Update in Multiple Myeloma

September 18th, 2024

Dr. Alfredo De la Torre MD

Division of Hematology; Department of Medicine

Dalhousie University

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Conflict of Interest

Honoraria, Advisory Board and or Educational Grant from:

- Janssen Pharmaceuticals
- AMGEN
- Forus Therapeutics
- Sanofi
- Apo-Biologics
- BMS
- Incyte
- Pfizer

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Agenda:

- **Introduction**
- Epidemiology
- Clinical Presentation
- Pathological Features and Imaging
- Diagnosis
- Prognosis
- Treatment

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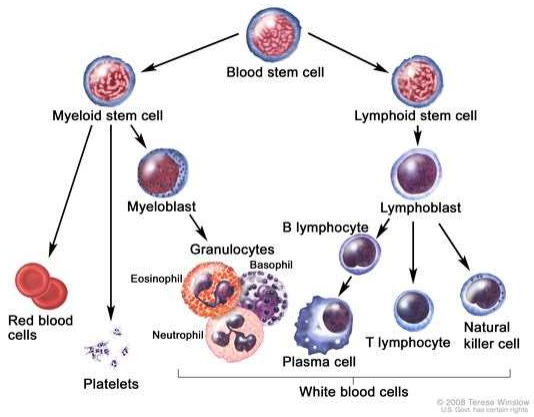
Multiple Myeloma



Multiple myeloma (MM) is characterized by the neoplastic proliferation of plasma cells producing a monoclonal immunoglobulin

Other plasma cell neoplasms

- Plasmacytoma
  - Solitary bone
  - Extramedullary
- Heavy chain disease
- WM
- Systemic AL amyloidosis
- POEMS syndrome

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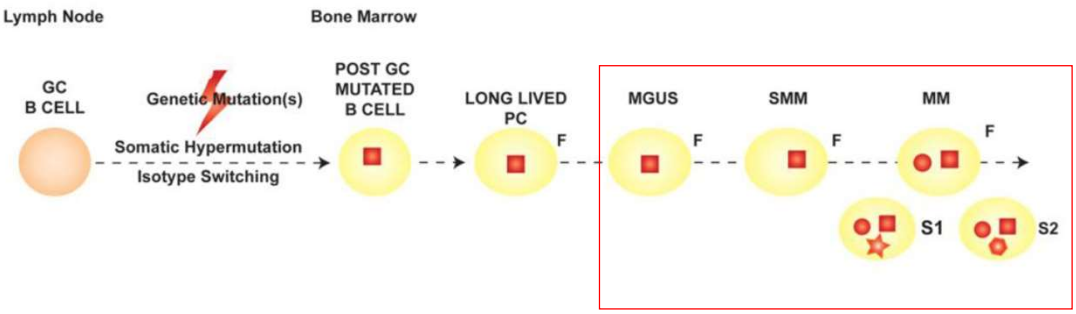
Pathogenesis



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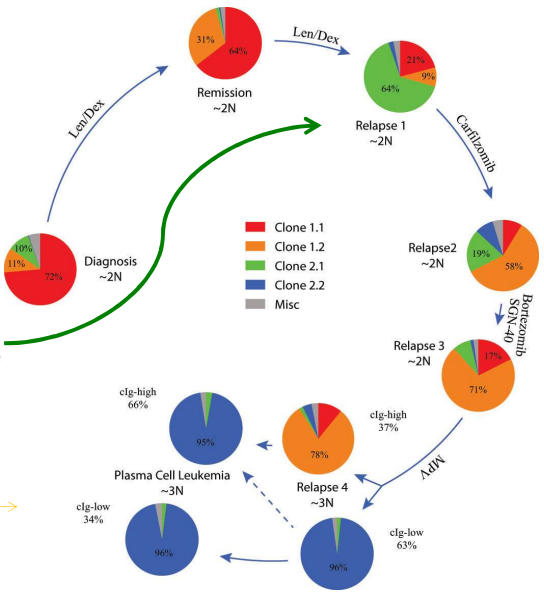
Clonal Tides



- 5 unique clones at diagnosis
- Variable chemotherapy response
- Minor drug resistant clone lethal

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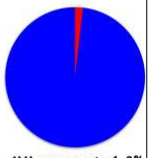
Epidemiology

- 1-2% of all cancers
- 2nd most common hematological malignancy
- Higher incidence in Males 1,4:1
- Median 65-74 years at diagnosis (only 2% are < 40 y/o)

2016

	Common Types of Cancer	Estimated New Cases	Estimated Deaths
1	Breast Cancer	246,660	40,450
2	Lung and Bronchus	224,390	158,080
3	Prostate Cancer	180,890	26,120
4	Colon and Rectum Cancer	134,490	49,190
5	Bladder Cancer	76,960	16,390
6	Melanoma of the Skin	76,380	10,130
7	Non-Hodgkin Lymphoma	72,580	20,150
8	Thyroid Cancer	64,300	1,980
9	Kidney/Renal Pelvis Cancer	62,700	14,240
10	Leukemia	60,140	24,400
14	Myeloma	30,330	12,650



CA Cancer J Clin. 2024;74(1):12. Epub 2024 Jan 17.
Mayo Clin Proc. 2003;78(1):21.
Leuk Lymphoma. 1998;30(5-6):493.

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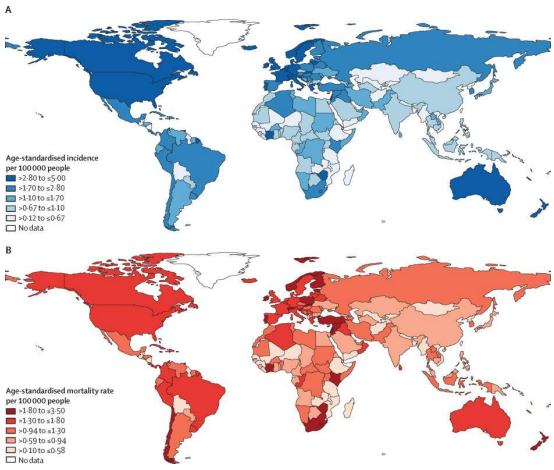
Epidemiology



Estimate:

- ✓ 4,100 Canadians will be diagnosed
  - ✓ 100 in NS
- ✓ 1,750 Canadians will die
  - ✓ 55 in Nova Scotia

1. The Lancet Haematology, Volume 9, Issue 9, e670 - e677
2. CMAJ 2024 May 13;196:E615-23

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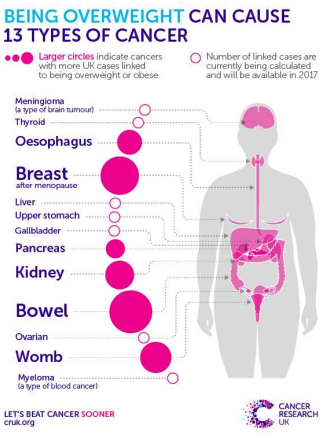
Risk Factors

- Risk increases with higher BMI
- Agent orange exposure
- Prior plasma cell disorder (MGUS, Plasmacytoma)
- Familial risk 3 cases per 1000 (3.7-fold higher in first degree relatives)



JAMA Oncol. 2019;5(3):384.
Clin Lymphoma Myeloma Leuk. 2020;20(5):305. Epub 2019 Dec 28.
N Engl J Med. 2008;359(2):152.

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Symptoms

A retrospective analysis of 1027 sequential patients diagnosed with MM at a single institution found the following symptoms and signs at presentation :

- Anemia – 73 percent
- Bone pain – 58 percent
- Elevated creatinine – 48 percent
- Fatigue/generalized weakness – 32 percent
- Hypercalcemia – 28 percent
- Weight loss – 24 percent, one-half of whom had lost ≥9 kg

paresthesia (5 percent), hepatomegaly (4 percent), splenomegaly (1 percent), lymphadenopathy (1 percent), and fever (0.7 percent).

Mayo Clin Proc. 2003;78(1):21.

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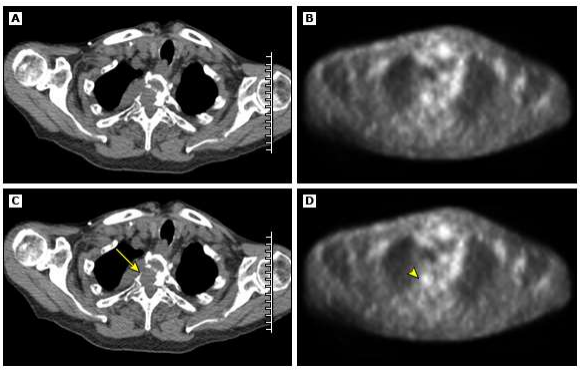
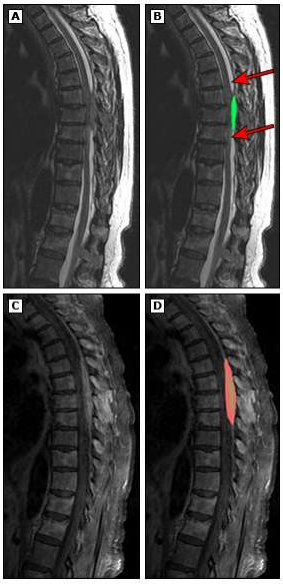
Neurological symptoms



Spinal cord compression from plasmacytoma or due to fracture happen in 5% of cases



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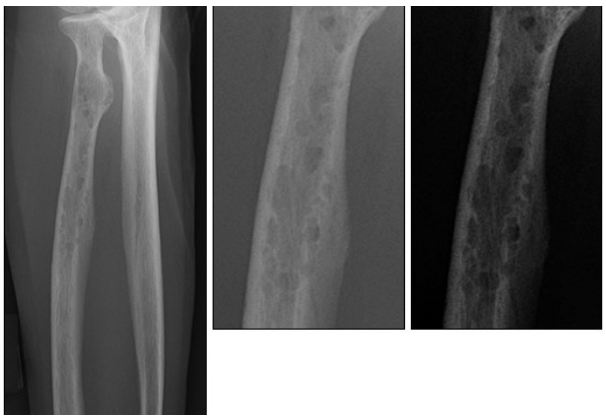
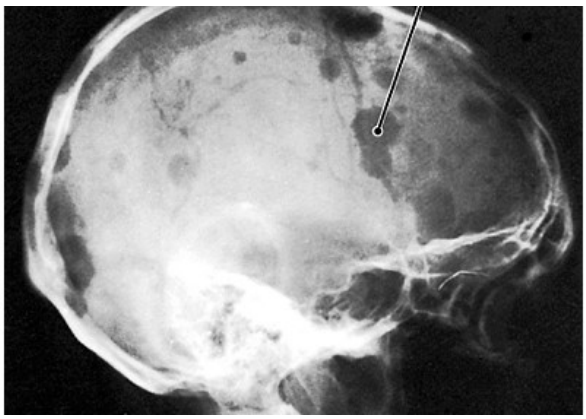
Other Radiological findings





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Infections

- Patients with MM are at increased risk for infection due to a combination of immune dysfunction and physical factors.
- Immune dysfunction results from impaired lymphocyte function, suppression of normal plasma cell function, and hypogammaglobulinemia.
- Physical factors include hypoventilation secondary to pathologic fractures and pain involving the rib cage and spine

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Clinical features of myeloma

HyperCalaemia (present in 13% at diagnosis)
- Increased osteoclastic bone resorption
- Increased renal tubular calcium reabsorption

Renal failure (present in 19% at diagnosis)
- Light chain cast nephropthy ("myeloma kidney")
- Hypercalcaemia (with or without nephrocalcinosis)
- Monoclonal immunoglobulin deposition disease
- Plasma cell infiltration of the kidneys
- Concurrent amyloidosis
- Drug-induced (NSAIDs, bisphosphonates)
- Recurrent urinary tract infections

Anemia (present in 35% at diagnosis)
- Bone marrow infiltration by plasma cells
- Cytokine-mediated suppresive effect on erythropoiesis (anemia of chronic disease-type of anemia)
- Renal failure (decreased erythropoietin production)

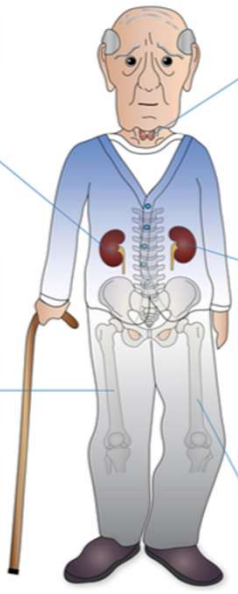
Bone pain (present in 58% at diagnosis)
- Increased osteoclast activity causing lytic bone lesions, osteoporosis and pathological fractures
- Plasmacytomas affecting the bone

Other features:

Spinal cord compression: (occurs in 5% of patients)
- Due to plasmacytomas or due to pathological fractures

Recurrent infections:
- Due to hypogammaglobulinemia and leukopenia

Hyperviscosity symptoms:
- Due to high levels of circulating paraprotein



Alternate diagnoses that can mimic myeloma

HyperCalaemia

PTH-mediated hypercalcaemia
- Primary hyperparathyroidism
- Tertiary hyperparathyroidism (eg, due to CKD or vitamin D deficiency)

Non-PTH-mediated hypercalcaemia
- Malignancy (bone metastases, humoral hypercalcaemia of malignancy)
- Drugs (eg, thiazides, lithium, vitamin D, vitamin A)
- Endocrine conditions (eg, thyrotoxicosis, Addison's disease)
- Granulomatous conditions (eg,sarcoidosis, tuberculosis)
- Other (eg, prolonged immobilisation, milk-alkali syndrome)

Renal failure

AKI (acute kidney injury)
- Prerenal causes – eg, dehydration, sepsis
- Renal causes – eg, drug-induced, infections
- Postrenal causes – eg, acute urinary retention

CKD (chronic kidney disease) (affects ~60% of >80 year olds)
- Age-related decrease in eGFR
- Hypertension
- Diabetic nephropathy
- Drug-induced (eg, diuretics, NSAIDs)
- Obstructive uropathy (eg, due to BPH)
- Glomerulonephritidies

Anemia (affects ~25% of >80 year olds)
- Anemia of chronic disease
- Iron deficiency (dietary and/ or blood loss)
- Vitamin B12 or Folate deficiency
- Chronic kidney disease
- Myelodysplasia
- Others (eg, bone marrow infiltration, haemolytic anemia, thalassemia)

Bone pain

Nonmalignant causes
- Osteoporosis
- Osteomalacia
- Osteomyelitis
- Paget's disease
- Injury (eg, fractures)

Malignant causes
- Primary bone cancer
- Bony metastases: – eg, breast, prostate, lung, thyroid kidney, testicular, ovarian

Zweegman, haematologica 2014; 99(7)

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Initial Investigations

- CBC (anemia)
- Extended Lytes (calcium)
- Creatinine
- Total protein, Albumin, LDH
- Uranalysis (proteinuria)
- Skeletal Survey (lytic lesions)

If possible:

- SPEP, immunofixation, Free light chains, immunoglobulins

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Investigations for diagnosis

- SPEP, immunofixation
- Free light chains
- Bone Marrow Biopsy (with FISH testing)
- Advance imaging (PET or MRI)
- 24 h urine w/UPEP
- Beta 2 macroglobulin/ LDH/Albumin

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Definition Monoclonal protein

- **M-protein = paraprotein = monoclonal protein**
  - *A monoclonal immunoglobulin secreted by an abnormally expanded clone of plasma cells*
  - Can be detected by Immunofixation and SPEP
- Size of clone in g/L
  - Larger the clone more likely it will
    - Be accompanied by symptomatic MM/Lymphoma
    - Cause hyperviscosity

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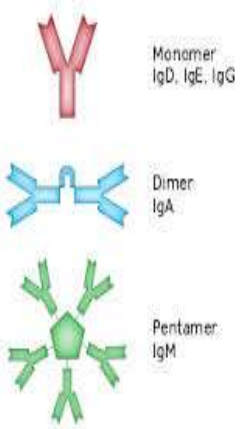
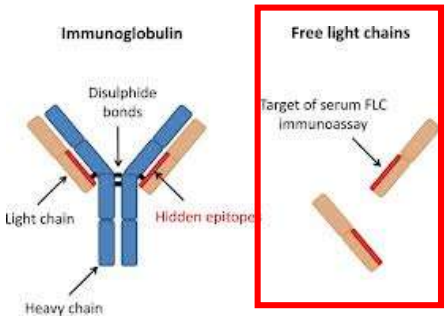
Immunoglobulins

Quantitative Immunoglobulin's

Heavy Chains
Light Chains



Serum Free light chains



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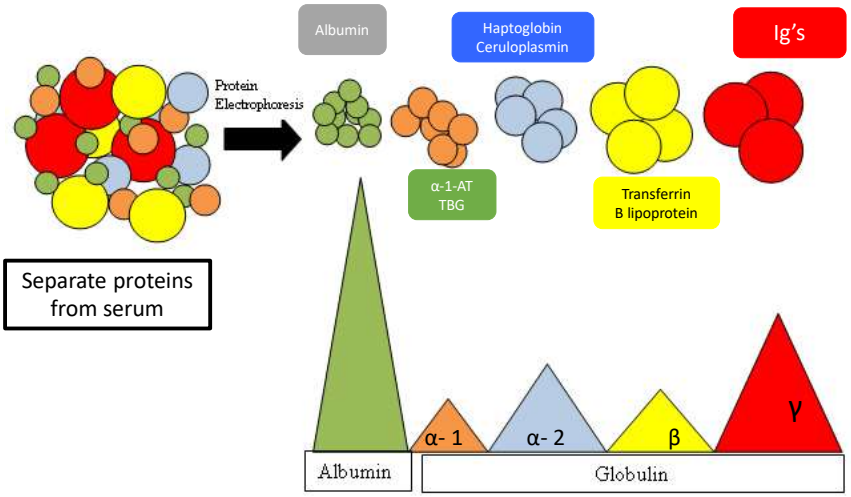
Serum protein electrophoresis (SPEP)



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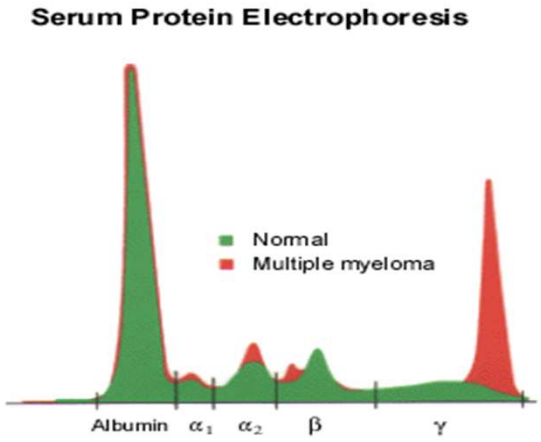
SPEP in Myeloma



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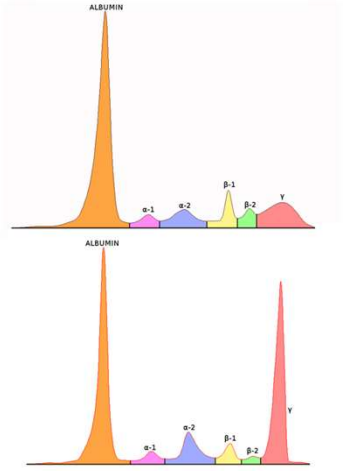
SPEP

- Lab doc reads and reports summary of electrophoresis on clinical portal (you don't need to interpret yourself!)
- SPEP takes time to be reported (ca take up to 3wks at times)



Alpha 1	4.1		Rel%
Alpha 2	8.3		Rel%
Beta 1	4.3		Rel%
Beta 2	2.2		Rel%
Gamma	38.0		Rel%
Albumin	35.8 Low		g/L
Alpha 1	3.4		g/L
Alpha 2	6.9		g/L
Beta 1	3.6		g/L
Beta 2	1.8 Low		g/L
Gamma	31.5 High		g/L

M peak = 31.2 g/L
Gamma 2 = 0.3 g/L.

Comment	A monoclonal protein continues
	(..)

A monoclonal protein continues to be seen in the gamma2 region, previously identified as IgG kappa since December 2007.

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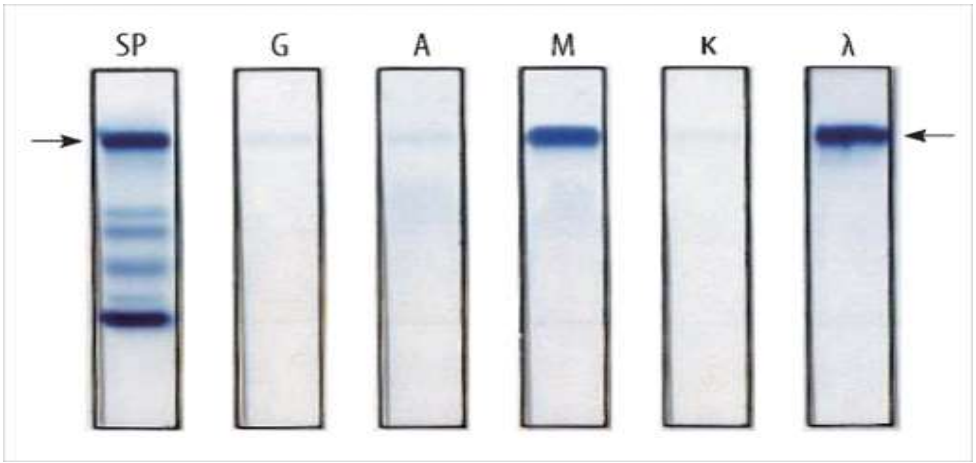
Immunofixation (IFE)



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Example 1 : Quant Ig's

Heavy chains **Light chains**

	Result Name	Results	Units	Result Name	Results	Units
☑	IgG	34.70 High	g/L	Kappa	26.10 High	g/L
☑	IgA	0.13 Low	g/L	Lambda	<0.30 Low	g/L
☑	IgM	0.08 Low	g/L	Kap Lam Ratio	See Note Abnormal	

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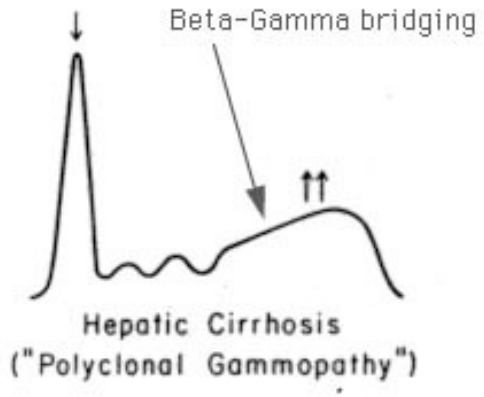
Beta Gamma bridging – not MGUS



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Myeloma Diagnostic Criteria

- **Myeloma:**
  - Clonal Bone Marrow Plasma Cells ≥10% or biopsy-proven plasmacytoma AND EITHER
  - A myeloma-defining end organ manifestation OR
  - A myeloma-defining biomarker of malignancy

IMWG updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014.15: e538

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Myeloma Diagnostic Criteria

Myeloma Defining Events:

- Hypercalcemia:
  - 2.75 mmol/L or 0.25 greater than ULN
- Renal insufficiency:
  - Creatinine greater than 177umol/L o CrCl < 40 mL/min
- Anemia:
  - Hemoglobin less than 100 g/L or 20 g/L less than lower limit of normal
- Lytic bone lesions:
  - One or more on standard skeletal survey, CT, PET

IMWG updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014.15: e538

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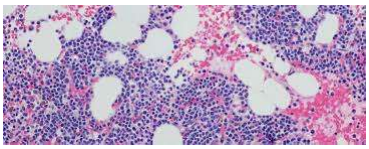
Myeloma Diagnostic Criteria



Myeloma Defining Biomarkers:

•Sixty percent or greater bone marrow plasma cells:

- •Mayo clinic cohort 6/276 SMM patients had BMPC>60% with 83% progression or death at 14 mo., median PFS 7.7 mo.
- •Validation cohort 21/651 SMM patients had BMPC>60% with 95% progression to myeloma at 2 years, TTP 7.0 mo.

Rajkumar et al. NEJM 2011. 365:474-475,

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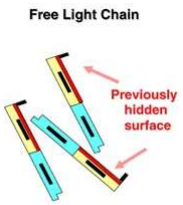
Myeloma Diagnostic Criteria



Myeloma Defining Biomarkers:

•Serum free light chain involved:uninvolved ratio >100

- •90/586 SMM patients had SFLC ratio >100 with 72% progressing to myeloma at 2 years
- •In patients who additionally had SFLC level > 1000 mg/L 82% progressed to myeloma at 2 years
- •27% presented with acute renal failure

Larsen et al. Leukemia 2013. 27:941-946.

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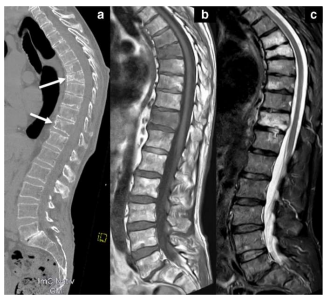
Myeloma Diagnostic Criteria



Myeloma Defining Biomarkers:

•<u>MRI bone lesions, 2 or more (at least 5mm):</u>

- •Of the 23/149 patients with >1 MRI lytic lesion, 70% progressed at 2 years with TTP 13 months

Hillengass et al. JCO 2010. 28:1606-1610

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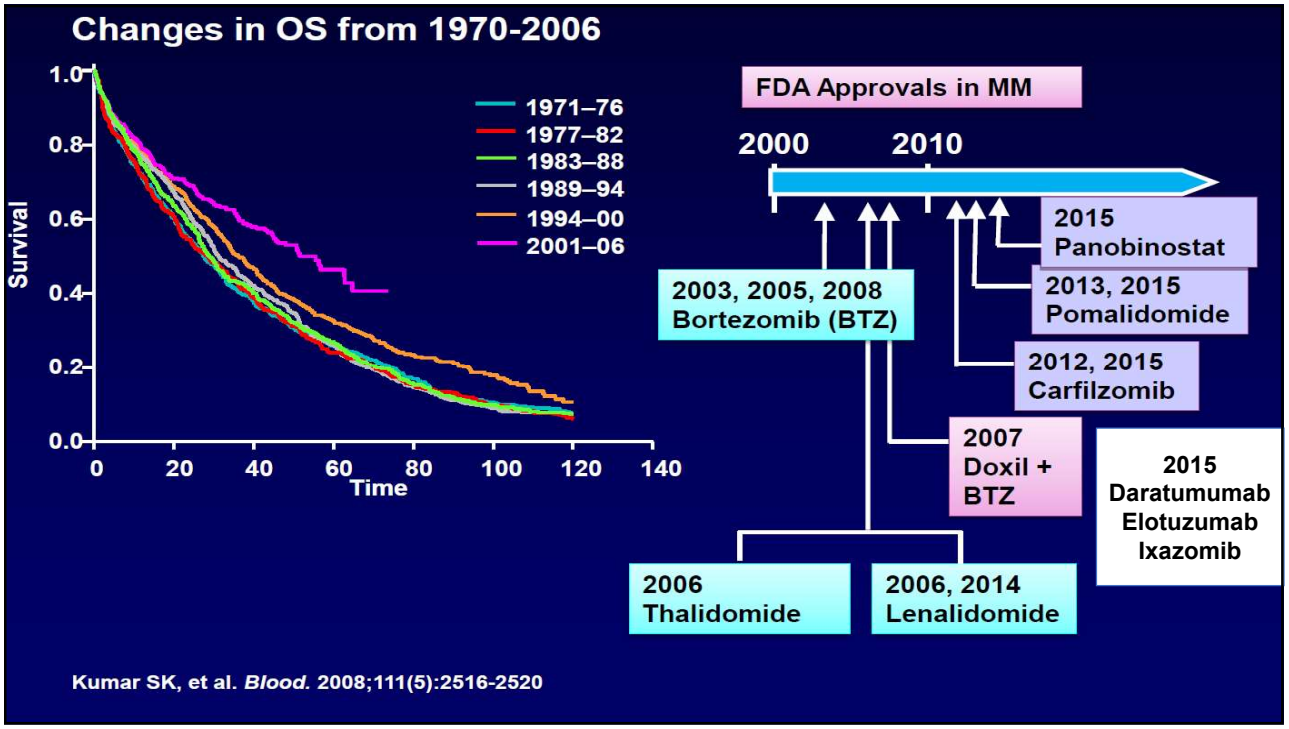

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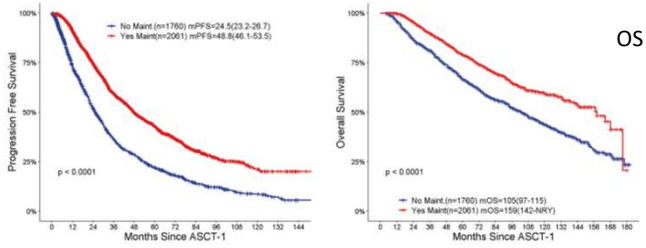
Real-world results of autologous stem cell transplantation in newly diagnosed multiple myeloma: a report from the Canadian Myeloma Research Group database

Treatments	mPFS	*p*-value	mOS	*p*-value
No. of induction regimens & maintenance				
1 regimen ($n = 1843$)	55.3 (52.1–60.5)		158.6 (142.5-NRY)	
2 regimens ($n = 218$)	51.1 (44.7 70.7)	0.11	NRY (135.1 NRY)	0.13
1 induction and maintenance				
Standard-risk ($n = 726$)	55.1 (48.4–61.5)	0.002	164.0 (158.4-NRY)	<0.001
High-risk ($n = 391$)	35.6 (30.9–47.3)		97.0 (81.2-NRY)	
2 inductions and maintenance				
Standard-risk ($n = 72$)	47.1 (27.3–57.1)	0.1	NRY (85.3-NRY)	0.001
High-risk ($n = 52$)	36.5 (22.6–60.9)		84.1 (59.9-NRY)	



OS 8-13 years

Blood Cancer Journal (2023) 13:137

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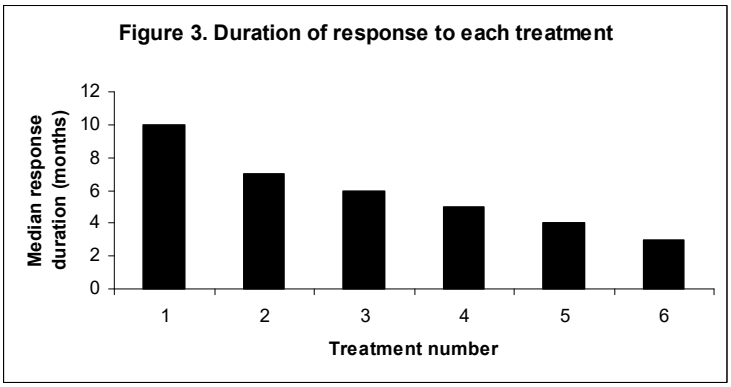
Duration of response in subsequent lines of treatment



Kumar SK, et al. Mayo Clin Proc. 2004;79:867-874.

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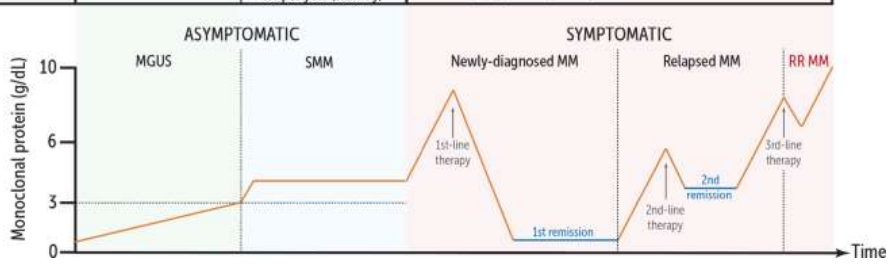
Natural History

Disease stage	MGUS	SMM	Active MM
Serum M-protein	<3 g/dL	≥3 g/dL	≥1 **myeloma defining events** + (1) or (2): End-organ damage (CRAB): any one of • Hypercalcemia, renal insufficiency, anemia, bone lesions Biomarkers of malignancy: • ≥60% clonal BM plasma cells, • Serum involved/uninvolved free light chain ratio ≥100 • >1 focal lesion on MRI ≥5mm in size (1) Clonal bone marrow plasma cells ≥10% or (2) Biopsy proven plasmacytoma
Urine M-protein	N/A	≥500 mg/day	
% BM plasma cells	<10%	10-60%	
Myeloma defining events	Absence of myeloma defining events or amyloidosis		
Progression risk	1% per year	10% per year (1st 5y) 3% per year (next 5y)	



Leukemia **34**, 3111–3125 (2020).

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Progression from MGUS to MM

MGUS to MM at a rate of 1% per year

Risk factors for progression to MM	No. of Factors	20-year risk of progression
Serum M-protein >1.5 g/dL	0	5%
Non-IgM MGUS	1	21%
Abnormal SFLC ratio <0.26 or > 1.65	2	37%
	3	58%

Rajkumar et al. Blood 2005. 10:812

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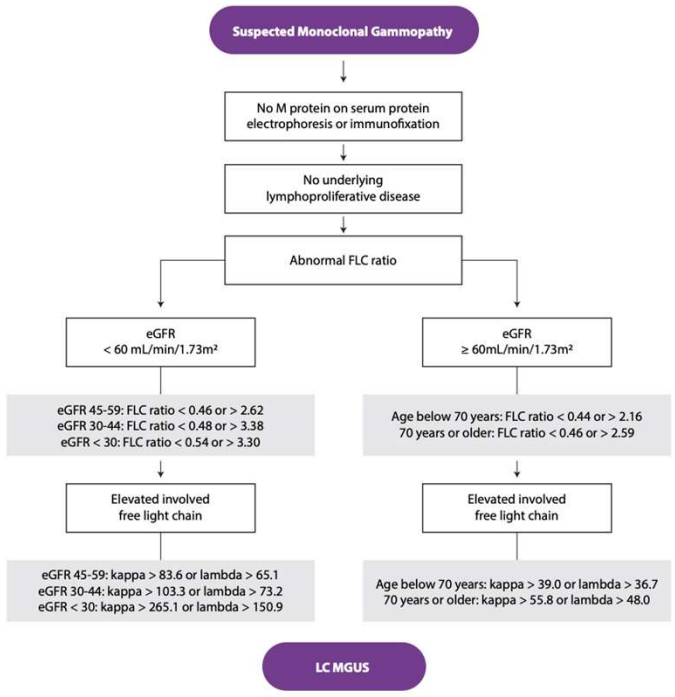

Blood (2023) 142 (Supplement 1): 535.

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Smoldering Myeloma

1348 THE NEW ENGLAND JOURNAL OF MEDICINE June 12, 1980

SMOLDERING MULTIPLE MYELOMA

ROBERT A. KYLE, M.D.,
AND PHILIP R. GREIPP, M.D.

MULTIPLE myeloma is characterized by an increase of abnormal plasma cells in the bone marrow and monoclonal protein in the serum, often with osteolytic bone lesions. Its course is progressive: anemia, weakness, fatigue, fractures, bone pain, hypercalcemia, renal insufficiency, recurrent infections, bleeding, and deterioration lead to death. However, we have seen six patients with illnesses that met the criteria for the diagnosis of multiple myeloma[1] but have not had a progressive course. Although no chemotherapy was given, their condition has remained stable for five or more years. We designate these cases as "smoldering multiple myeloma." We wish to call attention to this group because smoldering multiple myeloma should be recognized, and treatment withheld.

Table 1. Characteristics of Six Patients with Smoldering Multiple Myeloma.*

Characteristic	Patient Number					
	1	2	3	4	5	6
Age at diagnosis (yr)	70	73	61	57	63	61
Sex	M	M	M	F	F	F
Hemoglobin (g/dl)						
Initial	13.1	13.5	15.5	11.7	12.2	12.8
Last	12.8	13.8	14.2	12.6	12.7	13.5
Serum M protein						
Mobility	β-γ	β	γ	β	γ	β
g/dl	3.4	3.0	3.6	3.1	3.0	3.6
Class/subclass	$G_3\kappa$	$G_1\lambda$	$G_1\kappa$	$G_2\kappa$	$G_2\kappa$	Aλ
Urinary M protein						
Type	κ	λ	κ	κ	—	λ
g/24 hr	0.30	0.50	0.06	0.39	Negative	0.06
Immunoglobulins (mg/ml)						
IgG	65	25	65	27	23	5
IgA	0.32	0.35	0.9	1.7	0.75	26.6
IgM	0.00	0.23	0.4	0.5	0.67	0.29
Marrow plasma cells (per cent)	16	17	17	11	13	10
Labeling index (per cent)	0.0	0.0	0.0	0.0	0.0	0.0
Asynchrony	0.4	0.0	0.0	0.1	0.1	0.7
Myeloma 0.47±0.33 †						
MGUS ‡ 0.05±0.10 †						
Nucleolar size (μm)	1.4	1.2	0.5	0.7	0.8	1.1
Myeloma 1.6±0.76 †						
MGUS ‡ 0.47±0.44 ‡						
Follow-up (yr)	16	5	5	6	5	5

Kyle. NEJM. 1980;302:1347.

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Progression from Smoldering Myeloma

Risk of Smoldering Myeloma progressing to MM with end organ damage is:

- 10% per year for the first 5 years,
- 3% per year for the next 5 years,
- then 1-2% per year

Kyle et al NEJM 2007 356:2582

No. of risk factors	Patients, n (%)	Progression at 5 years
Mayo Clinic criteria*		
1	76 (28)	25%
2	115 (42)	51%
3	82 (30)	76%
PETHEMA criteria**		
0	28 (31)	4%
1	22 (25)	46%
2	39 (44)	72%

*N = 273[53,54]. Risk factors: (1) BMPCs >10%; (2) M-protein >3 g/L; and (3) FLC ratio <0.125 or >8.

**N = 89[55]. Risk factors: (1) ≥95% abnormal plasma cells, including decreased CD38 expression, expression of CD56, and absence of CD19 and/or CD45; and (2) immunoparesis.

Ghobrial and Landgren Blood 2014

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Staging

- **ISS staging**
  - I B2M <3.5 , albumin > 35
  - II neither I or III
  - III B2M > 5.5

- **R-ISS staging**
  - I B2M <3.5 , albumin > 35 and standard risk cytogenetics and normal LDH
  - II neither I or III
  - III B2M > 5.5 and high-risk ISS, high LDH

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IMWG Consensus[a]

FISH test CD138-selected cells for:
t(4;14); t(14;16); t(14;20); del(17/17p)

- High-risk disease is associated with poor outcomes
- Most respond to initial treatment, but relapse sooner
- The benefit of maintenance lenalidomide monotherapy is less clear in high-risk MM
  - In patients with del(17p) or t(4:14), lenalidomide maintenance did not improve OS in the meta-analysis[b]
  - Adding a proteasome inhibitor in the maintenance setting may provide a benefit for high-risk patients[c]

a. Sonndeveld P, et al Blood 2016;127;2955-62
b. McCarthy PL et al. J Clin Oncol. 2017; 35:3279-89
c. Sonneveld P, et al. J Clin Oncol. 2012; 113: 1-14

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Agenda:

- Introduction
- Epidemiology
- Clinical Presentation
- Pathological Features and Imaging
- Diagnosis
- Prognosis
- **Treatment**

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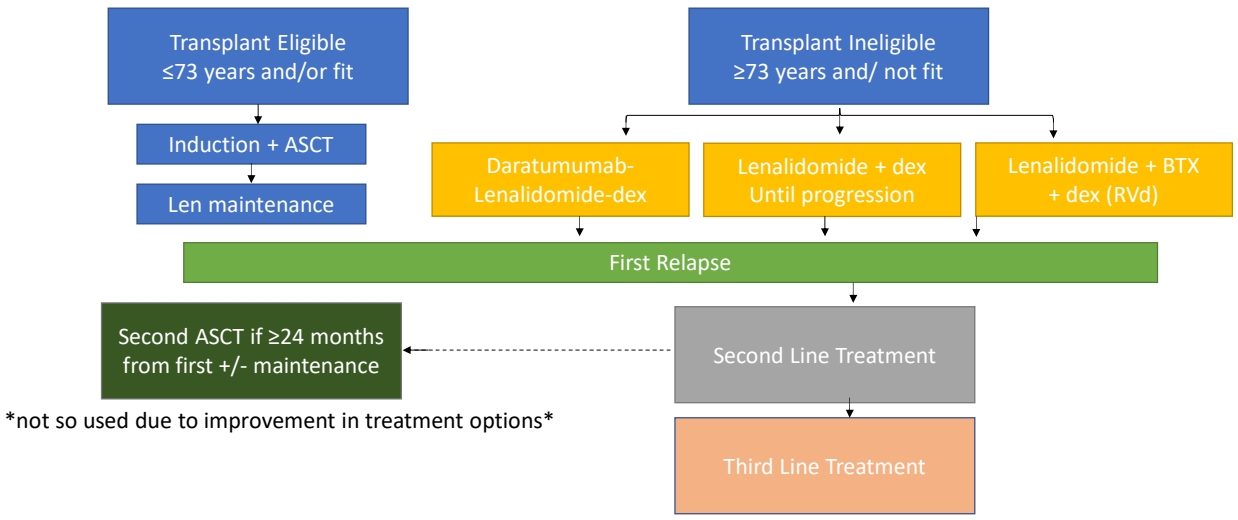
Current Canadian Algorithm for Initial Therapy in Myeloma



not so used due to improvement in treatment options

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Treatment options

- Proteosome inhibitors (PI): Bortezomib, Ixazomib, Carfilzomib
- Immunomodulators (IMIDs): Lenalidomide, Pomalidomide
- CD38 Antibodies: Daratumumab, Isatuximab
- Bispecific: Elranatamab, Teclistamab *
- CAR-T cells : Cilta-cel, Ida-cel **
- Other: Cyclophosphamide, Dexamethasone, Selinexor

*Access thru compassionate supply
** No Access but HC approved

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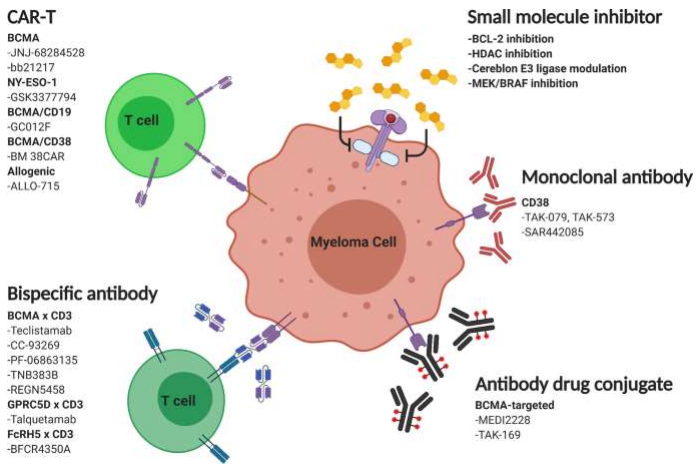
Other therapies



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Upfront bortezomib, lenalidomide, and dexamethasone compared to bortezomib, cyclophosphamide, and dexamethasone in multiple myeloma

- Retrospective analysis of patients treated with VRD and VCD
- 681 patients were included,
  - 117 receiving VRD (71 with, 46 without HDT)
  - 564 receiving VCD (351 with, 213 without HDT).
- ORR was higher with VRD compared to VCD (98% vs 88%, *P* < 0.001) in non-HDT group (98% vs 79%, *P* < 0.001).
- PFS at 18 months was longer with VRD 88% vs 63%,
- Overall survival at 18 months was better for VRD-treated (95% vs 89%, *P* = 0.048).

Eur J Haematol. 2019 Sep;103(3):247-254

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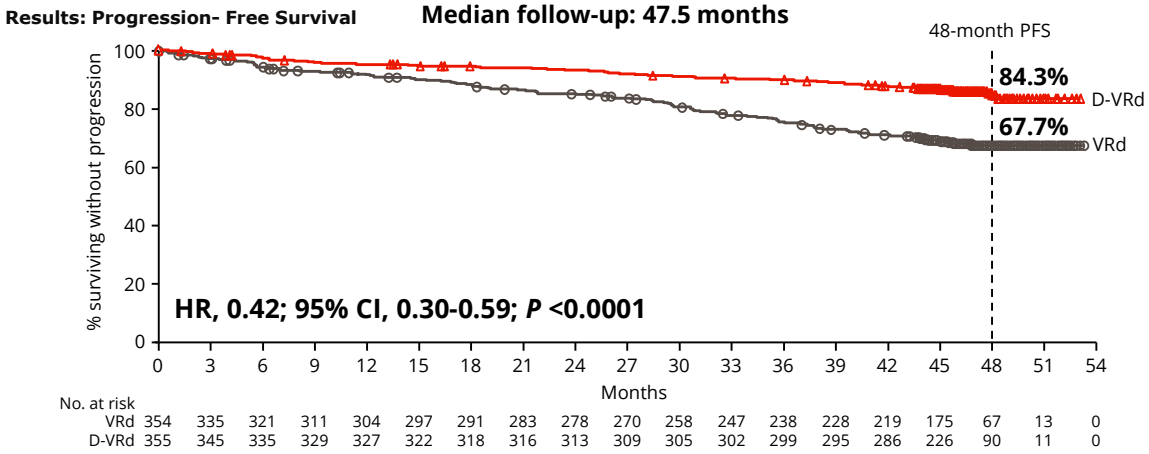
Phase 3 Randomized Study of Daratumumab (DARA) + Bortezomib, Lenalidomide, and Dexamethasone (VRd) Versus Vrd Alone in Patients (Pts) with Newly Diagnosed Multiple Myeloma (NDMM) Who Are Eligible for Autologous Stem Cell Transplantation (ASCT): Primary Results of the Perseus Trial

Results: Progression- Free Survival



58% reduction in the risk of progression or death in patients receiving D-VRd

HR, hazard ratio; CI, confidence interval

Sonneveld et al. #LBA-1 ASH 2023

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Master Trial

Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone (Dara-KRd), Autologous Transplantation and MRD Response-Adapted Consolidation and Treatment Cessation.

- 123 patients
- Treated until 2 readings showed MRD neg.

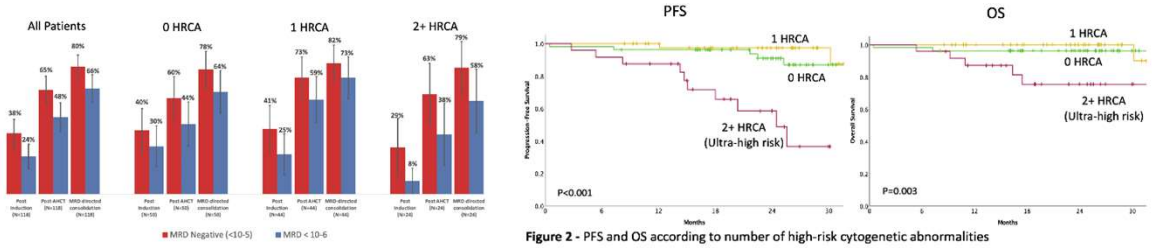

Figure 2 - PFS and OS according to number of high-risk cytogenetic abnormalities

Goldshmidt presented at ASH 2021 oral abstract 463

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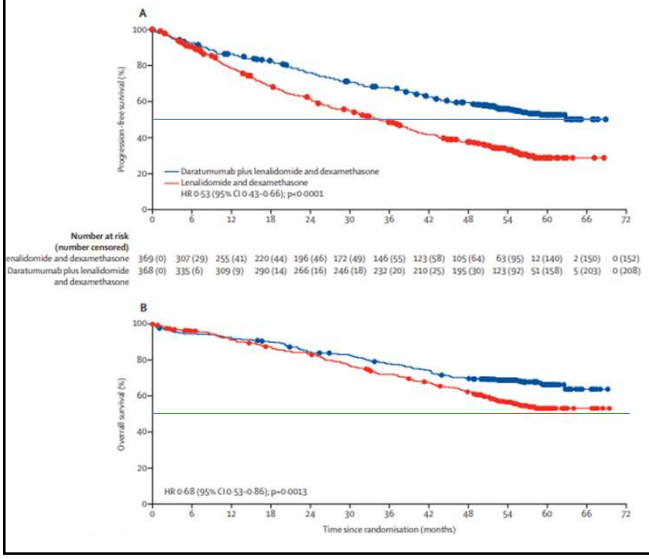
Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomized, open-label, phase 3 trial



- DRD increased overall survival and progression-free survival
- At 56.2 month follow up median PFS and OS was not reached

	Daratumumab plus lenalidomide and dexamethasone group (n=368)	Lenalidomide and dexamethasone group (n=369)	Odds ratio (95% CI)	p value
Overall response	342 (92·9%; 89·8–95·3)	301 (81·6%; 77·2–85·4)	3·00 (1·85–4·86)	<0·0001
Complete response or better	188 (51%)	111 (30%)	2·44 (1·80–3·30)	<0·0001
Stringent complete response	130 (35%)	56 (15%)	3·06 (2·14–4·38)	<0·0001
Complete response	58 (16%)	55 (15%)	..	..
Very good partial response or better	298 (81%)	210 (57%)	3·28 (2·34–4·59)	<0·0001
Very good partial response	110 (30%)	99 (27%)	..	..
Partial response	44 (12%)	91 (25%)	..	..
Stable disease	11 (3%)	55 (15%)	..	..
Progressive disease	1 (<1%)	0	..	..
Response could not be measured	14 (4%)	13 (4%)	..	..
Negative status for minimal residual disease[10]	114 (31%)	38 (10%)	3·91 (2·62–5·84)	<0·0001

Lancet Oncol 2021; 22: 1582–96

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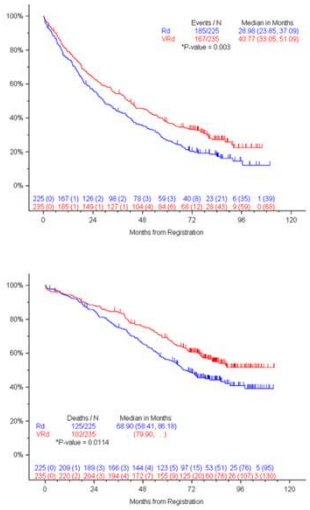
Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT)



- PFS and OS were improved with VRd versus Rd
- Median **PFS is 41 months** for VRd;29 months for Rd
- Median OS for VRd is still not reached with median OS for Rd being 69 months

Durie et al. Blood Cancer Journal (2020) 10:53

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2nd Line options

PI Based Regimens

	DVd- CASTOR(1)	KCd- MCR003(2)	KdD- Candor(3)	IsKd- IKEMA(4)	Kd-Endeavor(5)
Study phase	3	2	3	3	3
Median prior lines	2	1-2	2	2	2
ORR in Len-Ref (%)	81	83.6 (*exposed*)	77	87*	Not reported (NR)
Median PFS, mo. Len-Ref	16.7 9.3	17.0 Not reported (NR)	28.6 28.1	Not *reached (NYR)* Not *reached (NYR)*	18.7 8.6

1.- Haematologica. 2018;103(12): 2079-2087.
2.- Am J Hematol. 2021;96:552–560.
3.- Lancet Oncol 2022; 23: 65–76
4.- Lancet 2021; 397: 2361–71
5.- Leukemia. 2017;31(1):115-122.

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DITA1

3rd Line options

IMID Based Regimens

	PCd(1)	PVd- OPTIMISMM(2)	DPd- APOLLO(3)	IPd- ICARIA MM (4)
Study phase	2	3	3	3
Median prior lines	3	2	2	3
ORR in Len-Ref (%)	Not reported	Not reported	76.2	Not reported
Median PFS, mo. Len-Ref	7.3 Not reported	11.0 9.5 (17.8*)	12.4 9.9	11.5± Not reported

*Refractory to lenalidomide in first line therapy
± 94% of patients where refractory to lenalidomide

1.- Annals of Hematology (2019) 98:1441–1447
2.- Lancet Oncol. 2019; doi:10.1016/ S1470-2045(19)30152-4
3.- Lancet Oncol 2021; 22: 801–12
4.- Lancet Oncol 2022 https://doi.org/10.1016/ S1470-2045(22)00019-5

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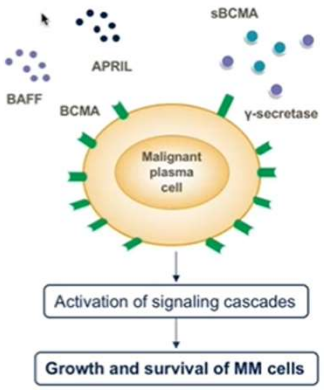
Targeting BCMA

- BCMA is a cell surface protein expressed on late-stage B cells and plasma cells but virtually absent on naïve and memory cells
- BCMA is highly expressed on malignant plasma cells in all patients with MM
  - ➢BCMA ligands, BAFF and APRIL, are detected in increased levels in circulation of patients with MM
- BCMA is essential for proliferation and survival of malignant plasma cells



APRIL a proliferation-inducing ligan; BAFF B cell activation factor, BCMA B cell maturation antigen

1.- Tai,YT immunotherapy 2015;7(11)1187-1199, 2. RyanMC, Mol Cancer Ther. 2007;6(11)3009-3018. 3 Cho S-F Fron Immunol 2019;9:1821, 4 NovakAJ Blood 2004;103(2):689-694, 5. Tai YT Blood 2014;123(20):3128-3138

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Slide 55

DITA1 De la Torre, Alfredo, 2022-02-18

Other phase 1 BCMA bispecific antibody studies

Target	Product	n	ORR	CR	Comment
BCMA	CC-93269	30	43%	17%	89%/44% at 10mg dose (n=9) dual BCMA binding sites Weekly IV x 12, q 2wks x 6, then q 4 weeks
BCMA	**Teclistamab**	149	n/a	n/a	68%/24% at 720-1500mcg/kg SC doses (n=37) Weekly SC dosing
BCMA	AMG701	85	26%	10%	83%/17% at 18 mg doses (n=6) Weekly IV
BCMA	REGN5458	49	39%	16%	63/0% at 96mh dose (n=8)/ Weekly IV x 16 then q2wks
BCMA	TNB-383B	58	47%	14%	80/13% at 40-60mg doses (n=15) dual BCMA binding sites. IV q3wks dosing
BCMA	**Elranatamab**	30	53%	20%	80/30% at 215-1000mcg/kg doses (n=20) weekly SC dosing

Usmani. ASCO 2020. Abstr 100. Sebag M, ASH 2021. Abstract 895

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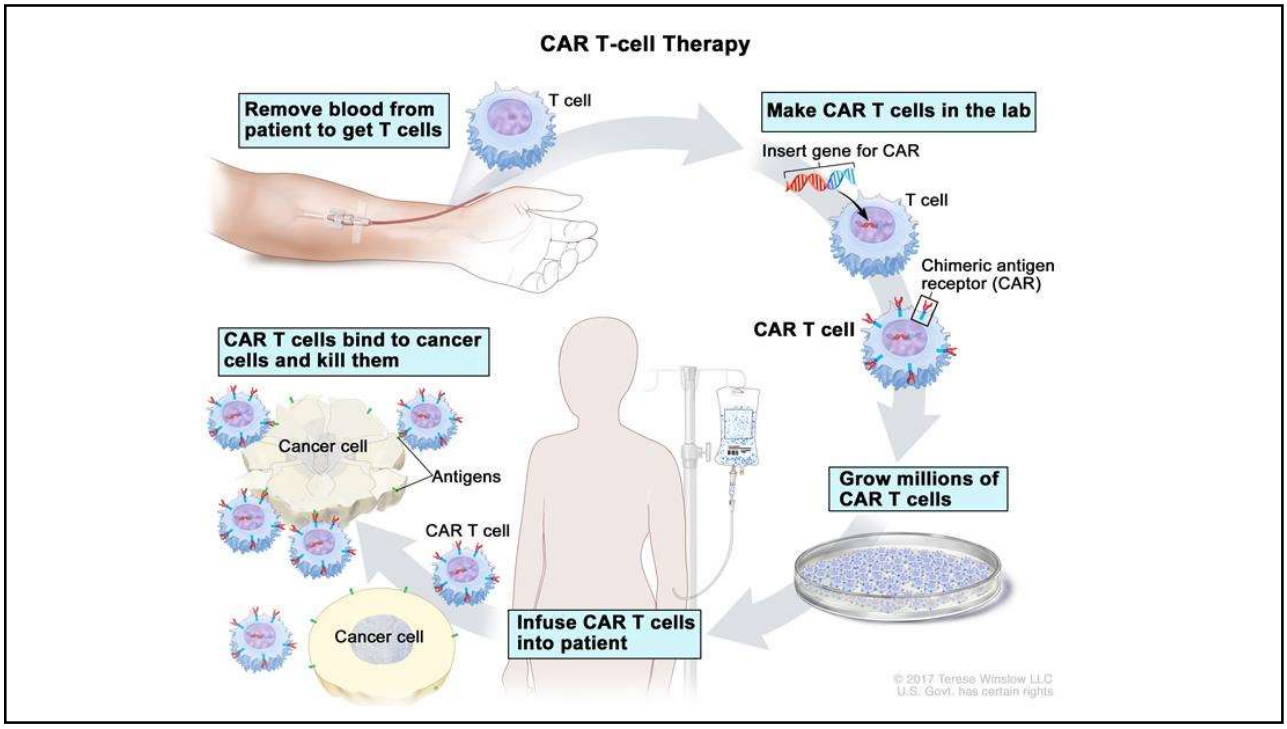

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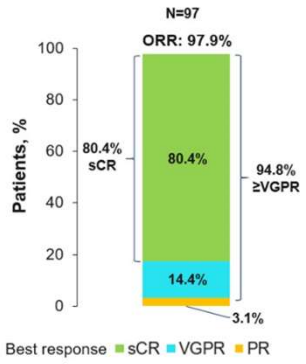
Updated Results from CARTITUDE-1

- At a longer median follow-up of 18 months, a single cilta-cel infusion led to early, deep, and durable responses in heavily pre-treated pts with MM
- ORR was 97.9% (95% CI: 92.7–99.7); 80.4% of pts achieved sCR, and 94.8% achieved very good partial response or better

Figure: Overall response rate (N=97)



Matin T, et al. ASH 2021 abstract 549

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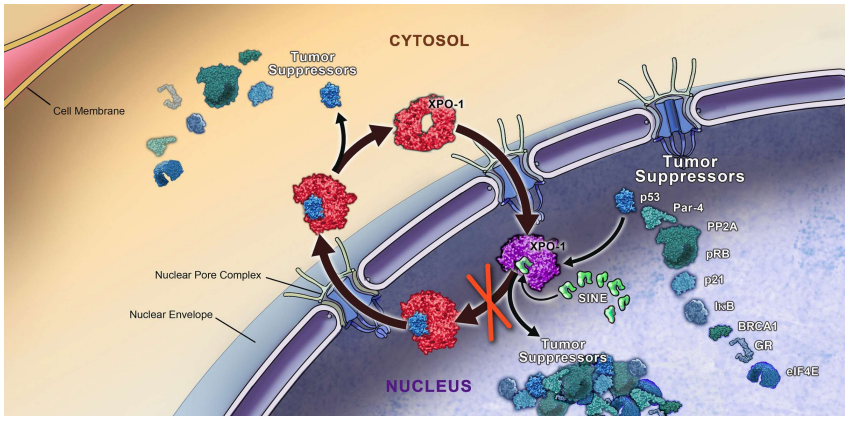
Selinexor: Novel Oral Anti-Cancer Agent Restores Tumor Suppressors & Reduces Oncoproteins



Selinexor and Low Dose Dexamethasone (Sd) in Patients with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib & anti-CD38 mAb Refractory MM: STORM Study

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QUESTIONS ??
alfredo.delatorre@nshealth.ca

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