Fred Hutch Cancer Center

UW Medicine

Newly Diagnosed Multiple Myeloma

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Disclosures

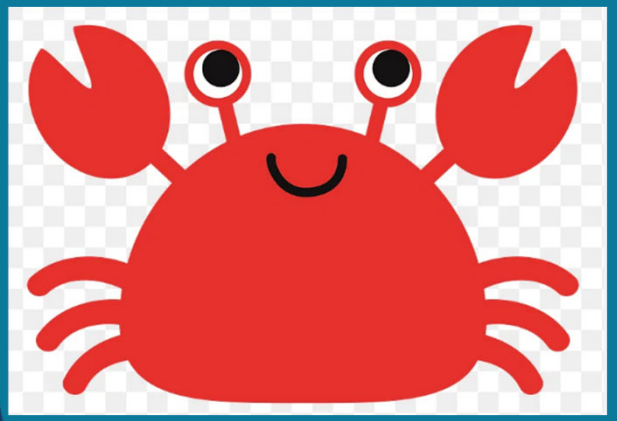
- Research: Bristol Myers Squibb
- Advisory Boards: Prothena, Johnson & Johnson

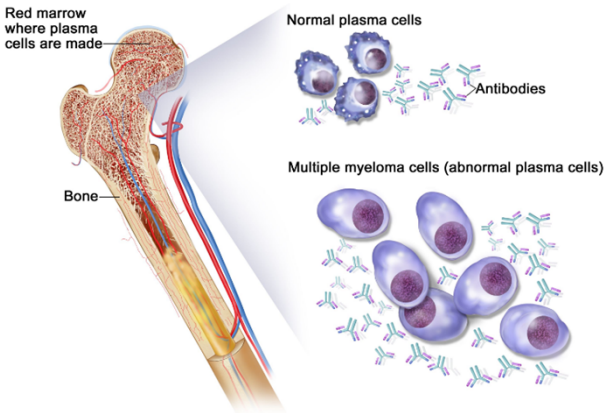
1 Diagnosis of Multiple Myeloma

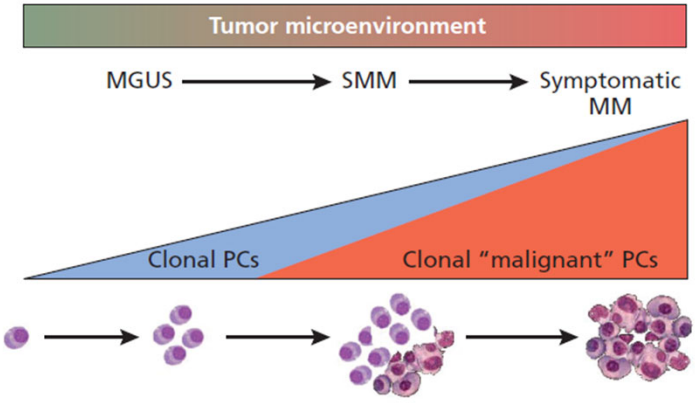
2 Plasma Cell Directed Therapy

3 Supportive Considerations

Diagnosis of Multiple Myeloma







Multiple Myeloma

SLiM-CRAB

Both criteria must be met:

- Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma
- Any one or more of the following myeloma defining events:
  - Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

C
- 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)

R
- Renal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >177 µmol/L (>2 mg/dL)

A
- Anemia: hemoglobin value of >2 g/dL below the lower limit of normal, or a hemoglobin value <10 g/dL

B
- Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography-CT (PET-CT)

S
- Clonal bone marrow plasma cell percentage ≥ 60%

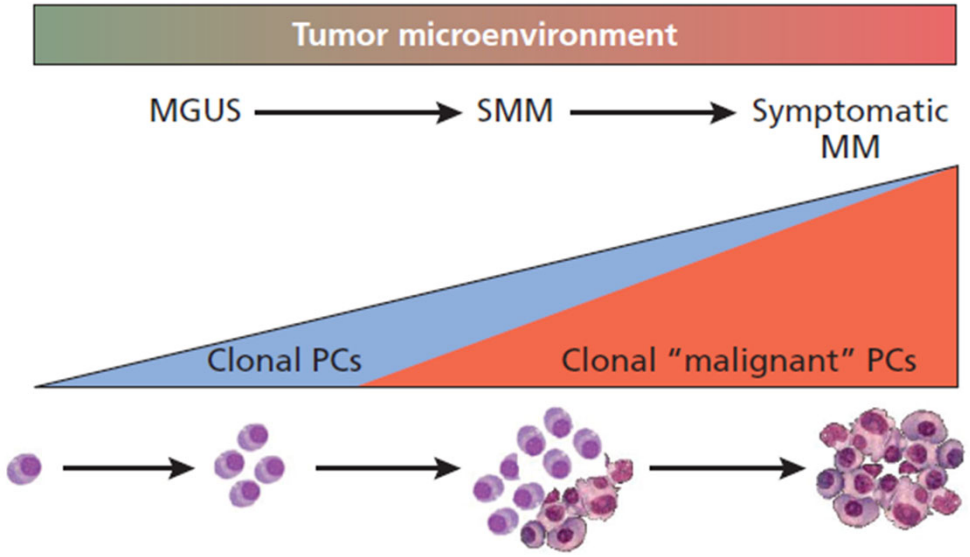
L
- Involved: uninvolved serum free light chain (FLC) ratio ≥ 100 (involved free light chain level must be ≥100 mg/L)

M
- >1 focal lesions on magnetic resonance imaging (MRI) studies (at least 5 mm in size)

ASH SAP 8th Edition; Rajkumar, *AJH*, 2022

Image: National Cancer Institute

Monoclonal protein ≠ End-organ damage

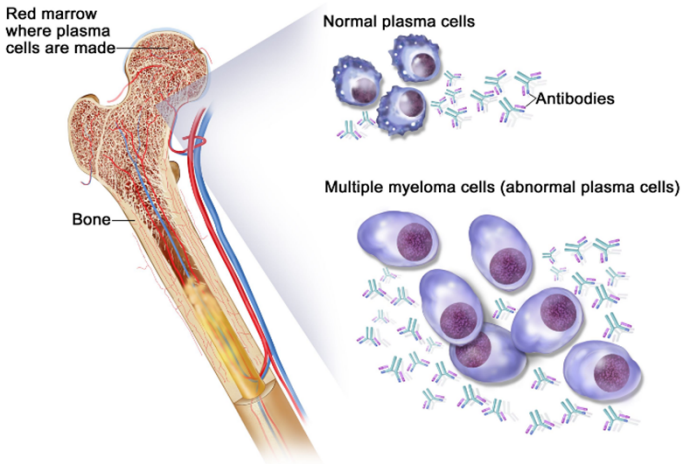


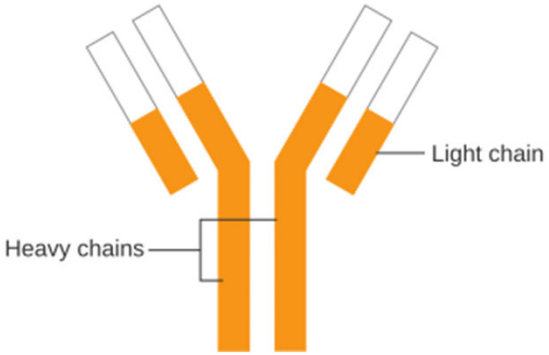
Renal Impairment as a Myeloma Defining Event

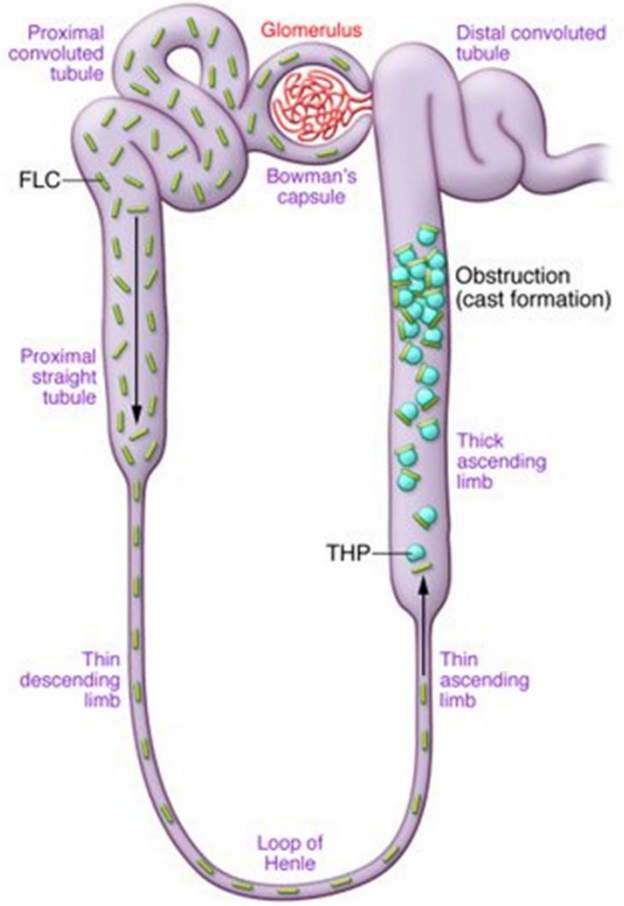
- **eGFR <40 *or* Cr >2 due to light chain cast nephropathy**
- Other causes of AKI must be excluded, for example:
  - Dehydration
  - Diabetes
  - High blood pressure
  - Other plasma cell disorders (i.e. AL amyloidosis)
  - *Hypercalcemia**

Leung & Rajkumar, *Blood Cancer Journal*, 202

Light Chain Cast Nephropathy



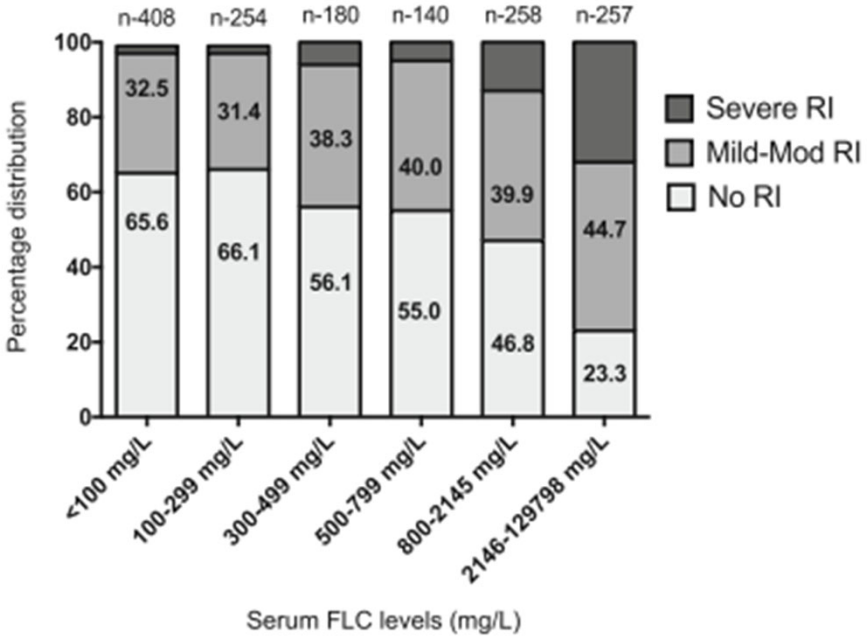


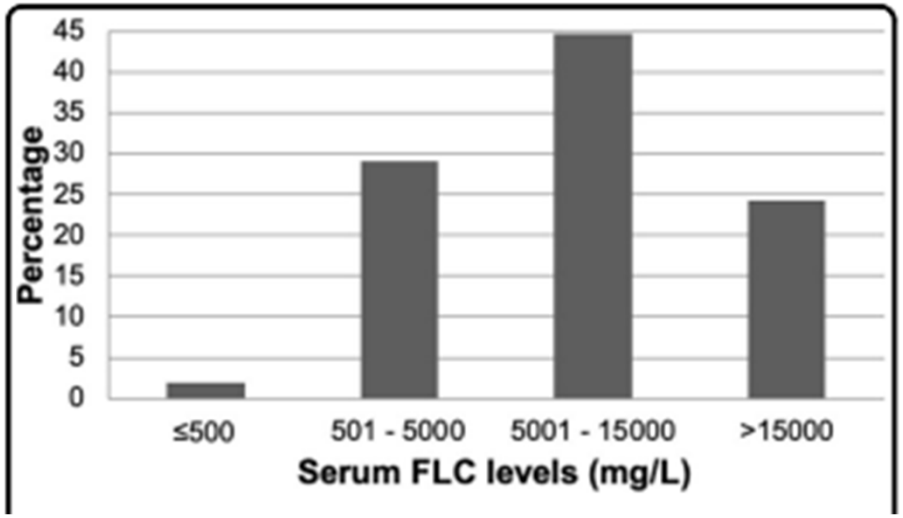


Leung & Rajkumar, *Blood Cancer Journal*, 2023

Images: National Cancer Institute; Leung, *J Clin Invest*, 2012

Levels of involved FLC & Kidney Function





- Since mechanism of kidney impairment is based on excess FLC being cleared through the kidneys, the higher the involved FLC, the worse the renal impairment
- Rare to have light chain cast nephropathy with iFLC <50 mg/dL

Yadav, et al., *BMC Nephrology,* 2018

Yadav, et al., *Blood Cancer Journal*, 2020

Renal Impairment as a Myeloma Defining Event

Kidney Biopsy?

- May be avoided if:
  - iFLC >150mg/dL *(higher the iFLC, greater the suspicion)*
  - Majority of proteinuria Bence Jones (<10% albuminuria)
  - No clear alternative etiologies for AKI
  - Not the only myeloma defining event necessitating treatment

Leung & Rajkumar, *Blood Cancer Journal*, 2023

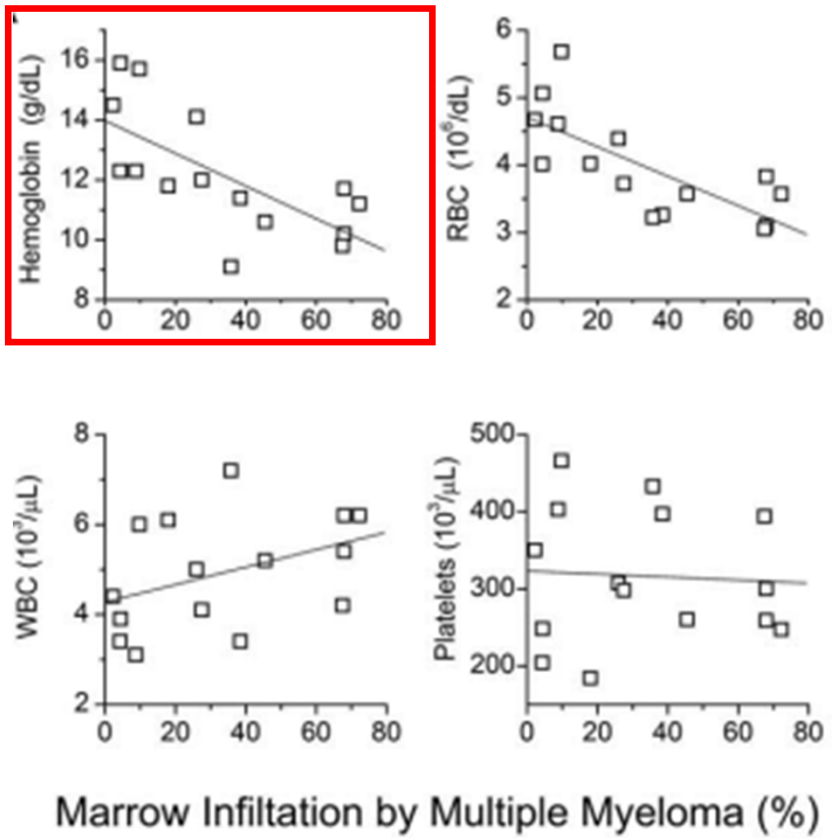
Treatment Considerations: Renal Insufficiency

- May be an emergency requiring hospitalization for immediate initiation of treatment
  - Rapid reduction of iFLC imperative to renal recovery
    - At least 50-60% reduction in iFLC; faster is better
    - Ideally <50 mg/dL by C1
- Plasmapheresis (PLEX) – controversial
  - Mixed results in terms of efficacy, but low risk procedure

Leung & Rajkumar, *Blood Cancer Journal*, 2023

Anemia as a Myeloma Defining Event

- **Hgb <10 *or* Hgb >2 below lower limit of normal due to the underlying clonal plasma cells**
- Other causes of anemia must be excluded:
  - Labs: iron/ferritin, B12, folate, TSH, haptoglobin, epo, etc.
  - BMbx



Rajkumar, *AJH*, 2022

Bouchnita, et al, *AJH*, 2016

Bone Lesions as a Myeloma Defining Event

- Advanced imaging preferred
  - Whole body PET/CT
  - Whole body MRI (ideally with diffusion weighting)
- One or more osteolytic lesion(s) ≥5mm
  - **If only one lytic lesion, then clonal bone marrow plasma cells must be ≥10%**
    - One lytic lesion with BMPC <10% = solitary bone plasmacytoma, *not multiple myeloma*
  - **Macrofocal myeloma = multiple lytic lesions (confirmed plasmacytomas) with BMPC <10% and no other MDE**
- Other causes of lytic lesions must be ruled out if indeterminate – bone biopsy
  - E.g. other malignancies, benign lesions
  - If without significant BMPC involvement but suspecting macrofocal myeloma
- Other bone abnormalities on imaging in absence of lytic lesions are *not* considered a myeloma defining event
  - E.g. osteoporosis, compression fractures, FDG avidity on PET
  - Exception: 2+ focal lesions ≥5mm on MRI = myeloma defining event

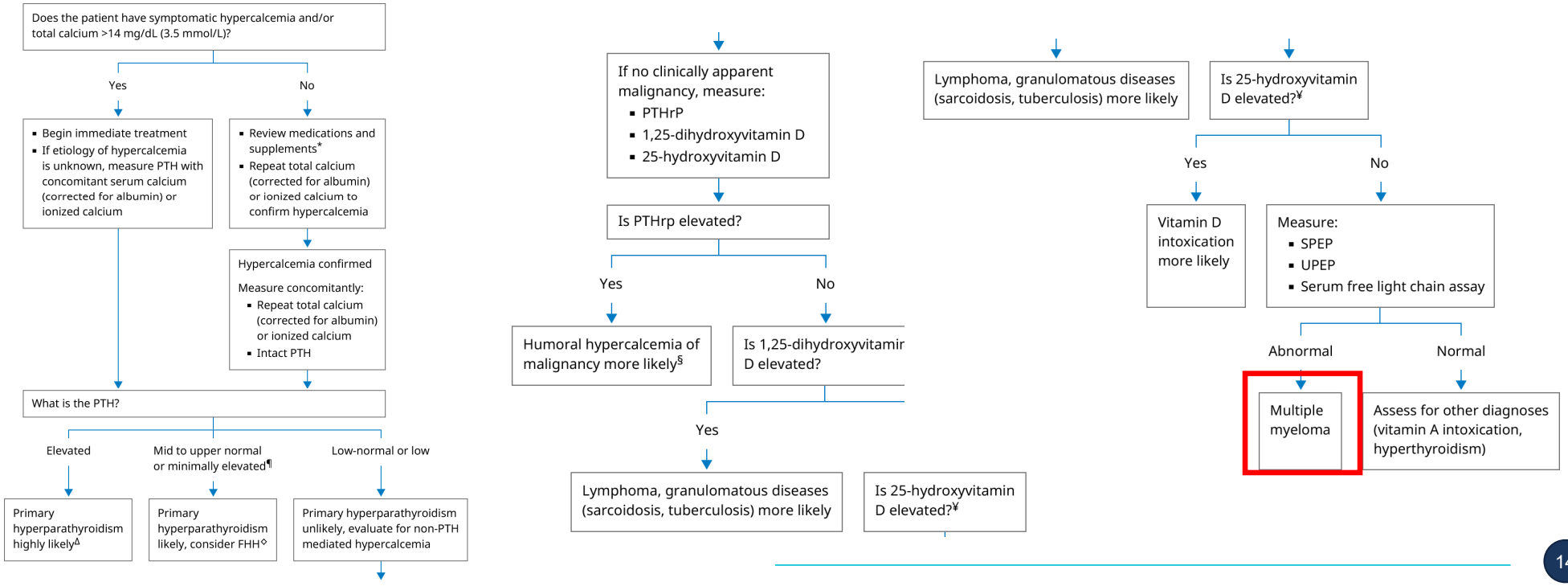
Rajkumar, *AJH*, 2022

UpToDate

Hypercalcemia as a Myeloma Defining Event

Severe hypercalcemia = emergency

- **Ca >11 mg/dL *or* >1 mg/dL above upper limit of normal due to the underlying clonal plasma cells**
- Other causes of hypercalcemia must be excluded:

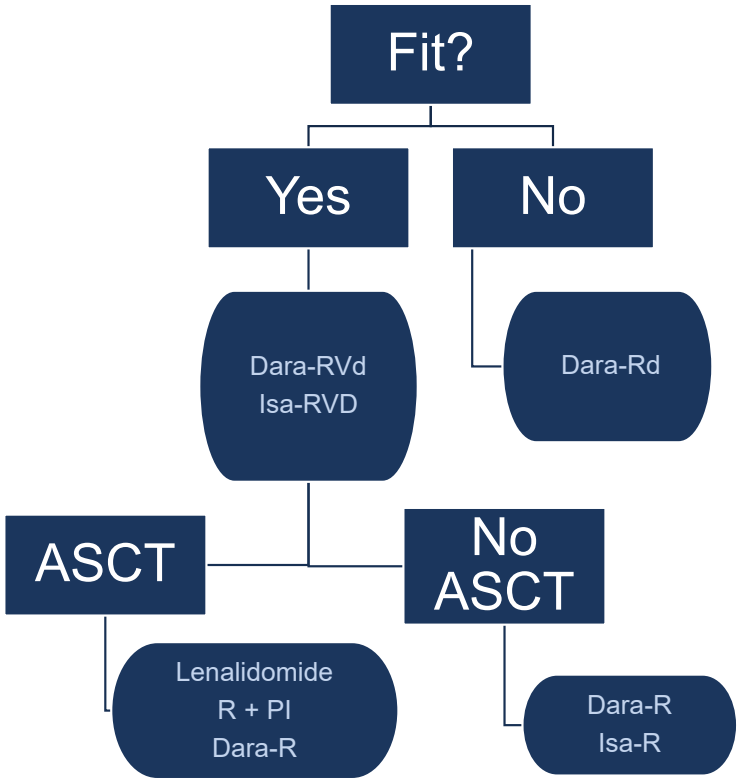


Rajkumar, *AJH*, 2022

UpToDate

Plasma Cell Directed Therapy

Newly Diagnosed Myeloma: First-line Treatment



Fit *with* ASCT: Dara-RVd or Isa-RVd

blood

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Daratumumab, lenalidomide dexamethasone for transplan multiple myeloma: the GRIF

Peter M. Voorhees,[1] Jonathan L. Kaufman,[2] Jacob Laubach,[3] Dougla Rebecca Silbermann,[8] Luciano J. Costa,[9] Larry D. Anderson Jr,[10] Nity Caitlin Costello,[15] Andrzej Jakubowiak,[16] Tanya M. Wildes,[17] Robert Z Yana Lutska,[21] Huiling Pei,[22] Jon Ukropec,[23] Jessica Vermeulen,[24] Carla for the GRIFFIN Trial Investigators

The NEW ENGLAND JOURNAL of M

ESTABLISHED IN 1812 JANUARY 25, 2

Daratumumab, Bortezomi and Dexamethasone for M

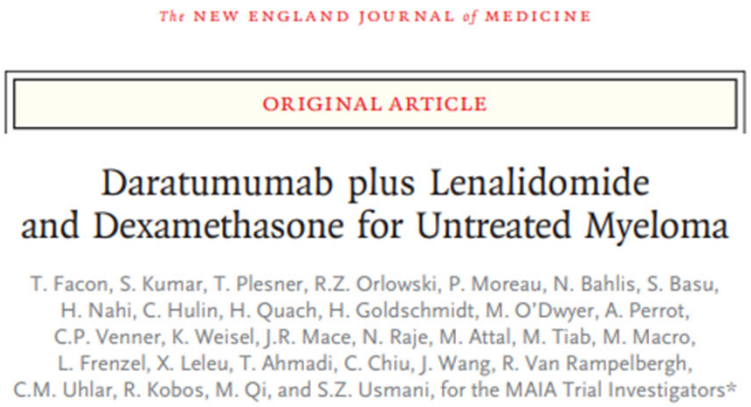
P. Sonneveld, M.A. Dimopoulos, M. Boccadoro, H. Quach, P.J. I S. Mangiacavalli, A. Perrot, M. Cavo, A. Belotti, A. Broijl, F. Gay, R. Mi F. Schjesvold, A. Sureda Balari, L. Rosiñol, M. Delforge, W. Roeloffz R. Hajek, A. Jurczyszyn, S. Lonergan, T. Ahmadi, Y. Liu, J. Wang, D. V A. Sitthi-Amorn, C.J. de Boer, R. Carson, P. Rodriguez-Otero, J. Bladé, a

Isatuximab, Lenalidomide, Bortezomib, and Dexamethasone Induction Therapy for Transplant-Eligible Newly Diagnosed Multiple Myeloma: Final Part 1 Analysis of the GMMG-HD7 Trial

Elias K. Mai, MD[1]; Uta Bertsch, MD[1,2]; Ema Pozek, MSc[3]; Roland Fenk, MD[4]; Britta Besemer, MD[5]; Christine Hanoun, MD[6]; Roland Schroers, MD[7]; Ivana von Metzler, MD[8]; Mathias Hänel, MD[9]; Christoph Mann, MD[10]; Lisa B. Leypoldt, MD[11]; Bernhard Heilmeier, MD[12]; Stefanie Huhn, Dr sc hum[1]; Sabine K. Vogel, PhD[1]; Michael Hundemer, MD[1]; Christof Scheid, MD[13]; Igor W. Blau, MD[14]; Steffen Luntz, MD[15]; Niels Weinhold, PhD[1]; Diana Tichy, PhD[3]; Tobias A.W. Holderried, MD[16]; Karolin Trautmann-Grill, MD[17]; Deniz Gezer, MD[18]; Maika Klaiber-Hakimi, MD[19]; Martin Müller, MD[20]; Evgenii Shumilov, MD[21]; Wolfgang Knauf, MD[22]; Christian S. Michel, MD[23]; Thomas Geer, MD[24]; Hendrik Riesenberg, MD[25]; Christoph Lutz, MD[26]; Marc S. Raab, MD[1]; Axel Benner, Dipl Stat[3]; Martin Hoffmann, MD[27]; Katja C. Weisel, MD[11]; Hans J. Salwender, MD[28]; and Hartmut Goldschmidt, MD[1,2]; for the German-Speaking Myeloma Multicenter Group (GMMG) HD7 Investigators

- Quad induction with anti-CD38 monoclonal antibodies improves **progression free survival** and **depth of response** compared to RVD alone
  - Isatuximab (isa) or daratumumab (dara) = anti-CD38 monoclonal antibody
  - Lenalidomide (R) = immunomodulatory drug (IMID)
  - Bortezomib (V) = proteosome inhibitor
  - Dexamethasone (D) = steroid

Frail: Dara-Rd



The NEW ENGLAND JOURNAL of MEDICINE

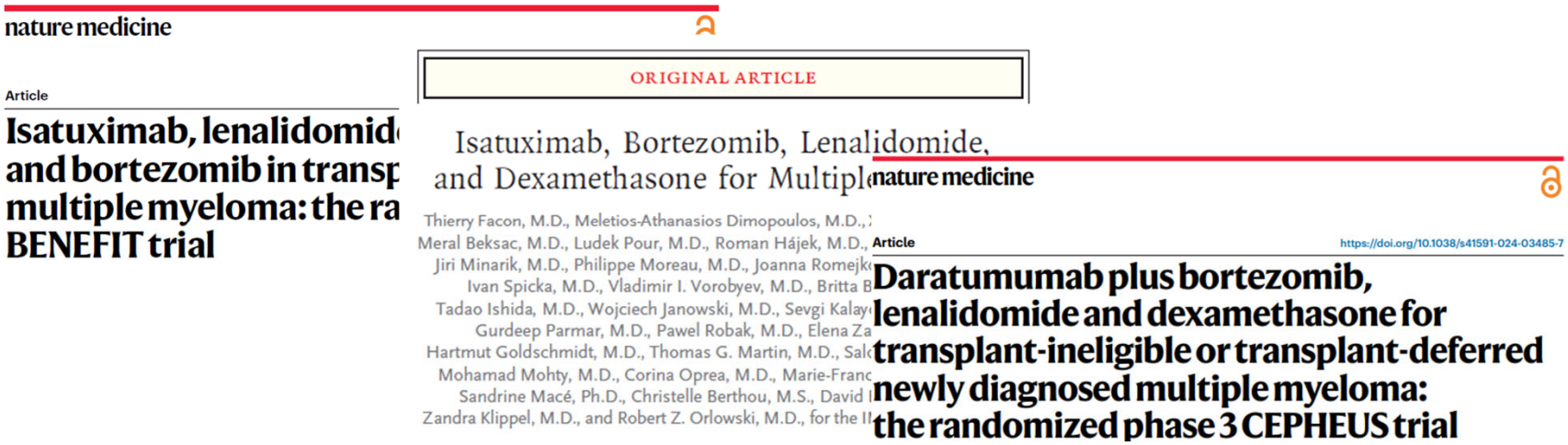
ORIGINAL ARTICLE

Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma

T. Facon, S. Kumar, T. Plesner, R.Z. Orlowski, P. Moreau, N. Bahlis, S. Basu, H. Nahi, C. Hulin, H. Quach, H. Goldschmidt, M. O'Dwyer, A. Perrot, C.P. Venner, K. Weisel, J.R. Mace, N. Raje, M. Attal, M. Tiab, M. Macro, L. Frenzel, X. Leleu, T. Ahmadi, C. Chiu, J. Wang, R. Van Rampelbergh, C.M. Uhlar, R. Kobos, M. Qi, and S.Z. Usmani, for the MAIA Trial Investigators*

- Dara-Rd improves **depth of response, progression free survival,** and **overall survival** compared to Rd for transplant-ineligible patients
  - OS benefit observed despite a substantial amount of crossover for dara in control group during subsequent lines of therapy

Fit *without* ASCT: Dara-RVd or Isa-RVd


nature medicine

Article

Isatuximab, lenalidomid and bortezomib in transp multiple myeloma: the ra BENEFIT trial

ORIGINAL ARTICLE

Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone for Multipl

Thierry Facon, M.D., Meletios-Athanasios Dimopoulos, M.D., Meral Beksac, M.D., Ludek Pour, M.D., Roman Hájek, M.D., Jiri Minarik, M.D., Philippe Moreau, M.D., Joanna Romejk Ivan Spicka, M.D., Vladimir I. Vorobyev, M.D., Britta B Tadao Ishida, M.D., Wojciech Janowski, M.D., Sevgi Kalay Gurdeep Parmar, M.D., Pawel Robak, M.D., Elena Za Hartmut Goldschmidt, M.D., Thomas G. Martin, M.D., Sal Mohamad Mohty, M.D., Corina Oprea, M.D., Marie-Franc Sandrine Macé, Ph.D., Christelle Berthou, M.S., David Zandra Klippel, M.D., and Robert Z. Orlowski, M.D., for the I

nature medicine

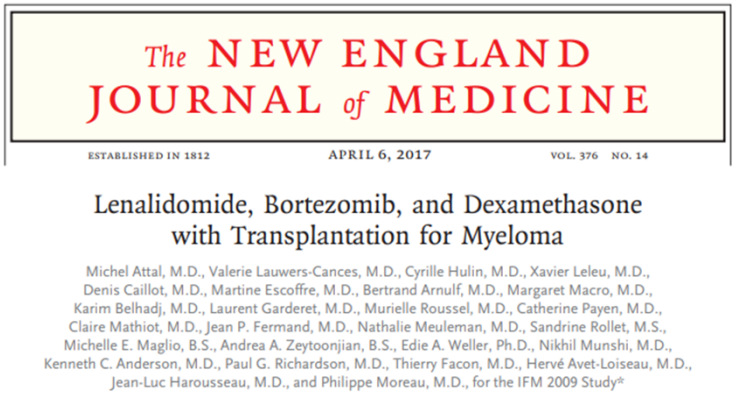
Article

https://doi.org/10.1038/s41591-024-03485-7

Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: the randomized phase 3 CEPHEUS trial

- Quad induction with anti-CD38 monoclonal antibodies improves **progression free survival** and **depth of response** compared to RVD alone
- Quad induction with bortezomib improves **MRD-negativity rates** compared to isa-Rd alone

ASCT for all who are transplant-eligible?

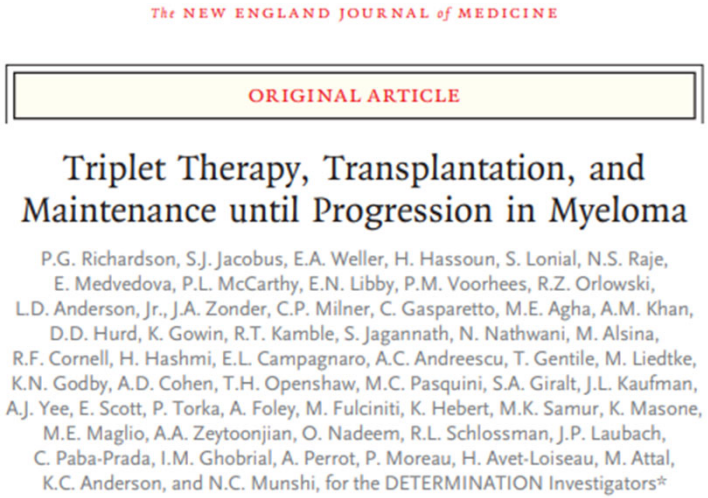


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 6, 2017 VOL. 376 NO. 14

Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma

Michel Attal, M.D., Valerie Lauwers-Cances, M.D., Cyrille Hulin, M.D., Xavier Leleu, M.D., Denis Caillot, M.D., Martine Escoffre, M.D., Bertrand Arnulf, M.D., Margaret Macro, M.D., Karim Belhadj, M.D., Laurent Garderet, M.D., Murielle Roussel, M.D., Catherine Payen, M.D., Claire Mathiot, M.D., Jean P. Fermand, M.D., Nathalie Meuleman, M.D., Sandrine Rollet, M.S., Michelle E. Maglio, B.S., Andrea A. Zeytoonjian, B.S., Edie A. Weller, Ph.D., Nikhil Munshi, M.D., Kenneth C. Anderson, M.D., Paul G. Richardson, M.D., Thierry Facon, M.D., Hervé Avet-Loiseau, M.D., Jean-Luc Harousseau, M.D., and Philippe Moreau, M.D., for the IFM 2009 Study*



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma

P.G. Richardson, S.J. Jacobus, E.A. Weller, H. Hassoun, S. Lonial, N.S. Raje, E. Medvedova, P.L. McCarthy, E.N. Libby, P.M. Voorhees, R.Z. Orlowski, L.D. Anderson, Jr., J.A. Zonder, C.P. Milner, C. Gasparetto, M.E. Agha, A.M. Khan, D.D. Hurd, K. Gowin, R.T. Kamble, S. Jagannath, N. Nathwani, M. Alsina, R.F. Cornell, H. Hashmi, E.L. Campagnaro, A.C. Andreescu, T. Gentile, M. Liedtke, K.N. Godby, A.D. Cohen, T.H. Openshaw, M.C. Pasquini, S.A. Giralt, J.L. Kaufman, A.J. Yee, E. Scott, P. Torka, A. Foley, M. Fulciniti, K. Hebert, M.K. Samur, K. Masone, M.E. Maglio, A.A. Zeytoonjian, O. Nadeem, R.L. Schlossman, J.P. Laubach, C. Paba-Prada, I.M. Ghobrial, A. Perrot, P. Moreau, H. Avet-Loiseau, M. Attal, K.C. Anderson, and N.C. Munshi, for the DETERMINATION Investigators*

- Upfront ASCT improves **progression free survival** but **not overall survival**
  - *Induction with RVd (not quad induction as would be standard of care today)*
  - *Substantial crossover between arms*
- Ongoing studies in today's modern era of therapy (i.e. quad induction) regarding role of ASCT

Post-Transplant Maintenance

- **Lenalidomide monotherapy**

- Special considerations
  - **Lenalidomide + proteosome inhibitor** if high-risk disease (i.e. RV)
    - FORTE clinical trial: KR maintenance improves PFS and conversion to MRD-negativity compared to lenalidomide monotherapy; benefit maintained for high-risk subgroup!
  - **?Daratumumab + lenalidomide** if MRD+ post-transplant (i.e. Dara-R)
    - AURIGA clinical trial: dara-R maintenance increased conversion to MRD negativity compared to lenalidomide monotherapy; however, patients were anti-CD38 naive when entering the maintenance setting
    - CASSIOPEIA clinical trial: trended towards increased rates of conversion to MRD negativity with daratumumab maintenance vs. observation for those who had previously been exposed to anti-CD38 during induction, but this did not meet statistical significance

Noteworthy Toxicities

- Infections, cytopenias, fatigue

Daratumumab Isatuximab	Lenalidomide	Bortezomib	Dexamethasone	HDM-ASCT
• Infusion reactions • Hypogamma-globulinemia	• VTE • Rash • Constipation or diarrhea • Nausea • Brain fog • Secondary malignancies	• Neuropathy	• Insomnia • Mood changes • Hyperglycemia • Gastritis • Fluid retention • Osteoporosis • Cataracts	• Secondary malignancies

What if treatment needs to be initiated urgently?

- E.g. hospitalization for acute renal failure or severe hypercalcemia
- Lenalidomide often takes some time to obtain; additionally, time to response may be delayed
- Daratumumab is often not available in the inpatient setting

CyBorD

Cyclophosphamide + Bortezomib + Dexamethasone

- *However, would switch to the preferred regimen as soon as able (i.e. once lenalidomide available – may renally dose – and/or upon discharge)*

Supportive Considerations

Bone Modifying Agents

Bone Modifying Agents: Zoledronic Acid & Denosumab

- Reduces skeletal-related events
- Improves survival outcomes

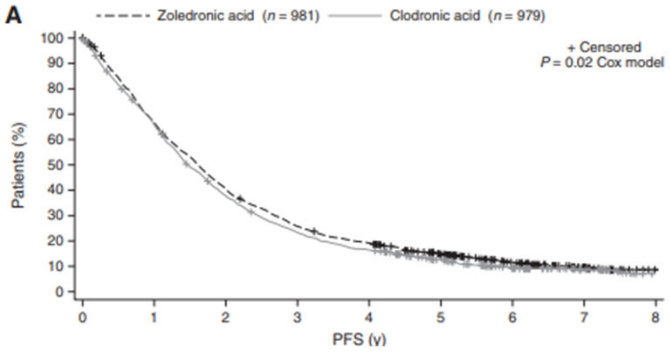
First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial

Gareth J Morgan, Faith E Davies, Walter M Gregory, Kim Cocks, Sue E Bell, Alex J Szubert, Nuria Navarro-Coy, Mark T Drayson, Roger G Owen, Sylvia Feyler, A John Ashcroft, Fiona Ross, Jennifer Byrne, Huw Roddie, Claudius Rudin, Gordon Cook, Graham H Jackson, J Anthony Child, on behalf of the National Cancer Research Institute Haematological Oncology Clinical Study Group

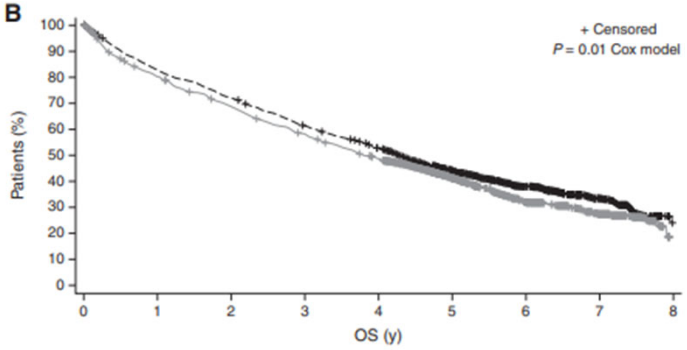
	Intensive pathway			Non-intensive pathway		
	Zoledronic acid (n=555)	Clodronic acid (n=556)	p value	Zoledronic acid (n=426)	Clodronic acid (n=423)	p value
CR, VGPR, or PR	432 (78%)	422 (76%)	0·43	215 (50%)	195 (46%)	0·18
CR or VGPR*	200 (36%)	193 (35%)	0·63	85 (20%)	60 (14%)	0·018
CR*	78 (14%)	69 (12%)	0·42	39 (9%)	27 (6%)	0·13

CR=complete response. PR=partial response. VGPR=very good partial response. *Exploratory analyses.

Table 5: Response rates after induction therapy (intention-to-treat population)



Median PFS: 19 vs. 18 mo



Median OS: 52 vs. 46 mo

Morgan, et al., *Lancet*, 2010

Morgan, et al., *Clinc Cancer Res*, 2013

Toxicities of Bone Modifying Agents

- Osteonecrosis of jaw
  - Dental clearance before starting!
- Severe hypocalcemia (denosumab > zoledronic acid)
- Bisphosphonates
  - Flu-like symptoms
  - Ocular symptoms
  - AKI, proteinuria
- Denosumab
  - Bone pain
  - Nausea, diarrhea
  - Shortness of breath
  - Rebound fractures

Teramachi, et al., *Journal of Bone & Min Metabolism*, 2023

Mirrakhimov, *North American Journal of Medical Sciences*, 2015

Questions?