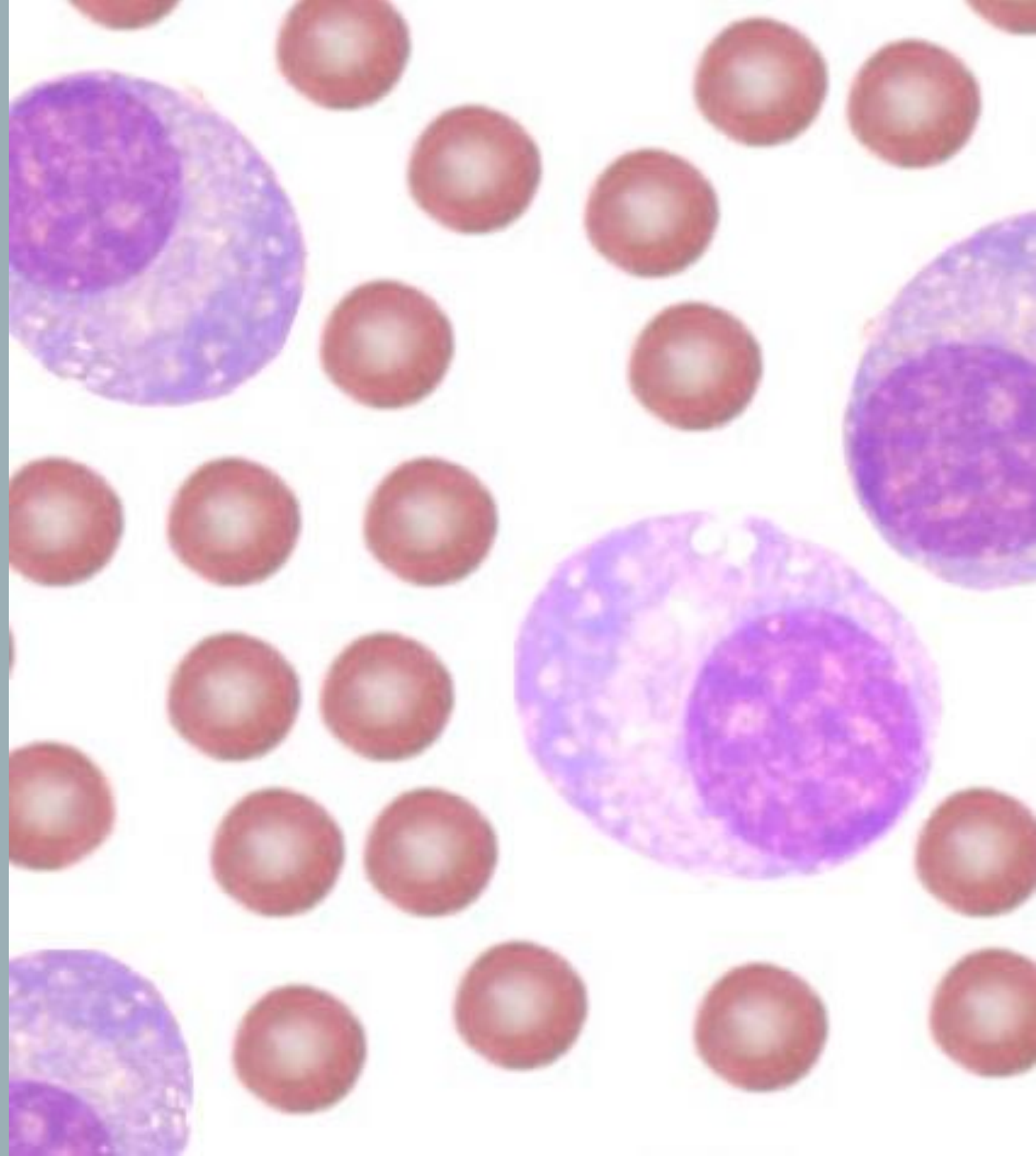
An Introduction to Plasma Cell Dyscrasias

Danyal Ladha

September 13th, 2025

GHEST Symposium

Oakville, ON



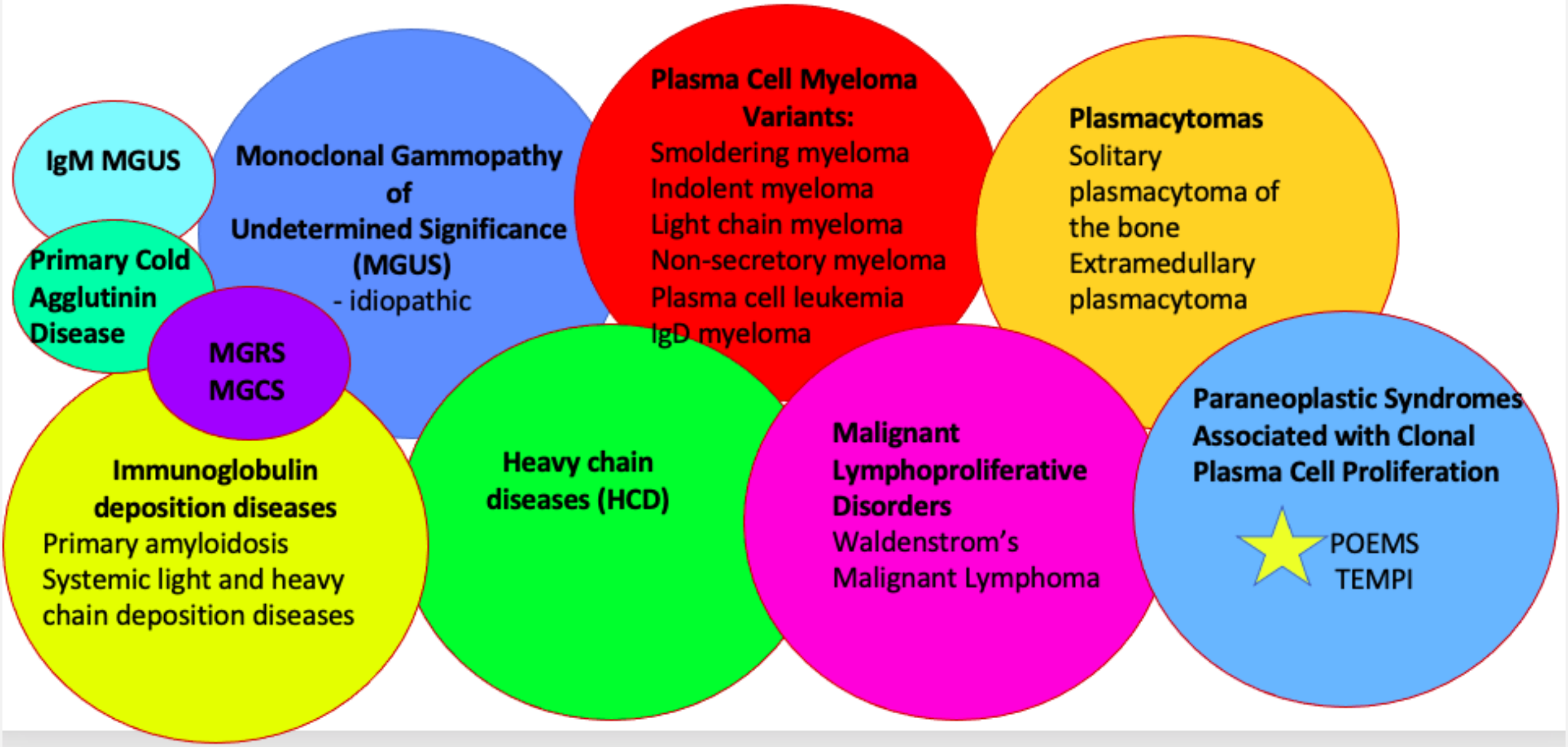
Learning Objectives

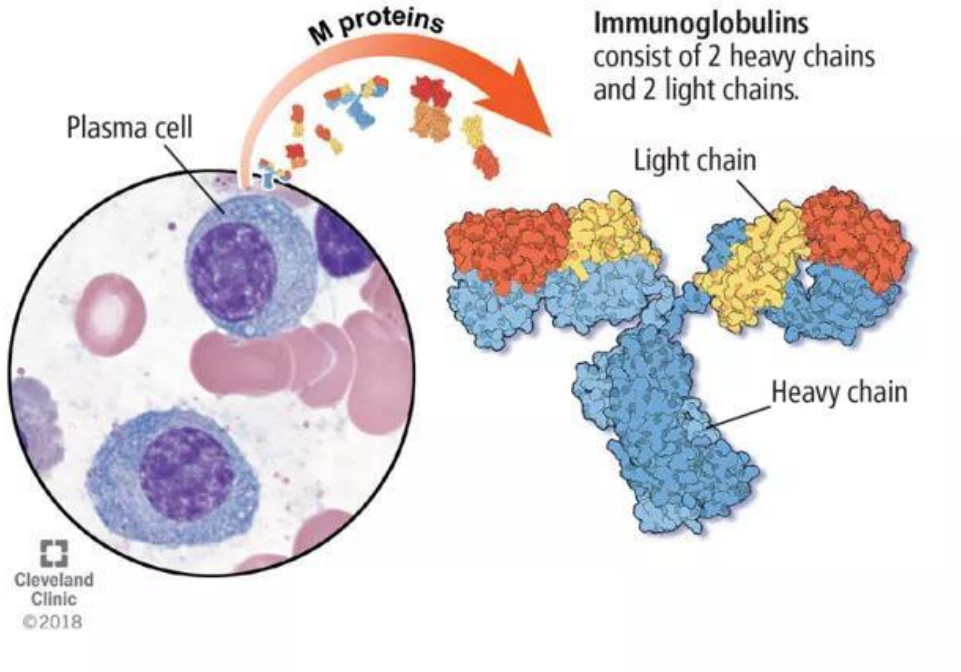
- **Describe** the key diagnostic criteria that distinguish MGUS, smoldering myeloma, and multiple myeloma
- **Identify** and **explain** the clinical manifestations of multiple myeloma
- **Outline** the key diagnostic tools and criteria for diagnosing multiple myeloma
- **Understand** the general approach to treatment of multiple myeloma

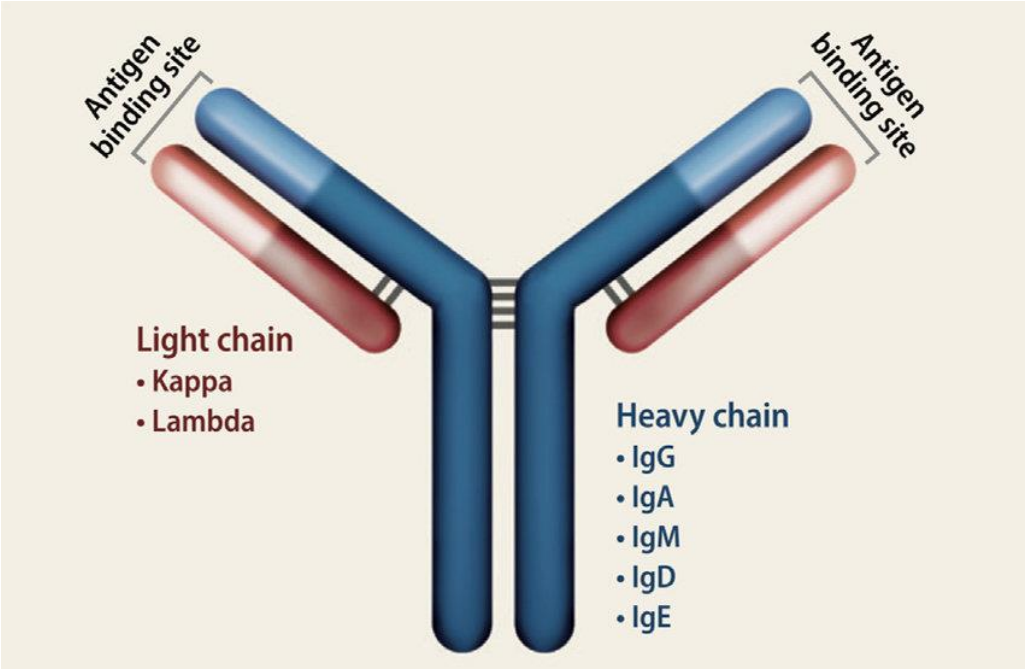
A Case…

- A 60M presents to the ED with back pain
  - Hemoglobin 134, Creati 105, Ca 2.45
  - SPEP – IgA kappa, **M protein 7.3 g/L**
  - IgG 8.5, IgA **18.42** (normal 0.7-4), IgM 0.32
  - Free kappa **1,141**, free lambda 8.6, ratio **132.71**
  - PET - **T10 lytic lesion and soft tissue mass**
- Treated with radiation to T10 lytic lesion, declined treatment for a few months → disease progressed
- Treated with RVD (induction chemotherapy) x3 cycles until November 2024 → declined treatment again and left the country

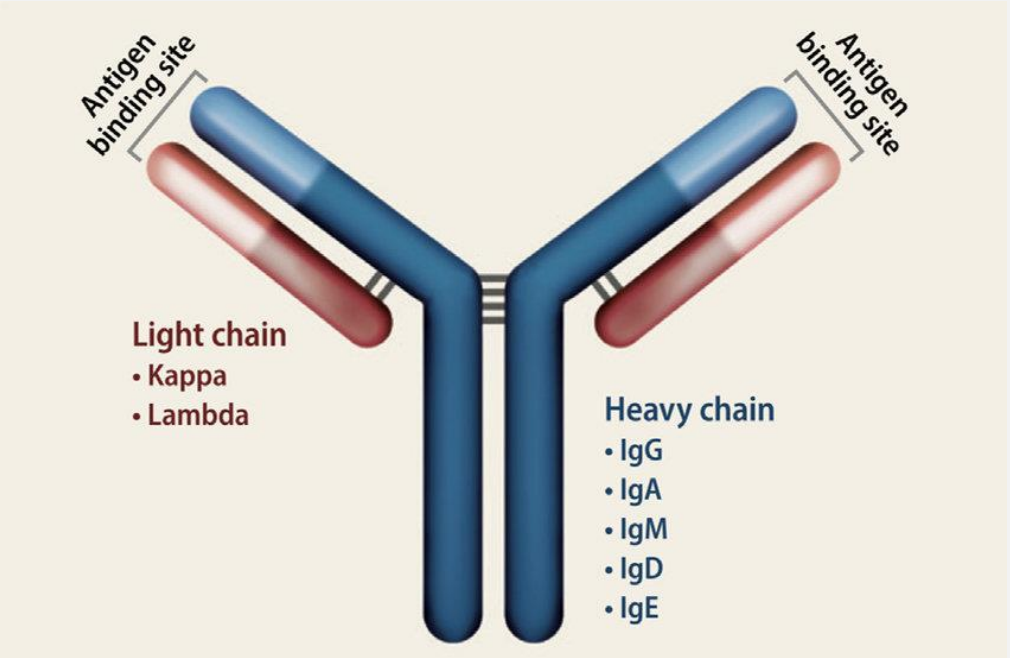
Spectrum of Plasma Cell Dyscrasias




M proteins
Immunoglobulins
consist of 2 heavy chains
and 2 light chains.
Plasma cell
Light chain
Heavy chain
Cleveland
Clinic
©2018


Antigen
binding site
Antigen
binding site
Light chain
• Kappa
• Lambda
Heavy chain
• IgG
• IgA
• IgM
• IgD
• IgE

- **Heavy chains**
  - 60% IgG
  - 20% IgA
  - <1% IgD, IgE, IgM
- **Light chains**
  - Lambda or kappa
  - Kappa more common in MM, lambda more common in amyloidosis, POEMS



****2-3%** of myelomas are NON-SECRETORY (i.e. no detectable heavy or light chain in serum)

Epidemiology

- Characterized by proliferation of malignant **plasma cells**
- Accounts for 1% of all cancers and ~10% of all hematologic malignancies
- Considered treatable but NOT curable (as of 2025*)
- Although median age is ~65, **NOT** a disease of only the elderly (can occur in 20s-30s, albeit less common)

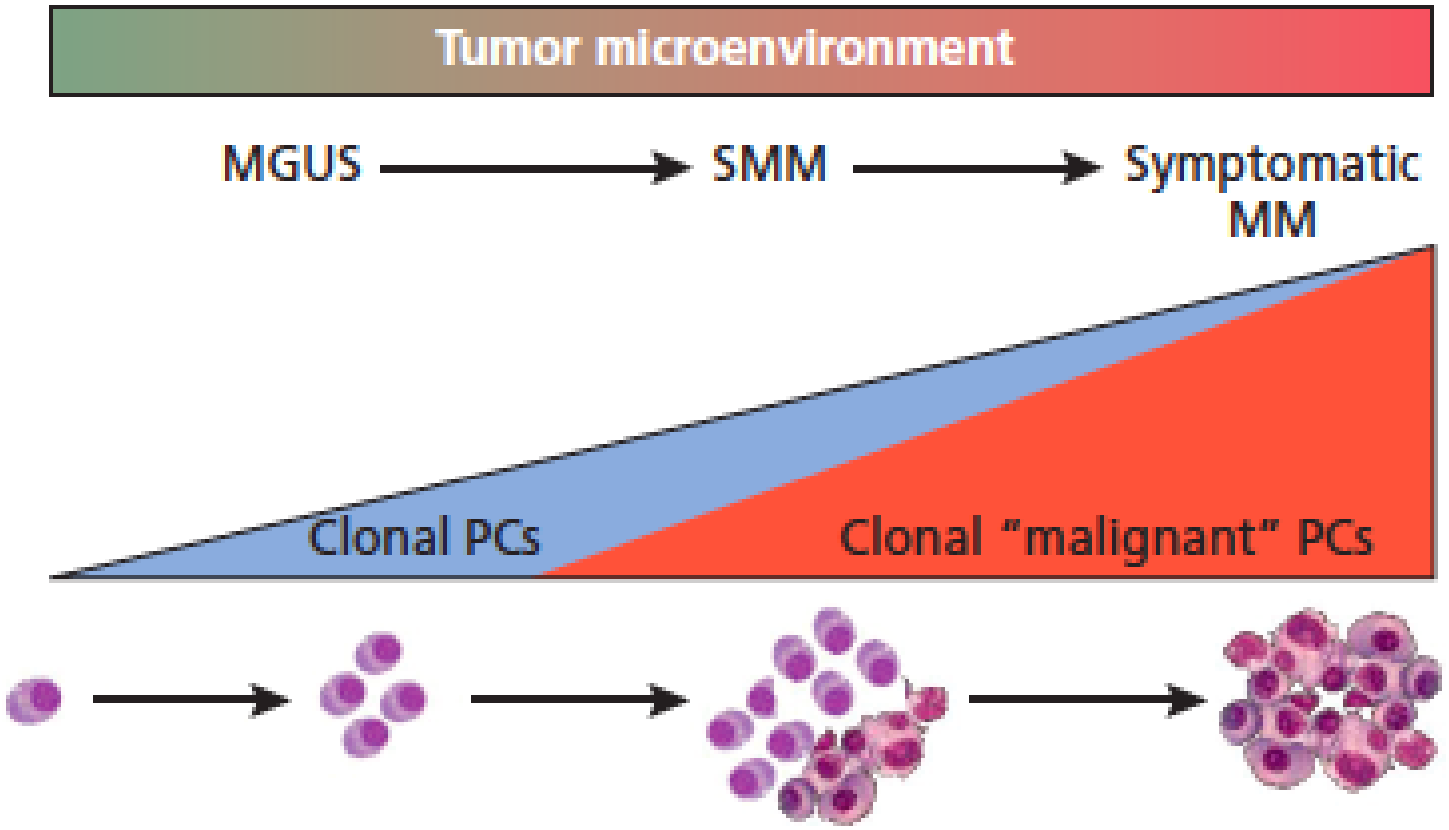
Learning Objectives

- **Describe** the key diagnostic criteria that distinguish MGUS, smoldering myeloma, and multiple myeloma
- **Identify** and **explain** the clinical manifestations of multiple myeloma

The Spectrum of Myeloma

- **MGUS (Monoclonal Gammopathy of Undetermined Significance)**
  - 3.2% incidence in patients >50, 5.3% of those >70 *(Kyle RA et al NEJM 2018)*
  - Risk of progression: 1% per year (constant over time)
- **Smoldering myeloma**
  - Risk of progression *(Rajkumar et al, Blood 2015)*
    - ~10% per year for first 5 years
    - ~3% per year for next 5 years
    - 1-2% per year thereafter

Figure 25-2 The transition from MGUS to myeloma.



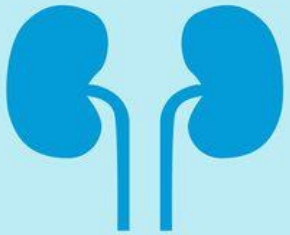
IMWG Criteria for Diagnosis of MM

MGUS	Smoldering Myeloma	Active or Symptomatic Multiple Myeloma
▪ M protein <3 g/dL ▪ Clonal plasma cells in BM <10% ▪ No myeloma-defining events	▪ M protein ≥3 g/dL (serum) or ≥500 mg/24 hr (urine) ▪ Clonal plasma cells in BM 10% to 60% ▪ No myeloma-defining events	▪ Underlying plasma cell proliferative disorder ▪ AND ≥1 SLiM-CRAB* features

*S: ≥60% clonal bone marrow plasma cells
Li: Serum free light chain ratio ≥100 (involved kappa) or ≤0.01 (involved lambda)
M: MRI studies with >1 focal lesion (≥5 mm in size)

C: Calcium elevation (>11 mg/dL or >1 mg/dL higher than ULN)
R: Renal insufficiency (CrCl <40 mL/min or serum creatinine >2 mg/dL)
A: Anemia (Hb <10 g/dL or >2 g/dL less than LLN)
B: Bone disease (≥1 lytic lesions on skeletal radiography, CT, or PET/CT)

Rajkumar. Lancet Oncol. 2014;15:e538.

C: HyperCalcaemia	R: Renal impairment	A: Anaemia	B: Bone lesions
			
Investigation: At least one clinical or referral record, and through laboratory tests (Calcium)	**Investigation:** At least one clinical or referral record and through laboratory tests (Serum creatinine)	**Investigation:** At least one clinical or referral records and through laboratory tests (Haemoglobin)	**Investigation:** At least one clinical or referral record, and include either plain radiograph(s) or other imaging studies, and on specific imaging investigations*
Confirmation: First record of clinical diagnosis of hypercalcaemia or serum calcium level > 2.75 mmol/L (> 11 mg/dL)	**Confirmation:** First record of clinical diagnosis of renal impairment or serum creatinine level > 177 µmol/L (>2 mg/dL)	**Confirmation:** First record of clinical diagnosis of anaemia or haemoglobin measurement < 110g/L (<11 g/dL) for Males, < 100 g/L (< 10 g/dL) for Females	**Confirmation:** At least one record of abnormal result on an imaging investigation **or** at least one record of pathological fracture, spinal cord compression, imaging-confirmed osteopenia, or imaging-confirmed osteoporosis

Seesaghur et al BMJ Open 2021

Summary Slide #1

- Myeloma occurs across a spectrum (MGUS → smoldering myeloma → multiple myeloma) – classifying the disease stage depends on the M-protein, bone marrow biopsy results, and absence/presence of clinical features
- Clinical features include:
  - **CRAB** – hyper**C**alcemia, **R**enal failure, **A**nemia, **B**one lesions
  - **SLiM** - **>60%** plasma cells in BM, **L**ight chain ratio >100 or <0.01, >1 **MRI** bone lesion (>5mm)
- Risk of progression is 1%/year for MGUS, 10%/year for SMM (within first 5 years)

Learning Objectives

- **Outline** the key diagnostic tools and criteria for diagnosing multiple myeloma

Investigations for suspected MM?

Investigations for suspected MM?

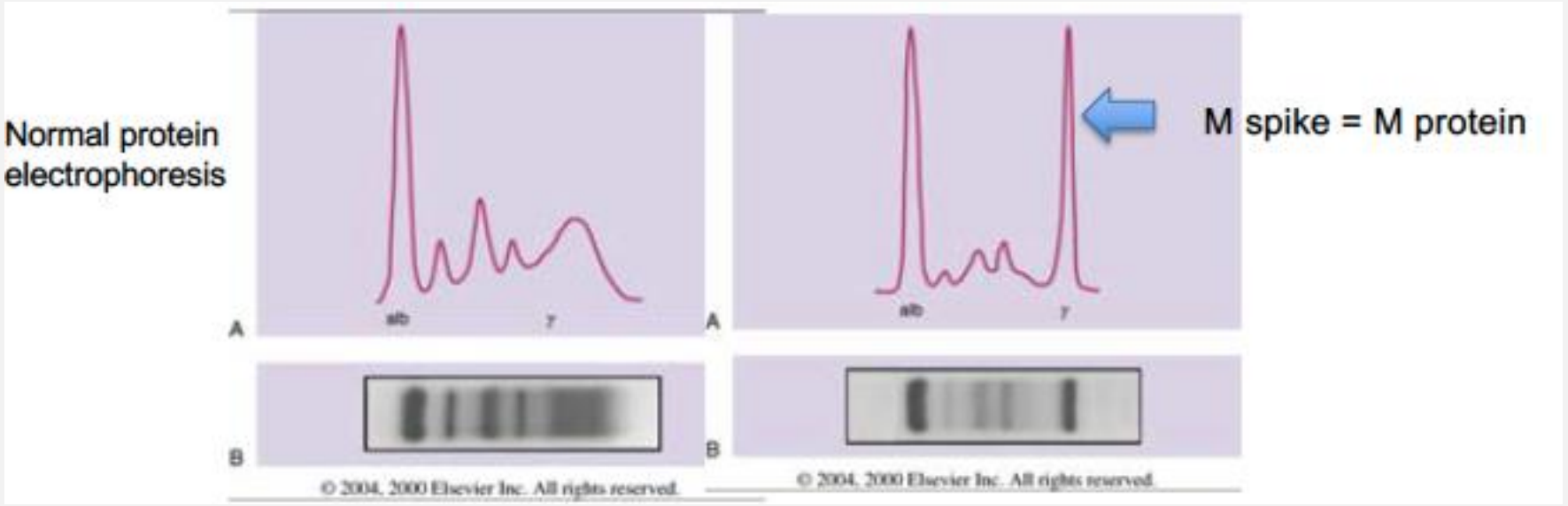
- **Labs**
  - CBC, blood film, creatinine, electrolytes including Ca
  - For staging (R-ISS): albumin, B-2 microglobulin, LDH
  - SPEP and immunofixation
  - Serum free light chains (~**15-20% of myelomas are light chain ONLY i.e. SPEP negative**)
  - Serum immunoglobulins (standard panel = IgG, IgA, IgM)
- **Imaging**
  - Low-dose CT or PET
- **Special tests**
  - Bone marrow aspirate + biopsy, including cytogenetics
  - 24-hour UPEP + immunofixation (looking for Bence Jones proteins, proteinuria)

Table 25-8 Revised International Staging System

Stage	Criteria	5-y overall survival (%)
R–ISS I	ISS–I (serum β_2-microglobulin <3.5 mg/L, serum albumin ≥3.5 g/dL) plus standard-risk genetics and no LDH elevation	82
R–ISS II	All others	62
R–ISS III	ISS III (serum β_2-microglobulin ≥5.5 mg/L) plus elevated LDH or high-risk genetics	40

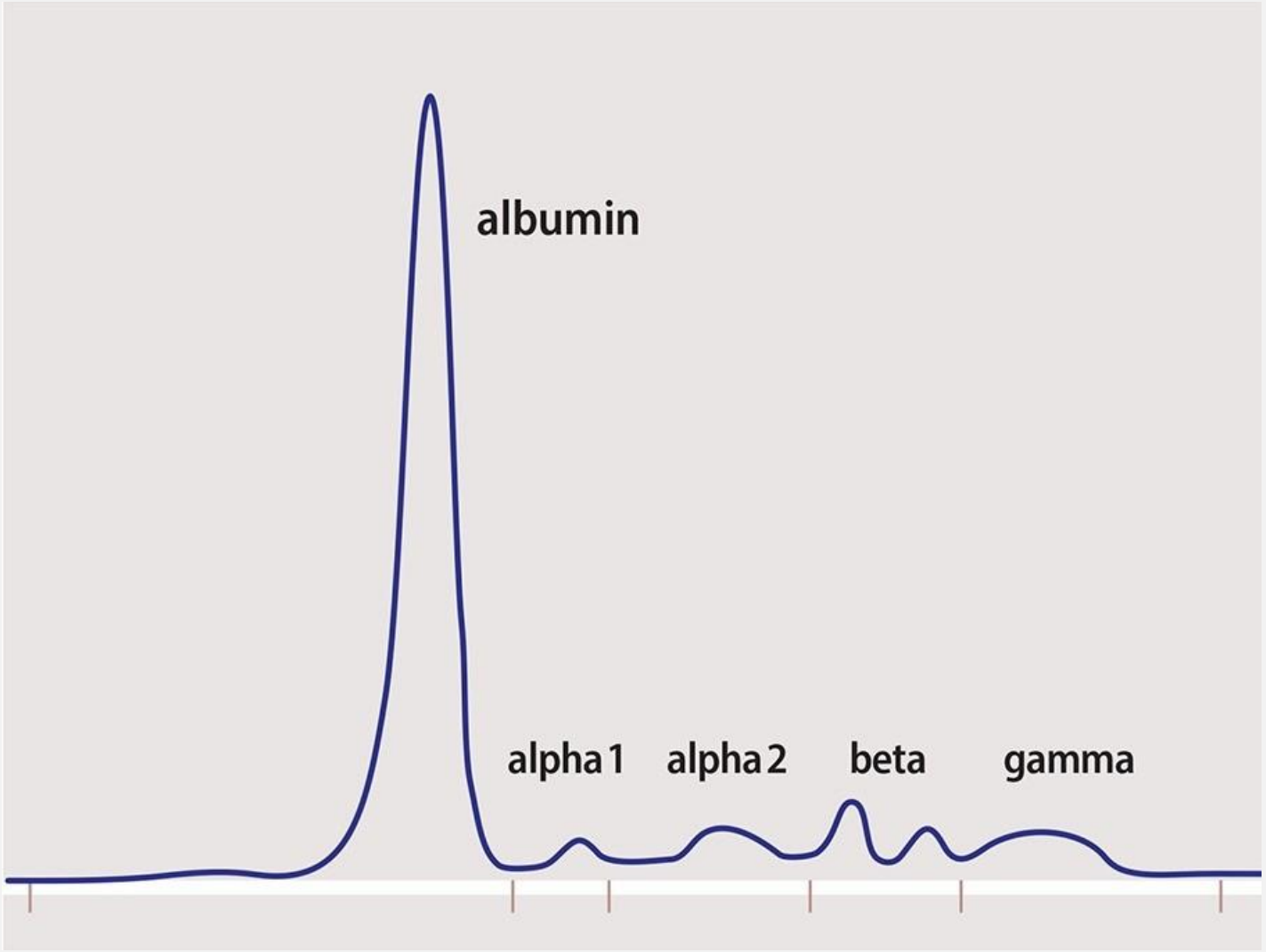
Serum protein electrophoresis (SPEP)

- Basic principle: proteins migrate to different locations in the gel based on size, shape, and charge
- SPEP is **quantitative** (tells you if there is an M protein and how much), immunofixation is **qualitative** (characterizes what type of M protein e.g. IgG, IgA, IgM…)

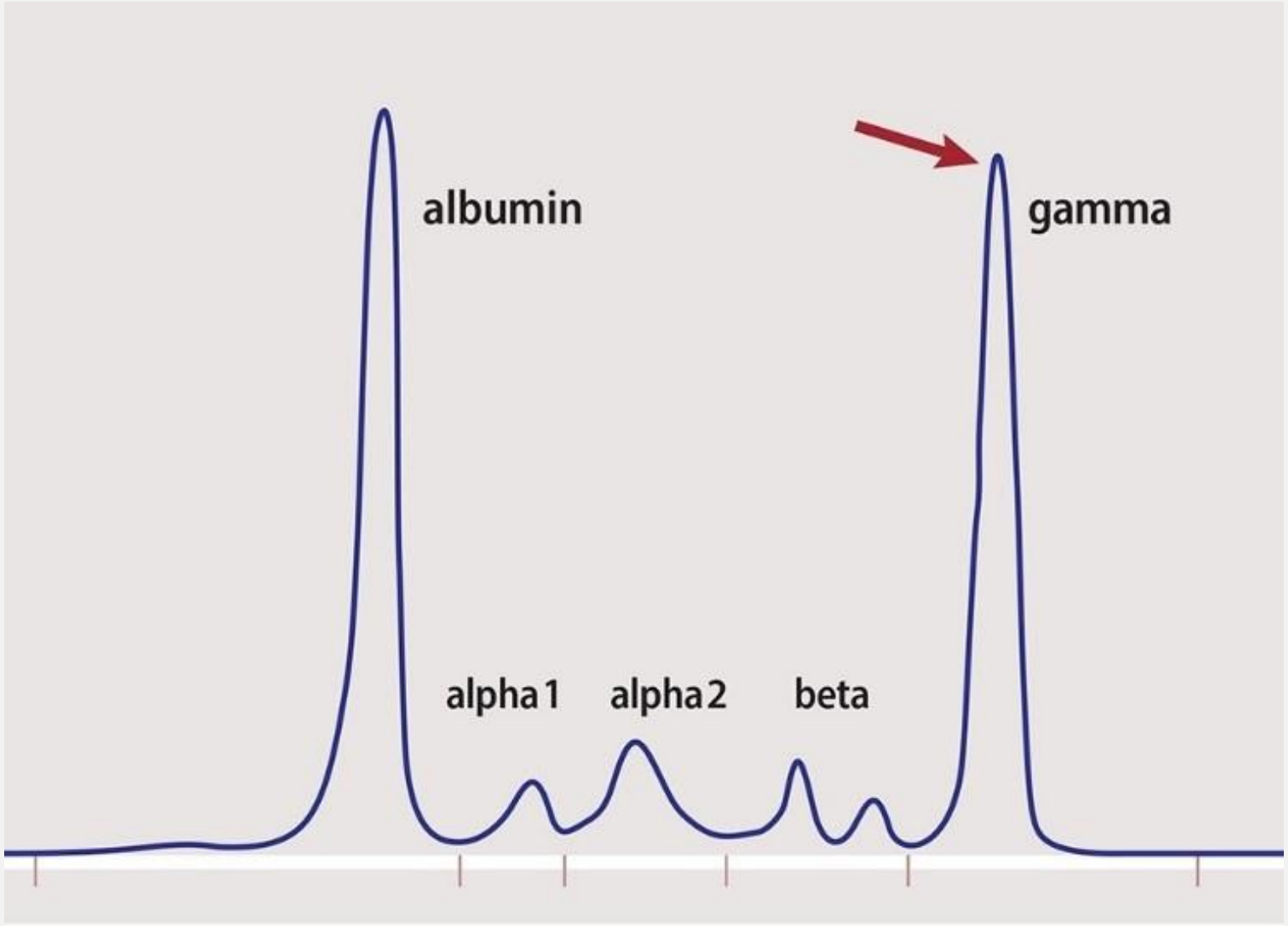


A normal SPEP

- **Albumin** – most prominent and fast-moving band, most abundant in blood
- **Alpha-1** – includes alpha-1 antitrypsin.
  - Often elevated in inflammation or acute infection
- **Alpha-2 globulins** – includes haptoglobin, ceruloplasmin.
  - Often elevated in liver disease or inflammation
- **Beta globulins** – includes transferrin, complement proteins, fibrinogen.
  - Often elevated in dysproteinemias, liver disease, anemias
- **Gamma globulins** – includes immunoglobulins
  - When elevated, can be MONOCLONAL or POLYCLONAL (infection, inflammation)



An ‘M-spike’



https://www.thebloodproject.com/ufaq/what-is-an-spep/

Serum free light chain assay (SFLC)

- Detects kappa and lambda levels (antibody detects epitopes which are hidden when light chains are bound to heavy chains)
- **Levels may be abnormal in patients with polyclonal hypergammaglobulinemia or renal failure
- Normal range = **0.26-1.65* (**up to 2.4 depending on age, renal function)
- Abnormal **RATIO** = likely monoclonal PC disorder

Serum free light chain assay (SFLC)

- **Clinical uses**
  - Making the diagnosis of plasma cell dyscrasia (MM, amyloidosis, etc.)
  - ‘Non-secretory MM’ – 70% have detectable FLC
  - Oligosecretory disease (very low paraprotein)
  - Light chain MM
  - MGUS and smoldering myeloma – risk stratification
  - AL amyloidosis
  - Monitoring response to treatment

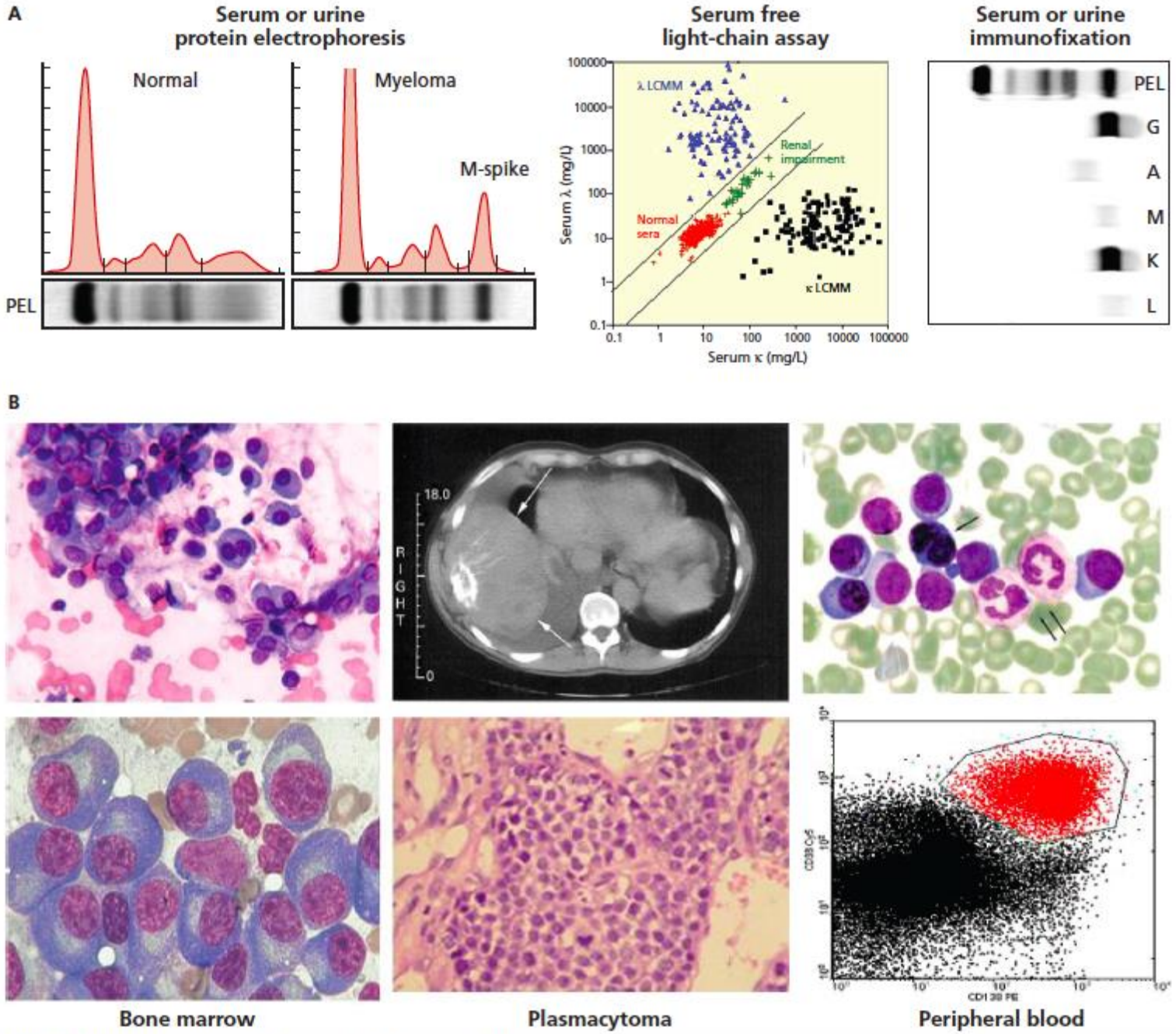


Figure 25-1 Diagnostic tests for monoclonal protein and PCs.

Summary Slide #2

- Myeloma is diagnosed with a combination of **labs** (CBC, Cr, Ca, SPEP + immunofixation, SFLC, immunoglobulins), **imaging** (CT/PET/MRI), and **special tests** (bone marrow aspirate + biopsy with cytogenetics, UPEP)
- Staging is by R-ISS system and involves **albumin, LDH, and B-2 microglobulin**

Learning Objectives

Understand the general approach to treatment of multiple myeloma

Drugs used in myeloma*

Drugs used in myeloma*

Alkylators – melphalan, cyclophosphamide

Steroids - backbone of most treatment regimens

Immunomodulators – **lenalidomide** (Revlimid), pomalidomide, thalidomide

Proteasome inhibitors – **bortezomib (Velcade),** carfilzomib, ixazomib

Autologous stem cell transplant (with melphalan conditioning)

Anti-CD38s – **daratumumab**, isatuximab

BITEs – teclistamab, elranatamab, talquetemab

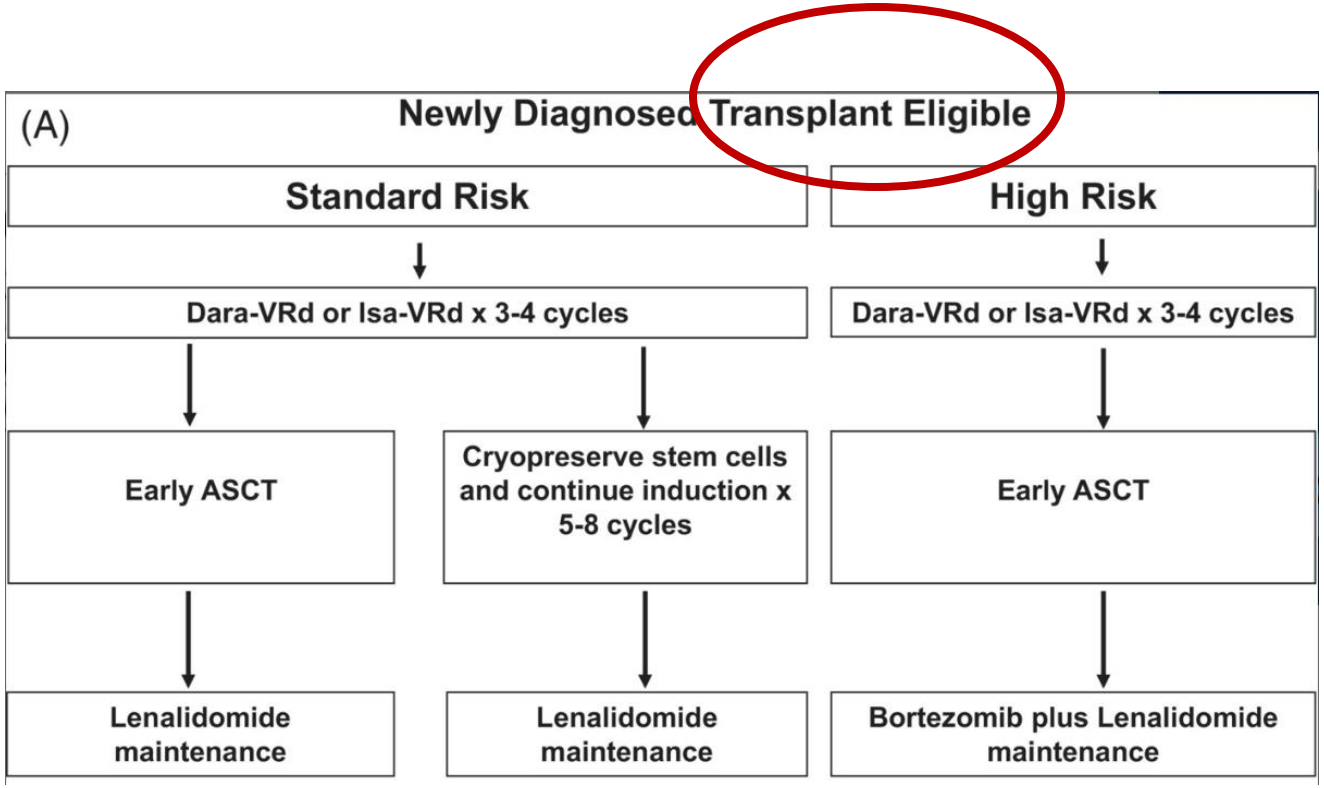
Antibody-drug conjugates – belantamab

Chimeric antigen receptor (CAR)-T-cell therapy – cilta-cel, ide-cel

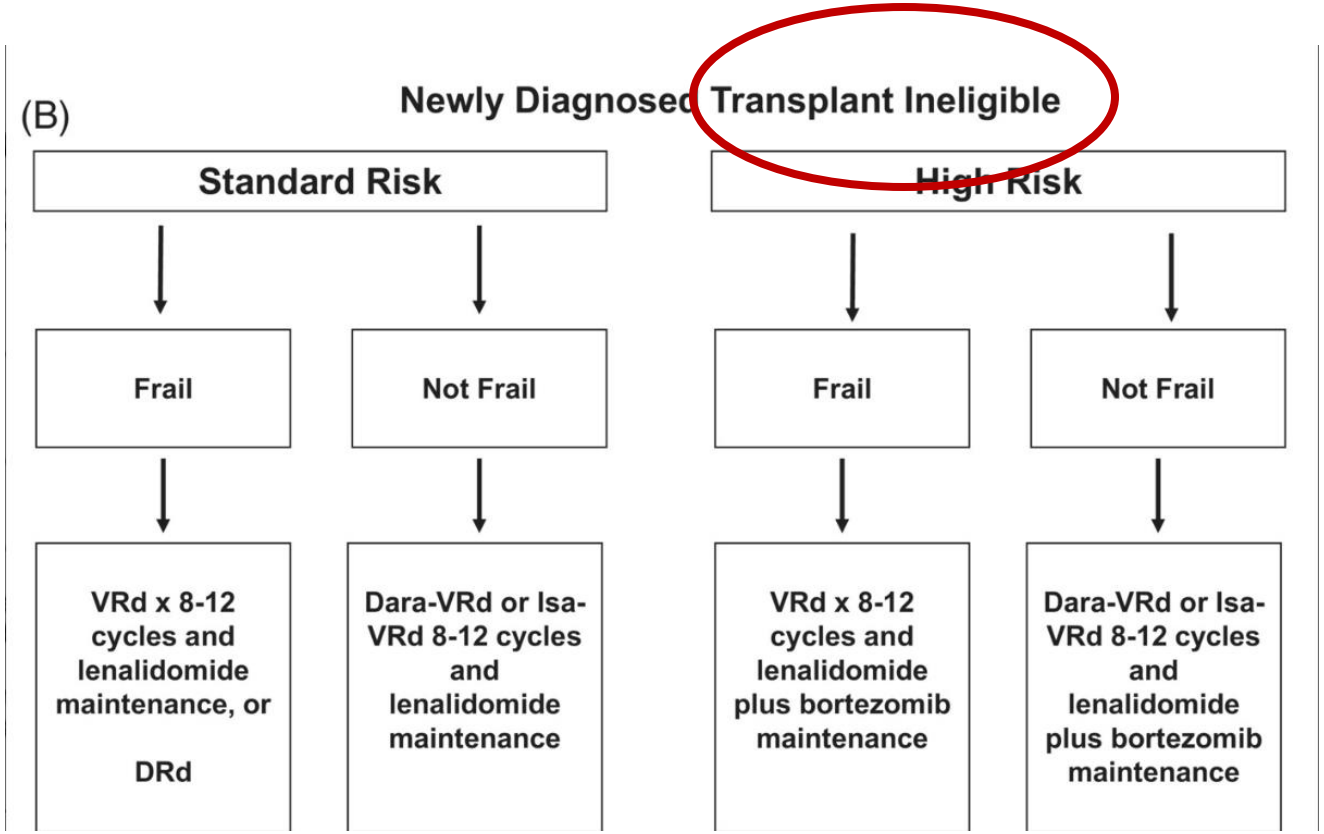
Anti-CD38's and transfusion medicine

- **Daratumumab** / **Isatuximab** are anti-CD38 monoclonal antibodies – this can be problematic if not known prior to testing as it interferes with routine pre-transfusion serologic testing by binding to CD38 on all the RBCs
- This manifests as **pan-agglutination** in the indirect Coomb's → can mask presence of clinically significant alloantibodies and make it difficult to provide compatible blood products
- How do we work around this?
  - **Prior to starting anti-CD38** → G+S for all patients, **some** guidelines (Australia, New Zealand) recommend performing extended red cell phenotyping or genotyping prior to initiation (although low risk of alloimmunization in these patients overall, so this is not universal)
  - **Use of dithiotreitol (DTT)** – denatures CD38 and eliminates daratumumab-induced panreactivity
    - ***Of note**, DTT also destroys Kell antigen (hence, if using DTT prior to testing → consider Kell-negative units)

OVERVIEW OF MYELOMA TREATMENT



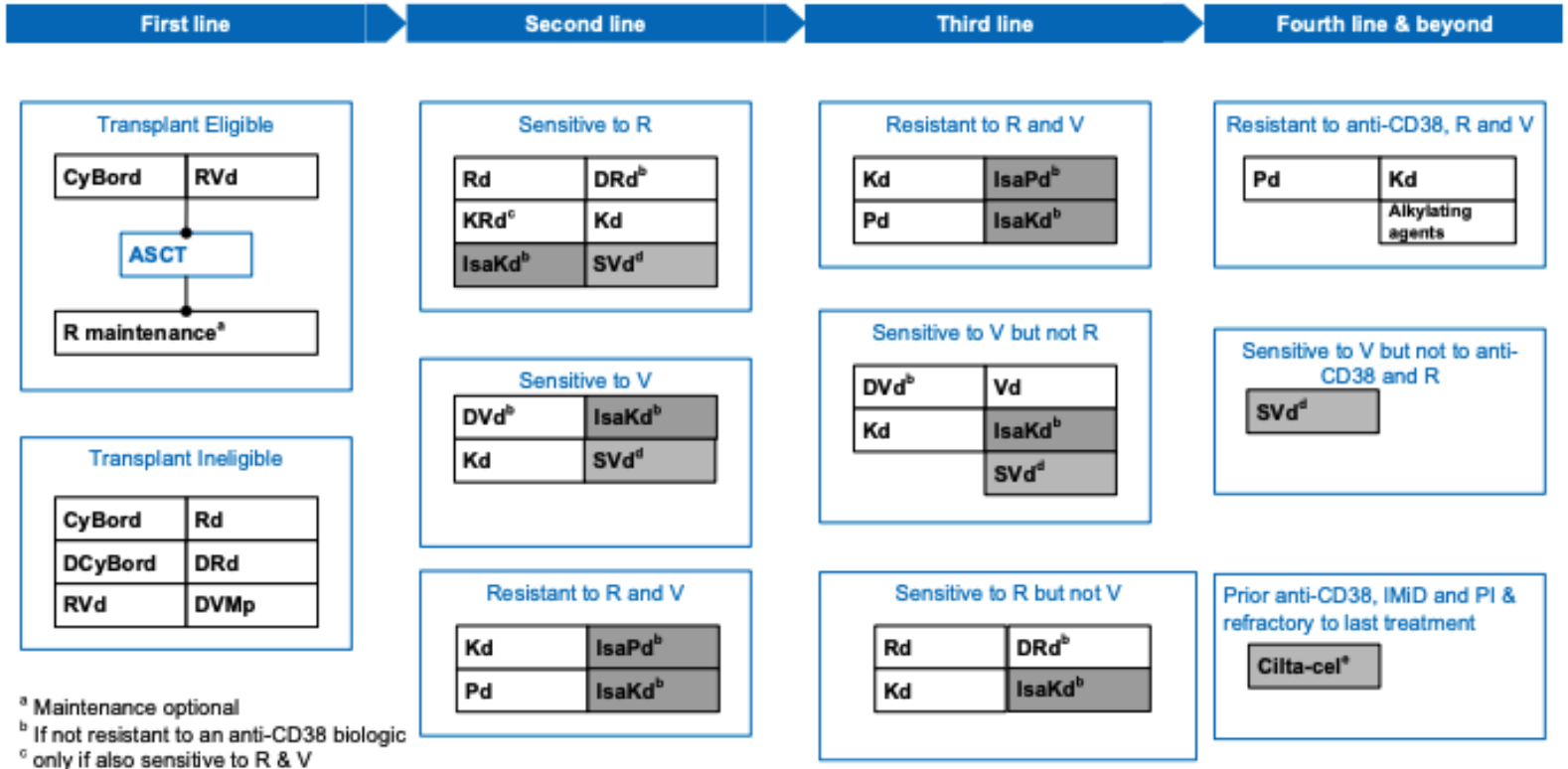
OVERVIEW OF MYELOMA TREATMENT



Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for Multiple Myeloma

Alt text: This funding algorithm depicts funding options for patients with multiple myeloma. In the first-line setting, the options are divided by whether patients are transplant eligible or ineligible. Subsequent lines of therapy are divided by their sensitivity and refractory status to different therapies.

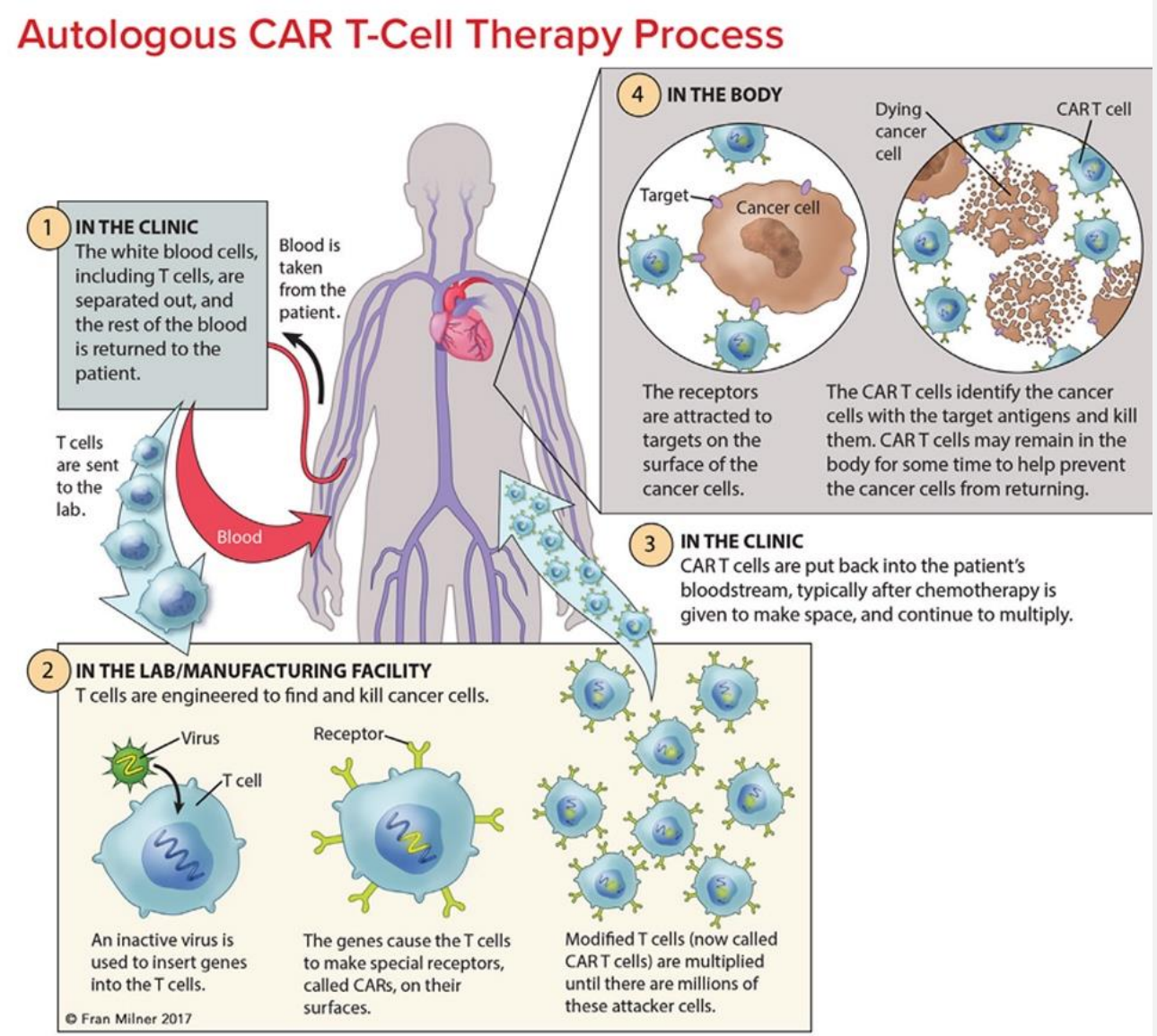


[a] Maintenance optional
[b] If not resistant to an anti-CD38 biologic
[c] only if also sensitive to R & V
[d] must have a proteasome inhibitor treatment-free interval of at least 6 months before 1st day of SVd
[e] If no prior treatment with any therapy that targets BCMA or any CAR-T cell therapy.

What's coming down the pipeline?

- **Immunotherapy** (BiTE's, CAR-T) will move into earlier lines of therapy (currently reserved for 4th line)
- **Monoclonal antibodies** (Dara/Isa) starting to be used in front-line setting
- **TRI**-specific antibodies (BCMA, GPRC5D, CD3)

CAR-T (Chimeric Antigen Receptor T-cell therapy)



OPEN ACCESS | CLINICAL TRIAL UPDATES | June 03, 2025

Long-Term (≥5-Year) Remission and Survival After Treatment With Ciltacabtagene Autoleucel in CARTITUDE-1 Patients With Relapsed/Refractory Multiple Myeloma

Authors: Sundar Jagannath, MD, FASCO, Thomas G. Martin, MD, Yi Lin, MD, PhD, Adam D. Cohen, MD, Noopur Raje, MD, Myo Htut, MD, Abhinav Deol, MD, ... SHOW ALL ... , and Peter M. Voorhees, MD | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 43, Number 25 • https://doi.org/10.1200/JCO-25-00760

27,539 / 5 | Am score 365 | PDF

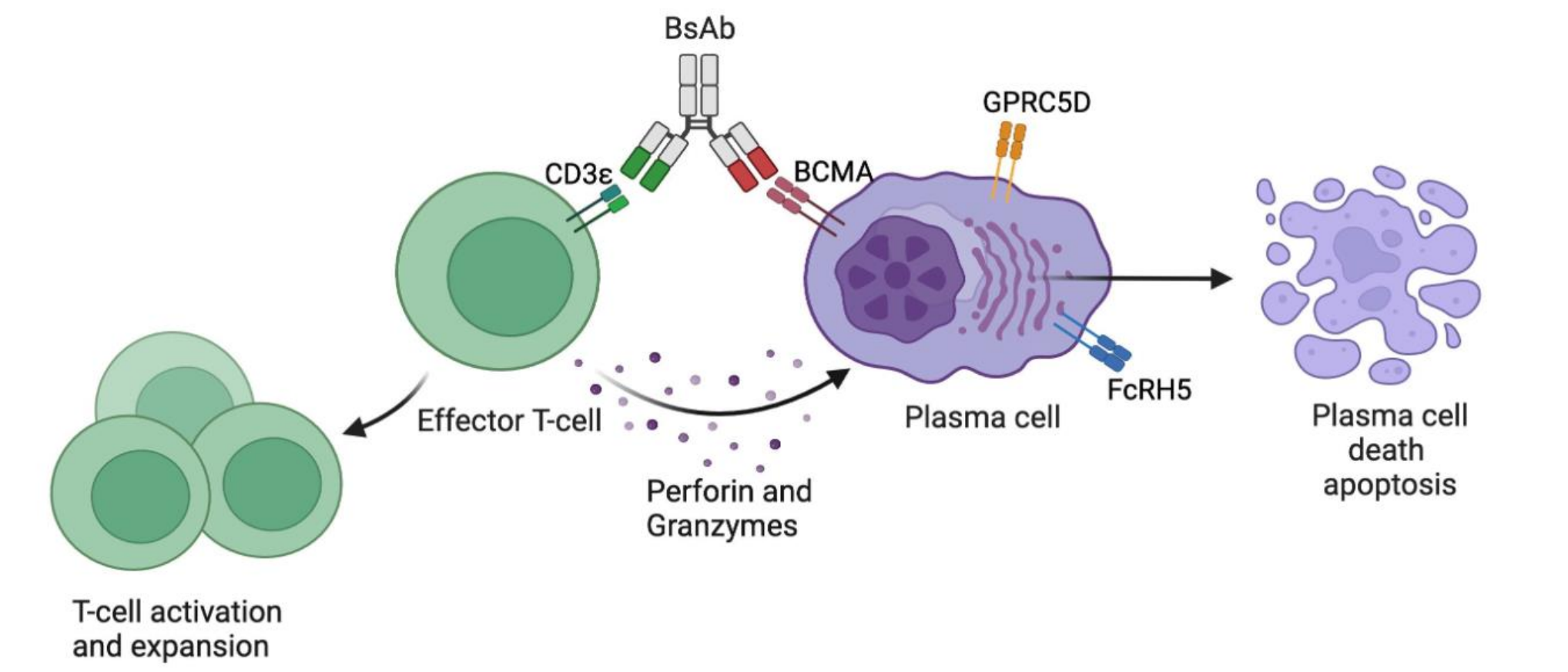
ORIGINAL ARTICLE

Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma

Authors: Jesús San-Miguel, M.D., Ph.D., Binod Dhakal, M.D., Kwee Yong, Ph.D., Andrew Spencer, M.D., Sébastien Anguille, M.D., Ph.D., María-Victoria Mateos, M.D., Ph.D., Carlos Fernández de Larrea, M.D., Ph.D., +35, and Hermann Einsele, M.D. Author Info & Affiliations

Published June 5, 2023 | N Engl J Med 2023;389:335-347 | DOI: 10.1056/NEJMoa2303379 | VOL. 389 NO. 4

BiTES (Bispecific T-cell engagers)



Summary Slide #3

- Myeloma treatment depends on if a patient is transplant ELIGIBLE or INELIGIBLE
- Myeloma is typically treated with a 3-drug (triplet) or **4-drug** (quad) regimen, typically with a steroid backbone
- **Myeloma outcomes have dramatically improved in recent years – average survival >10 years!**

Back to our case…

- 60M presented with back pain
  - Hemoglobin 134, Cr 105, Ca 2.45
  - SPEP – IgA kappa, **M protein 7.3**
  - IgG 8.5, IgA **18.42** (normal 0.7-4), IgM 0.32
  - Free kappa **1,141**, free lambda 8.6, ratio **132.71**
  - PET **T10 lytic lesion + soft tissue mass**
- Treated with radiation to T10 lytic lesion, declined treatment for a few months → disease progressed
- Treated with RVD (induction chemotherapy) x3 cycles until November 2024 → declined treatment again and left the country

Back to our case…

- Returned to Canada this month and seen on May 8th – **new lumps on head, bilateral wrist fractures, left hip pain, 20lb weight loss**
- Labs after 3 cycles of RVD (Nov 2024):
  - Hb 131, Cr 112, total protein 60, Ca 2.24, albumin 40
  - IgG 7.3, IgA 2.08, IgM 0.31
  - Free kappa 28, free lambda 15.2, ratio **1.84**
  - M protein not quantifiable (too low)
- Labs on returning (May 2025):
  - Hb **95,** Cr 117, total protein 99, Ca 2.76, albumin 33
  - IgG 9.0, IgA 37.42, IgM 0.51
  - Free kappa **2682.2,** free lambda 10.5, **ratio 255.45**
  - M protein 30.5

Last updated: 1 week ag

All Rows

ROUTINE IMMUNOLO...	29/7/24 14:03	27/5/24 13:49	25/4/24 13:43	21/3/24 13:18	11/1/24 16:21	2023 14/12/23 14:35	9/11/23 14:04
IgG Quantitation	6.5 ↓	7.5	8.1	8.5	8.3	8.1	8.5
IgA Quantitation	20.77 ↑	22.10 ↑	18.89 ↑	19.23 ↑	16.81 ↑	16.89 ↑	18.42 ↑
IgM Quantitation	0.25 ↓	0.25 ↓	0.28 ↓	0.30 ↓	0.26 ↓	0.27 ↓	0.32 ↓
Free Kappa	1,542.6 ↑	1,657.0 ↑	1,402.9 ↑	1,358.0 ↑	901.0 ↑	1,169.8 ↑	1,141.3 ↑
Free Lambda	5.7	10.4	10.7	12.6	9.7	8.0	8.6
Kappa/Lambda Ratio	270.63 ↑	159.33 ↑	131.11 ↑	107.78 ↑	92.89 ↑	146.23 ↑	132.71 ↑
Protein Electrophoresis, Serum	COMME...	COMME...	COMME...	COMME...	COMME...	COMME...	COMME...
M-protein Peak 1	7.4	6.7	5.9	7.9	6.6	6.6	7.3
M-protein Peak 2	2.2	6.2	1.6				
Isotype(s) - Immunofixation Electr...							IgA kappa p...

All Rows

ROUTINE IMMUNOLO...	2025 13/5/25 09:45	5/5/25 12:17	13/1/25 12:25	2024 25/11/24 15:39	28/10/24 16:20	30/9/24 12:55	26/8/24 12:50
IgG Quantitation	8.3	9.0	11.3	7.3	7.6	5.9 ↓	5.8 ↓
IgA Quantitation	36.72 ↑	37.42 ↑	4.38 ↑	2.08	6.13 ↑	16.84 ↑	27.90 ↑
IgM Quantitation	0.49	0.51	0.47	0.31 ↓	0.38 ↓	0.26 ↓	0.19 ↓
Free Kappa		2,682.2 ↑	295.8 ↑	28.0 ↑	30.5 ↑	102.4 ↑	2,448.1 ↑
Free Lambda		10.5	15.0	15.2	10.1	12.8	5.1 ↓
Kappa/Lambda Ratio		255.45 ↑	19.72 ↑	1.84 ↑	3.02 ↑	8.00 ↑	480.02 ↑
Protein Electrophoresis, Serum	COMME...	COMME...	COMME...	COMME...	COMME...	COMME...	COMME...
M-protein Peak 1	30.0	30.5	1.8	COMME...	2.2	9.7	13.9
M-protein Peak 2							2.7
Isotype(s) - Immunofixation Electr...					IgA kappa p...	IgA kappa p...	

Learning Objectives

- **Describe** the key diagnostic criteria that distinguish MGUS, smoldering myeloma, and multiple myeloma
- **Identify** and **explain** the clinical manifestations of multiple myeloma
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- **Understand** the general approach to treatment of multiple myeloma

5 TAKE-HOME POINTS

Myeloma is a treatable but incurable cancer

Myeloma must be distinguished from MGUS and SMM based on SPEP, bone marrow biopsy, and SLIM-CRAB features

Diagnosis includes standard labs (CBC, Cr, Ca), SPEP/UPEP, SFLC, immunoglobulins, and imaging

Myeloma is one of many plasma cell dyscrasias including amyloidosis, POEMS, etc.

Treatment depends on eligibility for autologous stem cell transplant and usually includes 3 or 4 drug regimens

Feedback/Questions?

Myte.org