Multiple Myeloma

8th Annual Living with Myeloma Conference
New Developments in Multiple Myeloma Treatment
Scottsdale, AZ
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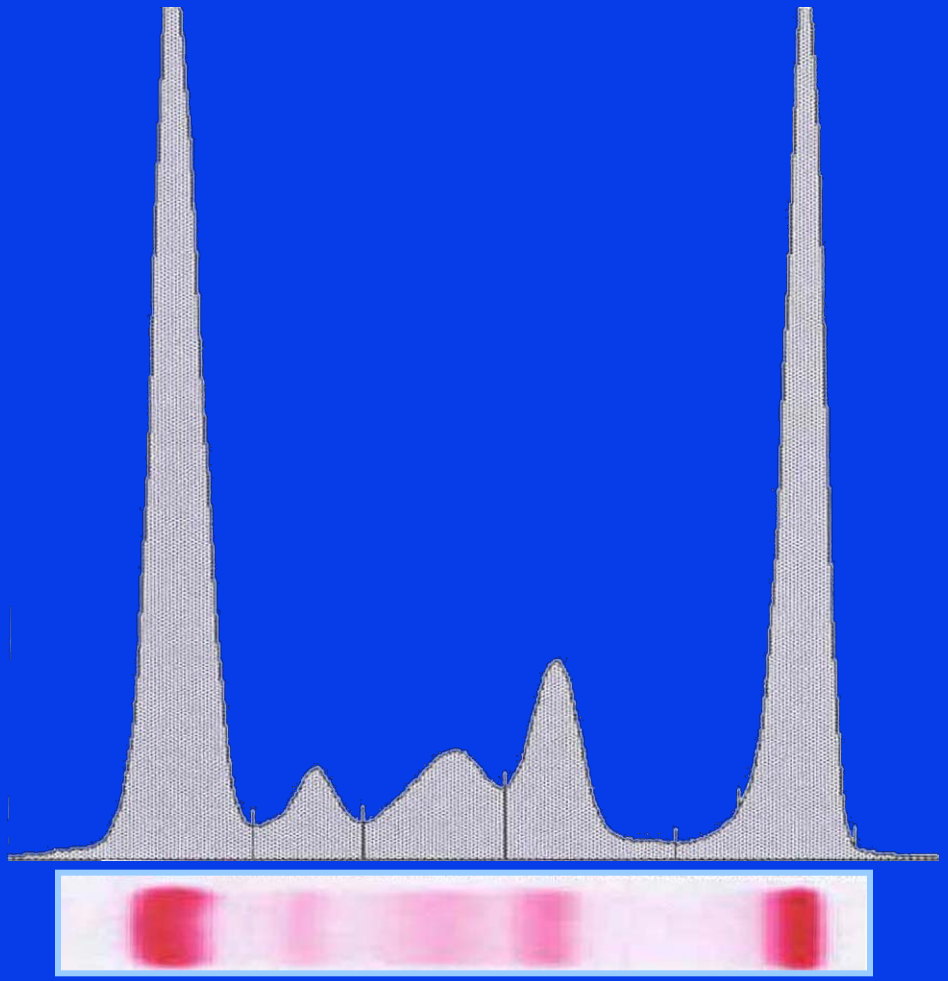
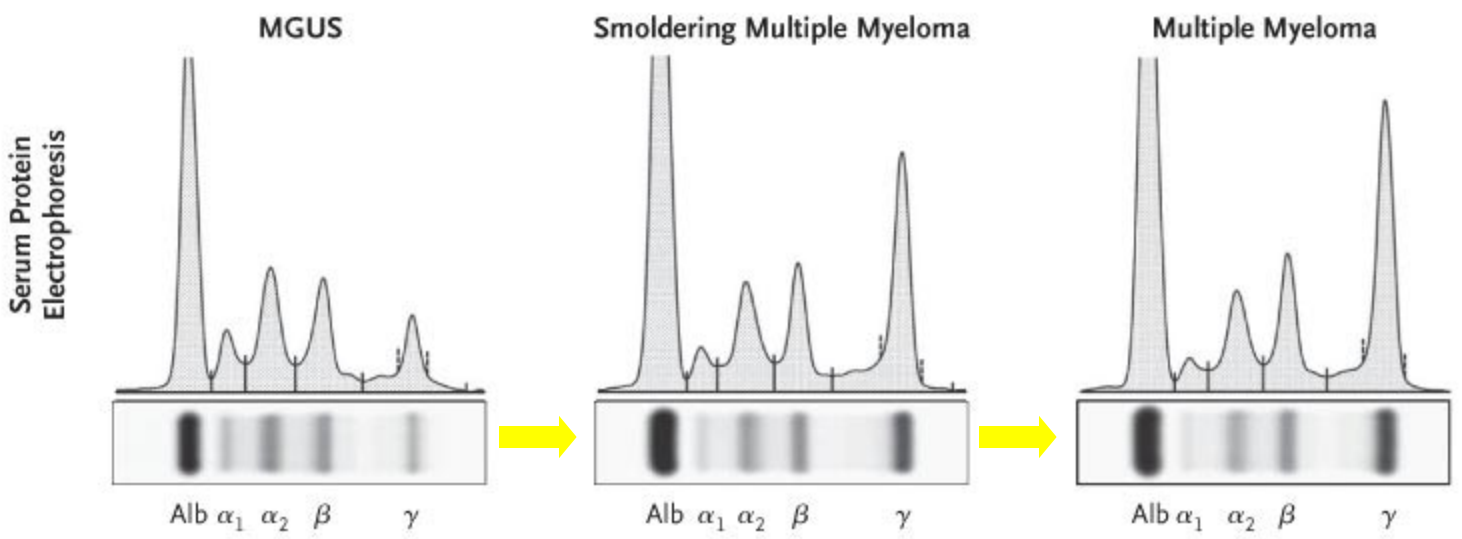
Disclosures for Robert A. Kyle

Johnson & Johnson	Disease Monitoring Committee
Celgene	Disease Monitoring Committees
Novartis	Disease Monitoring Boards
Merck	Data Monitoring Committee
Bristol-Myers Squibb	Independent Monitoring Committee
Aeterna Zentaris (Keryx)	Data & Safety Monitoring Board
Onyx	Data Monitoring Committee
Binding Site	Honoraria

Serum Protein Electrophoresis



Natural History



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

Kyle et al, NEJM, Volume 356:2582-2590, June 21, 2007

Multiple Myeloma
Criteria for Diagnosis

- M-protein in serum and/or urine
- Bone marrow clonal plasma cells or plasmacytoma
- End-organ damage: CRAB (hypercalcemia, renal insufficiency, anemia, bone lesions)

Brit J Haem 121:749, 2003

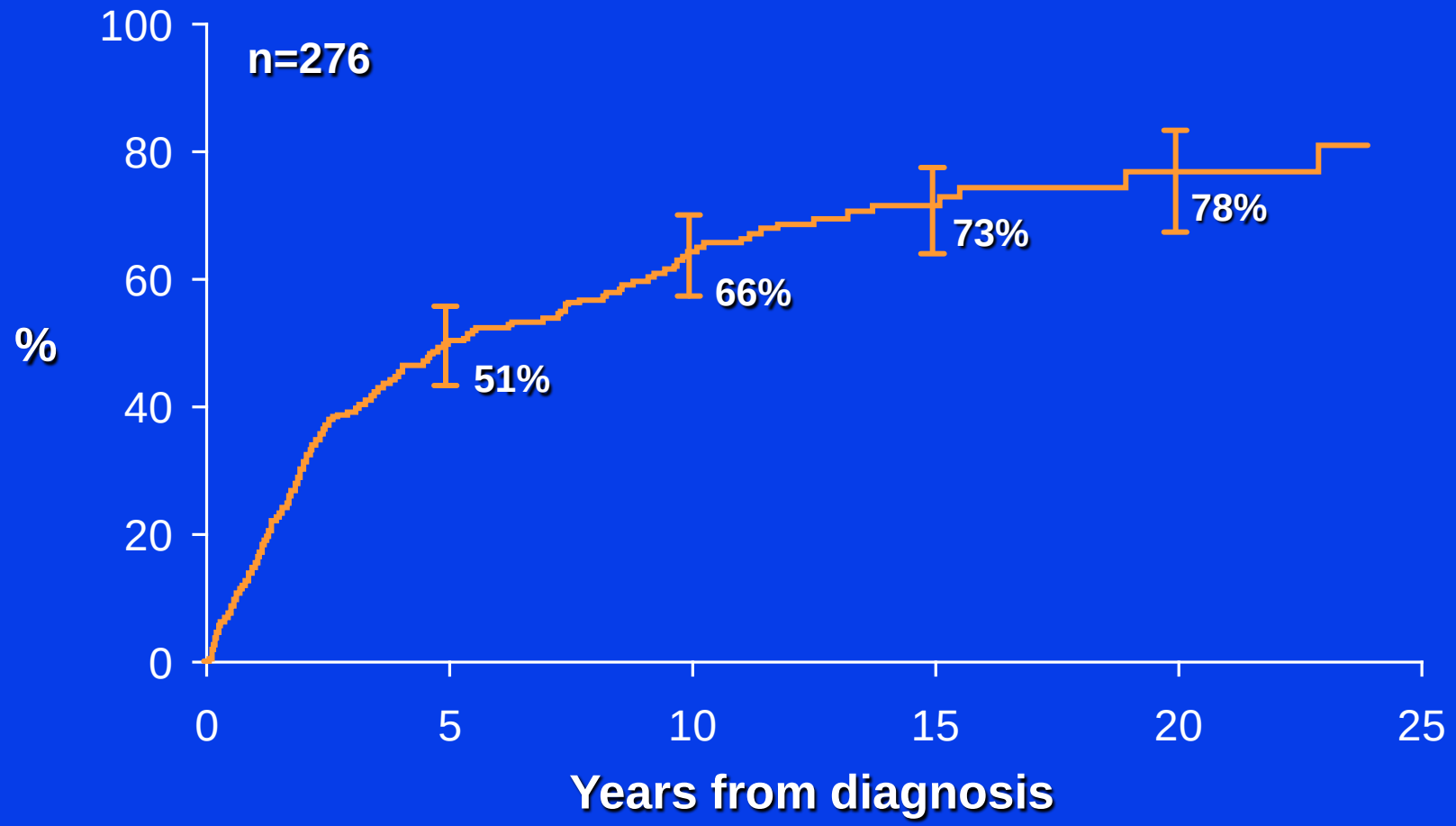
Smoldering Multiple Myeloma (SMM)

M-protein in serum and/or	≥3 g/dL
Plasma cells in marrow	≥10%
Anemia	None
Calcium	Normal
Creatinine	Normal
Lytic lesions	None

No end organ damage (CRAB)

Kyle and Greipp NEJM 302:147, 1980
Kyle et al NEJM 356:2582, 2007

Progression to Multiple Myeloma or Amyloid 1970-1995



Kyle et al: NEJM 356:2582, 2007

MAYO CLINIC

Multiple Myeloma. *Definition.* Multiple myeloma is a malignant tumor arising in the bone marrow which tends to occur in persons after the fifth decade. It is usually characterized by pain in the back and weakness, skeletal involvement especially of the trunk, pathological fractures, a normocytic anemia of moderate degree, and the presence of a peculiar type of protein (Bence-Jones) in the urine.

Although it has not received general acceptance, the most satisfactory tentative view is to consider multiple myeloma as a neoplastic process in which the myeloid cells are derived from the hematopoietic system. If this is true, the condition bears a close relationship to leukemia. The cells making up the tumors have been most commonly regarded as plasma cells although their identification is by no means definite. Possibly myeloma cells are a distinctive type varying from all other forms.

Symptoms and Signs. The condition is observed twice as commonly in males as in females. Almost all cases occur after the age of forty years. Pain of a vague, intermittent, shifting type, often referable to the spine, is commonly the earliest evidence of the disease. As the condition progresses this frequently is a severe and dominant symptom. Tumors and pathologic fractures, usually in bones containing red marrow, are common. Changes in the spine causing compression of the spinal cord with its resultant neurological manifestations is not a rare complication.

Blood. A moderately severe normocytic or slight macrocytic normochromic anemia is almost always present. The leukocyte count is ordinarily normal, slightly elevated or diminished, and the differential formula is usually not disturbed or may reveal only an occasional abnormal white blood cell. Rarely have many plasma cells been observed in the blood stream but these, when present, have caused the condition to be regarded as a plasma cell leukemia.

A finding of great diagnostic importance is the presence of Bence-Jones protein in the urine, which appears in about two-thirds of the cases. It may occur occasionally in the urine of patients with leukemia and polycythemia. This protein precipitates at temperatures of 50° to 60° C.; further heating causes it to go into solution at about boiling, and on cooling it reappears. Its presence appears to be limited to pathologic conditions attacking the bone or bone marrow. There may be a pronounced hyperproteinemia, as indicated by plasma protein determinations, which are often found to be 10 Gm. per 100 cc. of plasma, or above; figures twice as high as this have been reported. This is due entirely to an increase in the globulin fraction. Autohemagglutination, or spontaneous clumping of the erythrocytes, occurs in some cases. This accounts for the tendency to striking rouleau formation and an accelerated sedimentation rate. Serum calcium is frequently elevated to levels of 12 to 16 mg. per cent, but the serum inorganic phosphates are usually normal.

In addition to those mentioned above, there are two diagnostic procedures which are of great importance: (1) sternal puncture, which usually reveals the presence of typical myeloma cells, and (2) roentgen ray examination which demonstrates the characteristic punched out areas, without evidence of bone regeneration, in the ribs, spine, clavicles, skull and the shoulder and pelvic girdles.

Prognosis and Treatment. The disease is uniformly fatal after an average duration of life of between two and three years. Occasionally the course is prolonged with remissions and exacerbations. Roentgen ray exposures should be employed in all cases, as it frequently gives worth-while symptomatic relief and may prolong life in some instances. This, with blood transfusions, is the only known therapeutic agent of recognized value. Otherwise the treatment is symptomatic.

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"Cyrus C. Sturgis"

PH965519_1.Dig

Cecil Textbook of Medicine 7th Ed., 1948

Treatment of Multiple Myeloma

L-sarcolysin (L-phenylalanine mustard) (Melphalan) (Alkeran)

Blokhin et al, 1958
Bergsagel et al, 1962

Multiple Myeloma
Single (M/P) vs Combination Chemotherapy (CCT)

n=4,930 (20 trials)

Therapy	Response (%)
M/P	53
CCT	60

P<0.00001

No difference in survival

No subsets with benefit

Autologous Stem Cell Transplant

- Plasma cell leukemia
- Melphalan 140 mg/m^2 IV with good response
- Collected stem cells
- Relapsed and given Melphalan 140 mg/m^2 IV plus stem cells
- Treated 8 myeloma patients

McElwain TJ, Powles RL. Lancet 1983 Oct 8;2(8354):822-4.

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
- 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)

[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

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v12 //last reviewed March 2014

Multiple Myeloma
Autologous Transplant Eligibility

- Diagnosis of Multiple Myeloma with CRAB
- Age (physiologic) < 70
- Performance status (0-2)
- Bilirubin ≤ 2.0 mg/dL, creatinine ≤ 2.5 mg/dL & New York Heart Class I or II
- Adequate stem cells
- Concomitant diseases (heart, stroke, etc.)

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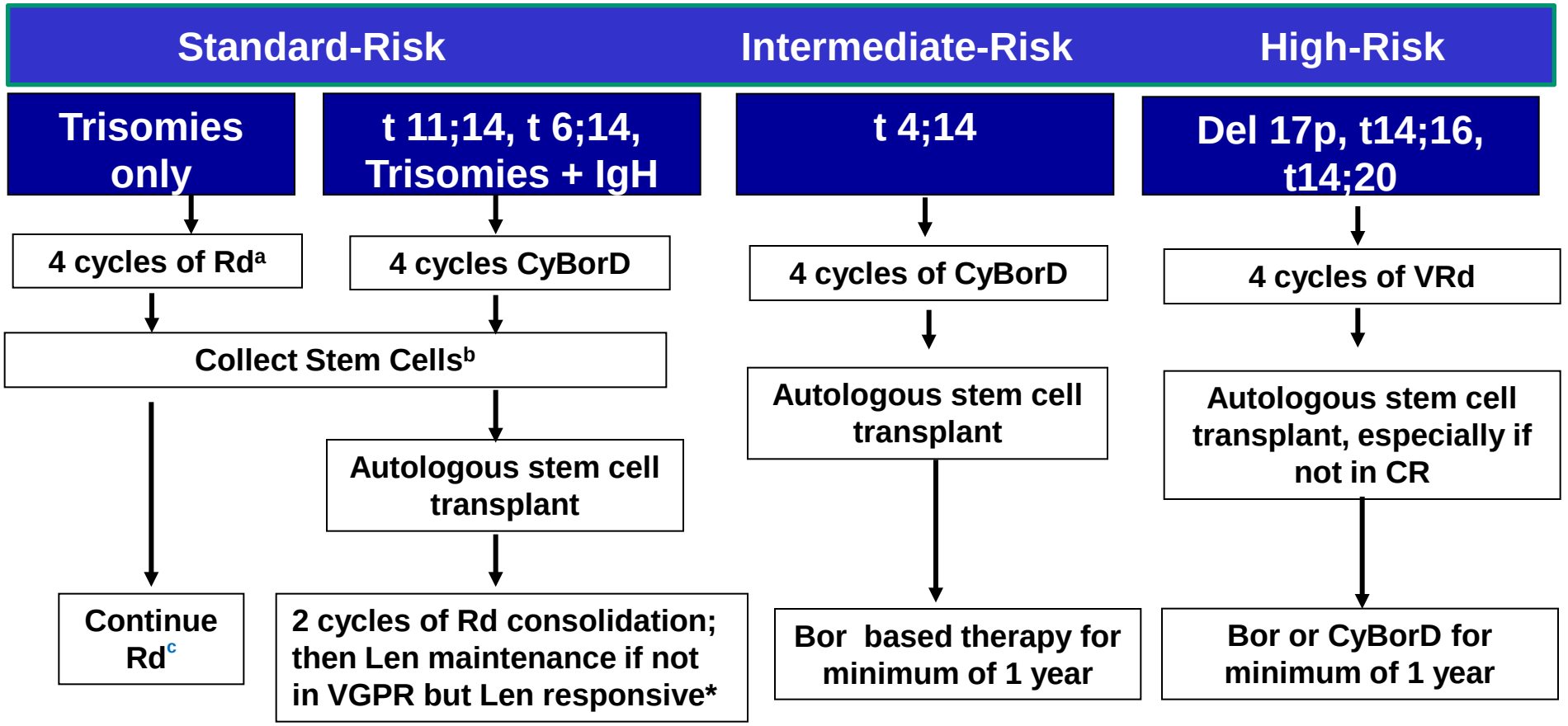
mSMART – Off-Study

Transplant Eligible



[a] *Bortezomib containing regimens preferred in renal failure or if rapid response needed*
[b] *If age >65 or > 4 cycles of Rd Consider G-CSF plus cytoxan or plerixafor*
[c] *Continuing Rd for patients responding to Rd and with low toxicities; Dex is usually discontinued after first year*
* *Consider risks and benefits; If used, consider limited duration 12-24 months*

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v12 //last reviewed March 2014

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mSMART – Off-Study

Transplant Ineligible

Standard-Risk		Intermediate-Risk	High-Risk
Trisomies only	**t 11;14, t 6;14, Trisomies + IgH**	**t 4;14**	**Del 17p, t14;16, t14;20**
↓	↓	↓	↓
Rd [a, b]	**Weekly CyBorD for ~12 months [c]**	**Weekly CyBorD for ~12 months [c]**	**VRd* for ~12 months**
↓	↓	↓	↓
Until progression [d]	**Followed by observation**	**Bor-based therapy maintenance for minimum of 1 year**	**Bor as maintenance for minimum of 1 year**

[a] In patients treated with Rd, continuing treatment is an option for patients responding well with low toxicities; Dex is usually discontinued after first year
[b] Bortezomib containing regimens preferred in renal failure or if rapid response needed
[c] CyBorD is considered a less toxic variation of VMP; VMP can be used as alternative
[d] Continuing Rd for patients responding to Rd and with low toxicities; Dex is usually discontinued after first year
**Clinical trials strongly recommended as the first option*

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v12 //last reviewed March 2014

Multiple Myeloma Untreated

Initial Therapy

Transplant eligible

Survival Rate

	N	Survival Probability	
		One-Year %	Two-Year %
Lenalidomide 25 mg d 1-21 + Dexamethasone 40 mg d 1-4, 9-12, 17-20	223	87	75
vs.			
Lenalidomide 25 mg d 1-21 + Dexamethasone 40 mg d 1, 8, 15, 22	222	96	87

Rajkumar, et al., Lancet Oncology 11:29, 2010.

Multiple Myeloma

Untreated
N = 48

	Response	
Bortezomib 1.3 mg/M2		**%**
2/wk x 2 q3 wks	**CR/NCR**	**19**
+		
Dexamethasone 40 mg		
Day of and day after Bortezomib	**PR**	**71**
if no response		
	Total	**90**

Overall survival 67% at 4 years

Jagannath et al., Blood 108: 238a, 2006; Jagannath et al., Br. J Haem 146:619, 2009

Multiple Myeloma
Bortezomib Therapy

- Give at weekly intervals (3 of 4)
- May give subcutaneously

Multiple Myeloma
Maintenance After Transplant
N=614

	PFS MOS (med)	OS 4 yr %	Second Cancer/ 100 patient years
Lenalidomide 10-15 mg daily	41	73	3.1
vs			
Placebo	23	75	1.2

MAYO CLINIC

Attal et al., N. Engl. J Med 366:1782, 2012

Multiple Myeloma Maintenance After Transplant N=460

	PFS MOS (med)	OS 3 yr %	Second Cancers %
Lenalidomide 10-15 mg daily	39	88	7.8
vs			
Placebo	21	80	2.6

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McCarthy et al., N. Engl. J Med 366:1770, 2012

Multiple Myeloma Transplant Ineligible Maintenance Therapy N=459

	PFS MOS	OS 3 yr %	Second Primary malignancies %
MPR-R	31	70	7
MPR	14	62	7
MP	13	66	3

Palumbo et al., N. Engl. J Med 366:1759, 2012

Multiple Myeloma Maintenance Considerations

- Meaningful OS
- Risk of second cancers
- Unforeseen adverse effects
- Need for physician visits on maintenance
- Quality of life
- Resistance of residual myeloma?
- Cost ($100,000 per year)

Kyle RA, Mayo Clinic Proceed 86:419, 2011

Multiple Myeloma Untreated

Initial therapy

Transplant ineligible

Multiple Myeloma Relapsed/Refractory

009,010
N = 704

	Response CR/PR %	TTP Mos (Med)
Lenalidomide 25 mg d1-21 + Dexamethasone 40 mg d 1-4, 9-12, 17-20	60.5	11.2
vs.		
Placebo d. 1-21 + Dexamethasone 40 mg d 1-4, 9-12, 17-20	22	4.7

Weber, et al., NEJM, 2007, 357:2133; Dimopoulos, et al., NEJM, 2007, 357:2123

Multiple Myeloma
Non-Transplant Candidates

Melphalan + Prednisone + Velcade (Bortezomib) (MPV)

vs.

Melphalan + Prednisone (MP)

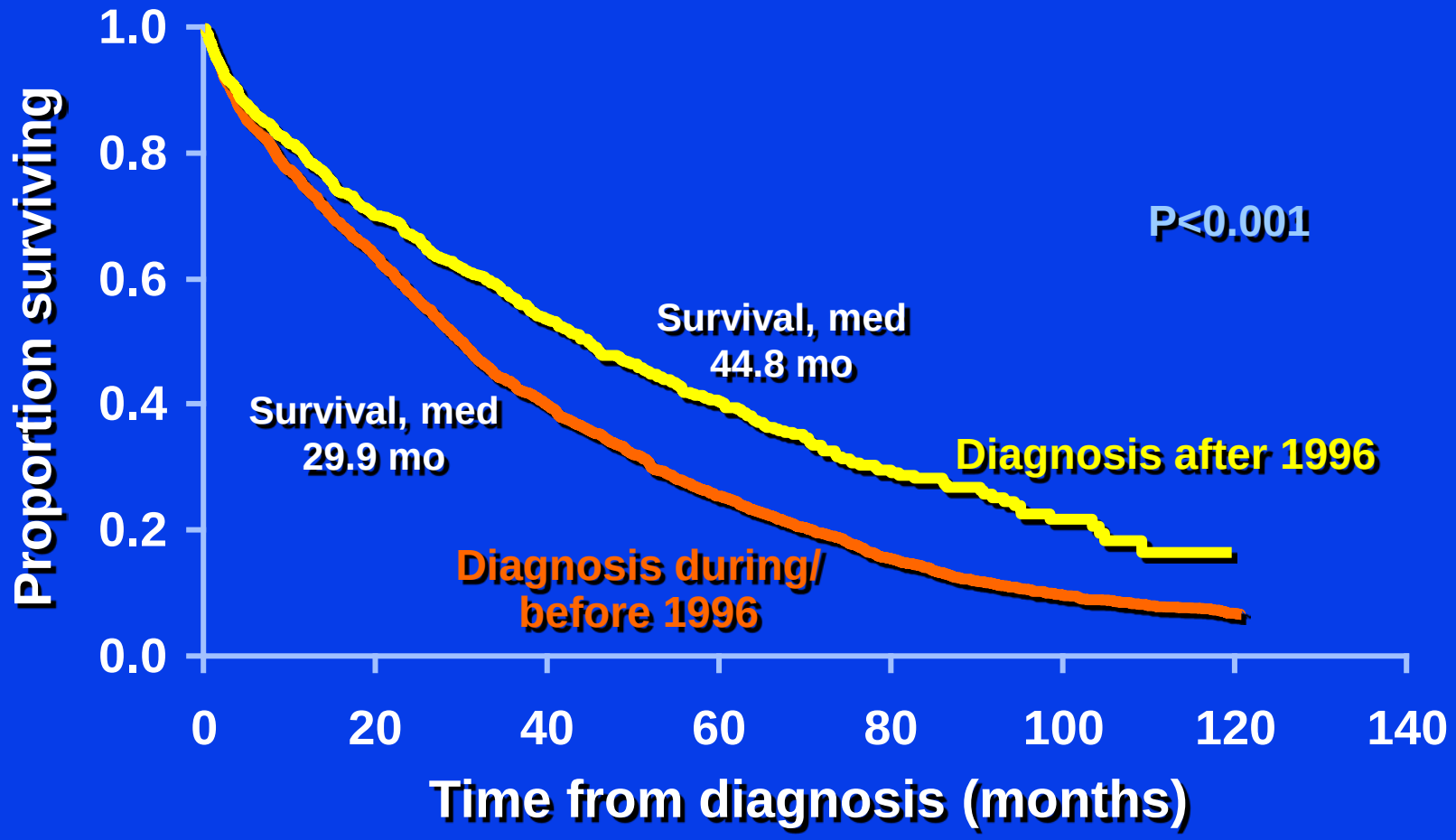
San Miguel, et al, NEJM 2008, 359:906

Multiple Myeloma
Response to Treatment

	MPV N=337	MP N=331
CR (IF-)	30%	4%
PR ≥	71%	35%
Duration of Response (Med, Mos)	19.9	13.1

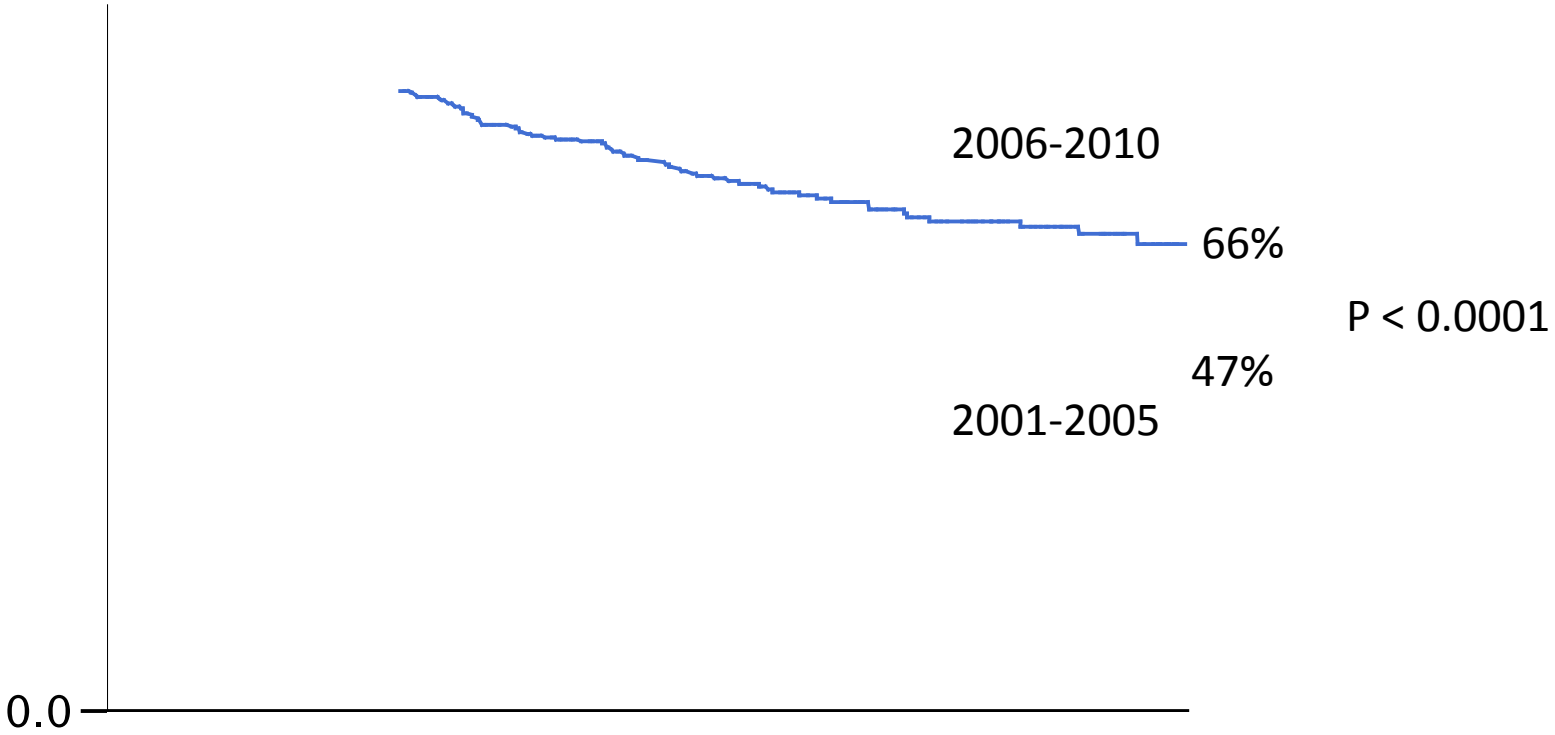
San Miguel, et al., NEJM 2008, 359:906

Multiple Myeloma 1971-2006
n=2,981



Kumar et al: Blood 111:2516, 2008

Multiple Myeloma
Mayo Patients



S. Kumar, 2012

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Novel Agents

- High Dose Therapy with stem cell transplant
- Thalidomide
- Bortezomib (Velcade)
- Lenalidomide (Revlimid)

Multiple Myeloma
Novel Agents

Pomalidomide (Pomalyst)

Carfilzomib (Kyprolis)

CC-4047

PR-171

Multiple Myeloma
Novel Agents

Proteosome inhibitor (oral/IV)	MLN-9708
Proteosome inhibitor (oral)	NPI-0052
Elotuzumab	
Bendamustine	
Histone deacetylase inhibitor	Vorinostat (SAHA)
Histone deacetylase inhibitor	Panobinostat

Multiple Myeloma Clinical Trials at Mayo Clinic Arizona

Open Trials:

Title	Therapeutic Status	Treatment Plan	Cycle Length	CRC Contact
MC1382 – Phase 1/2 trial of MLN9708 in combination with cyclophosphamide and dexamethasone in patients with previously untreated symptomatic multiple myeloma	Previously untreated symptomatic Multiple Myeloma	• MLN9708 PO days 1,8,15 • Cyclophosphamide PO days 1,8,15, 22 • Dexamethasone PO days 1,8,15,22 Given for 12 cycles then • MLN9708 PO days 1,8,15 maintenance (alone) until disease progression	1 cycle = 28 days	Anne Marie Allen
MC1181 – Phase II Trial of MLN9708 in Patients with Relapsed Multiple Myeloma Not Refractory to Bortezomib	Relapsed Multiple Myeloma	• Equal randomization odds to Arm B/C • Arm B: MLN9708 (4mg) plus Dexamethasone (40mg), PO days 1,8,15 • Arm C: MLN9708 (5.5mg) plus Dexamethasone (40mg), PO days 1,8,15 Continue until disease progression or unacceptable adverse events	1 cycle = 28 days	Cassandra Wolf
MC1082 – Phase I/II Trial of Pomalidomide (CC-4047), Bortezomib, and Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma	Relapsed or Refractory Multiple Myeloma	• Pomalidomide PO Days 1-21 • Bortezomib IV Days 1,8,15,22 • Dexamethasone PO Days 1,8,15,22 Given for 8 cycles then • Pomalidomide PO maintenance (alone) Days 1-21 until disease progression or unacceptable adverse events	1 cycle = 28 days	Kevin Morrison

Multiple Myeloma Clinical Trials at Mayo Clinic Arizona

Open Trials:

Title	Therapeutic Status	Treatment Plan	Cycle Length	CRC Contact
PrE1003 – Phase I/II Study of the Tolerability of Lenalidomide and Low Dose Dexamethasone in Previously Treated Multiple Myeloma Patients with Impaired Renal Function	Previously Treated Multiple Myeloma	• Patients registered to Group A/B/C based on renal function • Lenalidomide PO at assigned dose Days 1-21 • Dexamethasone PO 40mg Days 1,8,15,22 Continue until disease progression or unacceptable adverse events	1 cycle = 28 days	Kevin Morrison
MC1381 – Phase II Study of LCL161 Alone and in Combination with Cyclophosphamide in Patients with Relapsed or Refractory Multiple Myeloma	Relapsed or Refractory Multiple Myeloma	• LCL161 PO Days 1,8,15,22 • Given weekly for at least 2 cycles, then if less than minor response achieved, Cyclophosphamide PO added Days 1,8,15,22 Continue until disease progression or unacceptable adverse events	1 cycle = 28 days	Kevin Morrison
2011-001 – Phase 1b/2 Open-label Study of the Safety and Activity of Oprozomib in Patients with Hematologic Malignancies	Confirmed diagnosis of a hematologic malignancy that has relapsed standard therapy (excl. acute leukemia or MDS)	• Oprozomib PO on Days 1-5 Expected minimum duration 36 months *Multiple Myeloma and Waldenström's Macroglobulinemia patients enrolled at Mayo Clinic will be in Phase 2	1 cycle = 14 days	Anne Marie Allen

Multiple Myeloma Clinical Trials at Mayo Clinic Arizona

Open Trials:

Title	Therapeutic Status	Treatment Plan	Cycle Length	CRC Contact
MC1182 – Phase II Trial of nab-paclitaxel (Abraxane) in Patients With Relapsed or Refractory Multiple Myeloma	Relapsed or Refractory Multiple Myeloma	• Abraxane IV Days 1,8,15,22 • Given for 12 cycles then may continue at physician discretion Continue until disease progression or unacceptable adverse events	1 cycle = 28 days	Cassandra Wolf
FRF4998g – Phase I Trial of the Safety and Pharmacokinetics of Escalating Doses of DFRF4539A in Patients with Relapsed or Refractory Multiple Myeloma	Relapsed or Refractory Multiple Myeloma	• DRFR4539A given IV weekly or once every 3 weeks based on grouping Continue until disease progression or unacceptable adverse events	1 cycle = 21 days	JR Singh
M13-367 – A Phase 1 Study Evaluating the Safety and Pharmacokinetics of ABT-199 in Subjects with Relapsed or Refractory Multiple Myeloma	Relapsed or Refractory Multiple Myeloma	Two Portions: 1. Dose Escalation 2. Safety Expansion Cohort • ABT-199 PO day 1 of each cycle Study PK's and lead in days may be required	1 cycle = 21 days	Mike Anderton

Multiple Myeloma Clinical Trials at Mayo Clinic Arizona

Open Trials:

Title	Therapeutic Status	Treatment Plan	Cycle Length	CRC Contact
MC1113 – Phase I Trial of CDK Inhibitor Dinaciclib in Combination with Bortezomib and Dexamethasone	Relapsed Multiple Myeloma	• Dinaciclib IV Day 1 • Bortezomib SQ Days 1, 8 • Dexamethasone PO Continue until disease progression or unacceptable adverse events	1 cycle = 21 days	JR Singh
TED10893 – Phase I Dose Escalation Safety and Pharmacokinetic Study of Multiple Intravenous Administrations of a Humanized Monoclonal Antibody (SAR6509884) against CD38 in Patients with Selected CD38 Hematological Malignancies	Relapsed or Refractory Multiple Myeloma or other CD38+ Hematological Malignancies	• SAR6509884 IV every 2 weeks or weekly based on grouping Continue until disease progression or unacceptable adverse events	1 cycle = 21 days	Deborah Gallagher

Multiple Myeloma Clinical Trials at Mayo Clinic Arizona

Pending Trials:

Title	Therapeutic Status	Treatment Plan	Cycle Length	CRC Contact
MC1383 – Phase 1/2 Clinical Trial of MK-7965 (Dinaciclib) in Combination with Carfilzomib and Dexamethasone in Relapsed Multiple Myeloma	Relapsed Multiple Myeloma	Pending	Pending	Pending
MMRC-051 Phase I/II trial of MLN9708 plus Pomalidomide and Dexamethasone for Relapsed or Refractory Multiple Myeloma	Relapsed or Refractory Multiple Myeloma	Pending	Pending	Pending
A Randomized, Open-label Phase 3 Study of Filanesib (ARRY-520) + Carfilzomib Versus Single-agent Carfilzomib in Patients With Advanced Multiple Myeloma	Advanced Multiple Myeloma	Pending	Pending	Pending

Multiple Myeloma Clinical Trials at Mayo Clinic Arizona

Pending Trials:

Title	Therapeutic Status	Treatment Plan	Cycle Length	CRC Contact
OZM-440 Safety Study of the Selective Inhibitor of Nuclear Export (SINE) KPT-330 in Patients With Advanced Hematological Cancer (Phase 1 title)	Advanced Hematological Cancers	Pending	Pending	Pending

Questions about Clinical Trials?
Please call the Cancer Clinical Research Office
(480) 301-4268