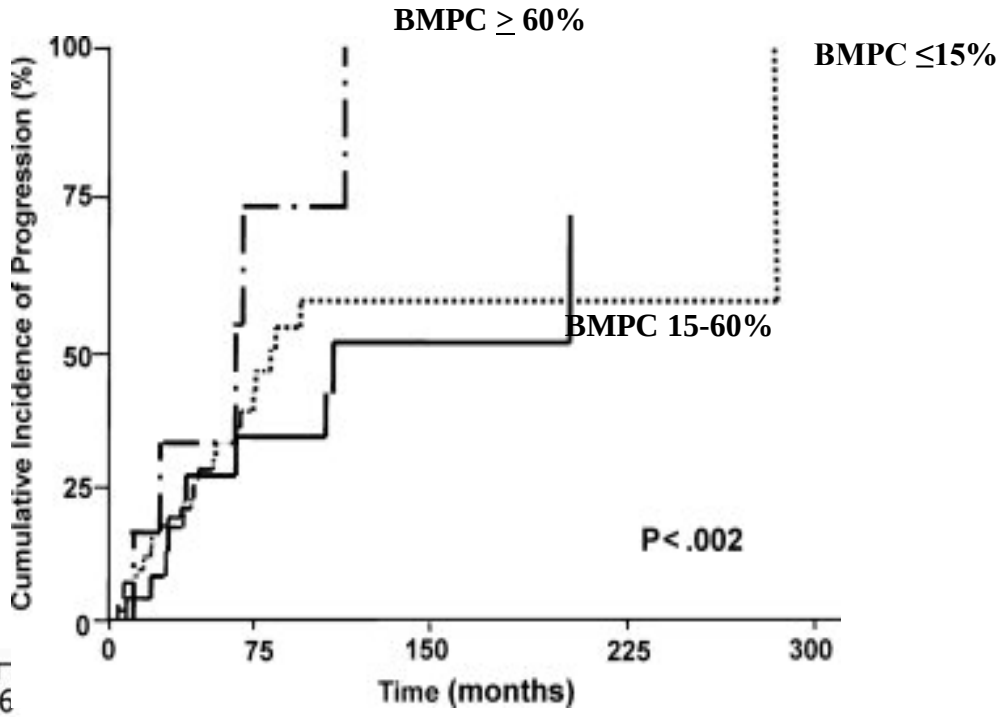


N = 276

N Engl J Med 2007;356:2582-90

(Very) High-risk AMM





Rajkumar V, NEJM 2011
Cancer. 2012

Definitions in Myeloma

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

  and

- Myeloma defining events:
  - **Hypercalcemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)**
  - **Renal insufficiency: creatinine clearance 177 μmol/L (>2 mg/dL)**
  - **Anemia: Hb >20 g/L below the lower limit of normal, or Hb < 100 g/dL**
  - **Bone lesions: one or more osteolytic lesions on skeletal radiography, CT/PET**

- Any one or more of the following biomarkers of malignancy:
  - **Clonal bone marrow plasma cell percentage* ≥60%**
  - **Involved:uninvolved serum free light chain ratio § ≥100**
  - **>1 focal lesions on MRI studies or PET scan**

Rajkumar Lancet Oncol 2014

Definitions in Myeloma

- Smoldering Multiple Myeloma (asymptomatic)
- **Both criteria must be met –**
  - **Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h**

    and/or

  - **clonal bone marrow plasma cells 10–60%**
  - **Absence of myeloma defining events or amyloidosis**

Rajkumar Lancet Oncol 2014

Durie-Salmon Criteria (Obsolete)

Major Criteria:

- Plasmacytomas
- Bone marrow showing > 30% plasma cells
- M-spike on SPEP: IgG > 3.5 g/dL or IgA > 2.0 g/dL; kappa or lambda light-chain excretion > 1.0 g/d on 24-h UPEP

Minor Criteria:

- Bone marrow showing 10–30% plasma cells
- M-spike present but of lesser magnitude than given above
- Lytic bone lesions.
- Normal IgM < 50 mg/dL, IgA < 100 mg/dL, or IgG < 600 mg/dL

Need at least one major and one minor or three minor including +BM and M spike.

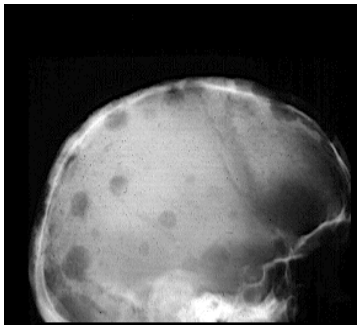
Initial Diagnostic Workup

INITIAL DIAGNOSTIC WORKUP

- H&P
- CBC, differential, platelet count
- BUN/creatinine, electrolytes
- LDH
- Calcium/albumin
- Beta-2 microglobulin
- Serum free light chain (FLC) assay
- Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)
- 24 h urine for total protein, urine protein electrophoresis (UPEP), urine immunofixation electrophoresis (UIFE)
- Skeletal survey
- Unilateral bone marrow aspirate + biopsy, including bone marrow immunohistochemistry and/or bone marrow flow cytometry
- Cytogenetics
- FISH [del 13, del 17p13, t(4;14), t(11;14), t(14;16), 1q21 amplification]

Useful Under Some Circumstances

- MRI
- CT scan (avoid contrast)
- PET/CT scan
- Tissue biopsy to diagnose a solitary osseous or extraosseous plasmacytoma
- Bone densitometry
- Plasma cell labeling index
- Staining of marrow and fat pad for amyloid
- Serum viscosity
- HLA typing



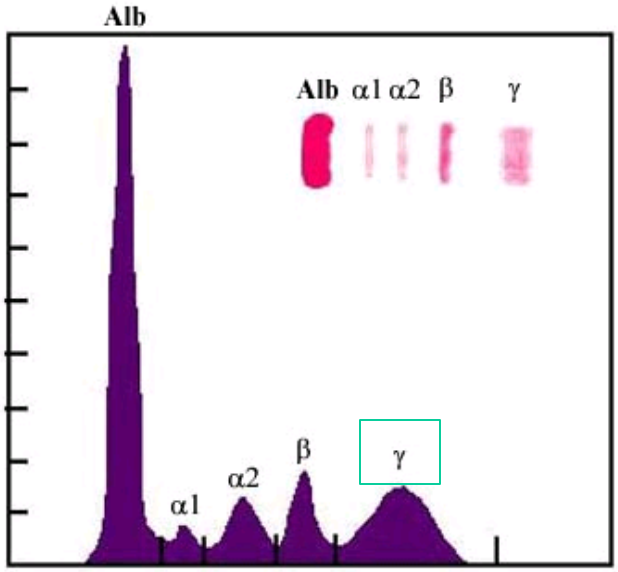
CLINICAL PRESENTATION

- Solitary plasmacytoma[a]
- Smoldering (asymptomatic)[a,
- Active (symptomatic)[a,d]

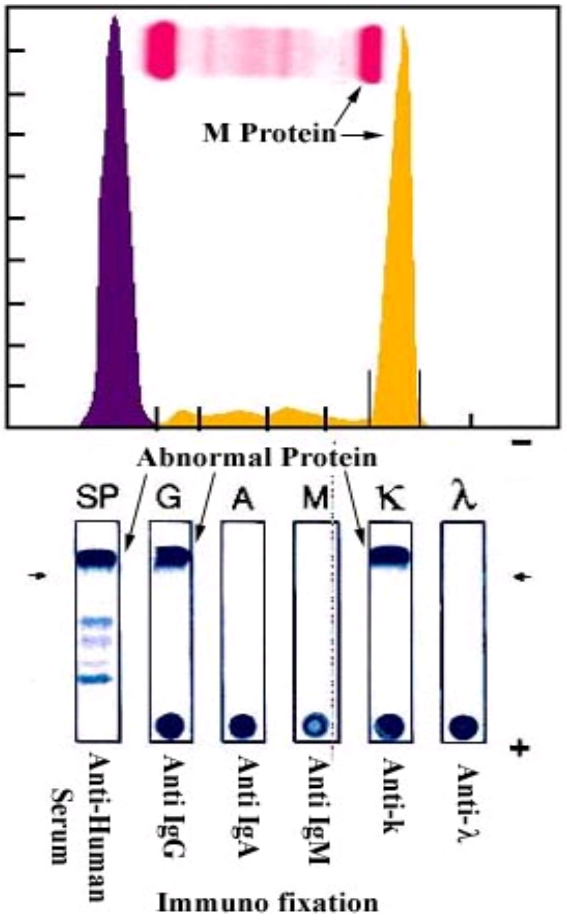
*NCCN® Practice Guidelines

QIM, SPEP & IFE should be done

- M-protein is detected by SPEP in 82% of the patients and by immunofixation in 93%



SPEP. Normal Pattern

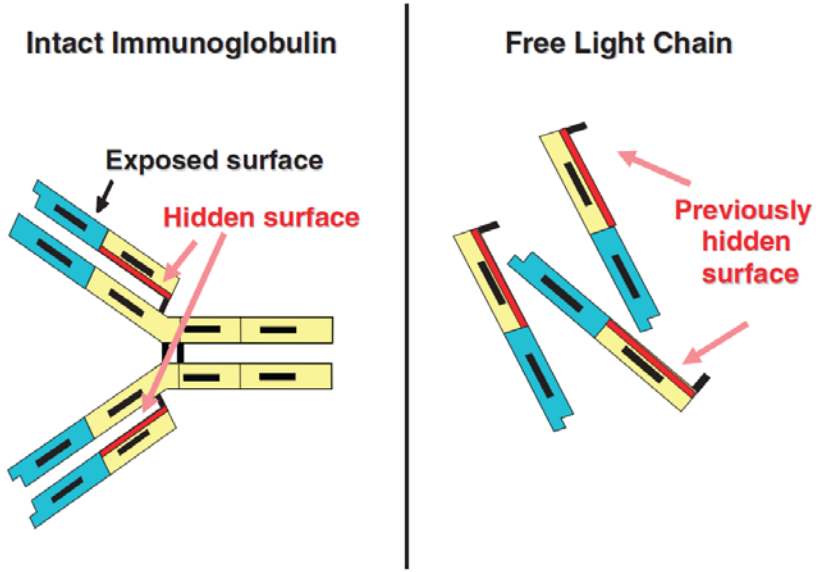


M-protein present

Kyle RA. Mayo Clinic Proc. 2003;78:21-33.

Rationale for Serum FLC Assay

- Diagnosis of LC myeloma can be missed if only SPEP and IFE are performed (but LC are always detectable in urine)
- Oligo-secretory MM cases where serum and urine electrophoresis and IFE are often normal
- Combination of SPEP, IFE and FLC is (99%) effective for screening all plasma cell dyscrasias (except AL or true non-secretory MM)
- After establishing diagnosis, 24hr urine studies are required



Dispenzieri et al. Leukemia 2009.

Durie-Salmon Staging (obsolete)

- Stage I
- Hemoglobin >10 g/dL
- Normal calcium
- No lytic bone lesions
- Low M-protein
  - IgG <5 g/dL
  - IgA <3 g/dL
  - Bence Jones <4 g/24h
- Stage II (not Stage I/III)
- Stage III
- Hemoglobin <8.5 g/dL
- Calcium >12 mg/dl (adjusted)
- Advanced lytic bone lesions
- High M-protein
  - IgG >7 g/dL
  - IgA >5 g/dL
  - Bence Jones >12 g/24h

- A) Creatinine <2 mg/dl
- B) Creatinine >2 mg/dl

Durie BGM et al. Cancer 1975.

International Staging System

Stage I:

- β2-microglobulin < 3.5 mg/L and albumin ≥ 3.5 g/dL
- (median survival of 62 months)

Stage II:

- Neither I nor III
- (median survival of 44 months)

Stage III:

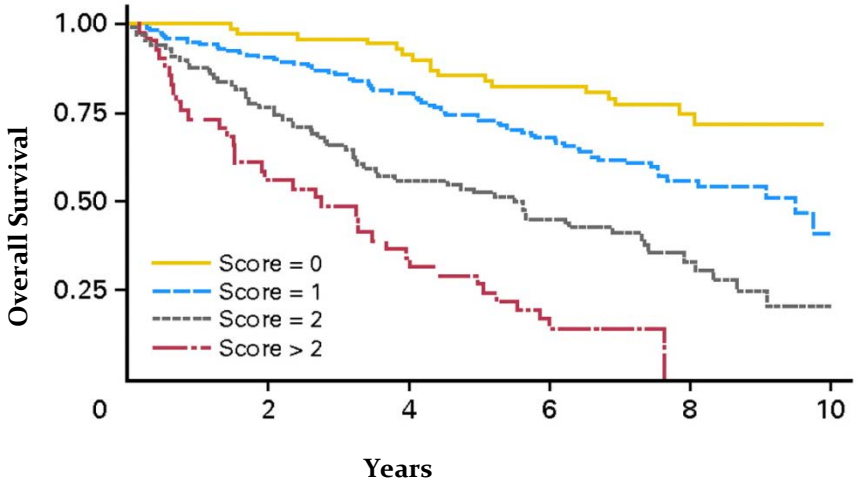
- Beta-2-microglobulin ≥ 5.5 mg/L
- (median survival of 29 months)

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

Prognostic Factors in Myeloma IFM99-02 & 99-04

OS According to Risk Factors

No. of Risk Factors	Frequency (%)	Median OS
0	19.5	Not reached at 10
1	44.3	9.5
2	25.5	5.6
> 2	10.7	2.8



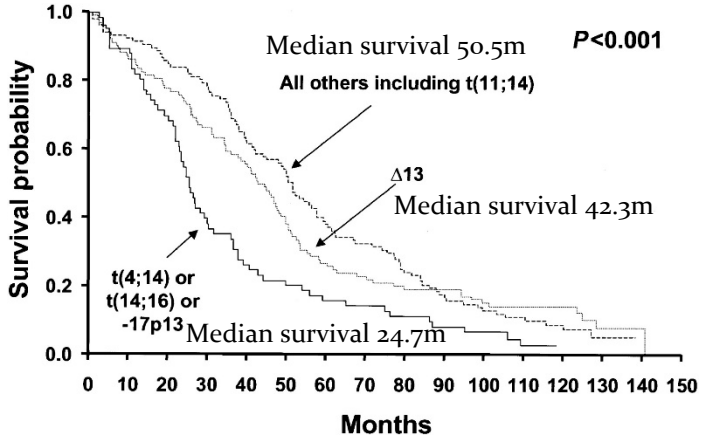
Poor-prognosis factors

- **age >55 years**
- **β2-microglobulin >5.5 mg/L**
- **t(4;14), del(17p), 1q gains**

Avet-Loiseau H. JCO 2012:30;1949-1952

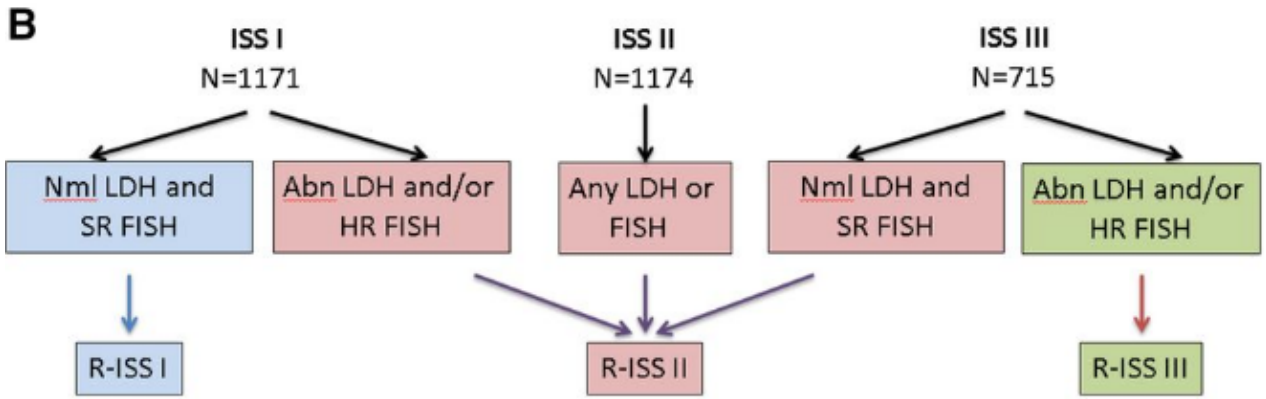
Prognostic Factors in Myeloma

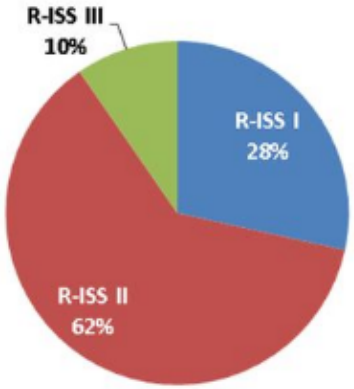
- Age and performance status
- LDH
- ISS stage
- Conventional cytogenetics
  - Monosomy 13
  - Hypo-diploidy
  - Chromosome 1 abn ('p' del / 'q' gain)
- Fluorescent in situ hybridization
  - **t(4;14)**(p16;q32)
  - **t(14:16); t(14;20)**
  - **del(17p)**
  - t(11;14)(q13;q32)
- Abnormal FLC ratio of <0.03 or >32
- Plasma cell labeling index ≥ 3%



Avet-Loiseau H. Blood. 2007;109:3489-3495.
Snozek CH. Leukemia 2008; 22: 1933–1937.
Fonseca R. Blood 2003; 101: 4569–4575.

Incorporating FISH into risk stratification of Myeloma





	R-ISS I (N=871)	R-ISS II (n=1894)	R-ISS III (n=295)
5-year PFS, % (n=3060)	54	36	22
5-year OS, %			
All (n=3060)	81	60	40
ASCT (n=1998)	83	62	39
No ASCT (n=1062)	75	52	47

ISS – no patients got PI or imid
HR-FISH - was defined as del(17p) and/or t(4;14) for ISS

R-ISS - incorporates the original ISS (B-2M and albumin), myeloma FISH (t[4;14], t[14;16], or del[17p]), and lactate dehydrogenase

Palumbo J Clin Oncol. 2015;33(26):2863-2869
Angela Dispenzieri Hematology 2016;2016:485-494

MAYO CLINIC

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
- High PC S-phase[f]

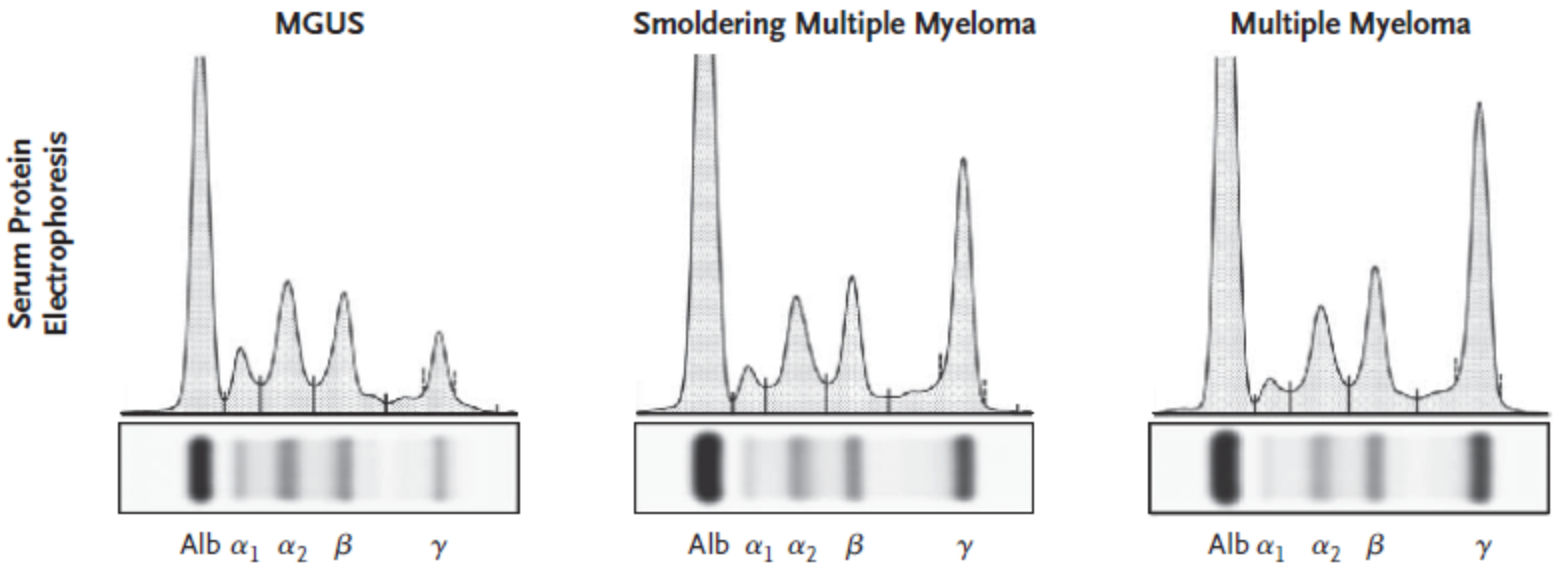
Standard-Risk[a,b]

All others including:

- Trisomies
- t(11;14)[e]
- t(6;14)

[a] Note that a subset of patients with these factors will be classified as high-risk by GEP
[b] LDH >ULN and beta-2 M > 5.5 may indicate worse prognosis; [c]Trisomies may ameliorate
[d] Prognosis is worse when associated with high beta-2 M and anemia
[e] t(11;14) may be associated with plasma cell leukemia; [f] Cut-offs vary

Therapeutic strategies



	MGUS	Smoldering Multiple Myeloma	Multiple Myeloma
Bone Marrow	<10% Plasma cells	≥10% Plasma cells	≥10% Plasma cells
Clinical Picture	Asymptomatic No end-organ damage	Asymptomatic No end-organ damage	Symptomatic End-organ damage present
Therapy	Observation only	Observation only	Therapy required

MGUS → Every 6-12 months
SMM/AMM → Every 3-6 months for 1-2 years → Evolving or Stable

N Engl J Med 2007;356:2582-90

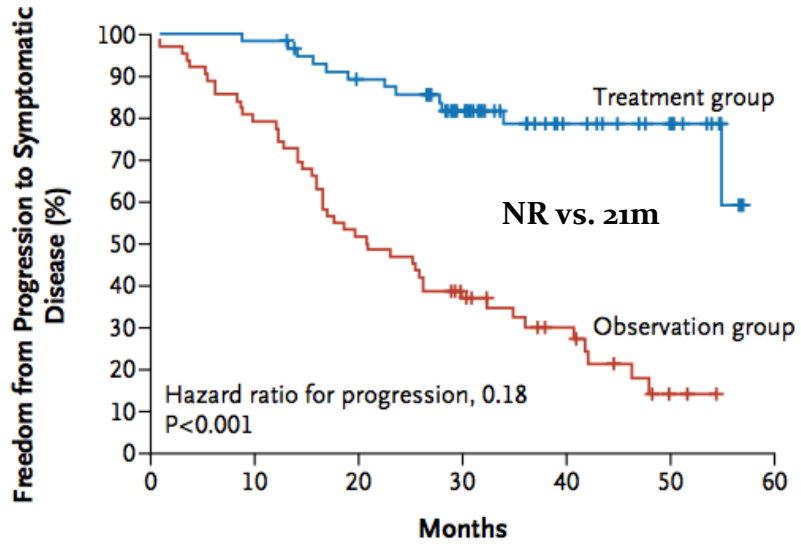
Early vs. Deferred Treatment

Trial	Year	Number	Regimen	PFS	OS	Toxicity	Comments
Hjorth	1993	50	Mel-Pred (early vs. deferred)	Imp	ND	2 acute leuk.	Median time to Rx in the deferred gp. was 12 months
Riccardi	2000	145	Mel-Pred (early vs. deferred)	Imp	ND	U/A	**Those randomized to observation and then progressed had worse survival**
Cochrane meta-analysis and review of 3 RCT – no survival advantage with early treatment							

Trial	Year	Number	Regimen	ORR	TTP	PFS	OS	Toxicity
Witzig	2013	68	Zometa +/- Thalidomide	0 Vs 37%	1.2 Vs **2.4**	55% Vs **86%**	**ND**	Neuropathy VTE

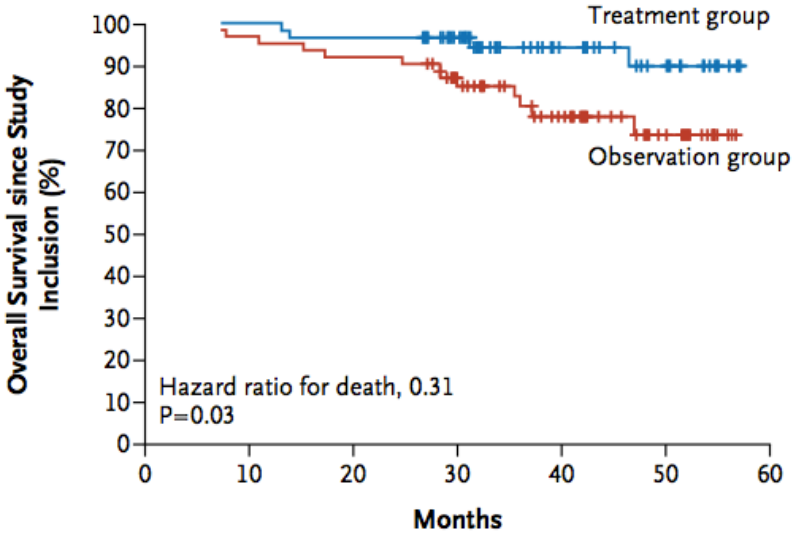
[1]Hjorth et al. Eur J Haematol.
Riccardi et al. Br J Cancer. 1994
[2]Riccardi et al. Br J Cancer. 2000 82(7), 1254–1260.
[3]Cochrane Database Syst Rev. 2003;(1):CD004023
[2]Leukemia (2013) 27, 220–225

A



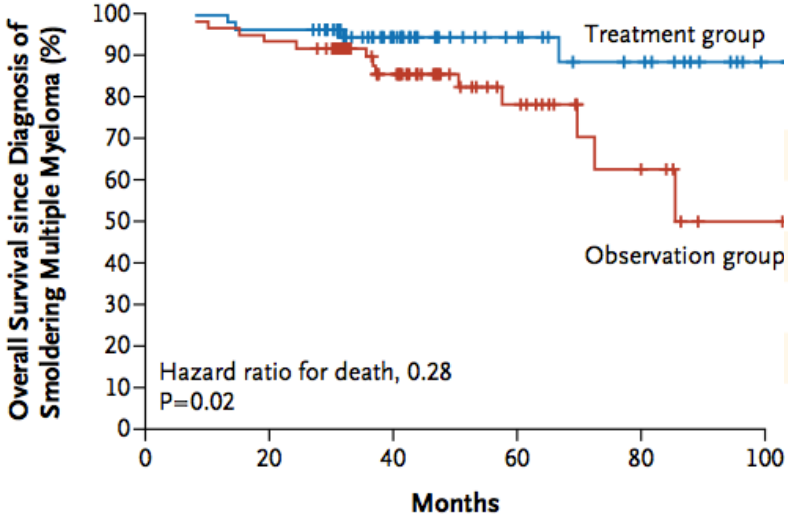
No. at Risk							
Treatment group	57	57	48	38	20	14	0
Observation group	62	49	32	21	11	3	0

B



No. at Risk							
Treatment group	57	57	55	48	26	17	0
Observation group	62	60	57	46	27	17	0

C



No. at Risk						
Treatment group	57	55	35	21	13	2
Observation group	62	58	39	19	7	1

Best Response†	Induction Phase (N=57)	Maintenance Phase (N=50)‡
	no. of patients (%)	
Complete or partial response	45 (79)	45 (90)
Stringent complete response	4 (7)	6 (12)
Complete response	8 (14)	13 (26)
Very good partial response	6 (11)	9 (18)
Partial response	37 (65)	32 (64)
Stable disease	12 (21)	5 (10)

ORR = 79% after induction
90% at maintenance

N Engl J Med 2013;369:438-47

Smoldering Myeloma – to treat or not to treat?

Table 2. Definition of high-risk SMM

Clonal BMPCs ≥10% and any one or more of the following:
Serum M protein ≥30g/L
IgA SMM
Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes
Serum involved/uninvolved FLC ratio ≥8 (but <100)
Progressive increase in M protein level (evolving type of SMM; increase in serum M protein by ≥25% on 2 successive evaluations within a 6-month period)
Clonal BMPCs 50%-60%
Abnormal PC immunophenotype (≥95% of BMPCs are clonal) and reduction of ≥1 uninvolved immunoglobulin isotypes
t(4;14) or del(17p) or 1q gain
Increased circulating PCs
MRI with diffuse abnormalities or 1 focal lesion
PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction

Table 3. Cytogenetically defined risk-based classification of SMM

Risk	Cytogenetic finding
High	t(4;14) del(17p) 1q gain
Intermediate	Trisomies without IgH translocation
Standard	Other IgH translocations including t(11;14), t(14;16), and t(14;20) Presence of trisomies and IgH translocation, except t(4;14) Monosomy13/del(13q)
Low	No abnormalities (normal or insufficient)

Apply the revised IMWG criteria – more patients eligible for therapy

Recommend MRI spine/pelvis or PET scan imaging in addition to skeletal survey – many in the observation arm of SMM progressed with bone disease

Case-by-case consideration to institute early treatment, especially rapidly increasing SPEP/IFE

Clinical trial referral

Observation for low and intermediate risk SMM; select HR-SMM

Rajkumar. Blood 2015

MM Therapeutic Principles

- Response to therapy = control disease
- Improve survival = PFS and OS
- Limit/resolve end organ damage
- Prevent or delay progression

- Considered treatable but incurable

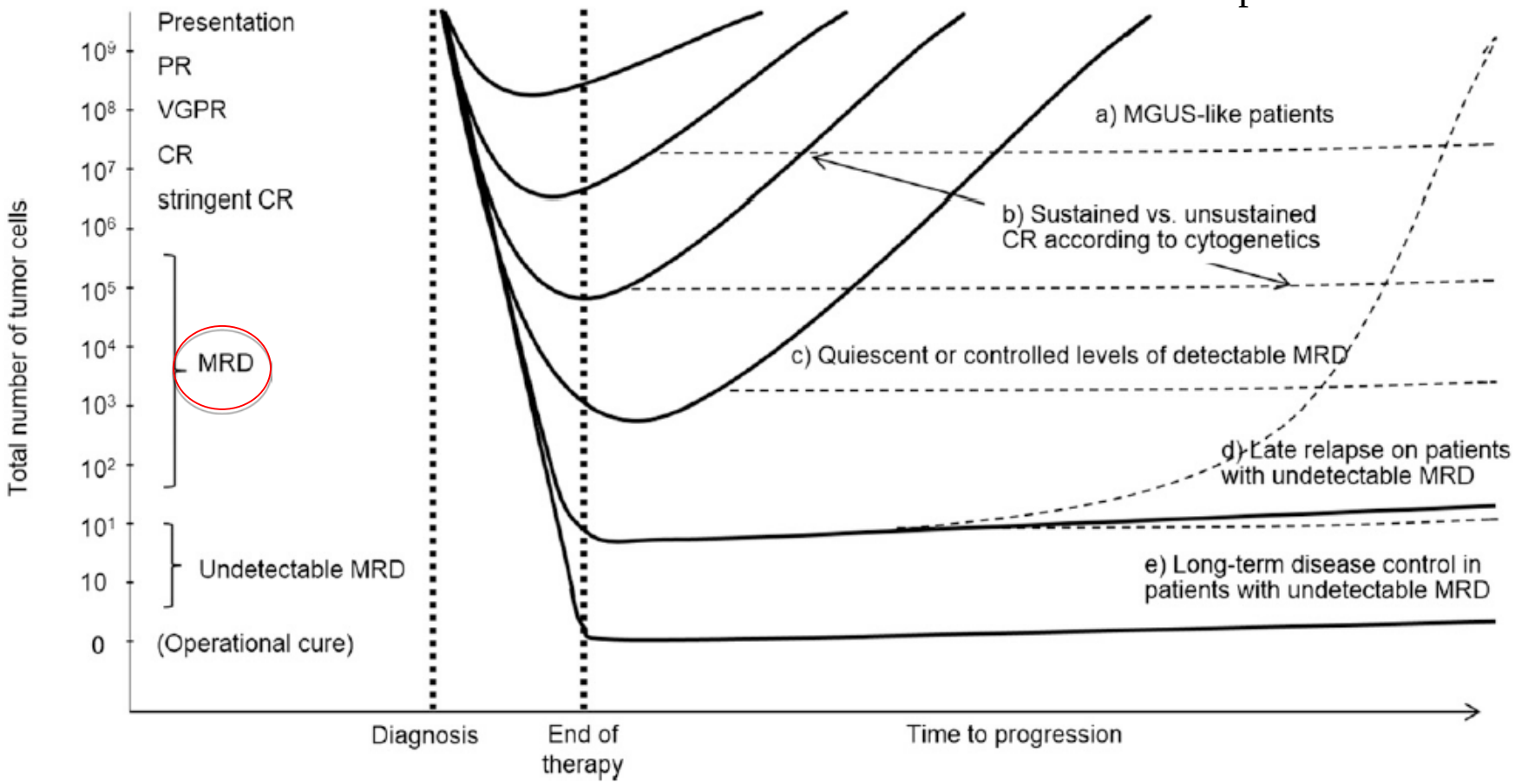
» ... OR IS IT ?

IMWG criteria for response assessment including criteria for minimal residual disease (MRD)	
Response Category	**Response Criteria**
IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	**MRD negativity in the marrow (next-generation flow [NGF], next-generation sequencing [NGS], or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)†**
Flow MRD-negative	**Absence of phenotypically aberrant clonal plasma cells by NGF‡ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher**
Sequencing MRD-negative	**Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using a validated equivalent method with a minimum sensitivity of 1 in 10^5 nucleated cells§ or higher**
Imaging plus MRD-negative	**MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool standardized uptake value (SUV) or decrease to less than that of surrounding normal tissue¶**
Standard IMWG response criteria‖	
Stringent complete response	**Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)†† **
Complete response	**Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates**
Very good partial response	**Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h**
Partial response	**≥50% reduction of serum M-protein plus reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (sum of the products of the maximal perpendicular diameters [SPD] of measured lesions)§§ of soft tissue plasmacytomas is also required**
Minimal response	**≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50%–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in SPD§§ of soft tissue plasmacytomas is also required**

NCCN guidelines ver 3.2017 based on IMWG

Is depth of response important

exceptions…



Paiva. Blood 2015

Is depth of response important

Techniques available

Multi-parametric flow cytometry
Ig allele specific oligonucleotide – PCR
Next generation sequencing
Functional Imaging with PET/CT

So, can myeloma be cured ??

Approx. 30% of patients undergoing HDT will achieve long term DFS (>10 years)

Total Therapy (1, 2, 3)
Majority of CR patients with 10-yr DFS (94%) were also MRD negative

Still a research question as MRD techniques are not widely available

Paiva. Blood 2015
Barlogie. Blood 2014

Considerations before starting therapy

- ? candidate for HDT and auto-HCT
- If yes, its best to avoid alkylator based chemotherapy regimens (esp prolonged Rx)
- Avoid prolonged immunomodulator therapy
- Also its prudent to collect enough stem cells for two autologous stem cell transplants
- **Age and renal functions** are not absolute contraindications for autograft

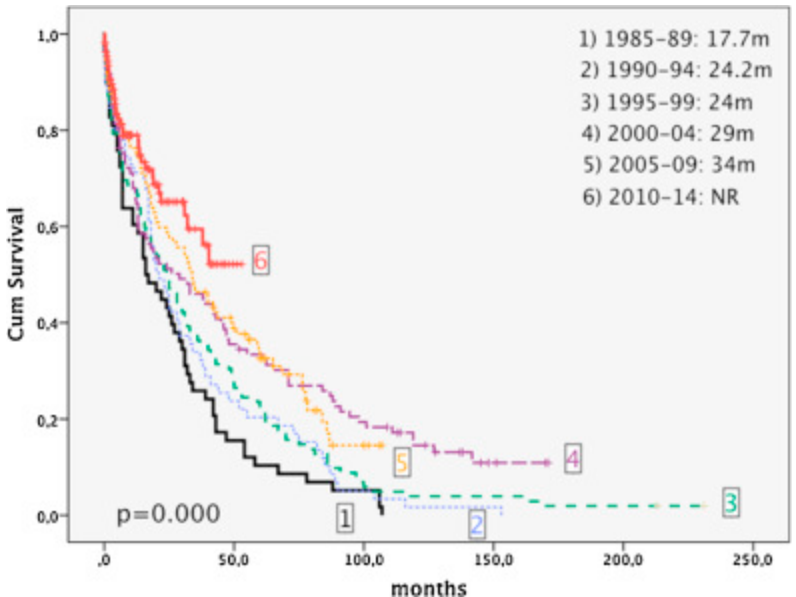
Treating elderly / transplant ineligible patients

- Melphalan and prednisone had been the *standard* chemotherapy in use for over 40 years
- Partial response rate 50-60%
- Complete response rate ~1%
- Median overall survival 3 years
- Until recently combination chemotherapy offered no survival benefit over MP and was more toxic

Alexanian R. JAMA. 1969;208(9):1680-5.
Myeloma Trialists' Collaborative Group. J Clin Oncol. 1998;16:3832.

- Bortezomib approved by FDA in 2003
- Lenalidomide approved by FDA in Dec 2005
- Thalidomide approved by FDA in May 2006

Study arm	Subclass of cohorts	Pre–bortezomib era (1991–2002)			Post– bortezomib era (2004–2011)			Z score	P Value
		N	RS (%)	Relative Standard Error (SE) (%)	N	RS (%)	Relative Standard Error (SE) (%)		
Gender	Male	13,066	34.6	0.5	17,765	46.1	0.6	15.904	<0.0001
	Female	11,580	32.1	0.5	14,917	43.7	0.6	14.765	<0.0001
Race	Caucasian	18,836	32.9	0.4	23,981	45.0	0.5	19.259	<0.0001
	African American	4,274	34.7	0.8	6,391	45.1	0.9	8.488	<0.0001
Age group	20–59	6,358	48.1	0.6	9,439	60.2	0.7	12.920	<0.0001
	>=60	18,288	27.8	0.4	23,243	38.4	0.5	16.606	<0.0001



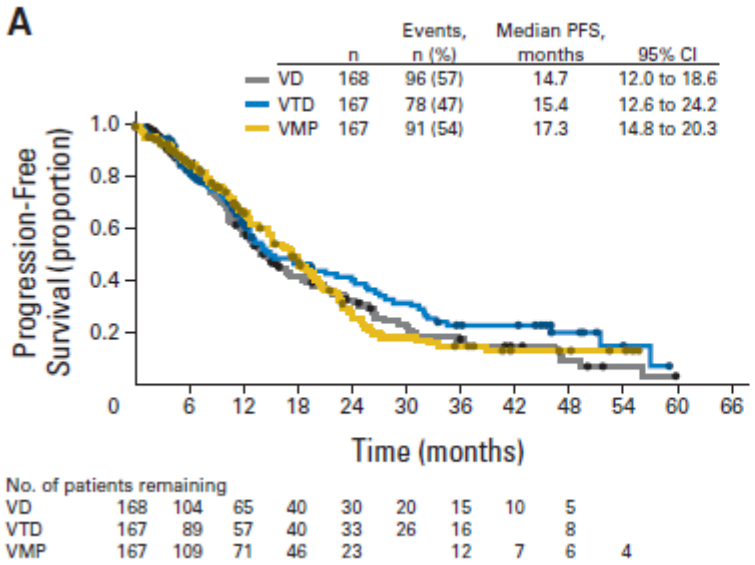
Blood 2014 124:2639
Cancer Epidimol 2015 Oct;39(5):693-9

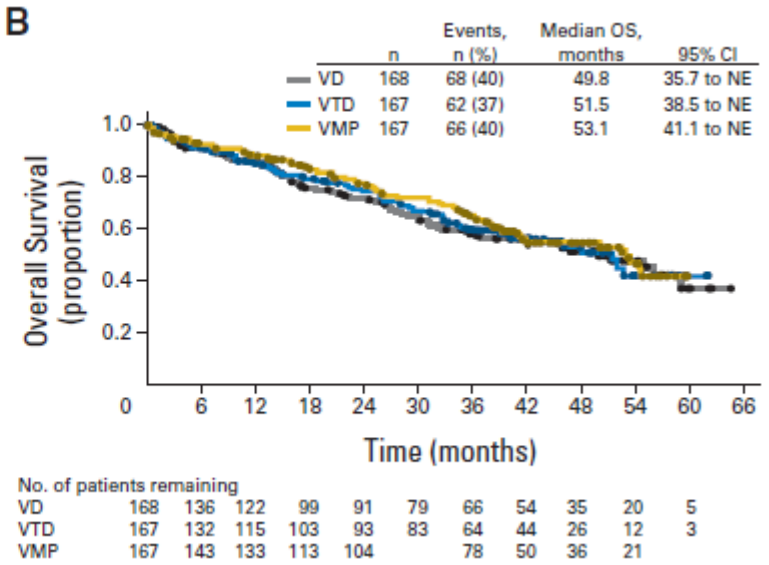
Study	Treatment schema/duration	No. of patients in treatment arm	Median follow-up	Best response	PFS	OS
MPT meta-analysis*[56]	MPT for 8 cycles, 12 cycles, or until relapse	1685 (total no. of patients included)	Not available	VGPR: 25%	20.3 mo	39.3 mo
MPT (FIRST trial)[74]	MPT for 12 cycles	547	37 mo	CR: 9.3%	21.2 mo	4-y OS: 51.4%
CTD[64]	CTD for up to 9 cycles (6 cycles minimum)	426	44 mo	CR: 13.1%	13 mo	33.2 mo
VMP (VISTA trial)[66]	VMP for 9 cycles	344	60.1 mo	CR: 30%	21.7 mo	56.4 mo
MPR-R[73]	MPR for 9 cycles, followed by R until disease progression	152	30 mo	CR: 9.9%	31 mo	4-y OS: 59%
VMPT-VT[67,69]	VMPT for 9 cycles, followed by VT for 2 y or until progression or relapse	254	54 mo	CR: 38%	35.3 mo	5-y OS: 61%
VMP/VTP-VT[68,70]	VMP or VTP for 6 cycles, followed by VT for up to 3 y	91	46 mo	CR: 46%	39 mo	5-y OS: 69%
Rd continuous (FIRST trial)[74]	Rd until disease progression	535	37 mo	CR: 15.1%	25.5 mo	4-y OS: 59.4%
BP[76]	BP until maximum remission or disease progression	68	Not available	CR: 32%	TTF: 14 mo	32 mo

MPT superior to MP – better PFS and OS
CTD superior to MP – UK regimen

VMP (standard dose) superior to MP – PFS and OS (overcame cytogenetics, 13% gr 3 PN)
Once weekly dosing of velcade or subcutaneous dosing of velcade

MPR-R
VMPT-VT
Rd

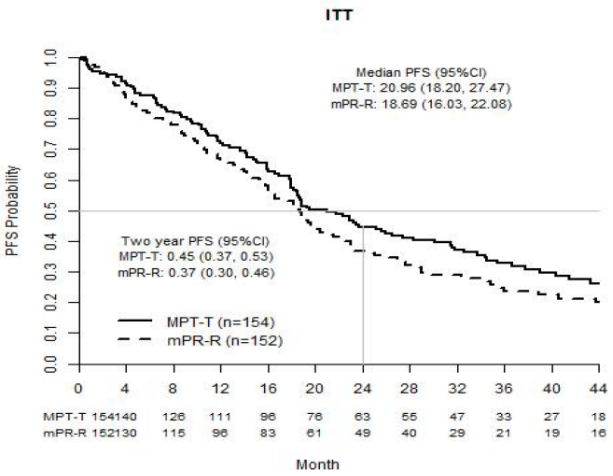




VD (n=168) iv, standard dose
VTD (n=167) ; iv, Thal 100 mg day 1-21
VMP (n=167); + oral MP

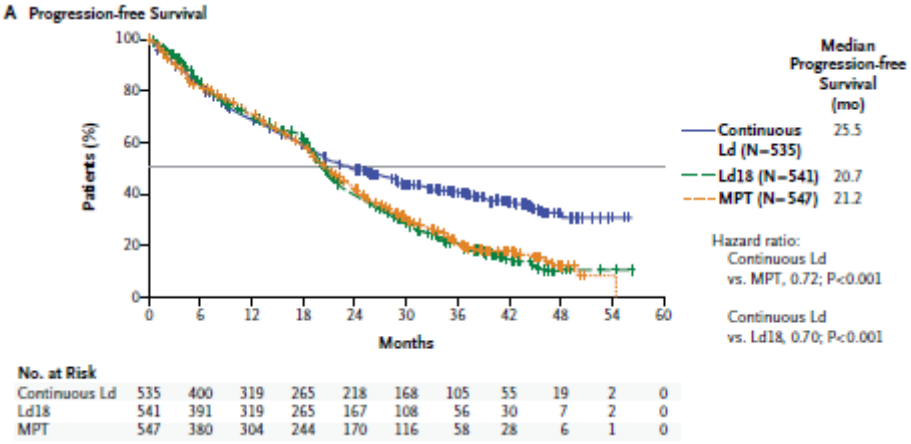
25 weeks of bortezomib maintenance (1.6 mg/m2, weekly)

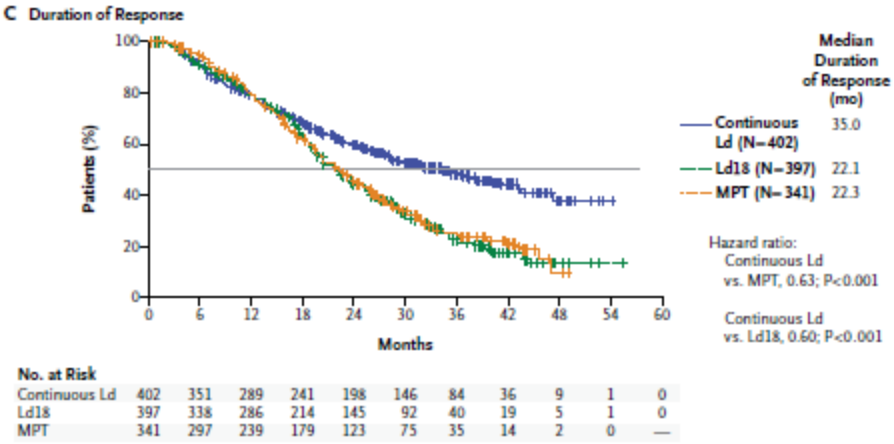
Similarly M (9mg/m2)PT-T = m (5m/m2) PR
mPR-R slightly better tolerated

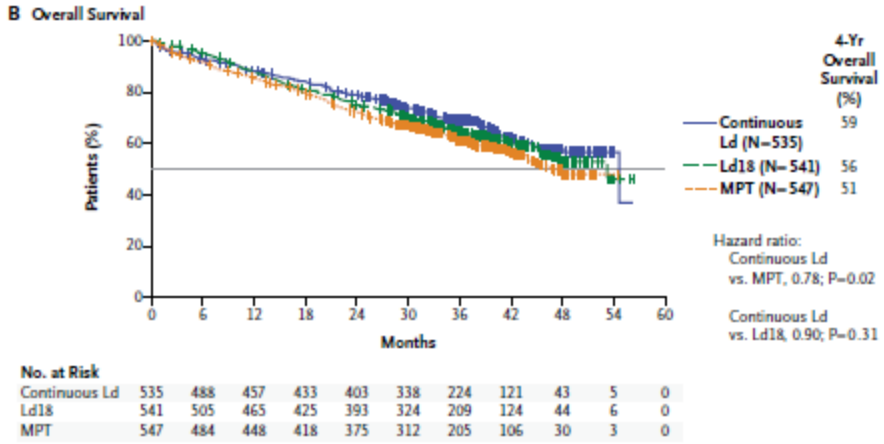


Niesvizky. JCO 2015
Raikumar Blood 2015

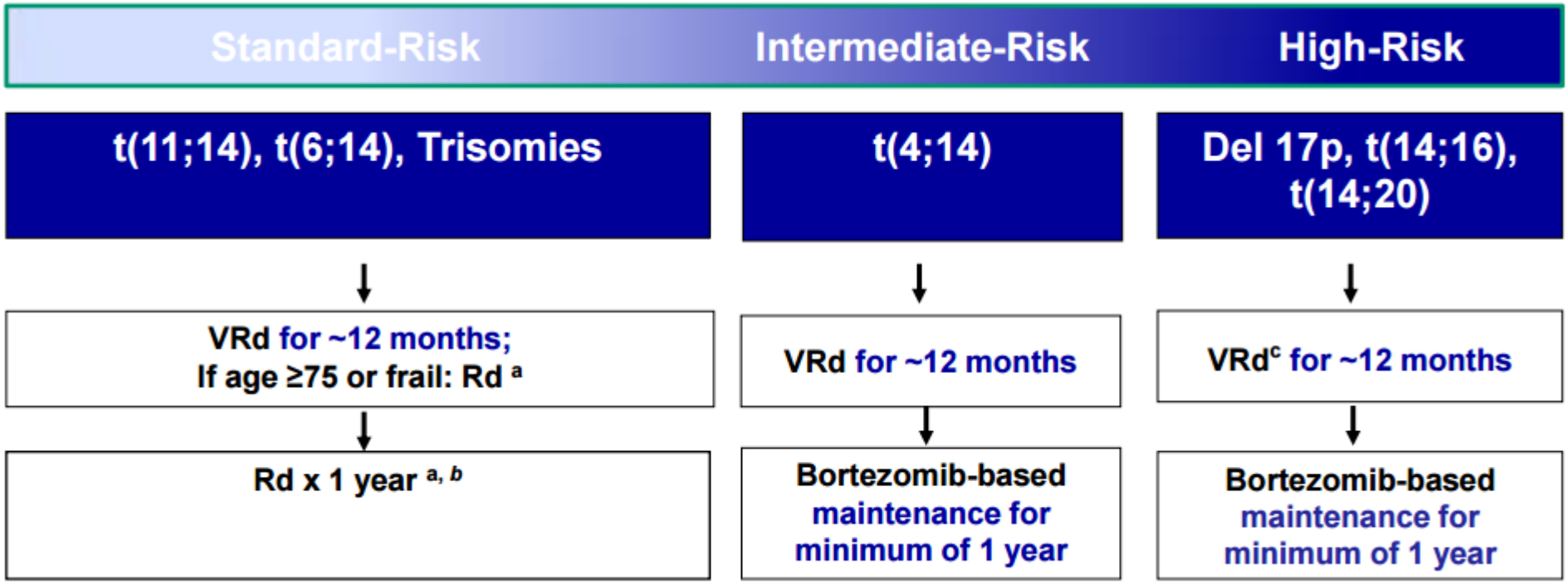
MPT vs. Rd(18) vs. Rd continuous







Rd continuous was superior
Secondary malignancy more in MPT



VMP and VTD are commonly used regimens

Subcutaneous velcade / weekly infusions of velcade

Rd is a good option as well

Continuous therapy or maintenance strategy useful to improved outcomes – stop alkylator and dexamethasone after 1 year

Depth of initial response correlates well with outcome – so should be the goal

Transplant Eligible Patients

Induction → High dose melphalan / auto-transplant → ? Consolidation → Maintenance

Induction regimen

Single or tandem (double) transplant

Early or late transplantation

Role of consolidation

Maintenance therapy

Obsolete induction regimens

- Vincristine; doxorubicin; dexamethasone (VAD)
- Vincristine; idarubicin; dexamethasone (VID)
- Dexamethasone
- Doxil; vincristine; dexamethasone (DVD)
- Thalidomide; dexamethasone (Thal/dex)

Thalidomide vs. Lenalidomide Induction

	Thal/Dex (n=183)	Rev/Dex (n=228)
CR (%)	3.3	13.6*
≥ PR (%)	61	80*
PFS (median)	17.1 m	26.7 m*
OS (median)	57 m	NR*
Grade 3-4 Neutropenia	0.6%	15%*
Grade 3-4 VTE	15%	9%
Grade 3-4 Peripheral neuropathy	10%	0.9%*

Gay F. Blood. 2010; 115: 1343 - 1350.

Lenalidomide induction - E4A03

- Symptomatic
- Untreated
- Non-inferiority trial

(N=445 patients)

→ RANDOMIZATION

RD = Lenalidomide 25 mg D1-21; dexamethasone 40 mg D1-4, 9-12, and 17-20, q 4wks

Rd = Lenalidomide plus; dexamethasone 40 mg D1, 8, 15, and 22, q 4wks

	RD	Rd
≥ VGPR (%)	50*	40
≥ PR (%)	79*	68
OS (1-yr)	87%	96%*

- Grade 3-4 DVT (26% vs.12%) and infections (16% vs. 9%) were higher with RD.
-3-year OS was 55% for patients not pursuing HCT and 92% in patients who underwent transplantation.
- OS superior in patients 65yrs or older too.

Rajkumar SV. Lancet Oncol. 2010;11:29-37.

Bortezomib induction – IFM 2005-01

- Symptomatic
- Untreated
- Non-inferiority trial

(N=445 patients)

→ RANDOMIZATION

→ VAD ± DCEP; followed by single or tandem HDT-HCT

→ VD ± DCEP; followed by single or tandem HDT-HCT

	VAD	VD
CR (%)	6.4	14.8*
≥ VGPR (%)	15.1	37.7*
pHCT-CR (%)	18.4	35%
pHCT-VGPR (%)	37	54%
PFS (median)	29.7 m	36 m´
OS (3-yr)	77%	81%

- Response < VGPR after induction negatively effect PFS
- Compared to VAD, VD improved PFS of patients with poor-risk cytogenetics, and ISS stage II/III

Harousseau JL. J Clin Oncol. 2010;28(30):4621-9.
Moreau P. Blood. 2011;117(11):3041-4.

TD vs. VTD – GIMEMA Trial

- Symptomatic
- Untreated
- Age 18-65yrs

(N=480 patients)

→ RANDOMIZATION

TD = T 100 mg/d for the 1st 14 days then 200 mg/d; dexamethasone 40mg D1–4 and 9–12, q 3wks followed by tandem auto and TD consolidation

VTD = Standard VD; plus T as above q3wks followed by tandem auto and VTD consolidation

	TD induction	VTD induction
CR (%)	6	22*
≥ VGPR (%)	31	62*
pAuto-CR (%)	40	49
pAuto-VGPR (%)	73	82*
PFS (3-yr)	56%	68%*
OS (3-yr)	84%	86%
	TD Consolid.	VTD Consolid.
CR (%)	47	61*
PFS (3-yr)	48%	60%*
OS (3-yr)	88%	90%

- Grade 3-4 PN with VTD 10%
- VTD improved outcomes of high-risk patients

Cavo M. Lancet. 2010;376(9758):2075-85.
Cavo M. Blood. 2012;120:9-19

So how do you treat (induction) your newly diagnosed symptomatic myeloma patient?

Velcade or lenalidomide based regimens
Triplet vs. doublet
Dexamethasone dose

Primary Therapy for Transplant Candidates (assess for response after 2 cycles)	
Preferred Regimens:	**Other Regimens:**
• Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/doxorubicin/dexamethasone (category 1) • Bortezomib/lenalidomide[5]/dexamethasone (category 1)	• Bortezomib/dexamethasone (category 1)[6] • Bortezomib/thalidomide/dexamethasone (category 1) • Carfilzomib[9,10]/lenalidomide[5]/dexamethasone • Ixazomib/lenalidomide[5]/dexamethasone • Lenalidomide[5]/dexamethasone (category 1)[6]
Primary Therapy for Non-Transplant Candidates (assess for response after 2 cycles)	
Preferred Regimens	**Other Regimens**
• Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/lenalidomide/dexamethasone (category 1) • Lenalidomide/low-dose dexamethasone (category 1)[6,7]	• Bortezomib/dexamethasone[6] • Carfilzomib[10]/lenalidomide/dexamethasone (category 2B) • Ixazomib/lenalidomide/dexamethasone
Maintenance Therapy	
• Bortezomib • Lenalidomide[8] (category 1)	

Velcade based triplets improve response rates, depth of response compared to doublets and are preferred

Phase I/II **VRD** – PR 100%; VGPR 74% and nCR/CR 54%

Phase II comparison **VD+Revlimid** = **VD+Cytoxan** (EVOLUTION study) and no additional benefit with VDCR

Meta-analysis of VDC vs. **VTD** showed CR 6% vs 34% and VGPR 27% vs 62% (Br J Hem'14)

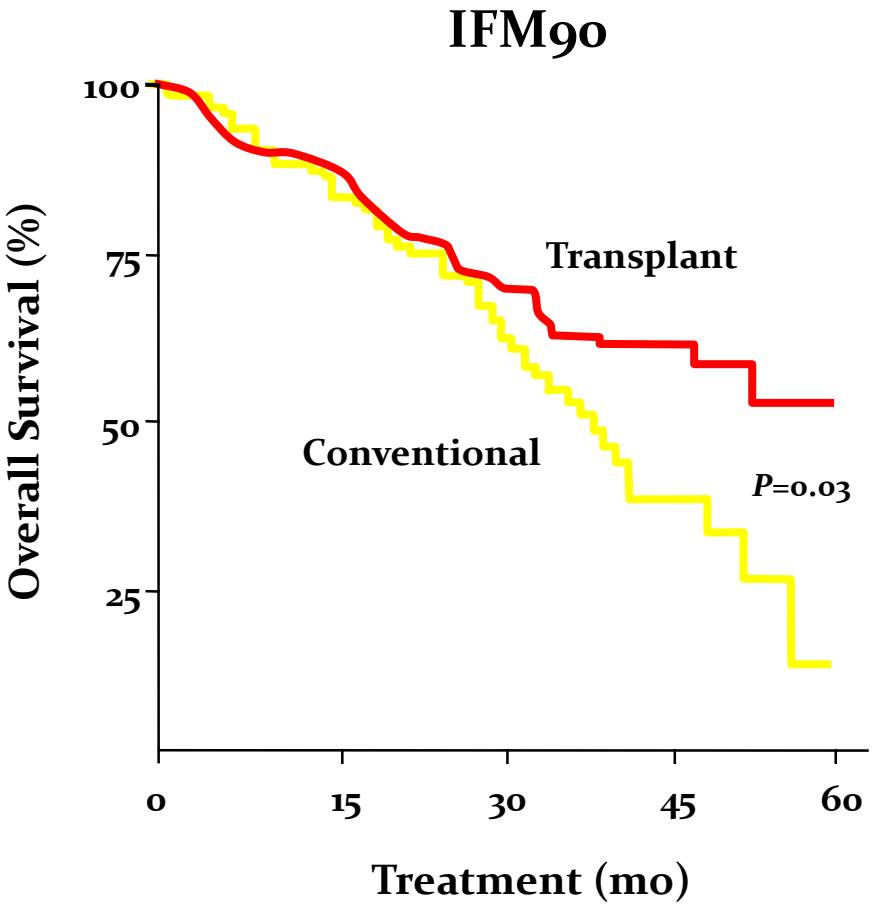
SWOG S077 – VRD vs RD – VRD improved OS, PFS and response rates

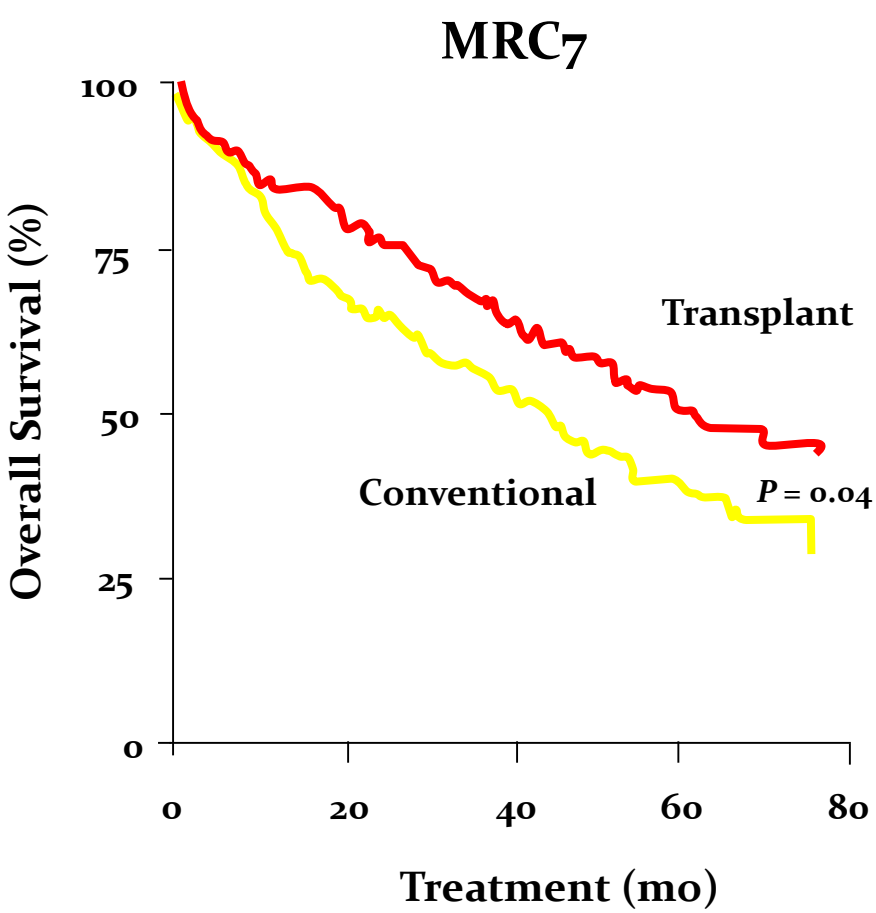
HOVON-65 – VAD (old) -> T vs. PAD -> velcade maintenance – better PFS and OS in velcade arm (especially pertinent in the high risk cytogenetics

CyBorD – 61% VGPR and 39% nCR/CR rated

Moreau Blood 2015
Kumar Blood 2012

Role of Autologous Transplantation

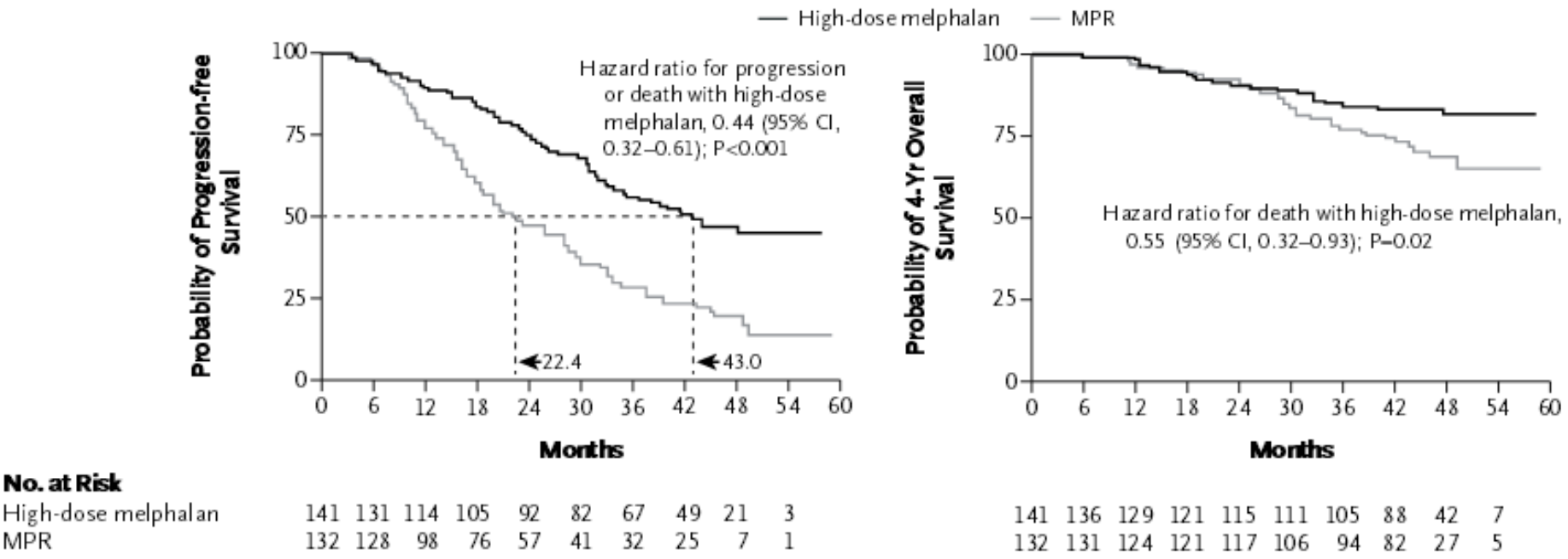




Palumbo et al MPR induction followed by MPR consolidation vs. HDM/auto-HCT
Superior OS and PFS in the transplant arm

Attal M . NEJM. 1996;335:91-7.
Child JA NEJM. 2003;348:1875-83.
Palumbo NEJM 2014

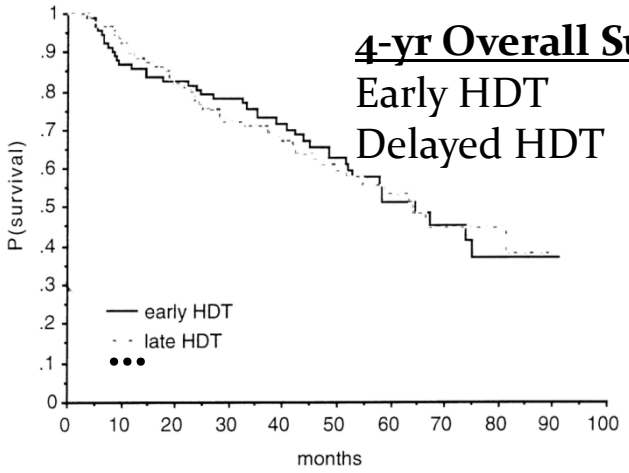
Role of Auto with newer agents



HDT/auto vs. VMP intensification (vel/mel/pred) after CyBorD in myeloma - better PFS and CR rates with auto suggesting upfront auto is still beneficial in fit myeloma patients (n=1510). https://ash.confex.com/ash/2016/webprogram/Paper91284.html

Palumbo, N Engl J Med 2014; 371:895-905

Early vs. delayed Transplantation



4-yr Overall Survival

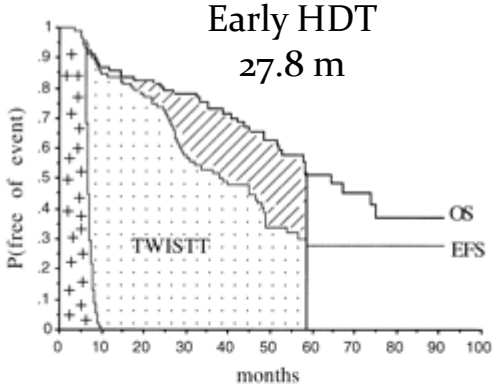
Early HDT 66%

Delayed HDT 61%

TWiSTT Analysis

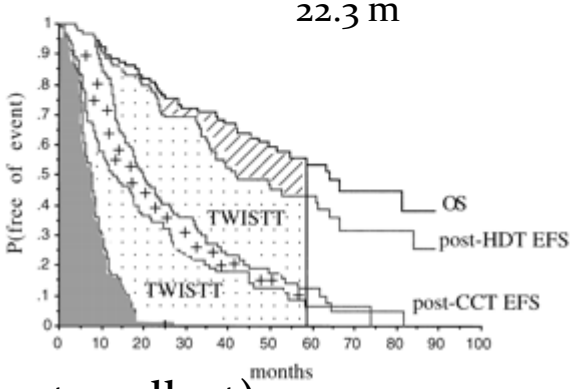
Early HDT

27.8 m



Late HDT

22.3 m

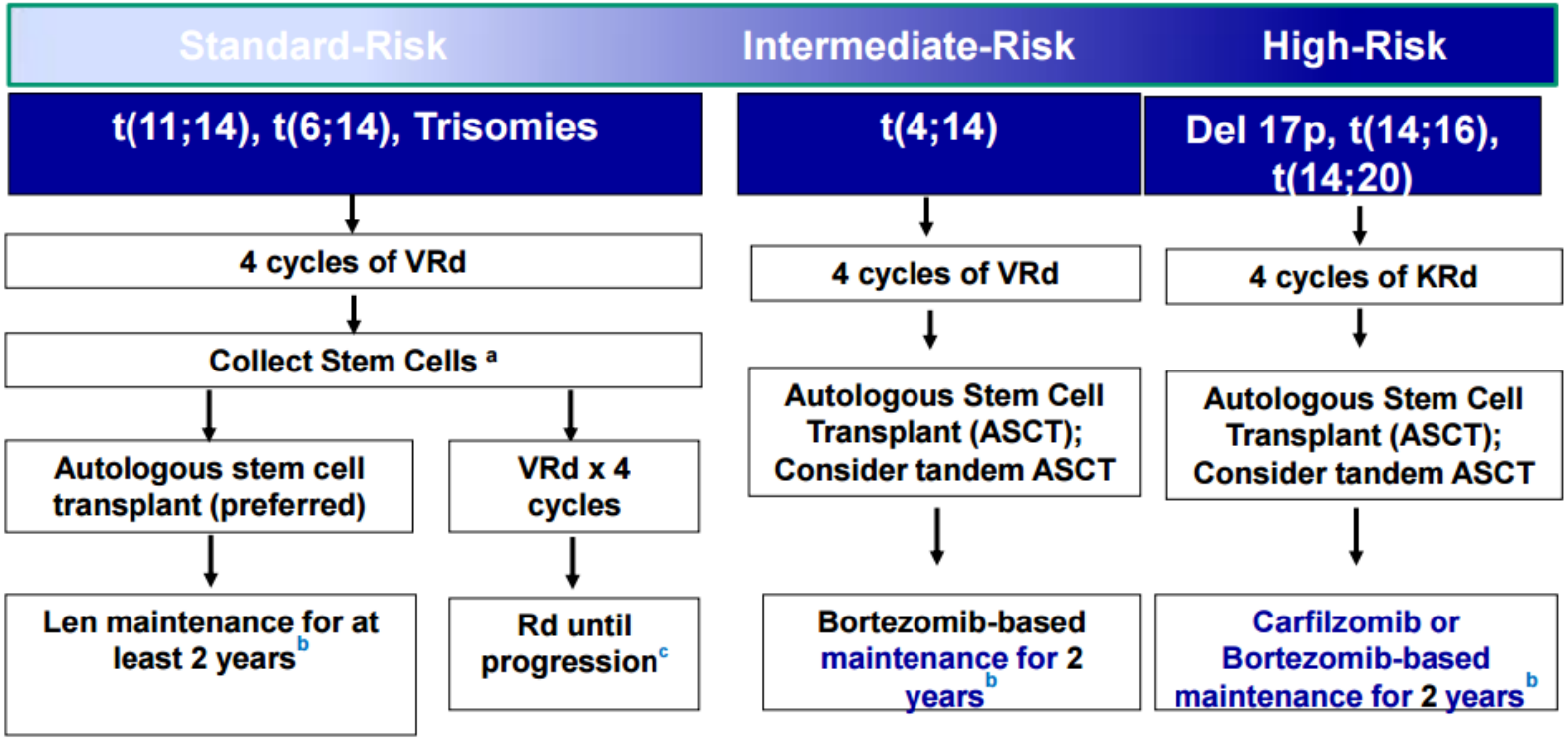


Time without symptoms, treatment, and treatment toxicity (TWiSTT) – QoL metric

In the era of novel agents:

- Retrospective studies x 2
- Early vs late auto-HCT had similar OS and PFS
- Delayed auto can be considered in standard risk (remember to collect)
- Ongoing phase III study is evaluating the question (DFCI 10-106)
- NCCN recommends early HCT based on Fermand data

Fermand JP. Blood. 1998;92(9):3131-6.



Induction: 3-drug regimens
VTD
VCD
RVD
PAD

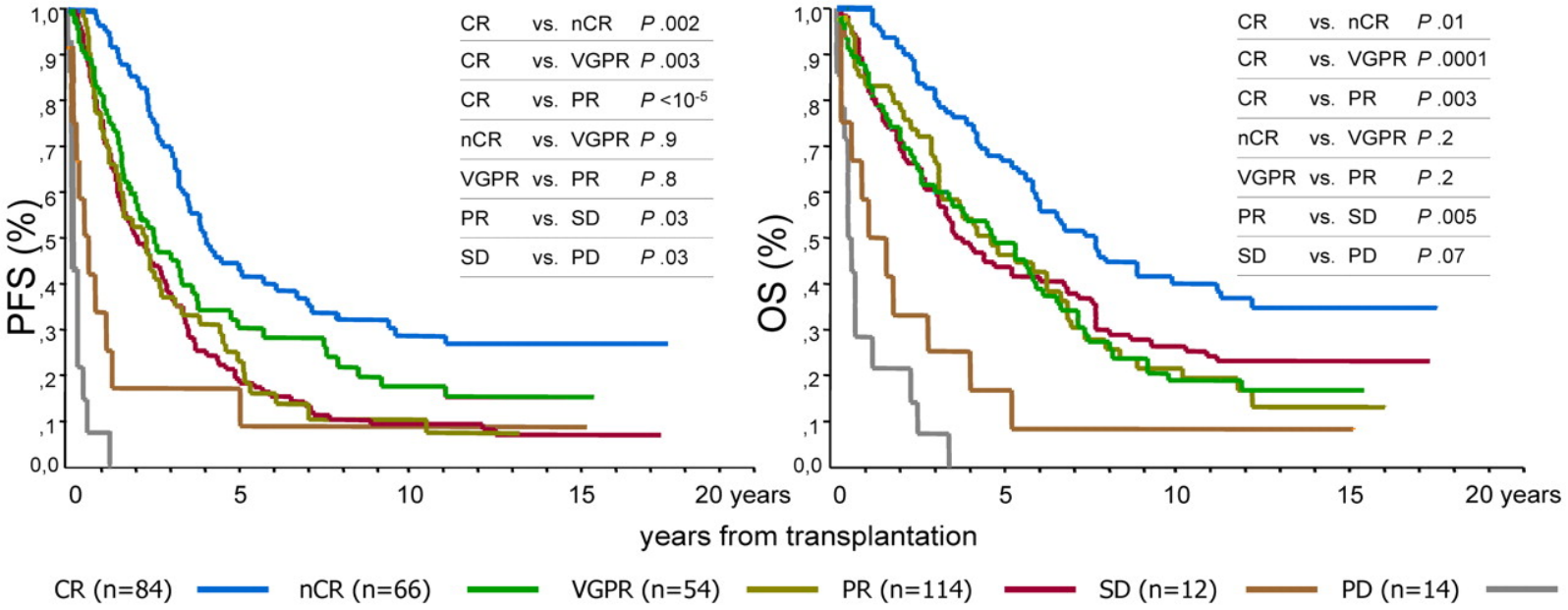
200 mg/m2 Melphalan followed by ASCT

Short-term consolidation*
VTD
RVD

Maintenance*
Lenalidomide
Bortezomib

msmart.org
Moreau Blood 2015

Is Autologous transplant curative?



12-yr PFS according to response to autologous transplant

CR	28%
nCR	19%
VGPR	10%
PR	11%
SD	8%
PD	0%

Martinez-Lopez J. Blood. 2011;118:529-534 .

Tandem Auto

Table 2. Randomized studies comparing single vs tandem ASCT

Study	First ASCT	Consolidation s/p first ASCT	Maintenance	EFS	OS	Salvage ASCT at relapse
IFM94[54]	MEL140 + TBI (single arm) MEL140 (tandem arm)	None vs MEL140 + TBI	Interferon α	Median EFS: 25 (single) vs 30 (tandem) mo (P = .03)	Median OS: 48 (single) vs 58 (tandem) mo (P = .01)	22% (single arm) vs 26% (tandem arm)
Bologna 76[55]	MEL200	None vs MEL120 + busulfan	Interferon α	Median EFS: 23 (single) vs 25 (tandem) mo (P = .001)	7-y OS: 46% (single) vs 43% (tandem) (P = .9)	33% (single arm) vs 10% (tandem arm)
GMMG-HD2[13]	MEL200	None vs second ASCT with MEL200	Interferon α	Median EFS: 25 (single) vs 28.7 (tandem) mo (P = .53)	Median OS: 73 (single) vs 75.3 (tandem) mo (P = .33)	26% (single arm) vs 24% (tandem arm)
BMT CTN 0702 (NCT01109004)	MEL200	None vs RVD ×4 vs second ASCT with MEL200	Len until progression for all arms	Not yet reported	Not yet reported	Not yet reported

s/p, status-post; TBI, total body irradiation.

BMTCTN 0702 – StaMINA https://ash.confex.com/ash/2016/webprogram/Paper98809.html

Tandem auto-HCT and post-auto VRd consolidation – similar PFS and OS compared to single auto-HCT

Unclear subsets of patients – those not achieving VGPR with 1st auto or HR-FISH will benefit from tandem auto.

Post-auto consolidation

Table 3. Randomized studies involving consolidation therapy post-ASCT

Reference	Consolidation regimen	Response rates (pre- and post-) %	PFS	OS
23, 56	VTD vs TD	nCR/CR rates VTD: 63→73 TD: 55→61	3-y PFS: 60% (VTD) vs 48% (TD) (P = .042)	3-y OS: 90% (VTD) vs 88% (TD) (P = .39)
24	V vs none	nCR/CR rates V: 20→45 None: 21→35	Median PFS: 27 (V) vs 20 (none) mo (P = .05)	Median OS not reached for either arm (P = .4)
25	V vs none	≥VGPR rates V: 55→62 None: 59→48	Median PFS: 33.6 (V) vs 27.8 (none) mo (P = .0058)	Median OS not reached for either arm (P = .75)

V, bortezomib; VGPR, very-good-partial response.

Intent of consolidation is to improve MRD status (depth of response)
Consolidation improves response but no OS benefit seen

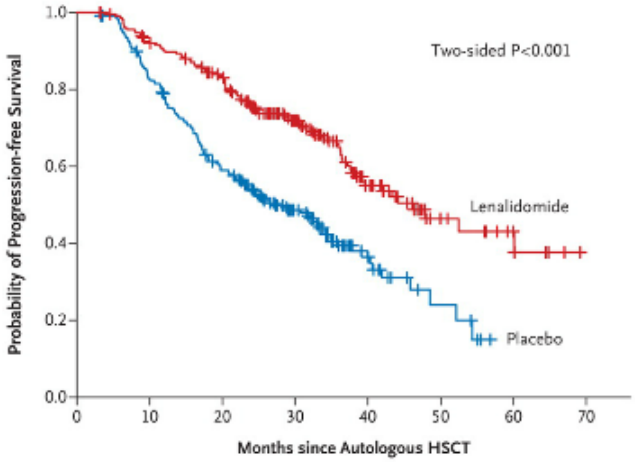
BMTCTN 0702 – StaMINA https://ash.confex.com/ash/2016/webprogram/Paper98809.html
- No PFS or OS benefit

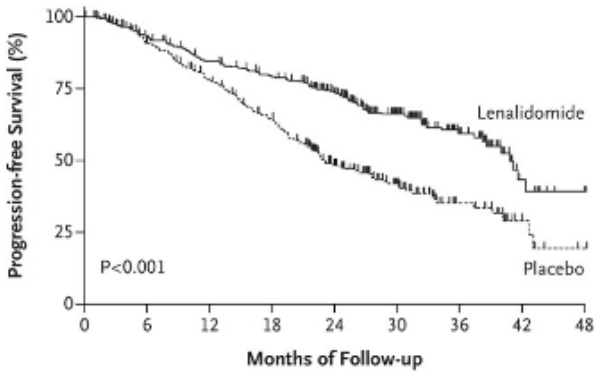
Improving nCR/CR rates in the placebo arm maybe due to long half life if Ig

Maintenance Therapy

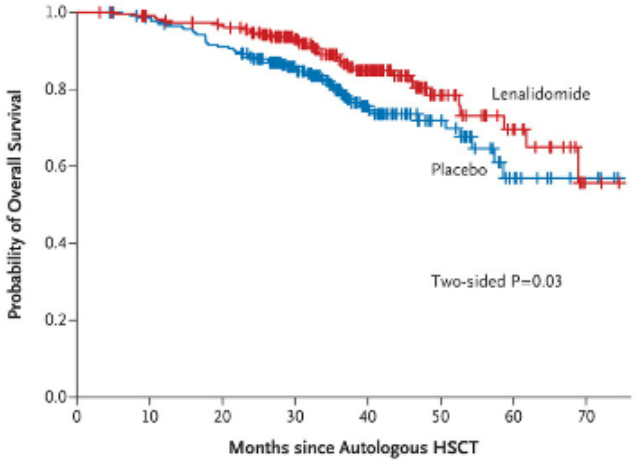
- Interferon and prednisone no longer appropriate
- Thalidomide maintenance after tandem autografting has shown survival benefit (IFM 99-02)
- Thalidomide maintenance after single autograft has PFS but no OS benefit
- Thalidomide maintenance not appropriate in patients with high-risk cytogenetics

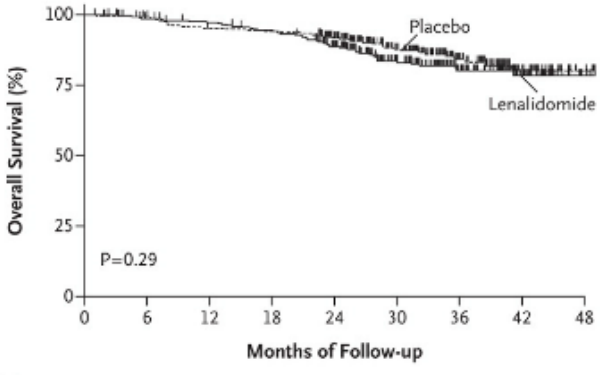
Lenalidomide Maintenance





No. at Risk									
Lenalidomide	307	267	236	216	172	103	49	10	1
Placebo	307	255	211	169	102	57	22	6	1





No. at Risk									
Lenalidomide	307	298	292	282	240	162	92	38	5
Placebo	307	297	282	279	247	167	87	31	6

McCarthy P. NEJM 2012; 366:1770-1781.
Attal M. NEJM 2012; 366:1782-1791.

Bortezomib Maintenance – HOVON-65/ GMMG-HD4 Trial

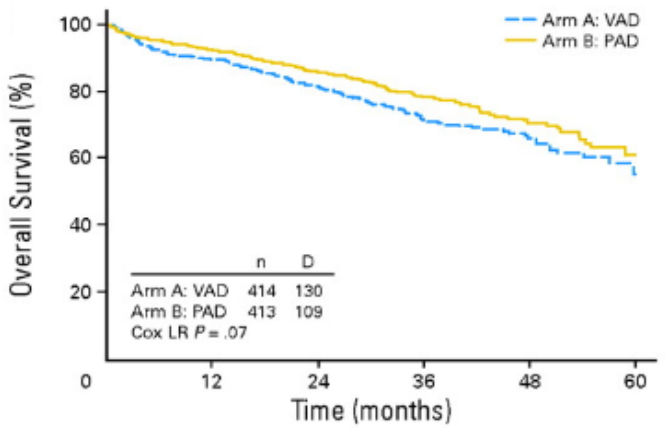
- Symptomatic
- Untreated

(N=827 patients)

→ RANDOMIZATION

→ VAD followed by single or tandem auto → Thalidomide maintenance

→ PAD followed by single or tandem auto → Velcade maintenance q2wks for 2 years



- CR + nCR, was superior after PAD induction (15% v 31%; P < .001) and bortezomib maintenance (34% v 49%; P < .001)
- 40% grade II-IV PNP with velcade

Sonneveld P. J Clin Oncol. 2012;30(24):2946-55.

A Practical Approach

- All transplant eligible patients receive 4-6 cycles of induction with intent to transplant
- Induction options include VRd, PAD, CyBorD and KRd, VD, Rd
- Refractory disease not contraindication for transplant
- Consider Maintenance therapy – consider velcade in high risk disease

Therapy for Previously Treated Multiple Myeloma	
Preferred Regimens:	**Other Regimens:**
• Repeat primary induction therapy (if relapse at >6 mo) • Bortezomib/dexamethasone (category 1)[6] • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Carfilzomib[10]/dexamethasone (category 1)[6,] • Carfilzomib[10]/lenalidomide/dexamethasone (category 1)[12] • Daratumumab[13,14] • Daratumumab[14]/bortezomib/dexamethasone (category 1) • Daratumumab[14]/lenalidomide/dexamethasone (category 1) • Elotuzumab[15]/lenalidomide/dexamethasone (category 1)[12] • Ixazomib[16]/lenalidomide/dexamethasone (category 1)[12] • Lenalidomide/dexamethasone[17] (category 1)[6] • Pomalidomide[18]/dexamethasone[17] (category 1)[6] • Pomalidomide[18]/bortezomib/dexamethasone • Pomalidomide[18]/carfilzomib[10]/dexamethasone	• Bendamustine • Bendamustine/bortezomib/dexamethasone • Bendamustine/lenalidomide/dexamethasone • Bortezomib/liposomal doxorubicin (category 1)[6] • Cyclophosphamide/lenalidomide/dexamethasone • Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)[19] • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE)[19] • Elotuzumab/bortezomib/dexamethasone • High-dose cyclophosphamide • Ixazomib[16]/dexamethasone[6] • Panobinostat[20]/bortezomib/dexamethasone (category 1) • Panobinostat[20]/carfilzomib[6,10] • Pomalidomide[18]/cyclophosphamide/dexamethasone

Table 2. Selected phase 3 trials in relapsed disease

Reference	Name of trial	No. prior lines	Arm	N	PFS*	HR	ORR	≥VGPR	≥CR
Dimopoulos et al[27]	ENDEAVOR	1-3	Kd	464	18.7	0.53	77%	54%	13%
			Vd	465	9.4		63%	29%	6%
Moreau et al[29]	TOURMALINE-MM1	1-3	IRd	360	20.6	0.74	78%	48%	12%
			Rd	362	14.7		72%	39%	7%
Lonial et al[42]	ELOQUENT-2	1-3	Elo-Rd	321	19.4	0.7	79%	33%	4%
			Rd	325	14.9		66%	28%	7%
Stewart et al[28]	ASPIRE	1-3	KRd	396	26.3	0.69	87%	70%	32%
			Rd	396	17.6		67%	40%	9%
San Miguel et al[36]	PANORAMA 1	1-3	Pano-Vd	387	11.99	0.63	61%		11%
			Vd	381	8.08		55%		6%
San Miguel et al[30]	NIMBUS (MM-003)	≥2†	Pd	302	4.0	0.48	31%	6%	1%
			D	153	1.9		10%	1%	0%
Palumbo et al[48]	CASTOR	≥1	Vd-dara	251	NE	0.39	82.9%	59.2%	19.2%
			Vd	247	7.2		63.2%	29.1%	9%
Dimopoulos et al[49]	POLLUX	≥1	Rd-dara	286	NE	0.37	93%	76%	43%
			Rd	283	18.4		76%	44%	19%

Thank you

QUESTIONS?

MP vs. MPT – Upfront Phase III Trials

	Arms	N	≥ PR (%)	CR (%)	PFS	OS	Dosing
Facon T (IFM 99-06) Lancet; 2007	MP MPT Mel100	196 125 126	35 76* 65	2 13 18*	18.7 m 27.5 m* 19.4 m	33.2 m 51.6 m* 38.3 m	M=0.25mg/kg; P=2mg/kg D1-4 ; T=400mg/d (max) repeated Q 6 weeks x 12
Hulin C (IFM 01/01) JCO; 2009	MP MPT	116 113	31 62*	1 7*	18 m 24 m*	29 m 44 m*	M=0.2mg/kg; P=2mg/kg D1-4 ; T=100mg/d (max) repeated Q 6 weeks x 12
Palumbo A (GIMEMA) Lancet 2006 & Blood; 2008	MP MPT	164 167	48 69*	4 16*	14.5 21.8*	47.6 m 45 m	M=4mg/m^2; P=40mg/m^2 D1-7; T=100mg/d repeated Q 4 weeks x 6; then maintenance T
Wijermans P (HOVON 49) JCO; 2010	MP MPT	168 165	45 66*	NR NR	14 % 2yr 34% 2yr*	30 % 4yr 43% 4yr*	M=0.25mg/kg; P=1mg/kg D1-5 ; T=200mg/d repeated Q 4 weeks
Waage A (Nordic Group) Blood; 2010	MP MPT	175 182	40 57*	7 23*	14 m 15 m	32 m 29 m	M=0.25mg/kg; P=100mg D1-4 ; T=200-400mg/d repeated Q 6 weeks