Multiple Myeloma Update: 2025

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Multiple Myeloma

- 7.6 cases per 100,000 persons
- Higher in males
- Median age of diagnosis is 72.6 years - > 80% patients diagnosed >60yoa
- People of African, Māori and Pacific Islander descent are more likely to develop MM
- Median life expectancy from time of diagnosis – 5.5 years

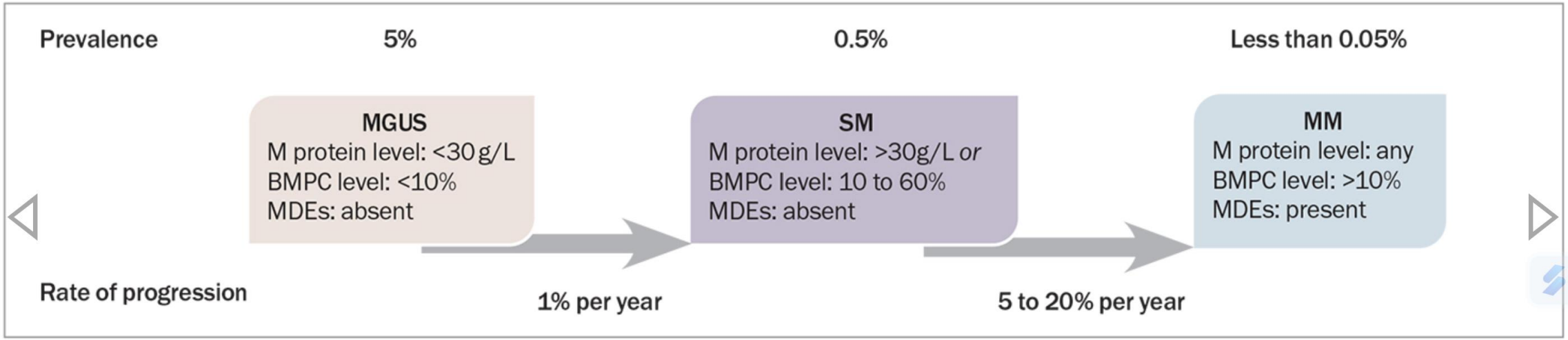
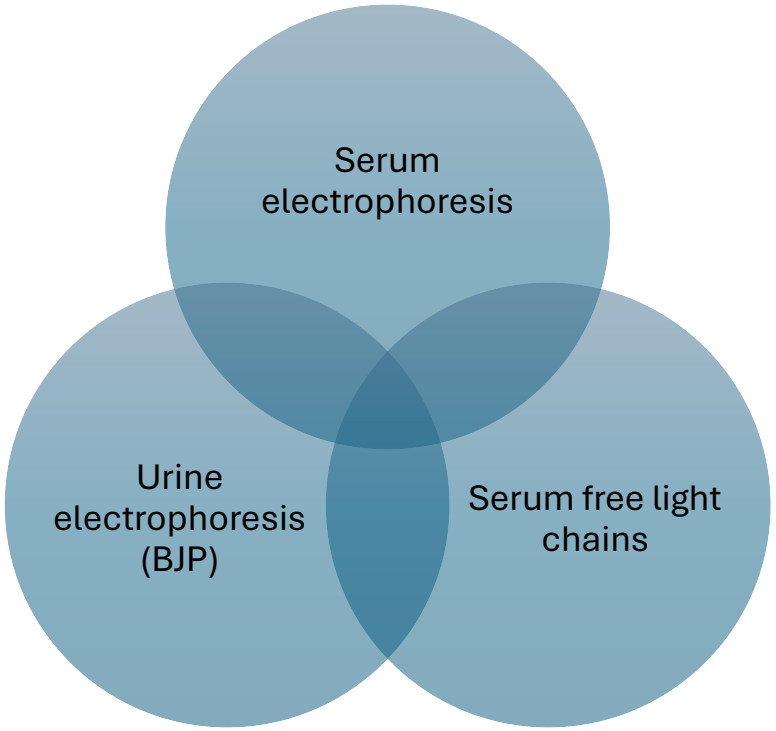
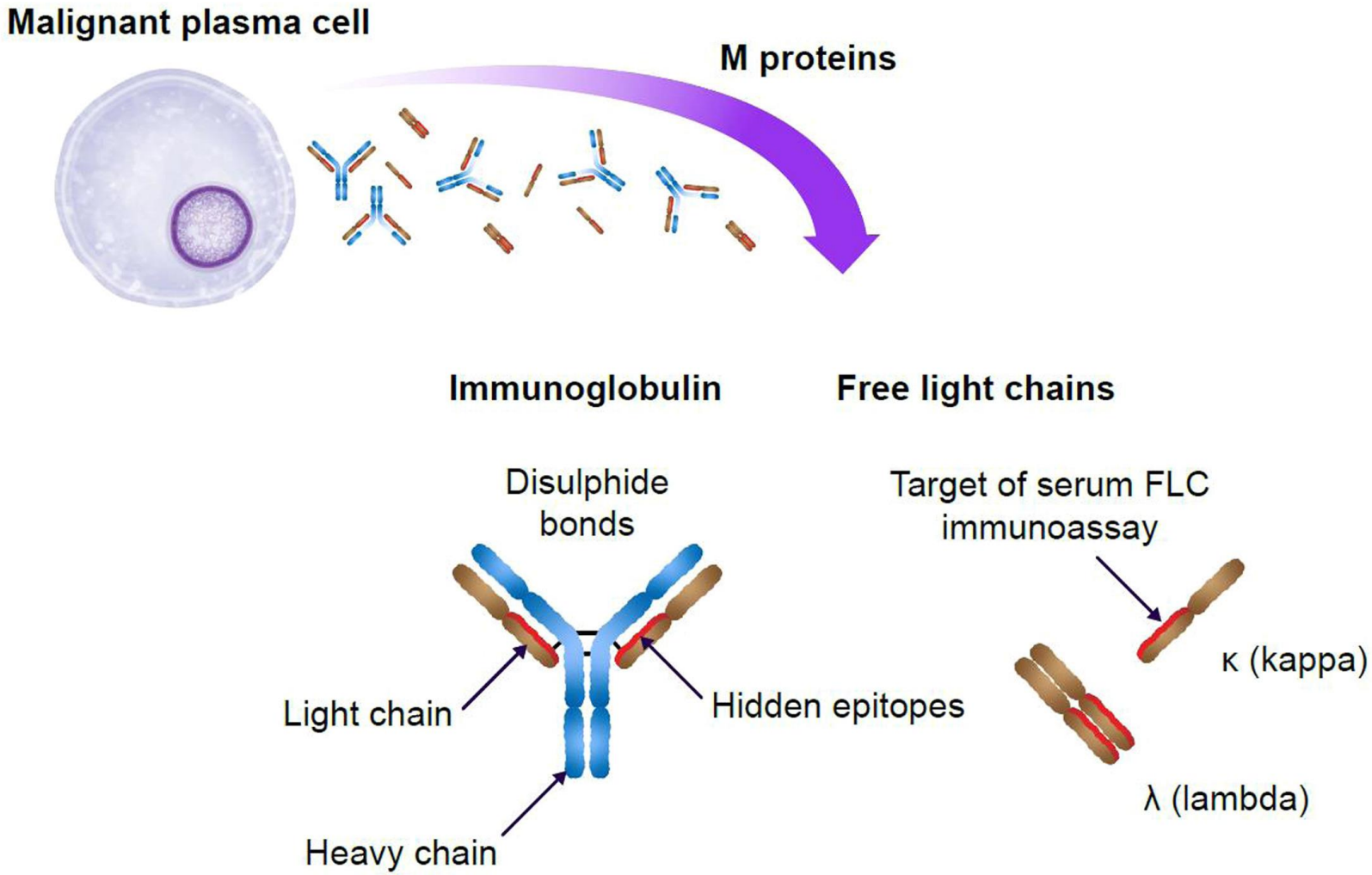


Figure 2. Developmental phases of multiple myeloma.[3,4]

Abbreviations: BMPC = bone marrow plasma cell; MDE = myeloma-defining event; MM = multiple myeloma; MGUS = monoclonal gammopathy of undetermined significance; SM = smouldering myeloma.

Multiple Myeloma





NB: polyclonal increase in globulins is **not** a feature of MM

Result	Interpretation
Kappa, Lambda and ratio all within reference range	Normal/no comment provided
Kappa and/or Lambda outside of reference range, but ratio within range	Likely causes include inflammation or abnormal renal function
sFLC ratio 1.66 to 3.1 (within expected range in CKD)	sFLC ratio falls within the reference range for CKD. In the presence of CKD no further action is required based on this result In the absence of renal disease consider MGUS, myeloma or amyloidosis. Recommend discussion with or referral to clinical haematology if any clinical features of myeloma. In the absence of any other features of myeloma recheck with immunoglobulins and electrophoresis in 2-3 months and refer to clinical haematology if >25% change. Refer urgently if any symptoms of myeloma develop

‘John’

60yo truck driver

Presents to GP with fatigue and new urticarial rash

Lives alone in Gin Gin

2 daughters live interstate

Drinks 2-4 beers most days

Past Medical History

- Hypertension
- BPH
- Non-melanoma skin cancers

Medications

- Perindopril 4mg
- Prazosin 1mg

Screening bloods

Test Name	Result	Units	Reference Interval
Haemoglobin	141	g/L	125 - 175
Haematocrit	0.43		0.38 - 0.54
Red cell count	4.2	10^12/L	4.2 - 6.5
● MCV	101 H	fL	80 - 100
White cell count	5.0	10^9/L	3.5 - 10.0
Neutrophils	2.51	10^9/L	1.5 - 6.5
Lymphocytes	1.76	10^9/L	0.8 - 4.0
Monocytes	0.65	10^9/L	0 - 0.9
Eosinophils	0.08	10^9/L	0 - 0.6
Basophils	0.04	10^9/L	0 - 0.15
Platelets	184	10^9/L	150 - 400

Protein Studies

Albumin	41	g/L	32 - 44
Alpha 1	2	g/L	2 - 4
Alpha 2	7	g/L	4 - 9
Beta 1	5	g/L	2 - 6
Beta 2	3	g/L	2 - 6
Gamma	7	g/L	6 - 15
IgG Type Kappa *	5 H	g/L	<0.1
Total Protein	70	g/L	63 - 80

Test Name	Result	Units	Reference Interval
Sodium	143	mmol/L	135 - 145
Potassium	4.3	mmol/L	3.5 - 5.5
Chloride	107	mmol/L	95 - 110
Bicarbonate	28	mmol/L	20 - 32
Anion Gap	8	mmol/L	<16
Calcium (Corrected)	2.42	mmol/L	2.10 - 2.60
Phosphate	0.97	mmol/L	0.80 - 1.50
Urea	8.3	mmol/L	3.5 - 9.5
Uric Acid	0.358	mmol/L	0.200 - 0.500
Creatinine	81	umol/L	60 - 115
eGFR	84		>59
Fasting Glucose	5.2	mmol/L	3.6 - 6.0
Total Protein	70	g/L	63 - 80
Albumin	41	g/L	32 - 44
Globulin	29	g/L	23 - 43
Bilirubin	17	umol/L	<21
Alk Phos	84	U/L	35 - 110
AST	26	U/L	10 - 40
ALT	26	U/L	5 - 40
Gamma GT	15	U/L	5 - 50
LDH	198	U/L	120 - 250
Cholesterol	3.3	mmol/L	<5.6
Haemolysis Index	5		<40

Monoclonal gammopathy of undetermined significance (MGUS)

Precursor state defined by:

- Monoclonal protein <30g/L
- Bone marrow plasma cells <10%
- Absence of myeloma-related organ damage

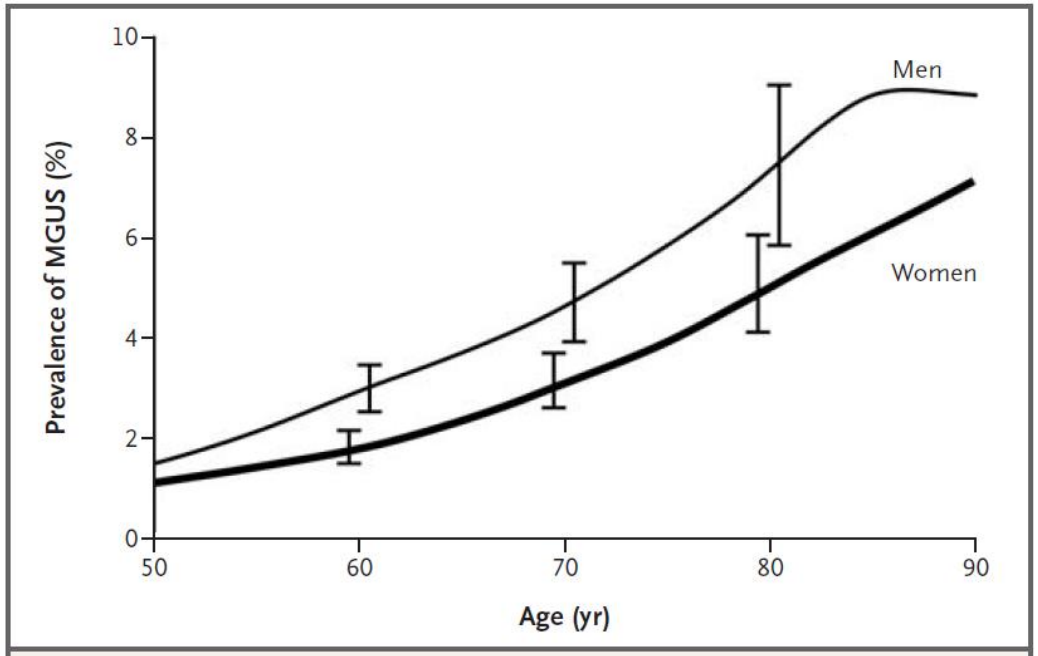


Figure 1. Prevalence of MGUS According to Age.

The I bars represent 95 percent confidence intervals. Years of age greater than 90 have been collapsed to 90 years of age.

Kyle R NEJM 2006; 354(13)

MGUS follow-up

- Goal = detect progression to multiple myeloma before significant end-organ damage

- History + examination (*esp. pain*)
- Bloodwork: FBC/ELFT/serum EPP/serum light chains

- Low-risk MGUS: Annually
- Intermediate-high risk MGUS: 6-monthly

Specialist referral indicated if:

1) New anemia/ renal dysfunction/ hypercalcemia

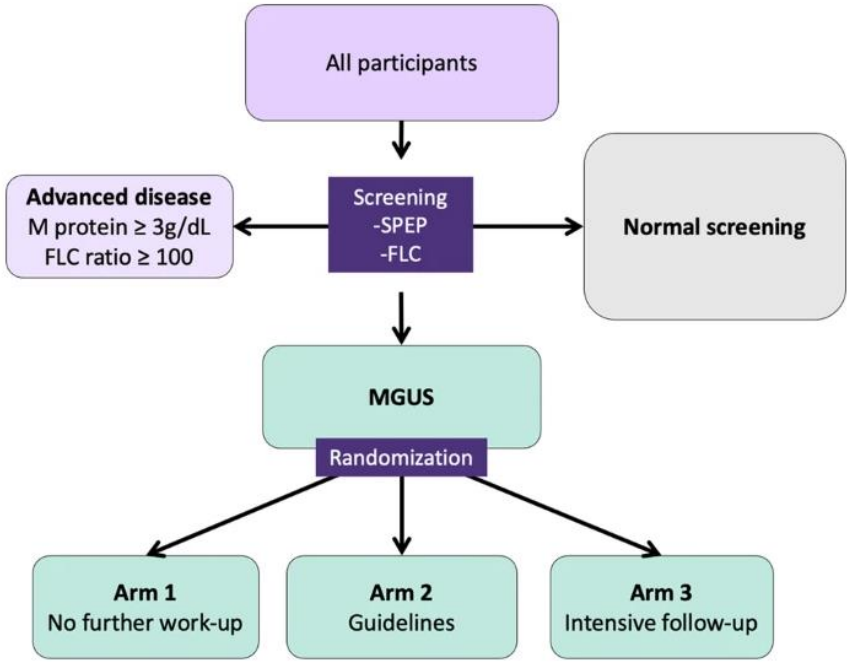
2) Lytic lesion on bone imaging

3) Paraprotein >15g/L

Iceland screens, treats, or prevents multiple myeloma (iStopMM) study

The largest scientific study ever conducted in Iceland

About the iStopMM study →



All individuals living in Iceland, born in 1975 or earlier, were invited to participate

148,704
offered participation

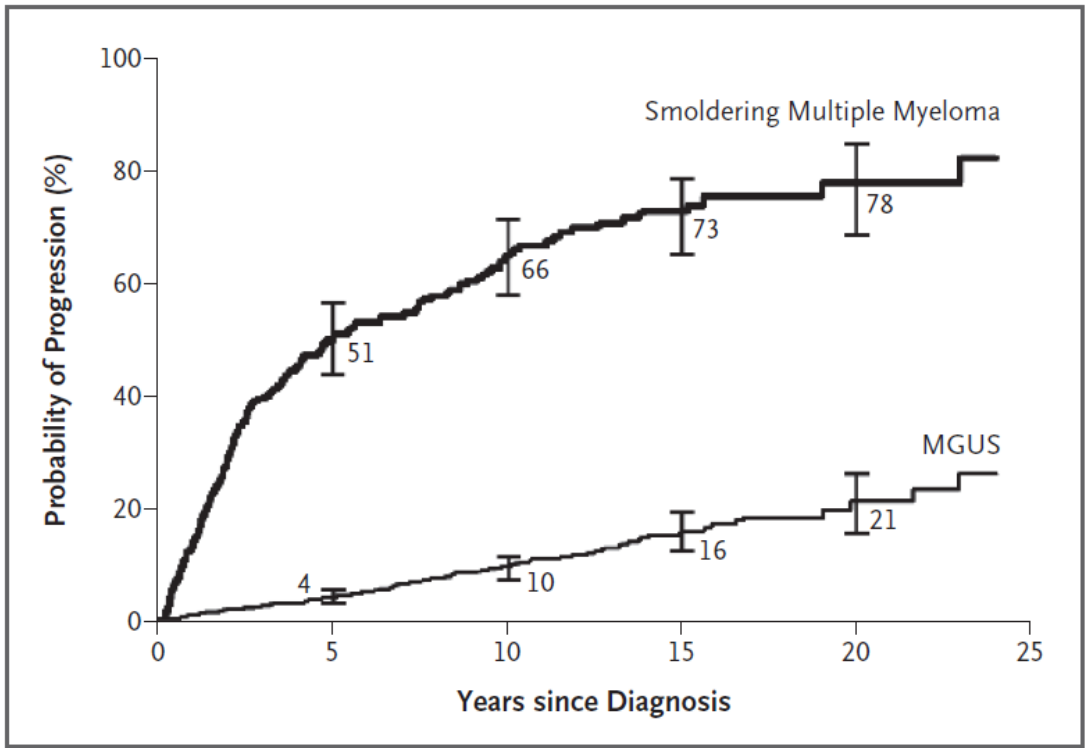
80,759
participated

75,422
blood samples collected

Smouldering myeloma

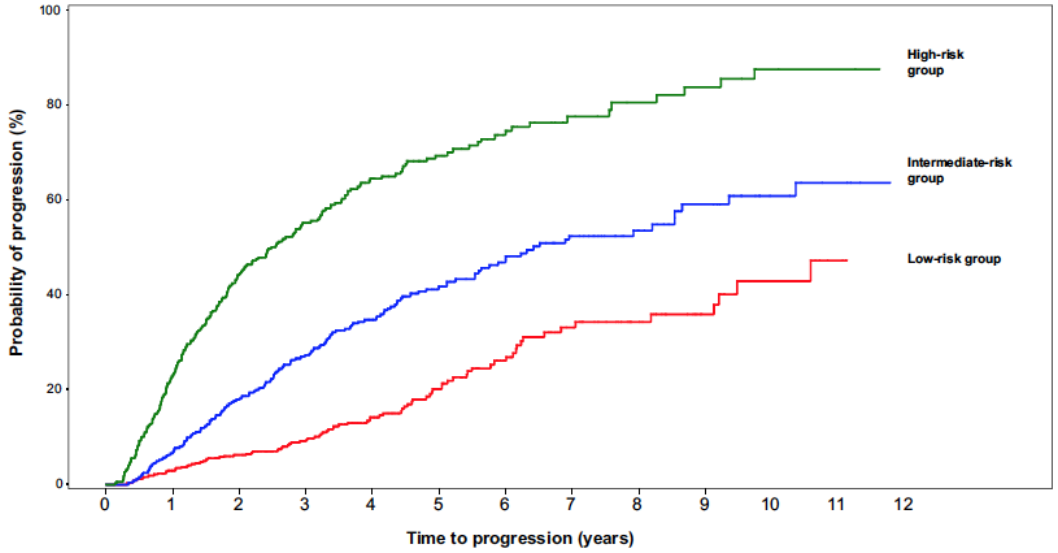
Asymptomatic stage of myeloma defined by:

- Monoclonal protein >30g/L, and/or
- Bone marrow plasma cells >10%, plus
- Absence of myeloma-related organ damage



Kyle R NEJM 2007; 356

Paraprotein > 20g/L
BM plasma cells
>20%
sFLC ratio >20



Risk Stratification groups	Number of risk factors	Hazard Ratio (95% CI)	Risk of progression (2 years)	# of patients
Low-Risk	0	Reference	6.2%	522 (38.3%)
Intermediate	1	2.99 (1.97 – 4.54)	17.9%	445 (32.7%)
High	2-3	9.02 (6.15 – 13.2)	44.2%	396 (29.1%)

Mateos Blood Cancer Journal 2020; 10:102

John's Progress

- Followed for 5 years by GP with annual clinical review + blood tests
- Review in August 2018
  - Now aged 65
  - Anorexia, increased lethargy
  - Some mild low back pain

Protein Studies

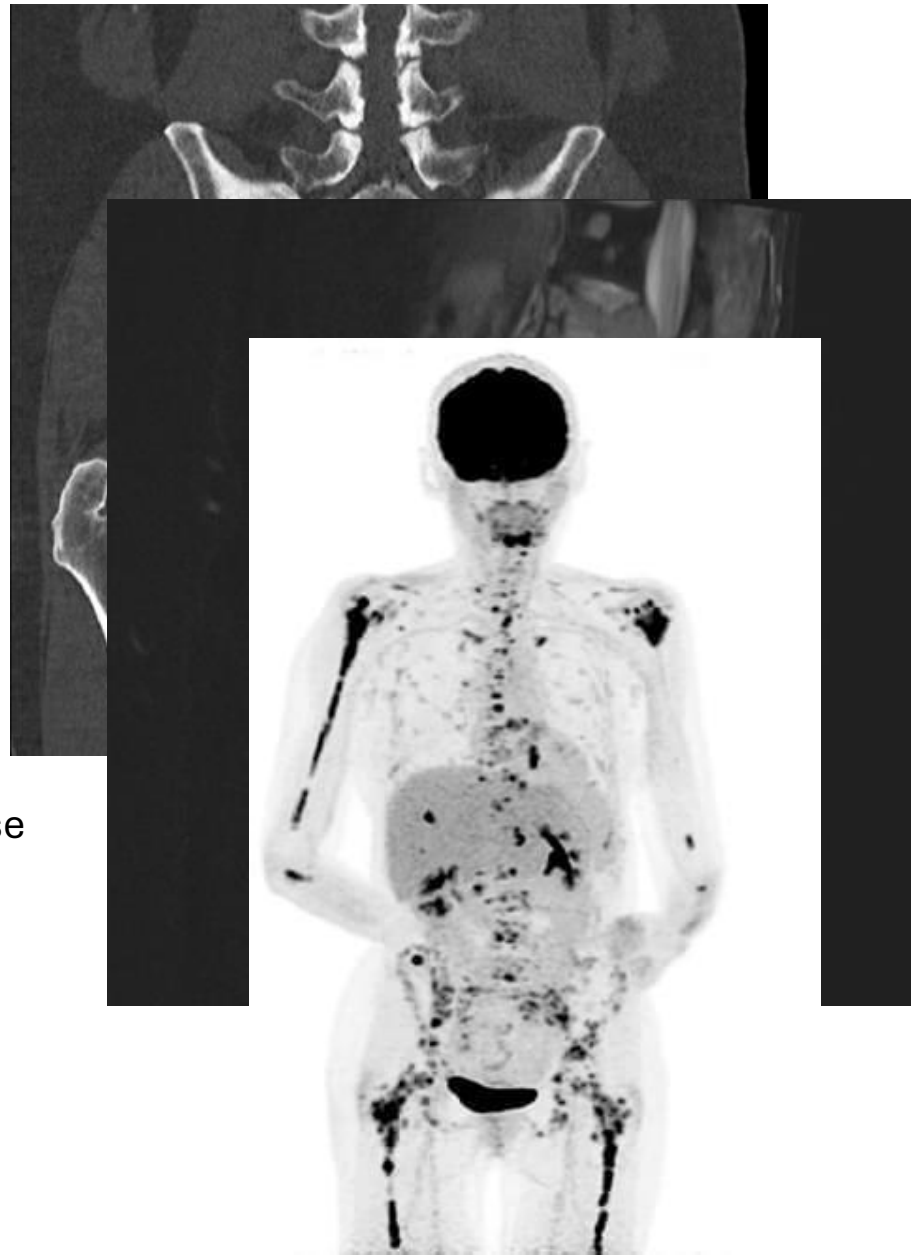
Albumin	22 L	g/L	32 - 44
Alpha 1	4	g/L	2 - 4
Alpha 2	9	g/L	4 - 9
Beta 1	3	g/L	2 - 6
Gamma	4 L	g/L	6 - 15
Band no longer detected.			
IgG Type Kappa *	22 H	g/L	<0.1
Total Protein	66	g/L	63 - 80
Immunofixation	Monoclonal IgG Kappa *		
Kappa Free Light Chains-N Latex	68 H	mg/L	7 - 22
Lambda Free Light Chains-N Latex	18	mg/L	8 - 27
K/L Ratio-N Latex	3.78 H		0.31 - 1.56

Test Name	Result	Units
Haemoglobin	126	g/L
● Haematocrit	0.36 L	
● Red cell count	3.6 L	10^12/L
MCV	100	fL
White cell count	6.1	10^9/L
Neutrophils	3.61	10^9/L
Lymphocytes	1.69	10^9/L
Monocytes	0.56	10^9/L
Eosinophils	0.21	10^9/L
Basophils	0.02	10^9/L
Platelets	186	10^9/L

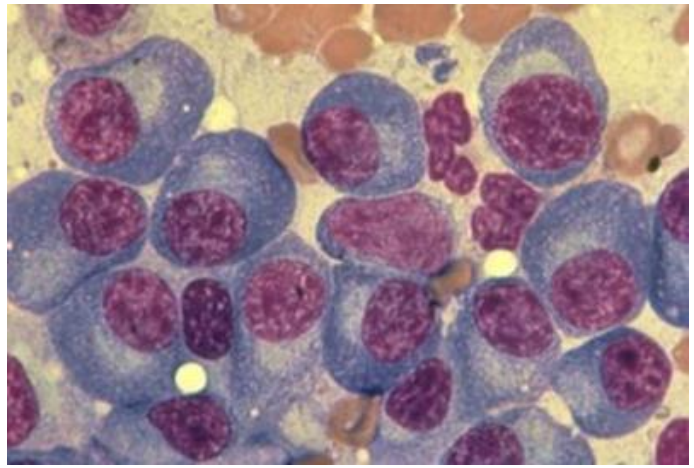
Test Name	Result	Units
● Sodium	133 L	mmol/L
Potassium	4.3	mmol/L
Chloride	100	mmol/L
Bicarbonate	21	mmol/L
Anion Gap	12	mmol/L
● Calcium (Corrected)	2.87 H	mmol/L
Phosphate	1.23	mmol/L
Urea	5.4	mmol/L
Uric Acid	0.422	mmol/L
Creatinine	110	umol/L
eGFR	63	
Random Glucose	6.5	mmol/L
● Total Protein	99 H	g/L
● Albumin	21 L	g/L
● Globulin	78 H	g/L

Skeletal imaging for myeloma

- Radiographic skeletal survey
  - insensitive, time-consuming
  - no longer recommended
- Whole-body, low-dose CT
  - quick, well-tolerated
  - more sensitive than plain x-ray
  - non-contrast
  - widely available
- MRI (whole body or spine/pelvis)
  - better resolution of pathological fracture, neurologic compromise
  - prognostic
- PET/CT
  - sensitive for extramedullary disease
  - relapsed and non-secretory disease monitoring
  - prognostic
  - difficult to access



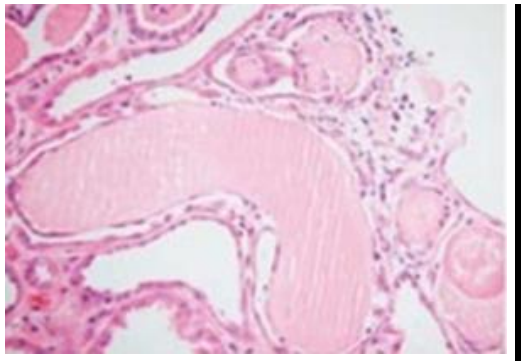
Multiple myeloma: Diagnosis



Biopsy-proven plasmacytoma, OR
>10% clonal bone marrow plasma cells, PLUS
one or more of:

- HyperCalcaemia: >2.75mmol/L
- Renal failure: eGFR < 40ml/min
- Anaemia: Hb <100
- Lytic Bone lesions

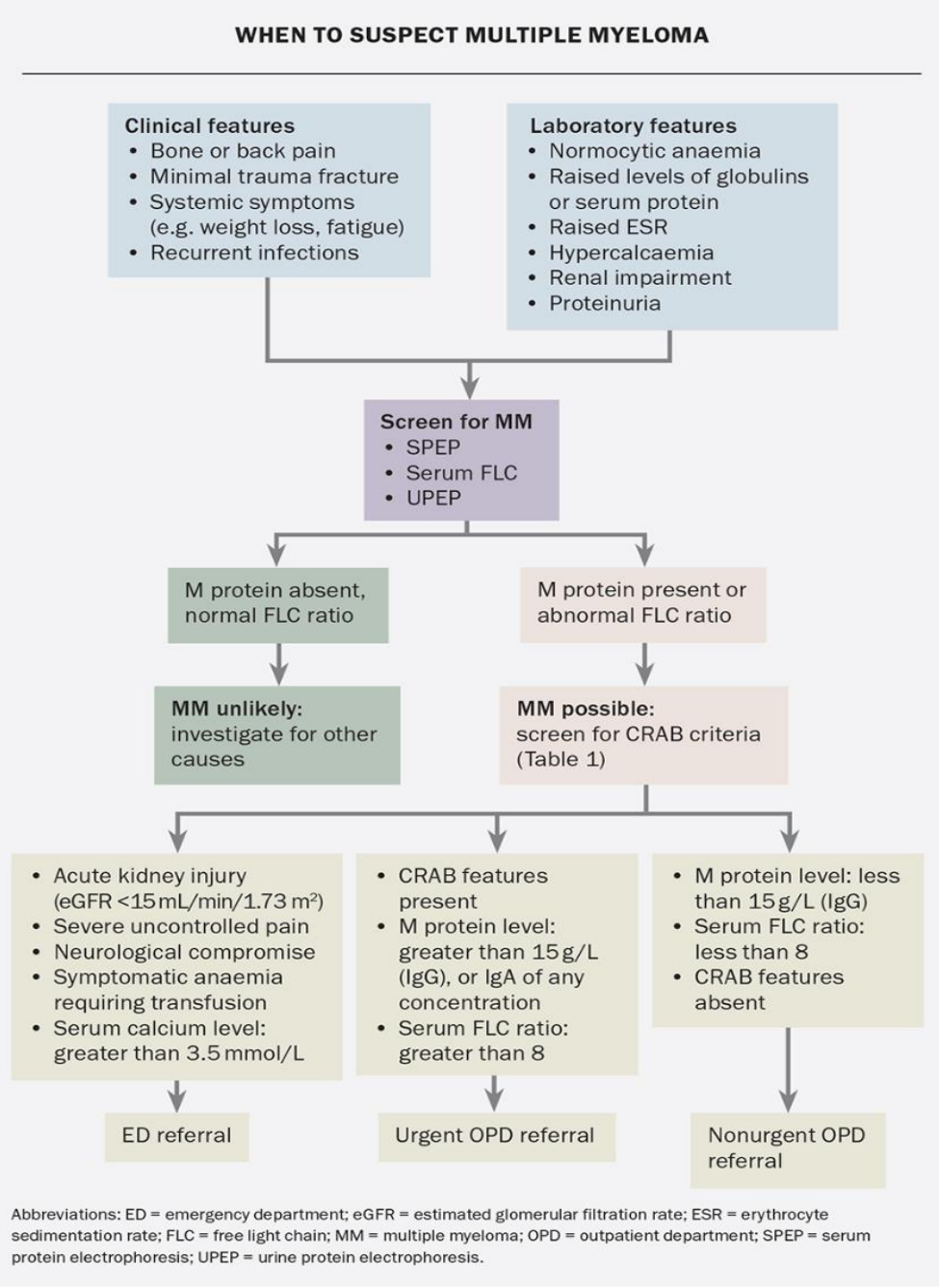
Symptomatic disease



- >1 focal lesion on MRI
- sFLC ratio >100
- >60% bone marrow plasma cells

Biomarkers of high risk for progression to symptomatic disease

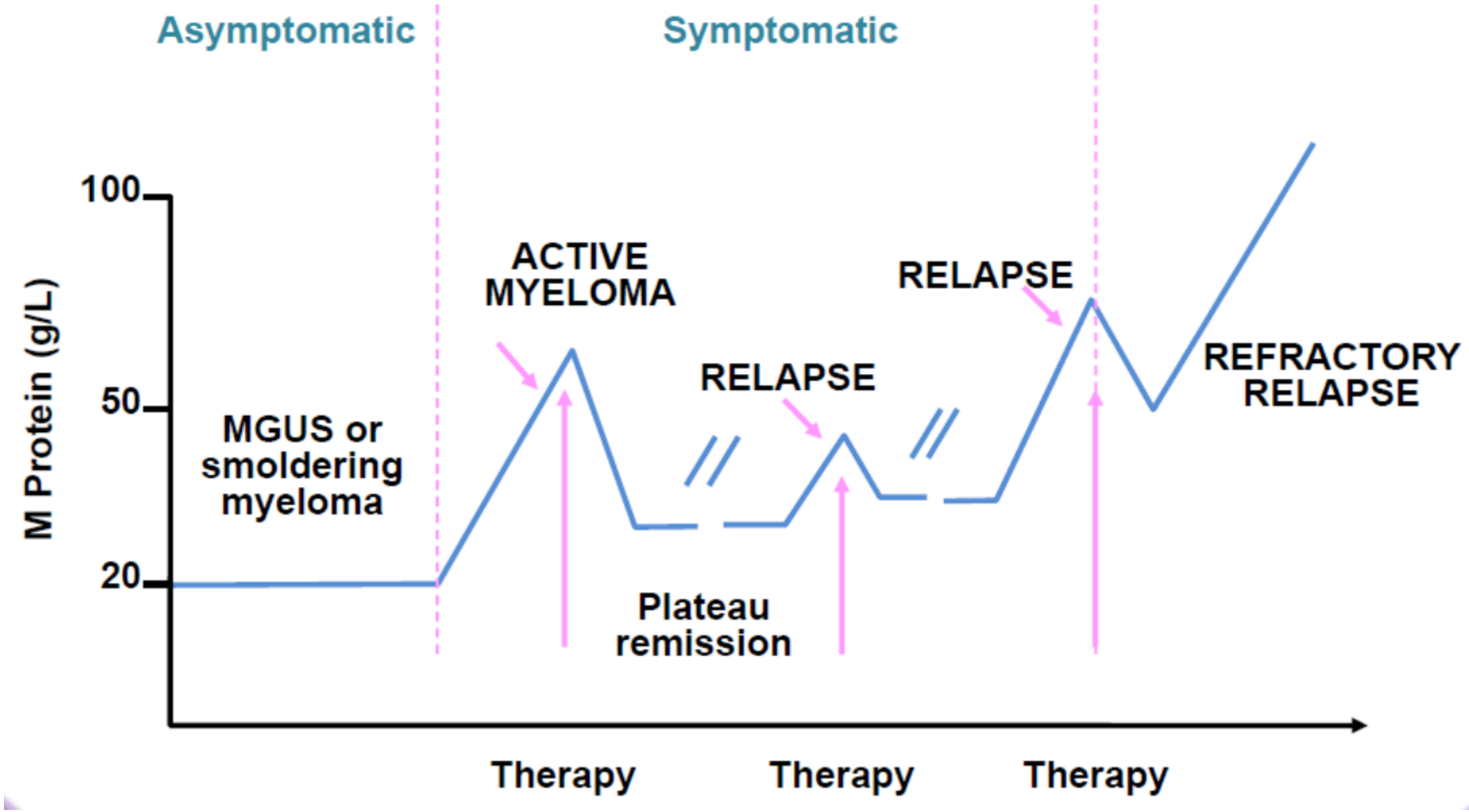
Lancet Oncol 2014; 15: e538-48



Abbreviations: ED = emergency department; eGFR = estimated glomerular filtration rate; ESR = erythrocyte sedimentation rate; FLC = free light chain; MM = multiple myeloma; OPD = outpatient department; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

There are several red flag symptoms that should lead to a suspicion of myeloma:

- Persistent or unexplained pain (>4–6 weeks, presenting as generalised or localised), particularly in the back or ribs
- Pathological or fragility fractures, e.g. of the vertebra
- Hypercalcaemia; reduction in renal function
- Recurrent or persistent infections
- Unexplained anaemia
- Nosebleeds or unexplained bleeding
- Unexplained breathlessness
- Generally unwell – fatigue, weight loss, suspicion of underlying cancer
- Unexplained peripheral neuropathy


Asymptomatic
Symptomatic
100
50
20
M Protein (g/L)
MGUS or smoldering myeloma
ACTIVE MYELOMA
Plateau remission
RELAPSE
RELAPSE
REFRACTORY RELAPSE
Therapy
Therapy
Therapy

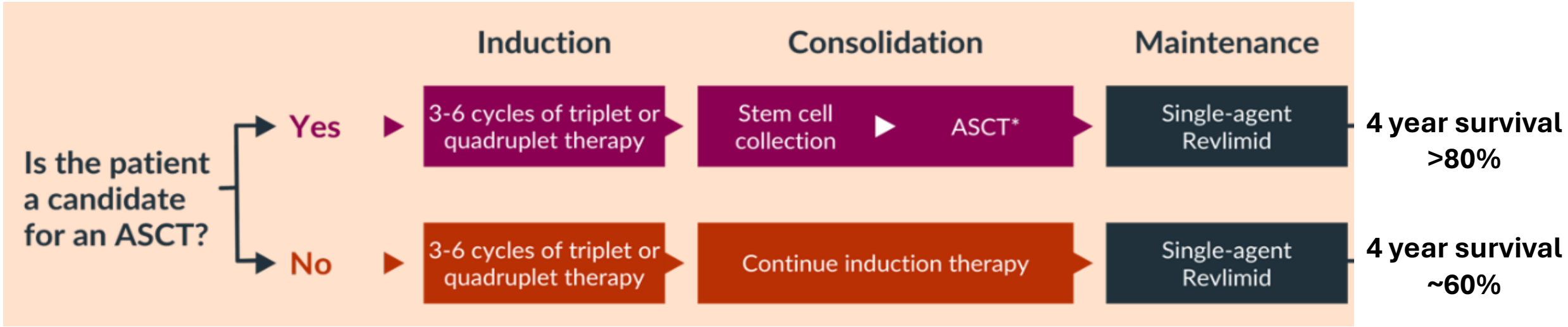
PBS-reimbursed agents for upfront treatment

- ***Proteasome inhibitors: "PIs"***
  - Bortezomib
- ***Immunomodulatory agents "IMiDs"***
  - Thalidomide
  - Lenalidomide
- ***Dexamethasone***
- Alkylating agents
  - Melphalan
  - Cyclophosphamide
  - Others (doxorubicin, etoposide…)

Therapy-related complications

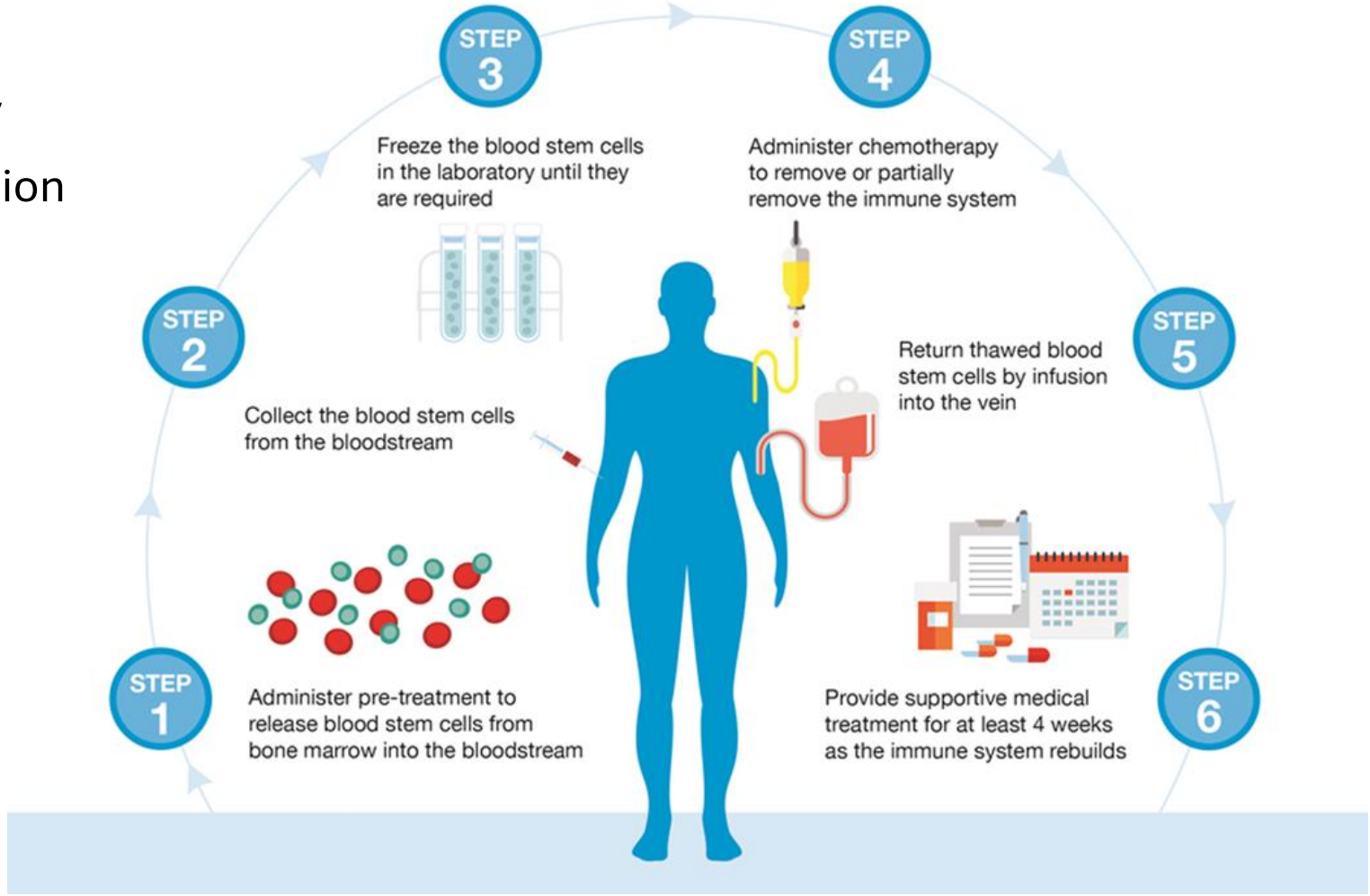
Complications	Prophylaxis/management
Peripheral neuropathy	Careful monitoring on treatment Bortezomib dose reductions/delays
Venous/arterial thromboembolism	Aspirin NOAC/LMWH if high risk
Infection	Valaciclovir (VZV), Bactrim DS (PJP) Vaccinations: Pneumovax, HiB, Influenza, CV19
Rash	Topical steroids
Corticosteroid complications	Proton pump inhibitor BSL monitoring and diabetes management Dexamethasone dose reduction
Cytopenia's	Dose adjustment Transfusion/growth factor support

Newly Diagnosed Multiple Myeloma frontline therapy



Autologous stem cell transplant

- Still considered important component of frontline therapy
- Extends duration of first remission by ~14mo
- Requires 2-3 week inpatient admission



John’s Progress

Induction therapy with VRD x 4 cycles

Peripheral blood stem cells collected

Further 4 cycles VRD

Autologous transplant performed at RBWH

= ***9 months of therapy***

- Unable to work during this time
- Weekly travel to RBWH
- Required daughter to relocate to perform carer role post-transplant

Supportive care: Infection Prevention

- Increased risk of infection due to impaired immune function from disease + treatment
- Most commonly – bacterial + viral respiratory infections
- Varicella Zoster reactivation can occur in up to 20%
- All patients should be vaccinated for: CV19, Influenza, Strep pneum, N.meningitidis
- Prompt treatment of intercurrent infection – low threshold to refer to hospital if there's mod-severe infection

Supportive care: Bone Protection

- Regular bisphosphonates reduce skeletal morbidity including bone pain, neural compression and pathological fracture
- Usual practice = monthly zoledronate or pamidronate for 12mo, then 3-monthly
  - **ONJ risk** – need initial and then ongoing dental review 6 monthly
- Monthly denosumab non-inferior to zoledronate but no PBS reimbursement
- Calcium and Vit D supplementation encouraged in the presence of normocalcaemia

Other supportive care

- **Analgesia**
  - Pharmacologic: opiates, pregabalin, paracetamol
  - Radiotherapy for focal lesions
- **Mental health + advanced care planning**
  - MM pts have a poor QOL compared to other cancer pts
  - Higher risk of depression, carer burnout
  - Mental healthcare plans are a valuable support
- **Secondary cancer screening** (esp. patients on lenalidomide maintenance)
  - Per standard guidelines
  - Regular skin checks

Back to our patient…

- Lenalidomide maintenance commenced post-transplant
  - Required dose reduction for neutropenia
  - Some late diarrhoea – responded to Questran lite
- Achieved complete response (undetectable paraprotein)
- Returned to work with 3-monthly phone reviews to RBWH clinic

- Routine review at 24mo post-transplant:

Protein Studies

Albumin	41	g/L	32 - 44
Alpha 1	2	g/L	2 - 4
Alpha 2	7	g/L	4 - 9
Beta 1	5	g/L	2 - 6
Beta 2	3	g/L	2 - 6
Gamma	7	g/L	6 - 15
IgG Type Kappa *	5 H	g/L	<0.1
Total Protein	70	g/L	63 - 80

Treatment for relapsed disease

Prolongation of survival while maintaining best quality of life for the patient

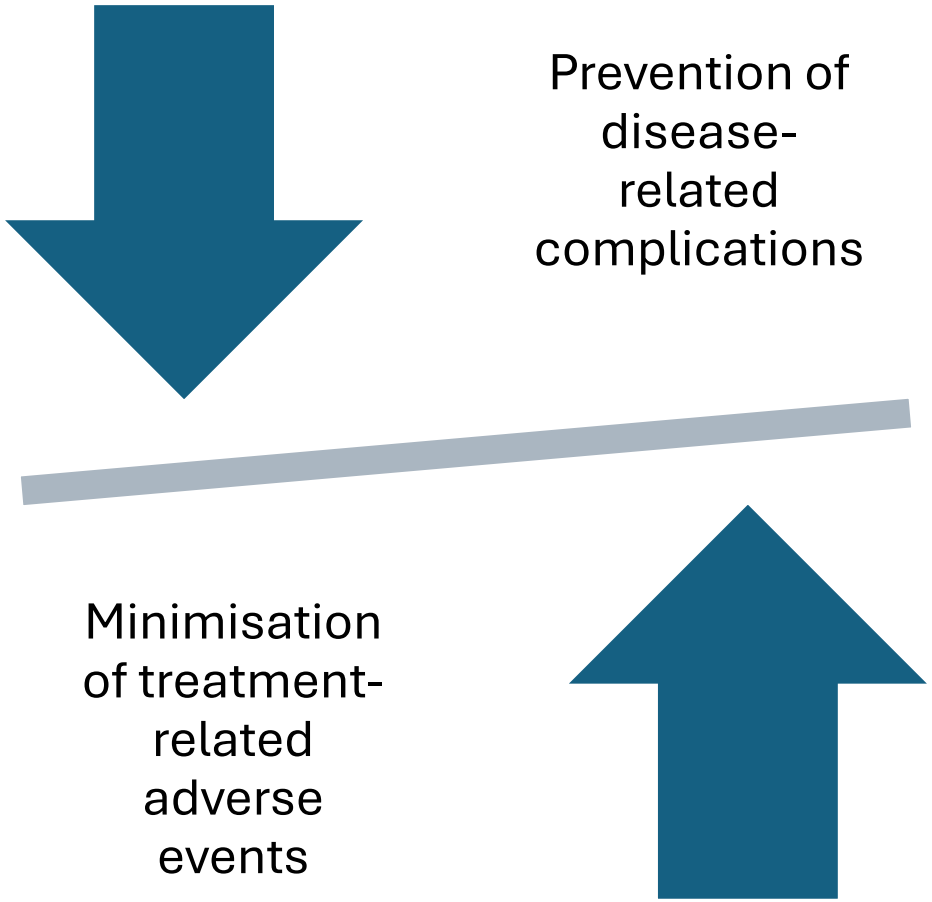
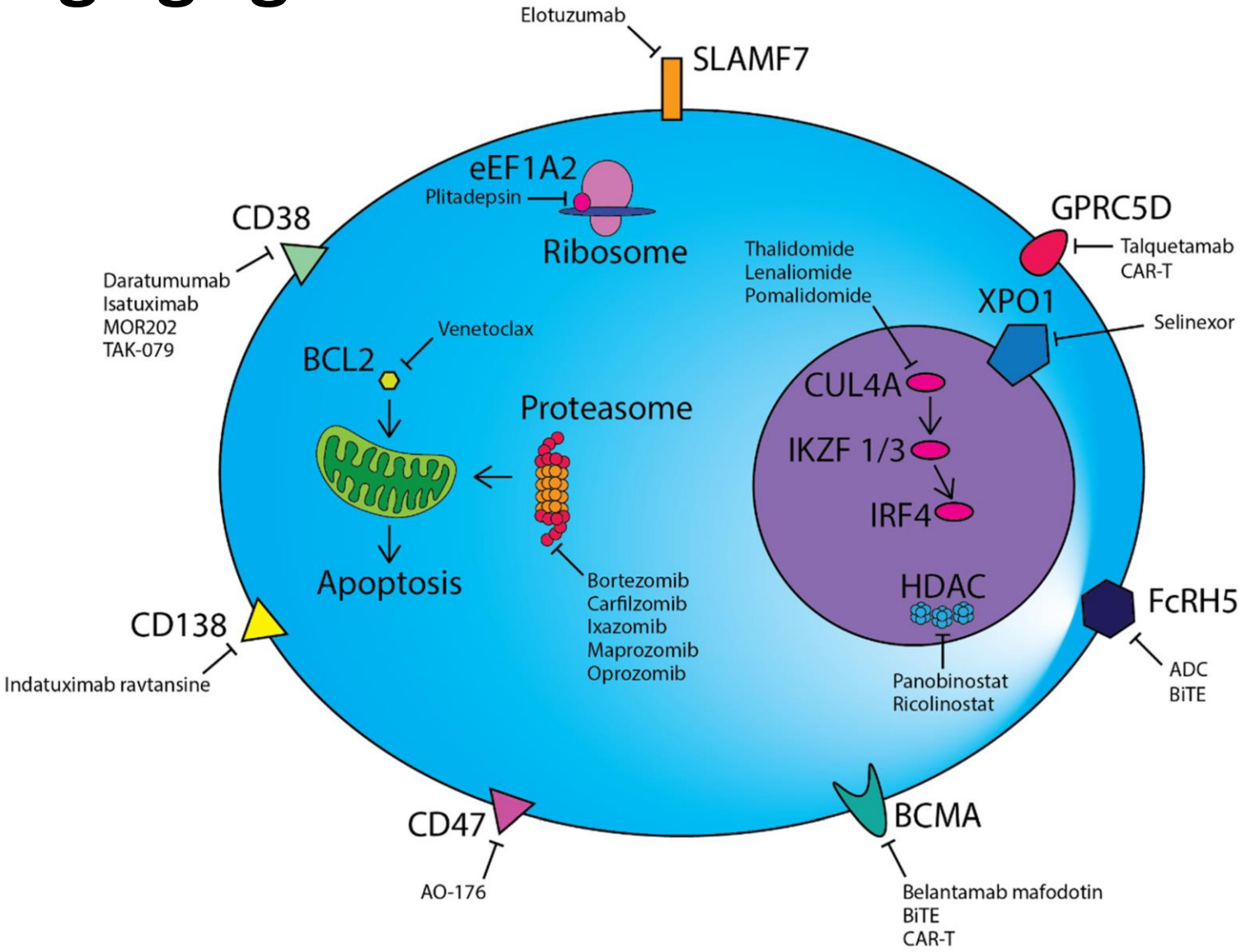


TABLE 2. COMMONLY USED TREATMENTS FOR MULTIPLE MYELOMA

Drug class	Examples	Common adverse effects
Corticosteroids	• Dexamethasone • Prednisone	• Insomnia • Mood disturbance • Proximal myopathy • Diabetes
Immunomodulatory agents	• Lenalidomide • Pomalidomide • Thalidomide	• Venous thromboembolism • Cytopenia • Skin rash • GI disturbance • Peripheral neuropathy
Proteasome inhibitors	• Bortezomib • Carfilzomib • Ixazomib	• Peripheral neuropathy • Thrombocytopenia • Dyspnoea
Monoclonal antibodies	• Daratumumab • Elotuzumab • Isatuximab	• Infusion-related reaction
Alkylating agents	• Melphalan • Cyclophosphamide	• Cytopenia • GI disturbance
T-cell-redirecting therapies (TCEs, CART)	• Teclistamab • Talquetamab • Cilta-cel • Ida-cel	• Cytokine release syndrome • Cytopenia • Neurotoxicity

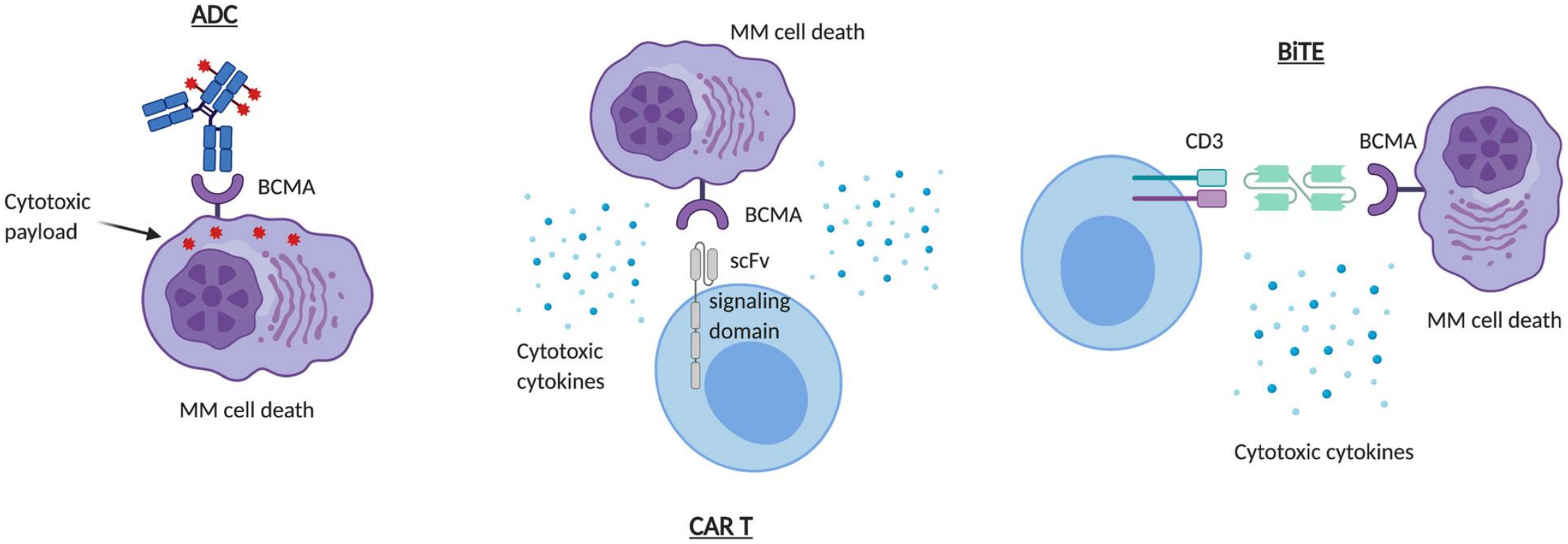
Abbreviations: CART = chimeric antigen receptor T-cell; GI = gastrointestinal; TCE = T-cell engager.

Emerging agents



J Pers Med 2021, 11(5): 334

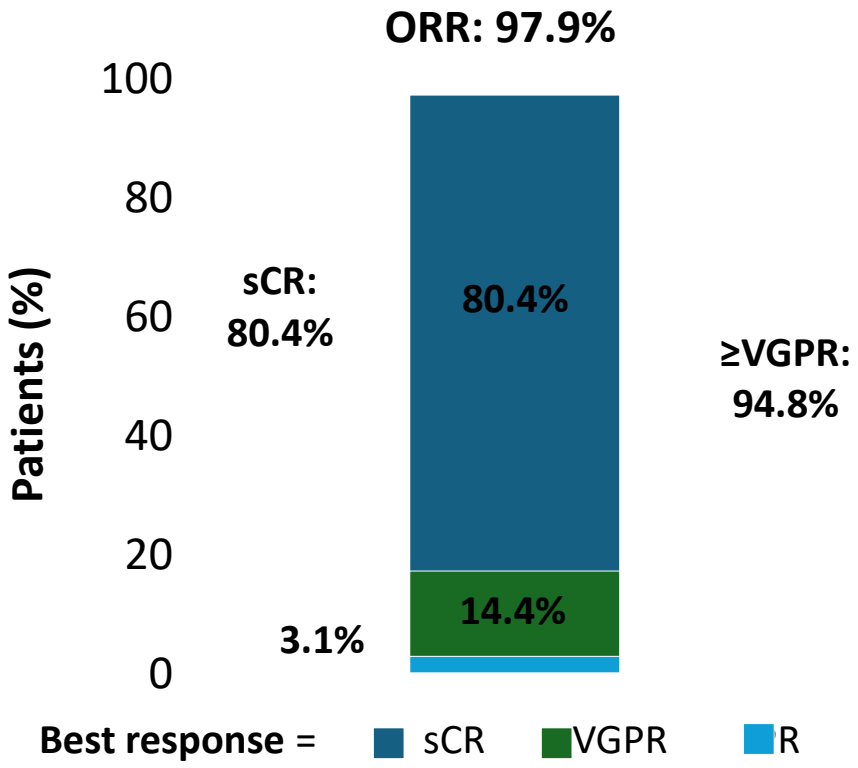
BCMA immunotherapies



Journal of Hematology & Oncology 2020; 13:125

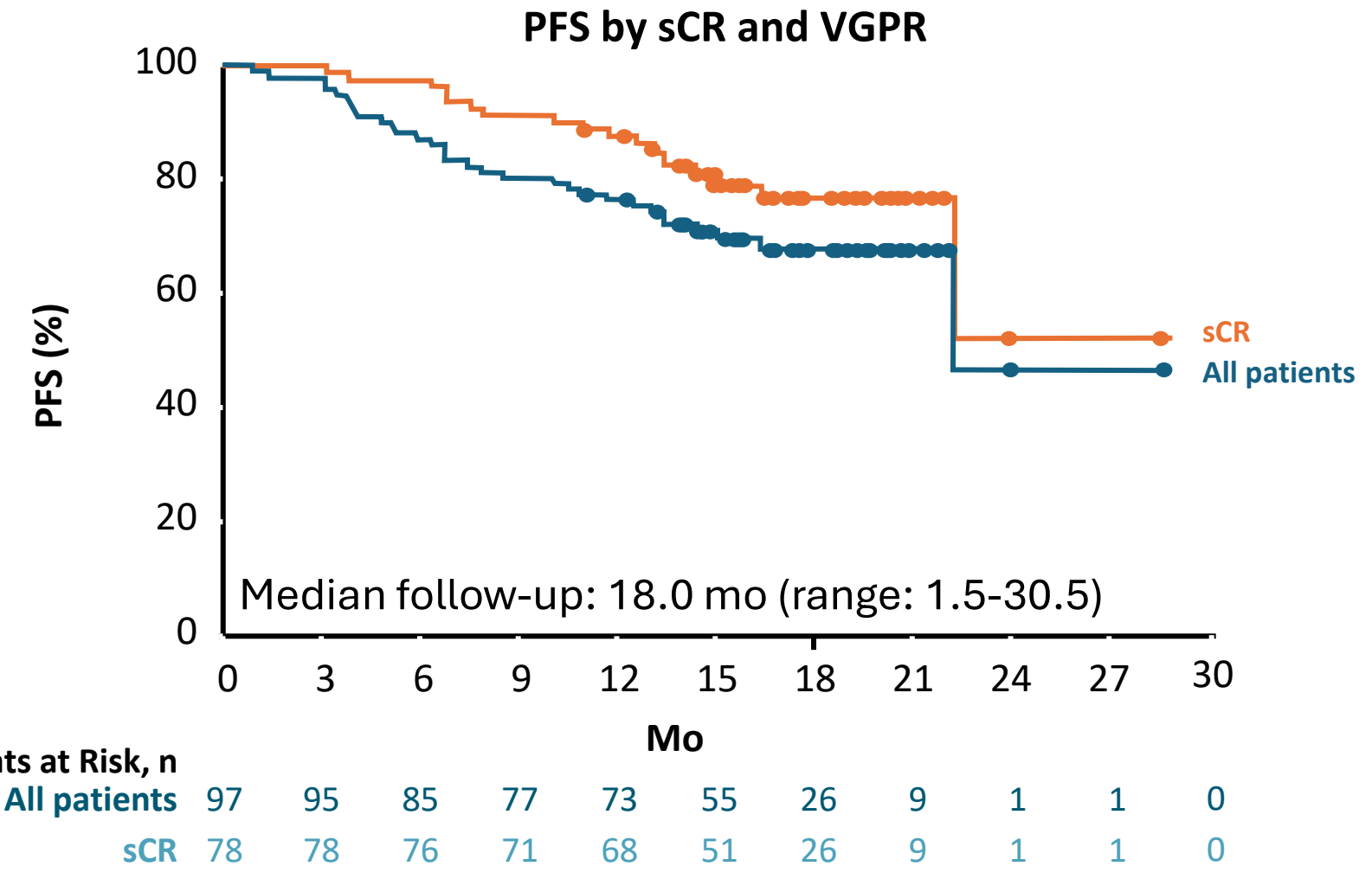
CAR-T: Cilta-cel

	N = 29
Median prior lines of therapy, n (range)	5 (3 – 18)
Prior autologous transplantation, n (%)	25 (86)
Triple-exposed,[d] n (%)	29 (100)
Penta-exposed,[e] n (%)	22 (76)
Refractory status, n (%)	
Carfilzomib	20 (69)
Pomalidomide	22 (76)
Daratumumab	27 (93)
Triple-refractory[d]	25 (86)
Penta-refractory[e]	8 (28)
Refractory to last line of therapy,[f] n (%)	28 (97)



Usmani. ASCO 2021. Abstr 8005.

CARTITUDE-1: PFS



Median PFS, Mos (95% CI)	18-Mo PFS, % (95% CI)
NR	75.9 (63.6-84.5)
22.8 (22.8-NE)	66.0 (54.9-75.0)

	18-Mo OS, % (95% CI)
All patients	80.9 (71.4-87.6)

Patients at Risk, n

All patients	97	95	85	77	73	55	26	9	1	1	0
sCR	78	78	76	71	68	51	26	9	1	1	0

Usmani. ASCO 2021. Abstr 8005.

Summary

Timely referral is important to avoid permanent organ damage and functional impairment

Please call us GP hotline
3646 1340

Increasing treatment complexity and move towards continuous therapy have improved outcomes but also imposed new challenges

GP role as important as ever

- psychosocial support
- analgesia
- preventative health
- advanced care planning

Emerging therapies are cause for hope that cure may be on the horizon