Updates on Diagnosis and Therapies for Myeloma

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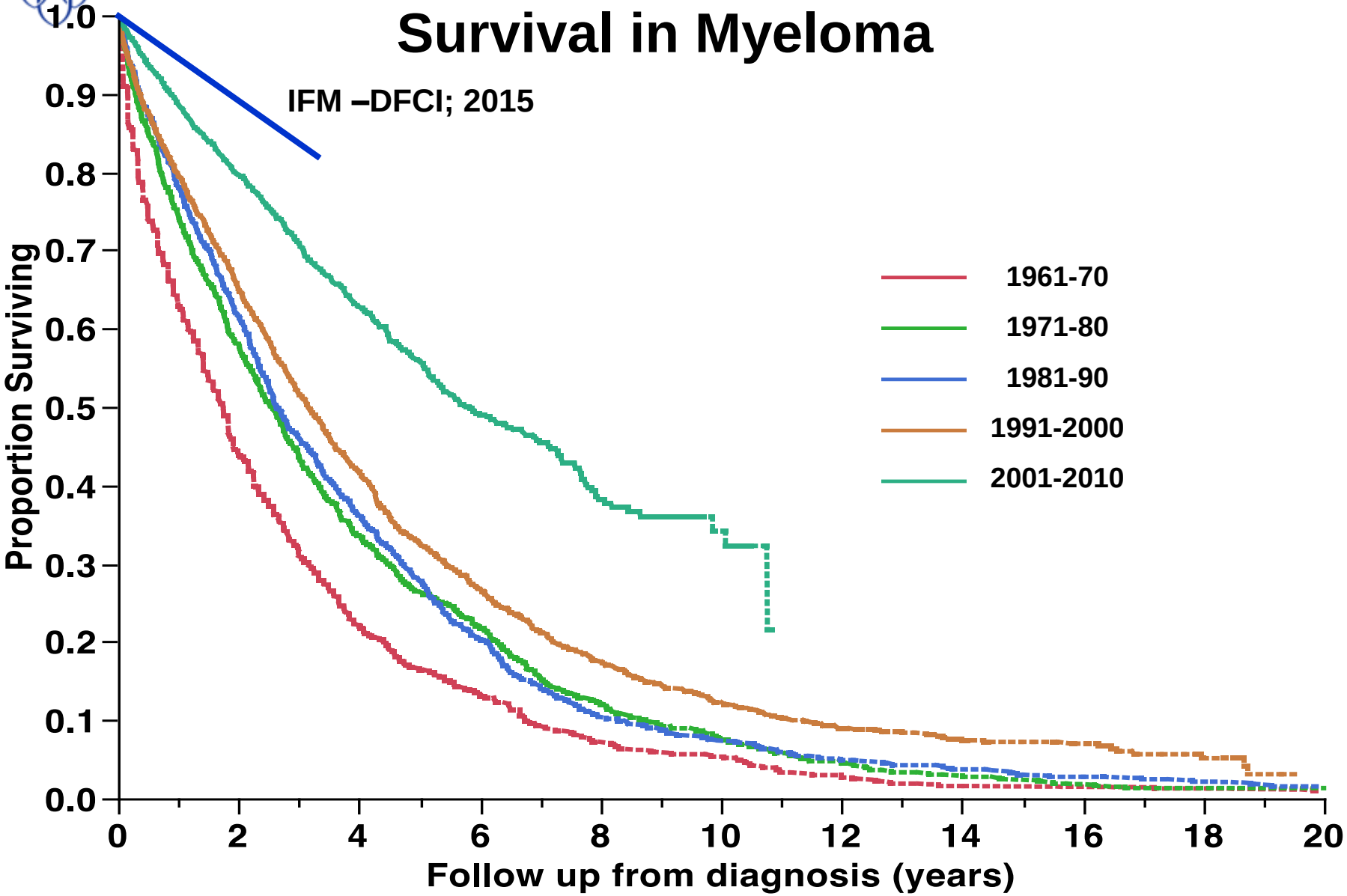
MAYO CLINIC

Survival in Myeloma



Kumar S. Blood 2008;111: 2516 – 2520; Kumar S. Leukemia (2014) 28, 1122–1128.

Previous Disease Definitions

- <10% BMPC AND
- <3gm/dL M protein

- ≥10% BMPC OR
- ≥3 gm/dL M protein

No CRAB

CRAB

C: Hypercalcemia; **R:** Renal failure; **A:** Anemia; **B**: Lytic bone lesions

Attributable to a clonal plasma cell disorder

Rajkumar SV. Cecil Textbook of Medicine, 25th Edition, 2015

Technologic/Research Advances

- Serum free light chain (FLC) assay
- Interphase Fluorescent *in situ* hybridization (FISH)
- Magnetic Resonance Imaging (MRI)
- Positron Emission Testing/CAT scan (PET/CT)

Interphase FISH

- Allowed for chromosome analysis in indolent hematologic malignancies
- Most myelomas have chromosomal abnormalities
- Categorization and risk stratification of myeloma based on cytogenetic abnormalities

2 Distinct Types of Myeloma

MGUS

Trisomic/Hyperdiploid	Hypodiploid (majority with IgH translocations)
Of 1 or more odd numbered chromosomes, 3, 7, 9, 11, 15, 17 except chromosomes 1, 13, 21	t(11;14)
	t(4;14)
	t(14;16)
	t(6;14)
% patients: 42%	t(14;20)

Kumar, et al. Trisomies in MM: Impact on survival in pts with high risk cytogenetics. **Blood** 2012; **119**: 2100-2105

Rajan AM and Rajkumar, V. Interpretation of cytogenetic results in multiple myeloma for clinical practice. **Blood Cancer J** (2015) **5**

Primary cytogenetic abnormalities in Active Myeloma

IgH (14q32) translocation	Gene Dysregulation	% new myelomas
t(11;14)	Cyclin D1	30
t(4;14)	FGFR/MMSET	15
t(14;16)	c-MAF	6
t(6;14)	Cyclin D3	5
t(14;20)	MAF-B	<1

Isolated monosomy 14	**?unknown partner chromosome**	**4.5%**
Normal		**3%**
Combined trisomic/IgH translocated		**15%**
Abnormalities not involving chromosome 14		**5.5%**

Table and data adapted from:

Kumar, et al. Trisomies in MM: Impact on survival in pts with high risk cytogenetics. **Blood** 2012; **119**: 2100-2105

Rajan AM and Rajkumar, V. Interpretation of cytogenetic results in multiple myeloma for clinical practice. **Blood Cancer J** (2015) **5**

Secondary Cytogenetic Abnormalities

Malignant transformation or disease progression:

- 1q amplification
- Deletion 17p
- 1p deletion
- MYC translocations
- Monosomies 13, 14

Developments in myeloma

1. Availability of multiple new highly active therapeutic agents

2. Identification of ultra-high risk smoldering myeloma patients; those with a probability of ≥ 80% of progressing within 2 years using 3 biomarkers: FLC ratio≥100; bone marrow clonal plasma cells ≥ 60%; > 1 focal lesion on whole body MRI

3. More advanced imaging modalities, including whole body CT, MRI, PET/CT

4. Randomized trial of high risk SMM patients demonstrating survival advantage for those treated with lenalidomide/dexamethasone versus observation.

Revised IMWG Criteria

- <10% BMPC AND
- <3 gm/dL M protein AND
- No MDE

- ≥10%-60% BMPC OR
- ≥3 gm/dL on SPEP OR
- ≥500 mg/24h Ur. M protein AND
- No MDE

- PCPD, AND
- 1 or more MDE
  - CRAB
  - ≥60% BMPC
  - ≥100 FLC ratio
  - >1 MRI focal lesion

No MDE

MDE

MDE, myeloma-defining events
PCPD; plasma cell proliferative disorder
BMPC; bone marrow plasma cells

Rajkumar SV, Dimopoulos M, Palumbo A, et al. *Lancet Oncol*. 2014;15(12):e538-e548.

IMWG Additional Diagnostic Changes

Imaging

Low dose body CT; PET/CT, whole body MRI

Bone myeloma defining event: 1 or more sites of osteolytic destruction ≥ 5 mm

Increased diffuse or focal FDG uptake on PET **NOT** sufficient

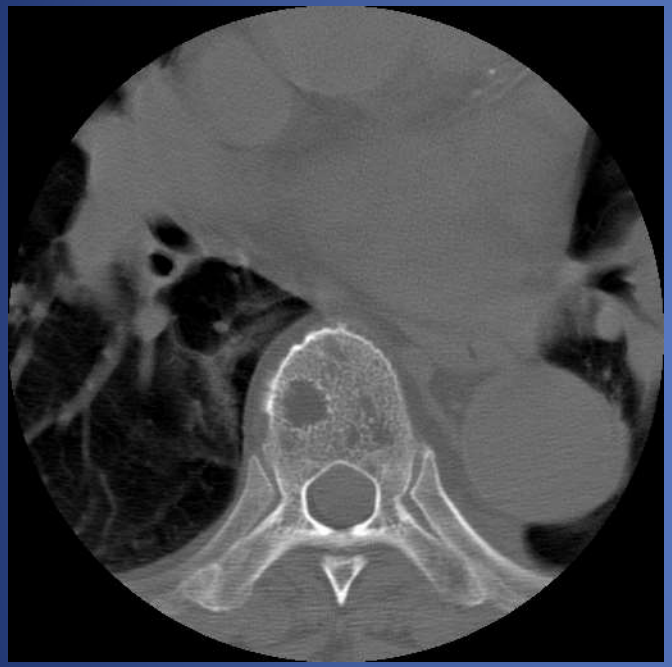
Renal Disease

ONLY suspected or biopsy proven cast nephropathy is a defining event

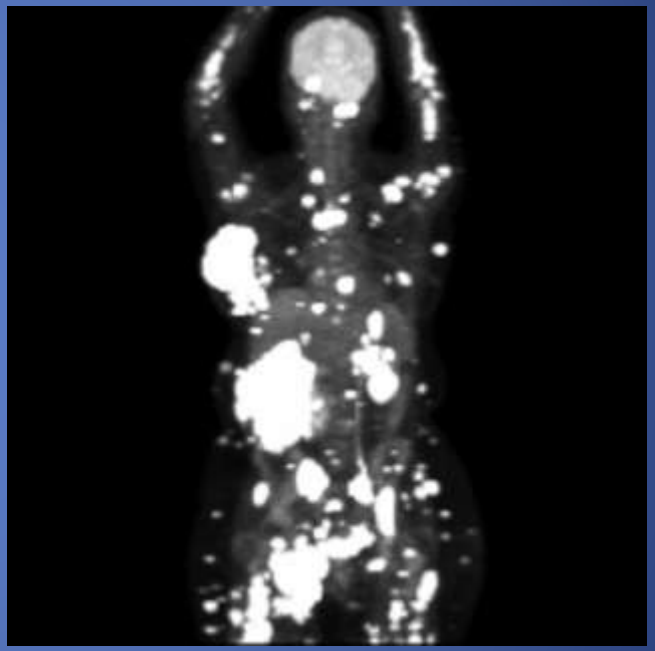
Biopsy recommended with involved serum FLC < 500 mg/L if cast nephropathy suspected

Advanced Imaging

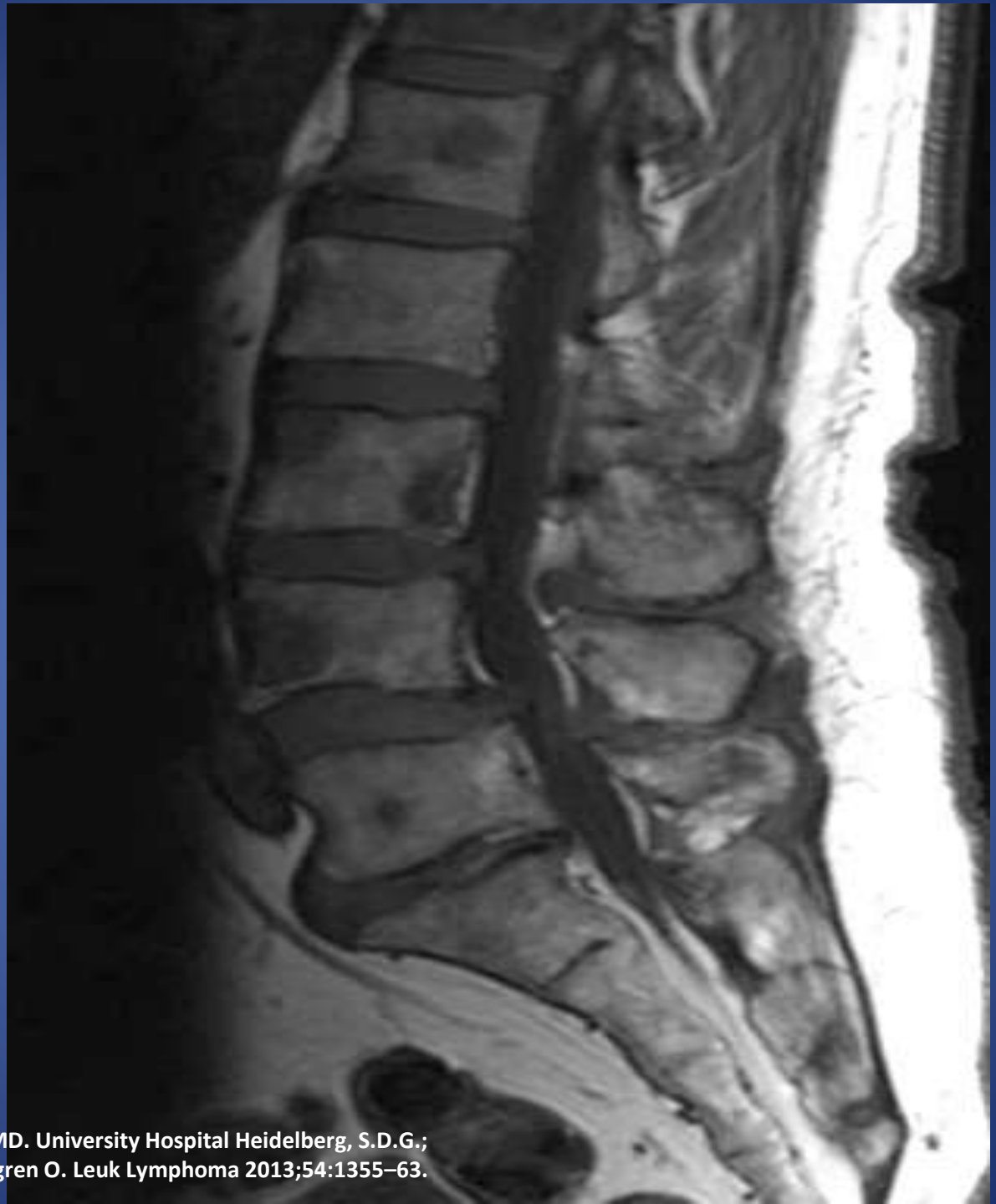
CT



PET-CT



Rajkumar SV, Dispenzieri A. In: Niederhuber JE, et al, eds. *Abeloff's Clinical Oncology*, 5th Edition; 2013.
Rajkumar SV. In: Goldman L and Schafer AI, eds. *Goldman's Cecil Medicine*, 24th Edition. 2012.



Images courtesy of Jens Hillengass MD. University Hospital Heidelberg, S.D.G.;
Hillengass J, Landgren O. Leuk Lymphoma 2013;54:1355–63.

IMWG Update Renal* 2016

Definition of Renal Insufficiency in symptomatic MM (IMWG): sCr > 2.0 mg/dL or Cr Cl < 40 mL/minute, as a result of disease.

**Rule out other causes of RI (>15% of myeloma patients with RI, not related to MM)

Evaluation of Cr Cl, eGFR, only for those with stable function:

MDRD
CKD-EPI

Classification using 5 stages of CKD

Acute Kidney Injury (AKI)

RIFLE and AKIN criteria, although limited usage in AKI in myeloma

*Dimopolous, M et al. IMWG Recommendations for the Diagnosis and Management of Myeloma Related Renal Impairment. JCO. 34(13). May 1, 2016.
**Nasr, SH et al. Clinicopathologic correlations in myeloma: A case series of 190 patients with kidney biopsies. Am J Kidney Dis 59: 786-794, 2012.

Criteria for Renal Response to Therapy*

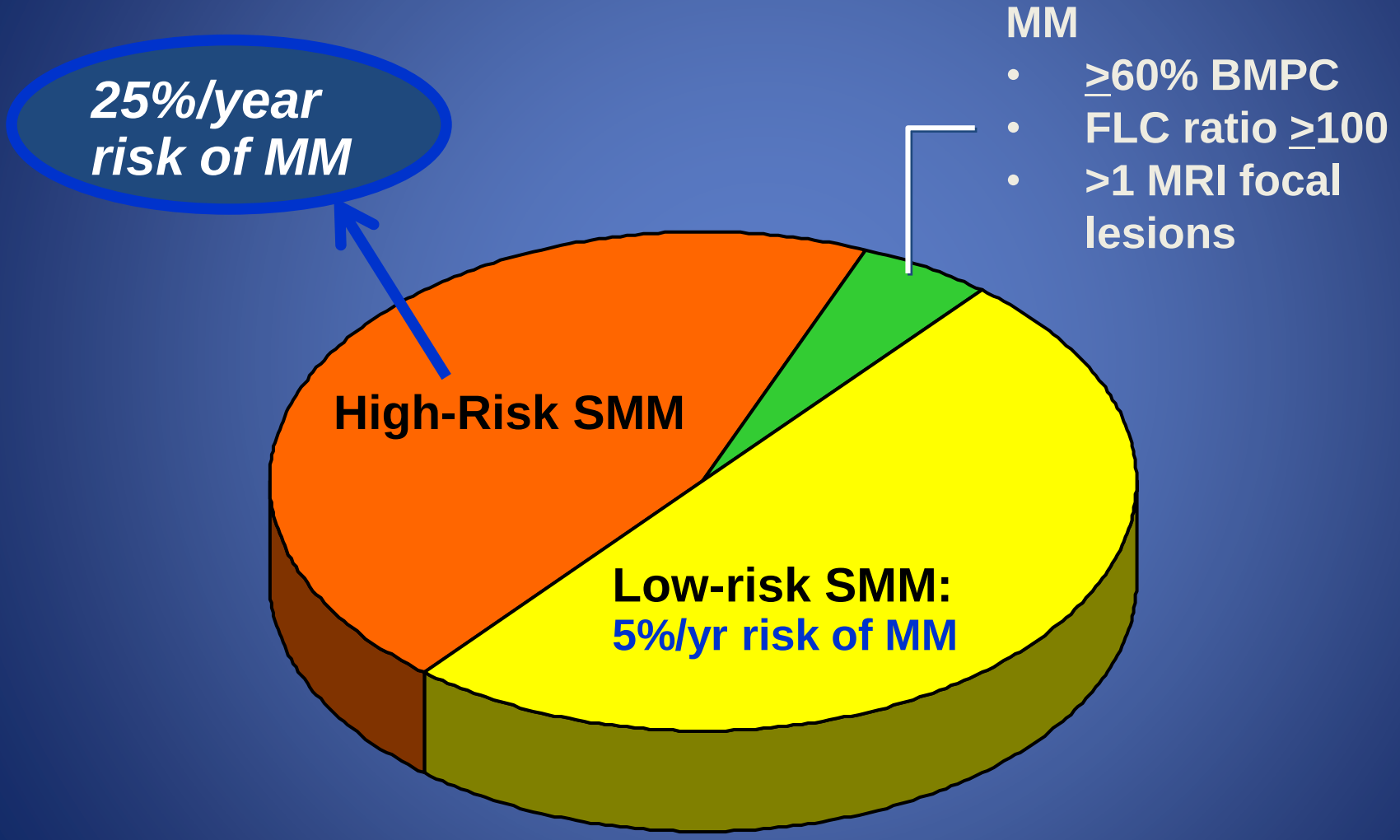
Response (renal)	Baseline eGFR (mL/min/1.73 m2)	Best Cr Cl response (mL/min)
CR	< 50	≥ 60
PR	< 15	30-59
Minor response	< 15 15-29	15-29 30-59

CR=complete response; PR=partial response

*__Dimopoulos, MA, et al__. Renal Impairment in patients with multiple myeloma: A consensus statement on behalf of the __IMWG. JCO. 28: 4976-4984. 2010.__

REVISED DEFINITION OF SMM

Smoldering Multiple Myeloma



BMPC=bone marrow plasma cells

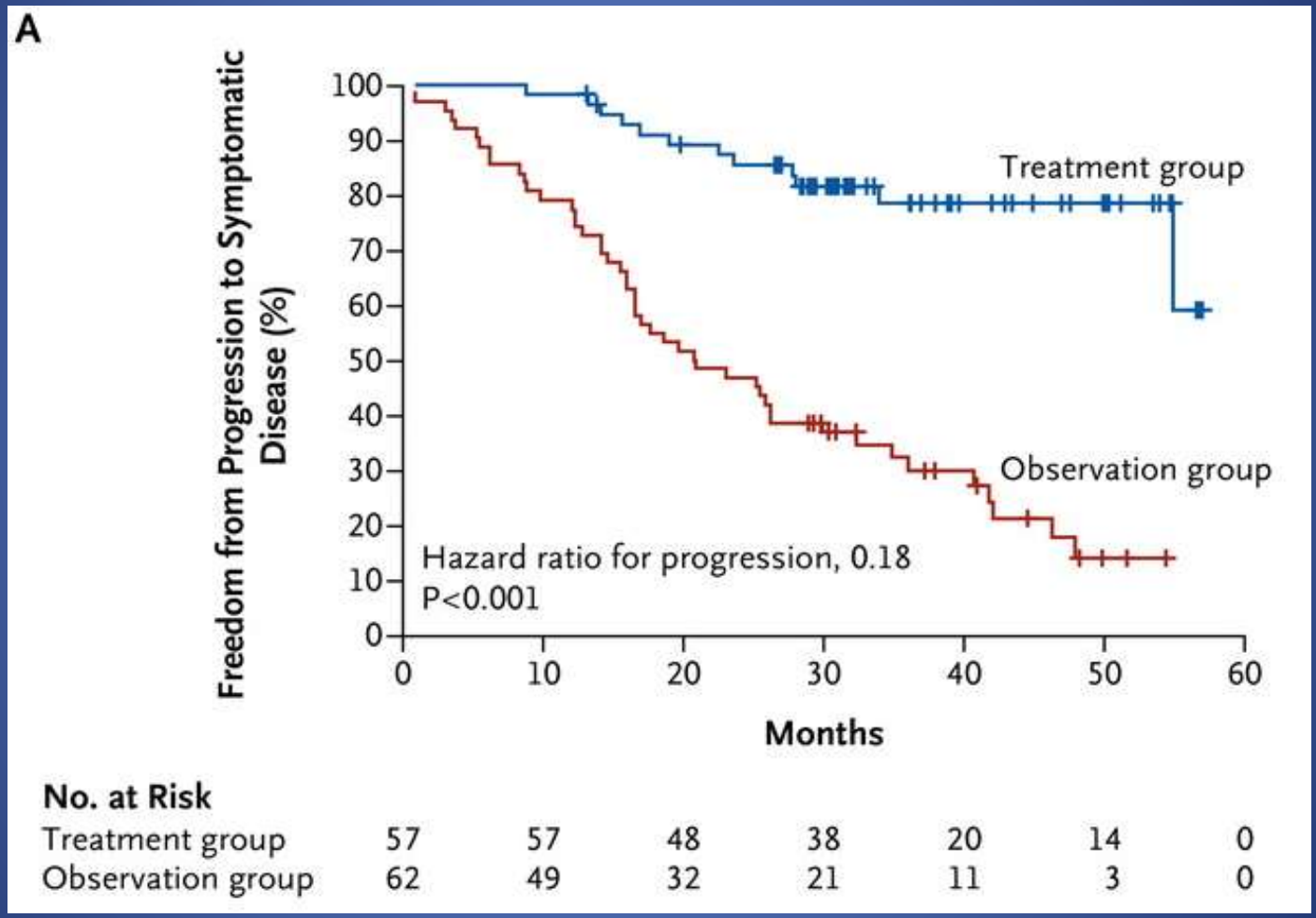
High Risk SMM: Median TTP ~2 years

≥10% Plasma cells (PC) plus ≥ 1:

- SMM with M protein ≥3 gm/dL
- Immunoparesis with reductions in 2 uninvolved Ig's
- Abnormal FLC ratio ≥ 8 but <100
- del(17p), t(4;14), gain(1q21)
- Bone marrow clonal plasma cells of 50-59%
- IgA SMM
- Evolving pattern (↑ M spike by ≥ 25%, 2 occasions within 6 months)
- Increased circulating plasma cells
- MRI with diffuse abnormalities or 1 focal lesion
- PET/CT with increased FDG uptake, but no osteolytic component
- Abnormal plasma cell immunophenotype (>95% of marrow PCs are clonal and reduction in ≥ 1 uninvolved Ig isotypes

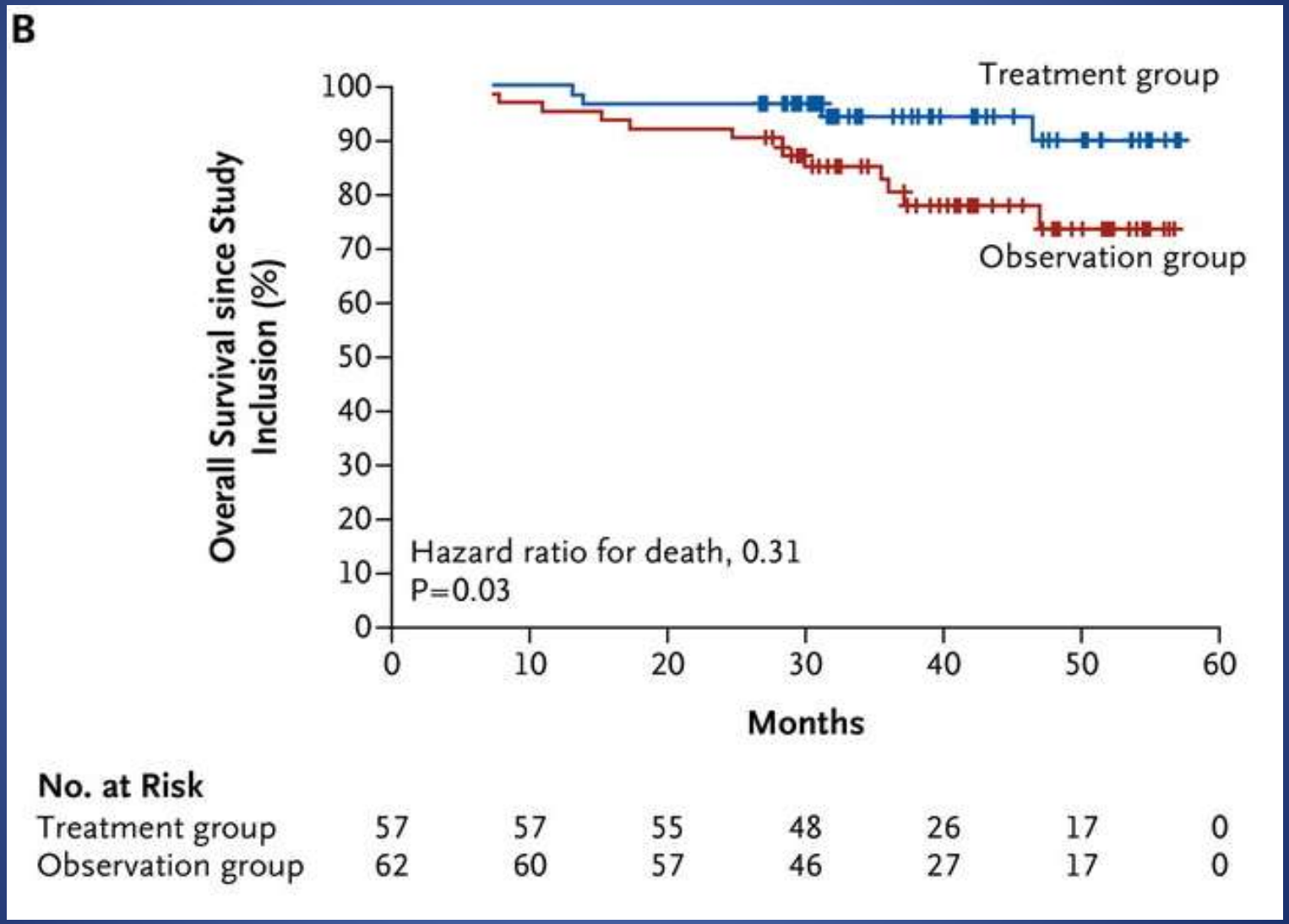
Reproduced from Rajkumar SV, et al. Blood 2015

Len/Dex versus Observation in High Risk SMM: TTP



Mateos M et al. N Engl J Med 2013;369:438-447.

Len/Dex versus Observation in High Risk SMM: OS



Mateos M et al. N Engl J Med 2013;369:438-447.

STAGING & RISK STRATIFICATION OF MYELOMA

Prognosis based on:

- Disease biology
- Response to therapy
- Host factors: Age, co-morbidities, performance status
- Stage of disease

Durie-Salmon Staging System

Stage	Criteria	Myeloma cell mass (x 10^{12} cells/m^2)
I	Hemoglobin >10 g/dL Serum Ca++ ≤12 mg/dL Normal or solitary plasmacytoma IgG <5 g/dL; IgA <3 g/dL Bence-Jones protein <4 g/24 hr	**<0.6 (low)**
II	Not fitting stage I or II	**0.6–12 (intermediate)**
III	Hemoglobin < 8.5 g/dL Serum Ca++ >12 mg/dL Multiple lytic bone lesions IgG >7 g/dL; IgA < 5 g/dL Bence Jones protein >12 g/24 hr	**>1.2 (high)**

Subclassification

A serum creatinine < 2.0 mg/dL

B serum creatinine ≥ 2.0 mg/dL

International Staging System for Myeloma

Stage	Survival in Months
Stage I β2M < 3.5 and albumin ≥3.5	62
Stage II Not meeting criteria for Stage I or III	44
Stage III β2M ≥5.5	29

Greipp PR. J Clin Oncol 2005;23:3412-3420

Disease Biology: Cytogenetic Impact on Prognosis

- 17 p- or deletion 17
- t(4;14)
- t(14;16)
- t(14;20)
- Gain of 1q associated with del 1p
- Combinations of ≥ 3 cytogenetic abnormalities < 2 year survival

Revised International Staging System

Stage	Frequency (% of patients)	5-year survival rate (%)
Stage 1 • Serum albumin >3.5 g/dL • Serum beta-2-microglobulin <3.5 • No high risk cytogenetics • Normal LDH	28%	82
Stage II • Neither Stage I or III	62%	62
Stage III • Serum beta-2-microglobulin >5.5 and • High risk cytogenetics [t(4;14), t(14;16), or del(17p)] *or* Elevated LDH	10%	40

Palumbo A, Avet-Loiseau H, Oliva S, et al. JCO, 2015;33:2863-2869.

Molecular Stratification of Myeloma and Smoldering Myeloma

Cytogenetic Abnormalities in SMM and MM and Time to Progression and Overall Survival

Abnormality	SMM	Myeloma
t(11;14)(q13;32) or t(6;14)(p21;q32)	Standard risk of progression (TTP 5 years)	Standard Risk; OS=7-10 years
t(4;14)(p16;q32)	High risk progression (TTP 2 years)	Intermediate (or high risk depending on study); OS 5 years
t(14;16)(q32;q23) or t(14;20)(q32;q11)	Standard Risk of progression TTP 5 years	High risk, median OS 3 years
Gain 1q21	High risk of progression; TTP 2 years	Intermediate Risk; OS 5 years
Del (17p)	High risk of progression; TTP 2 years	High risk; OS of 3 years
Trisomies	Intermediate risk of progression; TTP 3 years	Standard risk; OS 7-10 years
Trisomies + Ig H translocation	Standard risk of progression; TTP 5 years	Trisomies may ameliorate poor prognosis of high risk Ig H translocations
Isolated Monosomy 13 or 14	Standard Risk of progression; TTP 5 years	? Effect on prognosis
Normal	Low risk of progression; TTP 7-10 years	OS >7-10 years

Adapted from: **Rajan AM, et al**. Interpretation of cytogenetic results in myeloma for clinical practice. **Blood Cancer J 2015, 5, e365.**

Clinical Characteristics associated with cytogenetic abnormalities in MM

- IgH translocations associated with high FLC and renal failure as myeloma defining events (MDE)
- Especially t(14;16). 25% presented with renal failure as only MDE
- t(11;14) and t(6;14) more likely to present with bone disease as initial MDE
- t(4;14) associated with high FLC ratios

Greenberg, AJ et al. Relationship between initial clinical presentation and the molecular cytogenetic classification of myeloma. Leukemia, 2014; 28: 398-403
Kumar, S et al. Relationship between elevated free light chains and the presence of IgH translocations in myeloma. Leukemia, 2010. 24: 1498-1505.

Therapeutic Agents

Steroids

- Dexamethasone
- Prednisone
  Methylprednisolone

Chemo

- Alkylators/platinums
- Topoisomerase inhibitors
- Vinca alkaloids
- Stem cell transplant

Proteosome Inhibitors

- Bortezomib
- Carfilzomib
- Ixazomib

Immunomodulatory Agents

- Thalidomide
- Lenalidomide
- Pomalidomide

Monoclonal Antibodies

- Daratumumab
- Elotuzumab

Histone Deacetylase Inhibitors

- Panobinostat

New Agents

- Bcl-2 Inhibitors (venetoclax)
- Chimeric Antigen Receptor-T cells

PROTEOSOME INHIBITORS

Bortezomib:

- Reversible inhibitor of the chymotrypsin-like activity of the 26S proteosome
- SQ administration weekly; dosing 1.0-1.6 mg/m2
- No dose reduction with renal failure/dialysis
- Preferred agent in setting of renal failure, rapid response; use in all intermediate and high risk myelomas; t(4;14) particularly sensitive

Ixazomib: (4, 3, 2.3 mg); Once weekly x 3 weeks, off 1 week

- Oral. Reversible inhibition. Avoid with strong CYP3A inducers
- Mild to moderate renal failure: no dose reduction
- Severe renal failure <30 mL/min or dialysis: dose reduce
- Mild to moderate hepatic dysfunction: no dose reduction
- Severe hepatic dysfunction: dose reduce
- Can overcome bortezomib resistance

Carfilzomib: (20 mg; 27 mg/m2) Twice weekly x 3 weeks, 1 week off

Irreversible binding to 20 S subunit inhibiting chymotrypsin-like activity

- Much less risk of neuropathy than bortezomib
- Myelosuppression and GI symptoms
- *Cardiac side effects: pooled analysis 2 trials: ENDEAVOR and ASPIRE (7-10.6%); HF in 3.8-7.2%; HTN 4-14%
- *Renal side effects: AKI in 3.3-5.3%

Dimopoulos, et al; transient reductions in eGFR, but increase in eGFR in 55% in those with eGFR <60, with AKI due to myeloma

CLASS EFFECTS: Inhibit NF-KB, affects microenvironment, generates reactive oxygen species, pro-apoptotic

CLASS RISKS:

- Neuropathy
- GI side effects
- Myelosuppression, particularly thrombocytopenia
- Increased risk for Varicella zoster; anti-viral prophylaxis
- Upper respiratory infections/pneumonitis
- Case reports of thrombotic microangiopathy: No response to plasma exchange

Immunomodulatory Agents (IMiDs)

- **Thalidomide** (50, 100, 200 mg), daily, days 128
- Side effects: somnolence, peripheral sensory neuropathy, constipation, rash
- Renal: No dose reductions necessary

Lenalidomide: (5; 10; 15; 25 mg) days 1-21
q 28 days

Renal: dose reductions required

- Myelosuppression
- GI: diarrhea, occasional constipation, hepatitis
- Rash

- Peripheral neuropathy, usually mild
- May suppress ability to mobilize and collect stem cells

Pomalidomide: (4, 3, 2, 1 mg) days 1-21 q 28 days

- Overall response rate 25-30% in those refractory to bortezomib and lenalidomide
- Main side effect is myelosuppression
- No need for dose adjustments in renal failure

Class Risks:

Increased risk for venous thromboembolic events;

Prophylaxis with aspirin, warfarin, heparin,
low molecular weight heparin, thrombin inhibitors

Myelosuppression: Pomalidomide > Lenalidomide

Teratogenicity

Class Effects: anti-inflammatory, anti-angiogenic, activation of NK, T cells, anti-proliferative, induction of apoptosis. Inhibits: Il-6, TNF-alpha, VEGF, NF-Ƙβ

Cereblon: E3 ligase protein
Direct protein target for IMiDs
Mediates IMiD resistance

*IMiDs particularly effective in trisomic myeloma

*Not complete cross-resistance; Approx ½ of pts resistant to Thal Respond to lenalidomide. Approx ½ refractory to Lenalidomide respond to Pomalidomide

Monoclonal Antibodies

Daratumumab: IgGk1 human antibody against CD38

Activity as a single agent or in combination with IMiD or PI

Mechanisms of action:

- Complement mediated cytotoxicity
- Antibody-dependent cell mediated cytotoxicity
- Antibody-dependent cellular phagocytosis
- Apoptosis

Side effects: Infusion reactions, cytopenias

**Interference with SPEP/IF testing especially IgG k, co-migration on electrophoresis.

**Interference with blood compatibility testing. False + indirect Coombs due to binding of CD38 on red blood cells.

- **Elotuzumab**: anti-SLAMF7 (CD319) IgG1k monoclonal antibody
  SLAMF7 (Signaling lymphocytic activation molecule): Superfamily of immunoglobulins

- Expressed on normal and myeloma plasma cells, Less so on NK cells

- No single agent activity

- *__Phase III ELOQUENT-2 Trial__: Elotuzumab/lenalidomide/dex vs lenalidomide/dex in relapsed or refractory MM. PFS 19.4 months vs. 14.9 months (P<0.001)

Mechanisms of Action:

- NK cell activation

- Antibody dependent cellular cytotoxicity

- Interference with SPEP/IF interpretation

- No interference with blood compatibility testing

* Lonial, S et al. NEJM. 373: 621-631. Aug 13, 2015

HISTONE DEACETYLASE (HDAC) Inhibitors

Panobinostat: Pan histone deacetylase inhibitor

Hyperacetylation of proteins: cell cycle arrest, apoptosis, anti-angiogenic

Down regulates **aggresome pathway**

Aggresome pathway: Alternative protein degradation pathway**.** Mechanism of resistance toward PI. Theoretical benefit to adding to proteosome inhibitor

SIDE EFFECTS

QTc interval prolongation

Diarrhea

Elevation in liver function tests

No dose adjustments for severe renal failure, however, not tested in those on hemodialysis

INITIAL TREATMENT of NEWLY DIAGNOSED MYELOMA

IS THE PATIENT A POTENTIAL STEM CELL TRANSPLANT CANDIDATE?

IF YES:

INDUCTION THERAPY with STEM CELL SPARING REGIMEN
(NO melphalan based regimens)

Most of the time, bortezomib as part of a triplet regimen

- Bortezomib/lenalidomide/dexamethasone
- Bortezomib/thalidomide/dexamethasone
- Bortezomib/cyclophosphamide/dexamethasone

For High risk disease consider:

- Carfilzomib/lenalidomide/dexamethasone; Ph II data indicating may be beneficial compared to bortezomib containing regimen

- Triplet regimen with IMiD and PI better PFS than doublet
- Bortezomib/lenalidomide/dex showed OS benefit compared to lenalidomide/dexamethasone
  (Durie, BGM, et al. Ph III SWOG S0777, ASH abstract, 2015; 126:A25)
- Usually 4 cycles followed by autologous stem cell transplant in transplant eligible patients

Autologous Stem Cell Transplant

*Increases overall survival in myeloma by approximately 1 year based on studies performed prior to novel agents

Still remains standard of care, despite novel agents

Eligibility: up to age 76 in patients with good performance status and adequate organ function (excluding renal function)

- Patients with renal failure, including HD, are candidates assuming no other significant organ dysfunction

- Elevated creatinine does not affect TTP of disease or rates of CR

*Higher creatinine levels associated with higher day 100 mortality (3.8%), shorter OS (62% at 30 months), delayed platelet engraftment.

Single vs tandem auto transplantation

Most studies do not show survival advantage with tandem up front

*Gertz, M et al. Impact of age and serum creatinine on outcome after autologous blood stem cell transplantation for patients with myeloma. **BMT. 2007; 39 (10)**

Lee, CK. Dialysis dependent renal failure in patients with myeloma can be reversed by high dose myeloablative therapy and auto transplant. **BMT. 2004. 33(8)**

Badros, et al. Results of autologous stem cell transplant in multiple myeloma patients with renal failure. **Br J Haematol. 2001; 114(4).**

Maintenance Therapy after autologous stem cell transplant

*__Lenalidomide:__ Improves PFS and OS in most patients.
PFS 52.8 v 23.5 months; Median follow up of 79.5 months, OS not reached vs 86 mo

Questions: subgroup to most benefit; ?utility in HR disease; dosing and length of time

*Increased risk of second primary hematologic and solid tumors
Heme: Len vs placebo before PD 5.3% v 2.8%; after PD 6.1 vs 2.8%
Solid: before PD 5.8% and 2.0 %; after PD 7.3% vs 4.2%

Bortezomib: Administered every other week; preferred for Intermediate and high risk myelomas; t(4;14) particularly sensitive

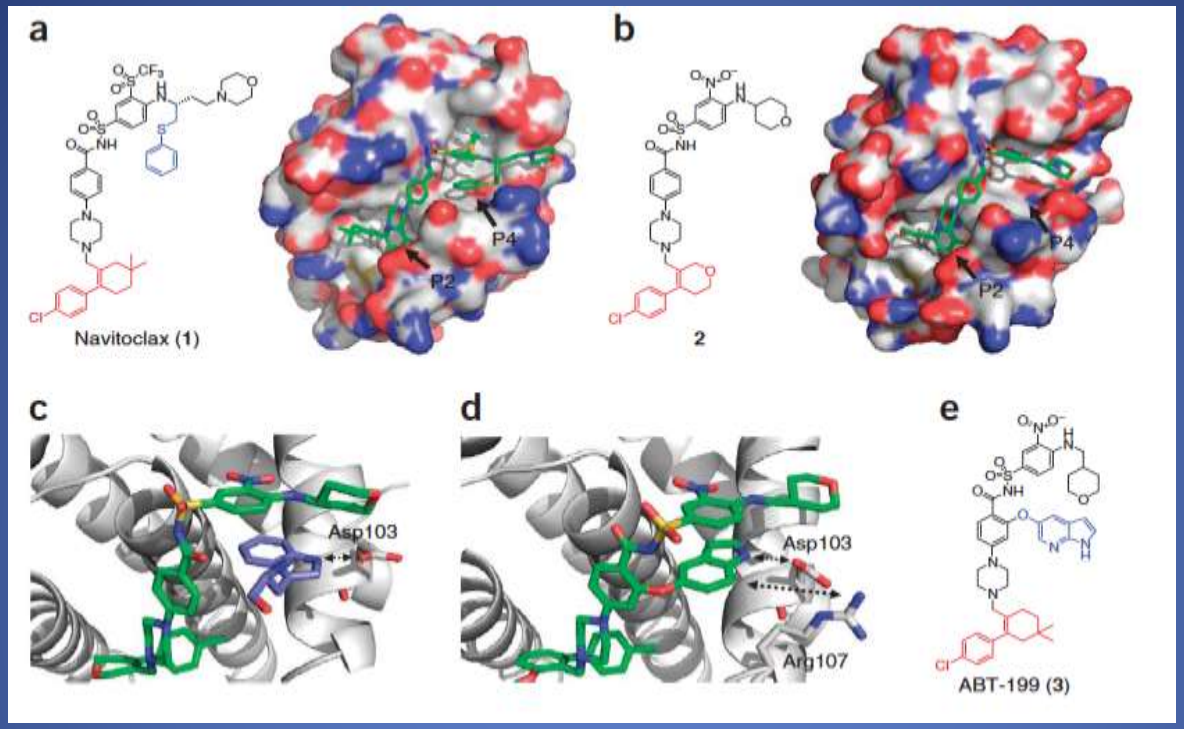
*McCarthy, PL et al. Meta-analysis, JCO, July, 201; Italian, American, French Trials

Treatment of Relapsed Disease

- Triplet or Doublet Therapy depending on aggressiveness and host factors
- Consider stem cell transplantation if patient has never had one or as salvage if previous transplant lasted extended period of time (> 1 year)
- Matched pair analysis comparing second transplant to systemic chemo after relapse demonstrated improved OS (55.5 vs 25.4 months, p=0.04), especially in those whose first transplant lasted > 18 months. (Yhim, HY, et al. BMT, 2013; 48(3))
- If relapse occurs off therapy for extended period of time, consider re-treatment

Newer Therapeutic Agents

Venetoclax: Bcl-2 inhibition

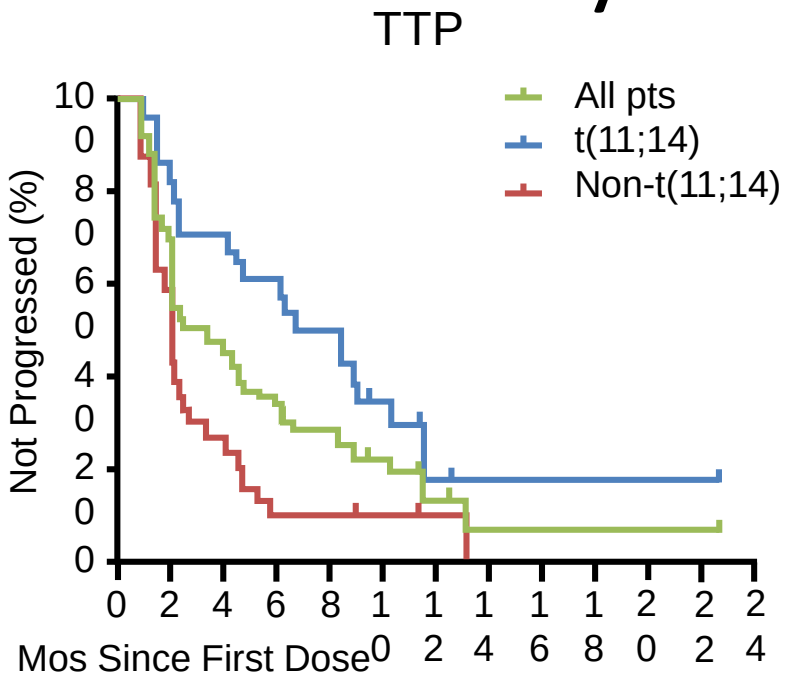


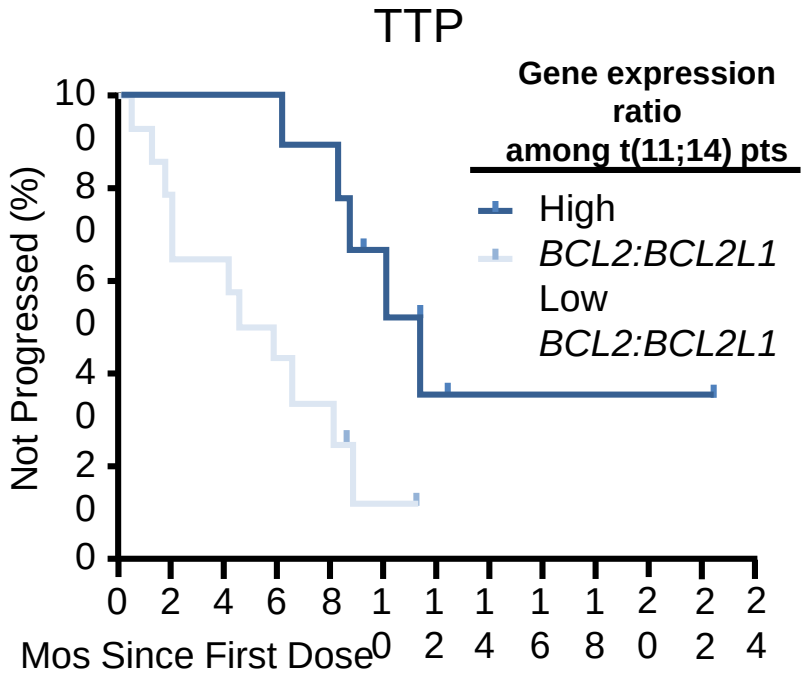
Selective, orally available, small-molecule BCL-2 inhibitor; **t(11;14)**

Major dose modifications required in setting of CYP 3A inhibitors and inducers and P-gp inhibitors

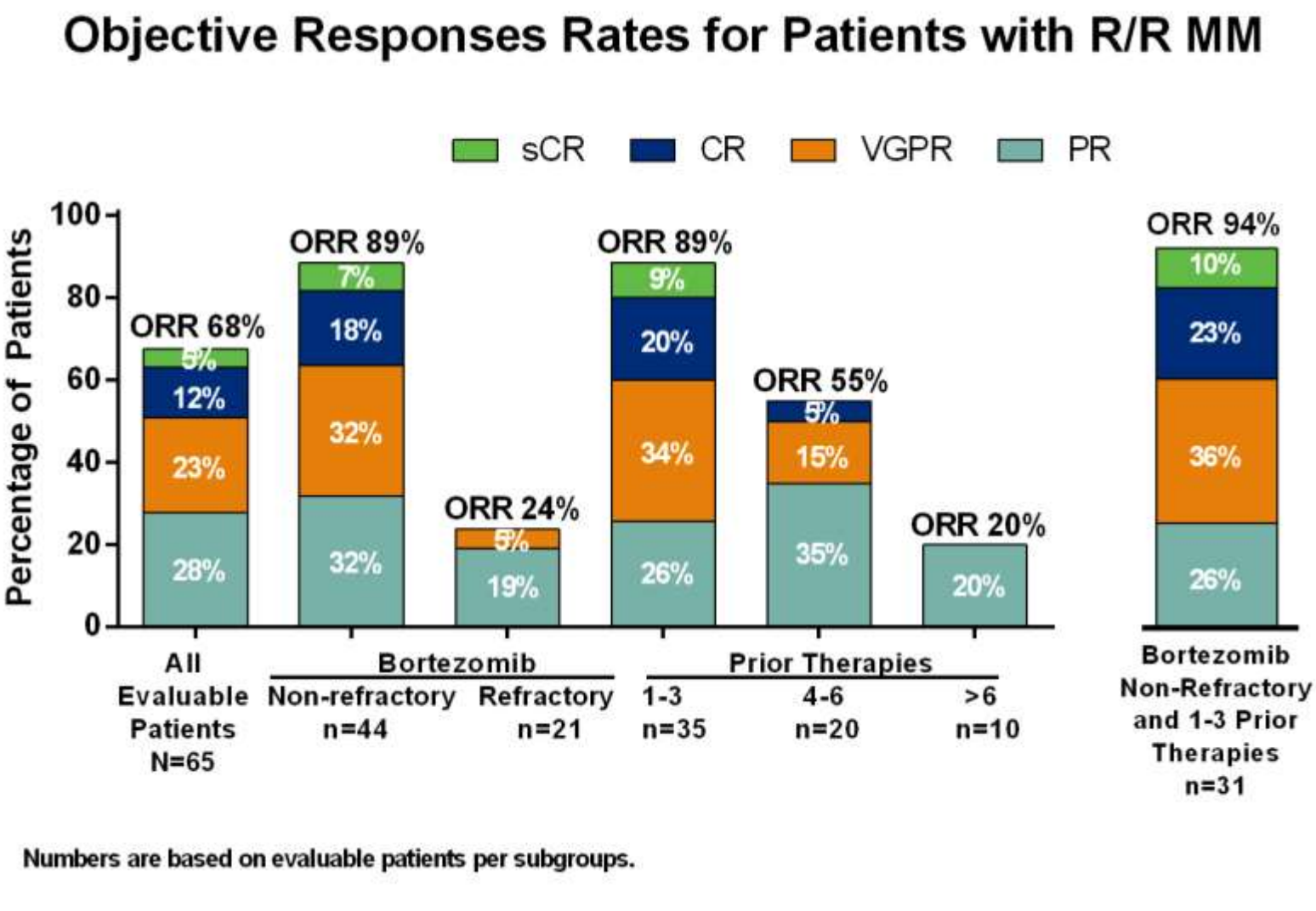
Cr Cl > 30 mL/minute; no dose adjustments; severe RI/HD, no data

Venetoclax Monotherapy for Relapsed/ Refractory MM: TTP and DoR





Kumar S, et al. ASH 2016. Abstract 488. *Reproduced with permission.*



975 Venetoclax Combined with Bortezomib and Dexamethasone for Patients with Relapsed/Refractory Multiple Myeloma

Phase III trial ongoing

Adoptive Cell Therapy

Chimeric Antigen Receptor-T (CAR-T) cells:

Autologous T cells transduced with lentivirus vector to encode CAR

- **Consists of extracellular receptor, co-stimulatory and activation domains**
- **HLA independent**

- FDA approved for refractory acute lymphocytic leukemia, ages 3-25

- Very promising results in non-Hodgkin lymphomas expressing CD19

- Multiple myeloma in patients whose plasma cells express BCMA (B cell maturation antigen); member of tumor necrosis factor superfamily

LCAR-B38M CAR-T*
ASCO, 2017

- Single arm study of 19 patients with relapsed, refractory myeloma
- 7 patients monitored for > 6 months; 6 of whom achieved complete response and minimal residual disease negative.
- 12 patients followed for < 6 months: near complete response
- Objective response rate of 100%
- Side effects: 74% with Cytokine Release Syndrome; 1 case gr 3 and 1 case gr 4

*Zhao, et al. Second Affiliated Hospital of Xi'an Jiaotong University, China

CRB-401 Multicenter Phase I Dose Escalation trial of bb2121 in RRMM*

- ≥ 3 prior therapies, including IMiD and Proteosome Inhibitor or both
- ≥ to 50% expression of BCMA (B cell maturation antigen)
- Lymphodepletion: Fludarabine (30 mg/m2) and CY (300 mg/m2) x 3 days
- Dosing levels of 5, 15, 45, 80, and 120 x 10(7) CAR-T cells
- ORR 100% in 9 evaluable patients at dose of 5.0 x 10(7) cells or higher

Side Effects: Cytokine Release Syndrome 73%, gr 1-2. No > gr 2 CRS or neurotoxicity.

*Trial: NCT02658929
Presented Lin, Yi, et al. European Hematology Association, Madrid, Spain, 2017

Main Side Effects of CAR-T cell Adoptive Cell Therapy

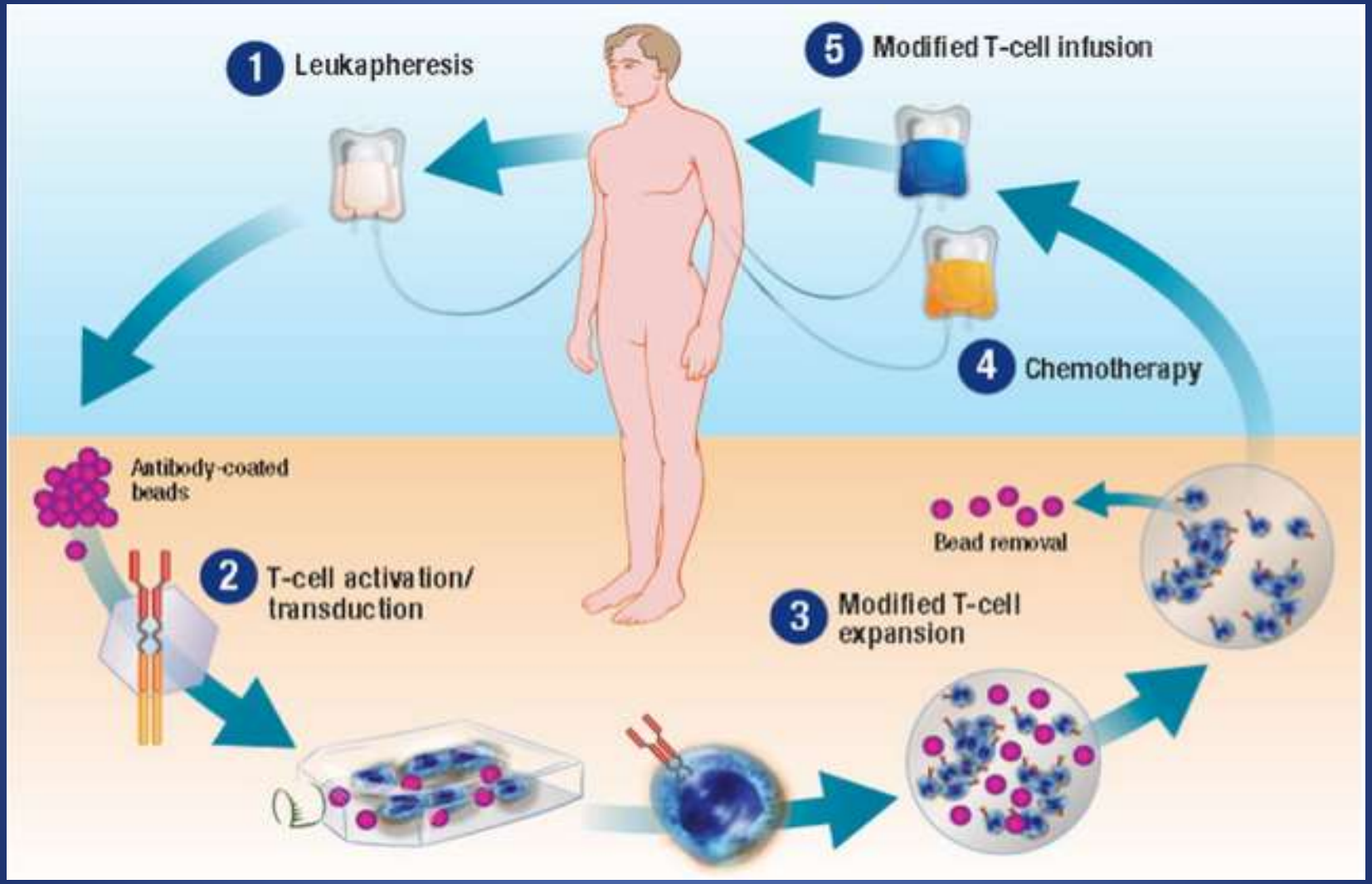
Immediate: Cytokine Release Syndrome: Fever, hypotension, AKI, elevated liver function tests, reduced left ventricular ejection fraction, coagulopathy, pneumonitis/dyspnea, pulmonary edema, elevated levels of creatine kinase, dysrhythmias, electrolyte abnormalities, gastrointestinal symptoms

Longer term: B cell aplasia, hypogammaglobulinemia

Neurotoxicity: May occur with or without CRS. May be delayed.

Headaches, confusion, obtundation, tremors, dysphasia, ataxia, seizures

CAR-T Cell Therapy Process



http://www.oncologynurseadvisor.com/leukemia/reprogramming-immune-system-to-target-cancer/article/461164/

Treatment of CRS/Neurotoxicity

- Supportive Care/ICU
- Tocilizumab: IL-6R antagonist
- Steroids: especially neurotoxicity

Treatment Cast Nephropathy

Mechanical Removal of Light Chains:

Plasma Exchange: Meta-analysis of 3 randomized studies, comparing patients who Received chemo alone (n=63), or chemo + PLEX (n=84): 6 month dialysis dependency ratio significantly lower in the combination group (15.6% v 37.2%; P=0.04). No OS difference.

(Yu, X, et al. Chemotherapy with or without plasmapheresis in acute renal failure due to multiple myeloma: A meta-analysis. **Int J of Clin Pharmacol Ther 53: 391-397, 2015)**

High Cut-off Hemodialysis: (molecules ≤ 60-65 kD)

67 myeloma patients dialysis-dependent: decreased FLCs in approx 2/3 by day 12 and dialysis independence in 63%. Treated with HCO and myeloma therapy.
HD-independence factors: 1. Time to initiation of HCO; 2. degree of FLC reduction on days 12 and 21.

(**Hutchison, CA, et al**. Immunoglobulin free light chain levels and recovery from Myeloma kidney on treatment with chemotherapy and high cut-off haemodialysis. **Nephrol, Dial, Transplant 27:3823-3828, 2012.**

Treatment of Myeloma Cast Nephropathy (MCN): A Randomized Trial Comparing Intensive Haemodialysis (HD) with High Cut-Off (HCO) or Standard High-Flux Dialyzer in Patients Receiving a Bortezomib-Based Regimen (the MYRE Study, by the Intergroupe Francophone du Myélome (IFM) and the French Society of Nephrology (SFNDT)

EuLITE Study (European Trial of Free Light Chain Removal by Extended Hemodialysis in Cast Nephropathy)

Randomized, Controlled. Evaluating HCO-HD and bortezomib based therapy

Single Center Outcomes in 52 consecutive new MM patients requiring dialysis January 1995-January 2016

Age	69 (37-88) 68% > 65 years of age
Male/female	54/46%
Calcium > 11.5 mg/dl	25%
LDH >250 IU/L	48%
Serum albumin	Median 3.5 g/dL (2.1-4.6)
Involved serum FLC mg/L	9080 (1190-201,000)
High risk cytogenetics	40% (38)
R-ISS	25% stage II and 75% stage III
Hemoglobin < 10 g/dL	95%
Platelets < 100 x 10(9)/L	10%
IgG/A/D/light chain only	30/26/2/42%
Beta-2 microglobulin mg/L	21.7 (6-60)
Bence-Jones proteinuria (g/24 hr)	2.2 (0.5-8.8)

Dimopoulos, MA et al. Blood Cancer J (2017) 7, e571. Table adapted.

- Treatments: Bortezomib based in 43 patients (82%)
- 26/52 patients became dialysis independent, median 158 days (4-336)
- Median eGFR=45.5 mL/min/1.73 m2 (18-84)
- Age ≤ 65 associated with higher probability of renal response (75 vs 38%) and shorter time to response, 51 vs 336 days (p=0.027)
- Renal recovery rate 27% in those > 75 years old
- Patients treated with bortezomib regimen (21/43): dialysis independence of 49%

Data above from Dimopoulos, MA et al. Blood Cancer J (2017)

- Bortezomib triplets (n=32) vs Bortezomib/dex (n=11): higher probability of renal response (57 vs 27%) p=0.06.
- 5 while on dialysis underwent transplant, 4/5 dialysis independent within 1 month
- Median follow up all patients: 33 months; median survival 29 months
- Early mortality (within 2 months) 16%, mostly infection complications
- Patients who achieved at least ≥ PR to therapy by 2months, greater dialysis independence (68 vs 27%) p=0.004.

Data above from Dimopoulos, MA et al. Blood Cancer J (2017)

Myeloma Therapies in Acute Renal Insufficiency

- Bortezomib based.
- Triplet therapy beneficial (bortezomib-IMiD-Dex; bortezomb-Cy-Dex)
- Dex 40 mg daily, 4 days on and 4 days off for 1 cycle; modified for age, tolerance and co-morbidities.
- Carfilzomib as PI also an option, particularly with Cr Cl ≥ 15 mL/min

MM Patients on Long Term HD*

- 15-30% increased risk of death within first months of diagnosis
- Median survival approx 2 years, 30% > 3 years

*Dimopolous, MA, et al. Significant improvement in the survival of patients with multiple myeloma presenting with severe renal impairment after the introduction of novel agents. Ann Oncol 25: 195-200, 2014.
*Torra R, et al. Patients with multiple myeloma requiring long term dialysis: Presenting features, response to therapy, and outcome in a series of 20 cases. Br J Haematol 91: 854-859. 1995
*Irish, AB, et al. Presentation and survival of patients with severe renal failure and myeloma. QJM 90: 773-780. 1997
*Gonsalves, WI, et al. Improvements in renal function and its impact on survival in patients with newly diagnoses multiple myeloma. Blood Cancer J. 5:e296, 2015.