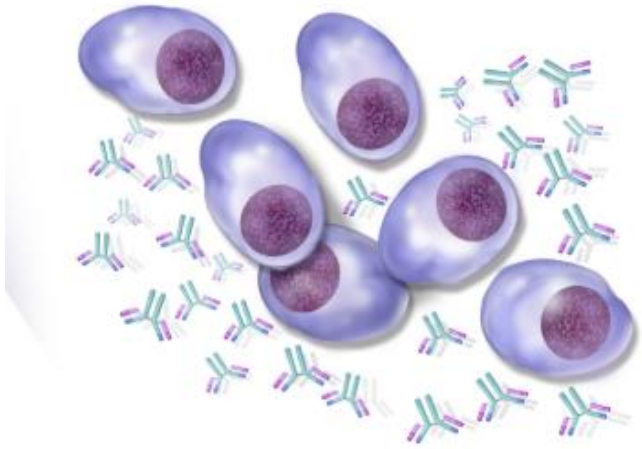
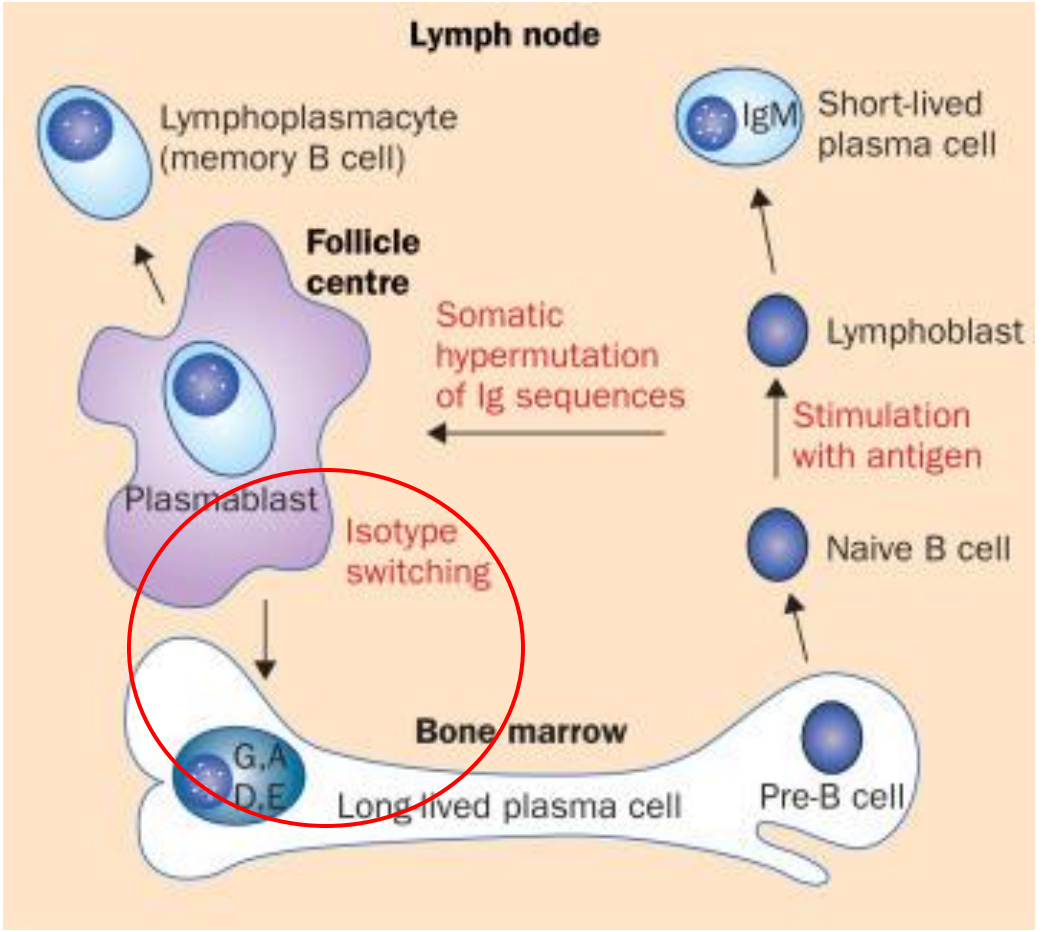
Advancing Myeloma Care: A Patient Case of High-Risk Disease Under a Novel Treatment Protocol.

Ewan Jones

Myeloma

Multiple myeloma cells (abnormal plasma cells)





New insights into the pathophysiology of multiple myeloma
Seidl, Sonja et al.
The Lancet Oncology, Volume

Myeloma

MyelomaUK

Myeloma, MGUS & related conditions

A Guide for GPs

About myeloma

- Myeloma is a blood cancer that arises in the plasma cells of the bone marrow
- On average 5,900 people are diagnosed with myeloma every year in the UK
- 73% of myeloma diagnoses are in people aged over 65, but it affects younger people too
- Myeloma is 2–3 times more common in black people compared with white and Asian people
- Complications of myeloma include bone damage, anaemia, infections, and renal impairment
- Diagnosis after GP referral has a better survival than after diagnosis via emergency routes

https://www.myeloma.org.uk/?gad_source=1&gad_campaignid=17544995264&gbraid=0AAAAAou3qzfb5nLFgW9mRzoMhrNQrFVyU&gclid=EAIaIQobChMI-JqZl6jvkAMV7IhQBh23KwF6EAAYASAAEgKmfvD_BwE – **Myeloma UK Website**

Myeloma testing - When, What and How?

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

Requesting tests

Some GPs have the option to request a 'myeloma screen' while others need to request the combination of individual tests, listed below:

- Full blood count
- Adjusted/corrected serum calcium
- Serum creatinine
- Plasma viscosity or ESR*
- Serum protein electrophoresis (to check for a paraprotein)
- sFLC assay (or urine BJP if sFLC is unavailable)**
- Serum immunoglobulins (IgG, IgA, and IgM)

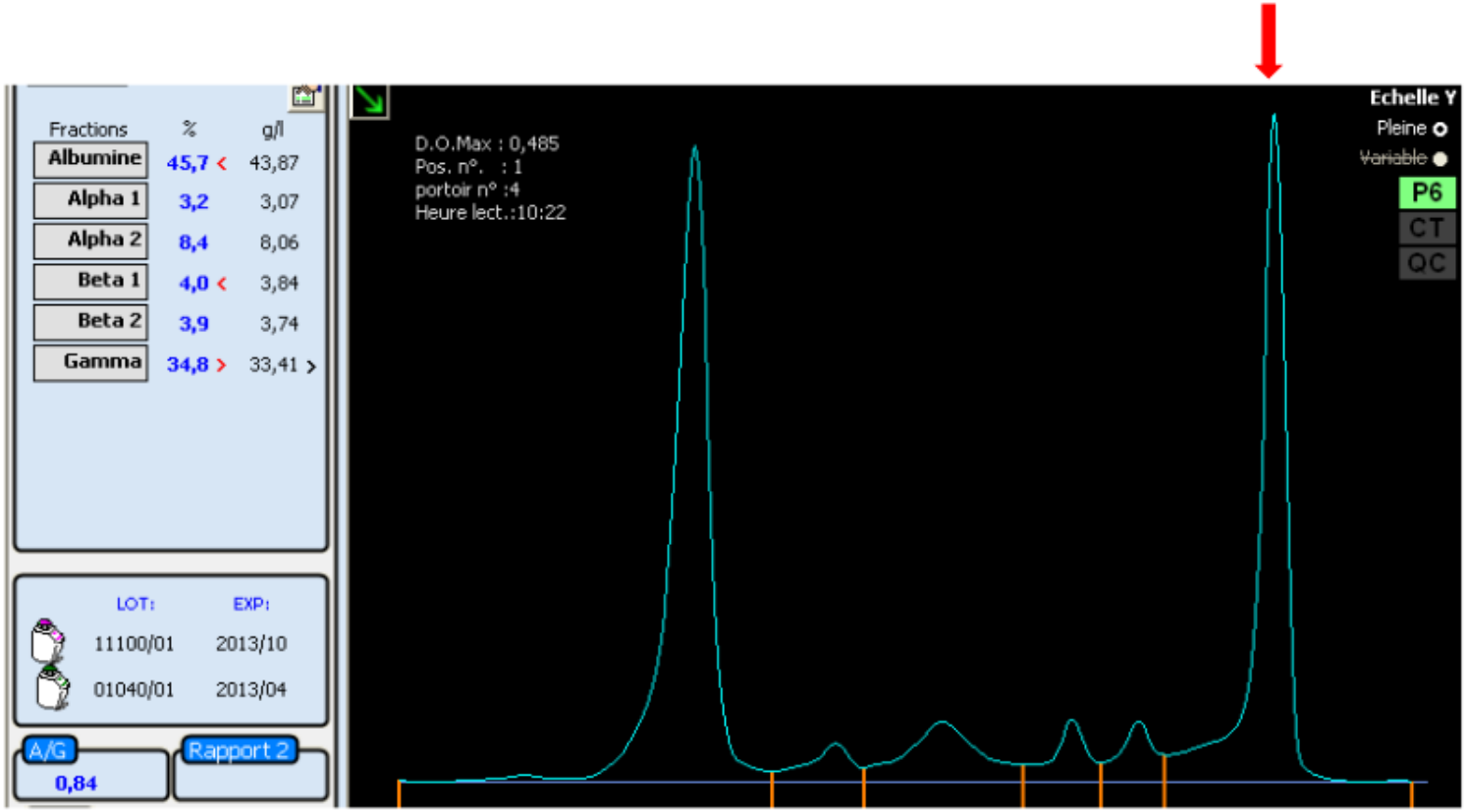
Table 1. Diagnostic criteria for active myeloma

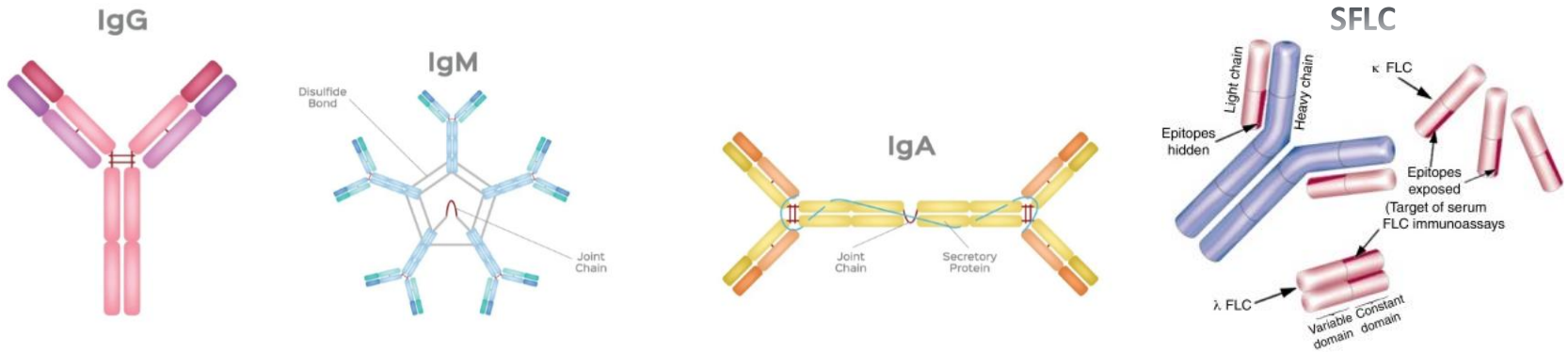
Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and one or more of the following **myeloma-defining events:**

- **C**a: Hyper**C**alcaemia: >2.75 mmol/L serum calcium or >0.25 mmol/L higher than the upper limit of normal
- **R**enal insufficiency: serum creatinine >177 µmol/L or creatinine clearance <40 ml/min
- **A**naemia: haemoglobin <100 g/L or >20 g/L below lower limit of normal
- **B**one lesions: ≥1 osteolytic lesion on X-ray, CT or PET/CT (>5 mm in size)

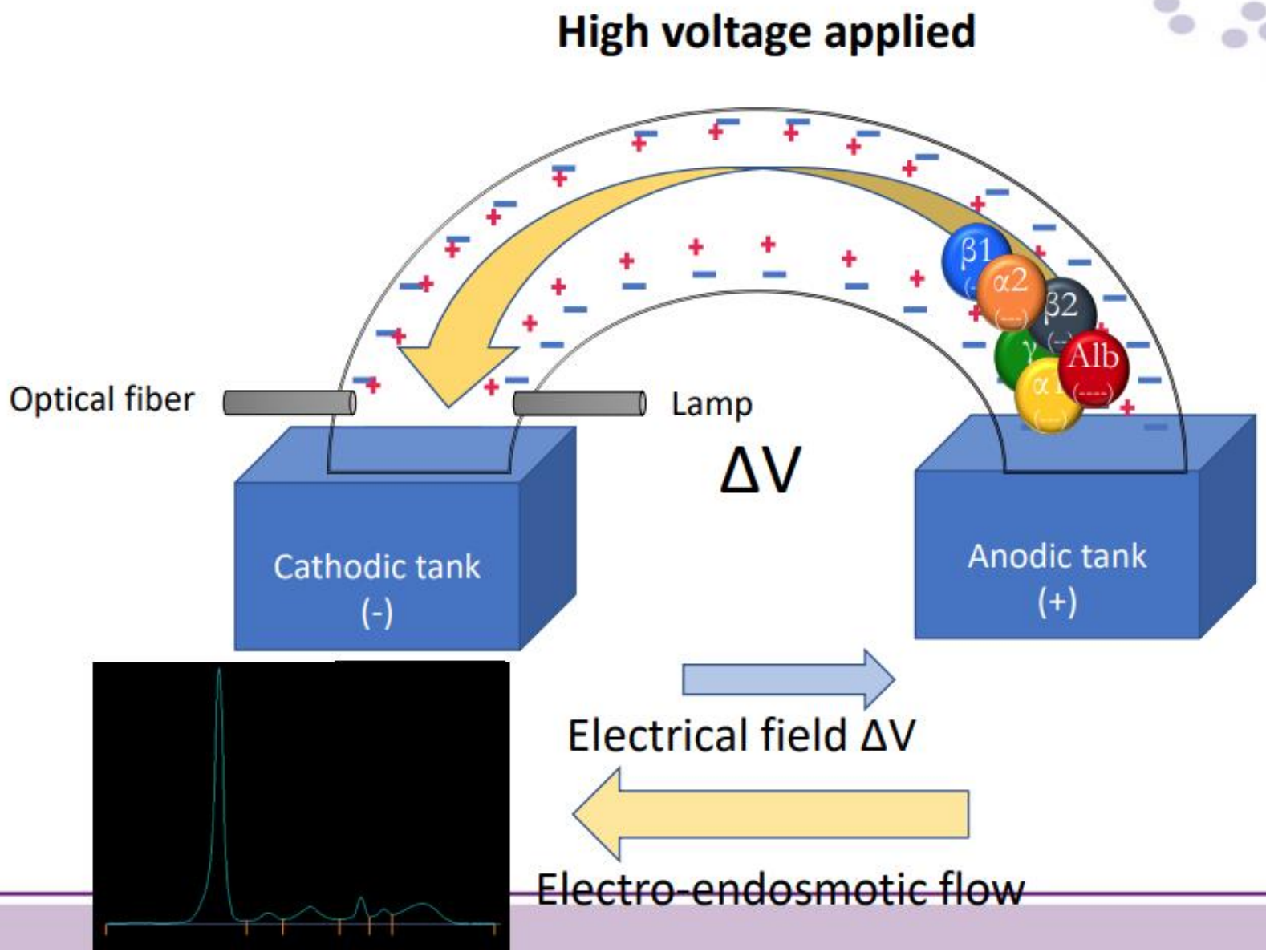
- **S**ixty percent or greater (≥60%) clonal plasma cells in bone marrow
- Ratio of abnormal **Li**ght chains/normal light chains ≥100, provided the involved light chain is >100 mg/L
- >1 focal lesion on **M**RI (>5 mm in size)

Laboratory analysis



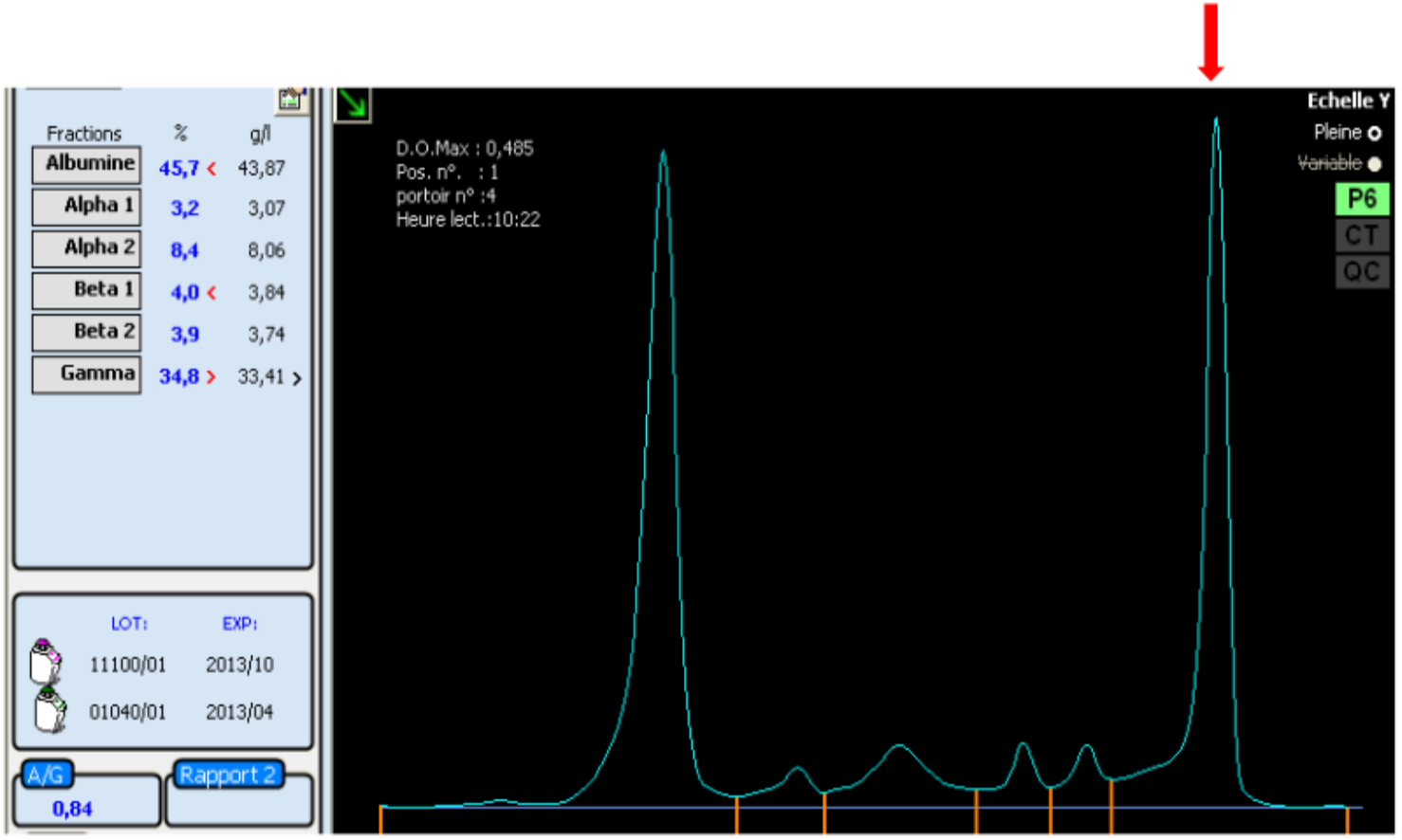


Principle of capillary protein electrophoresis



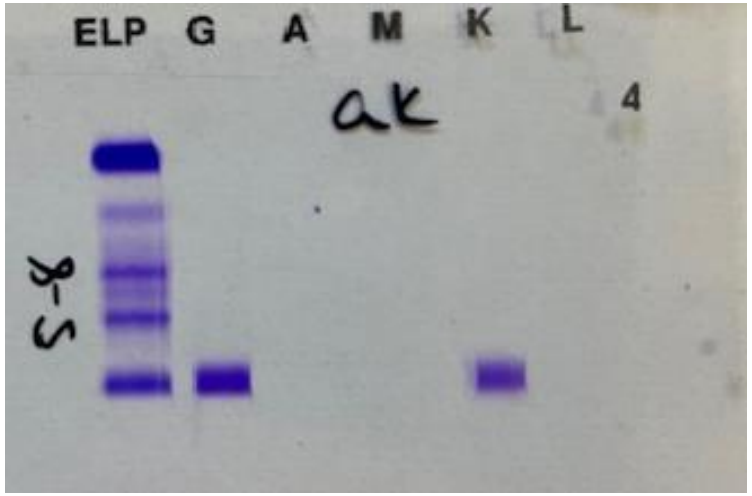
Capillary Electrophoresis

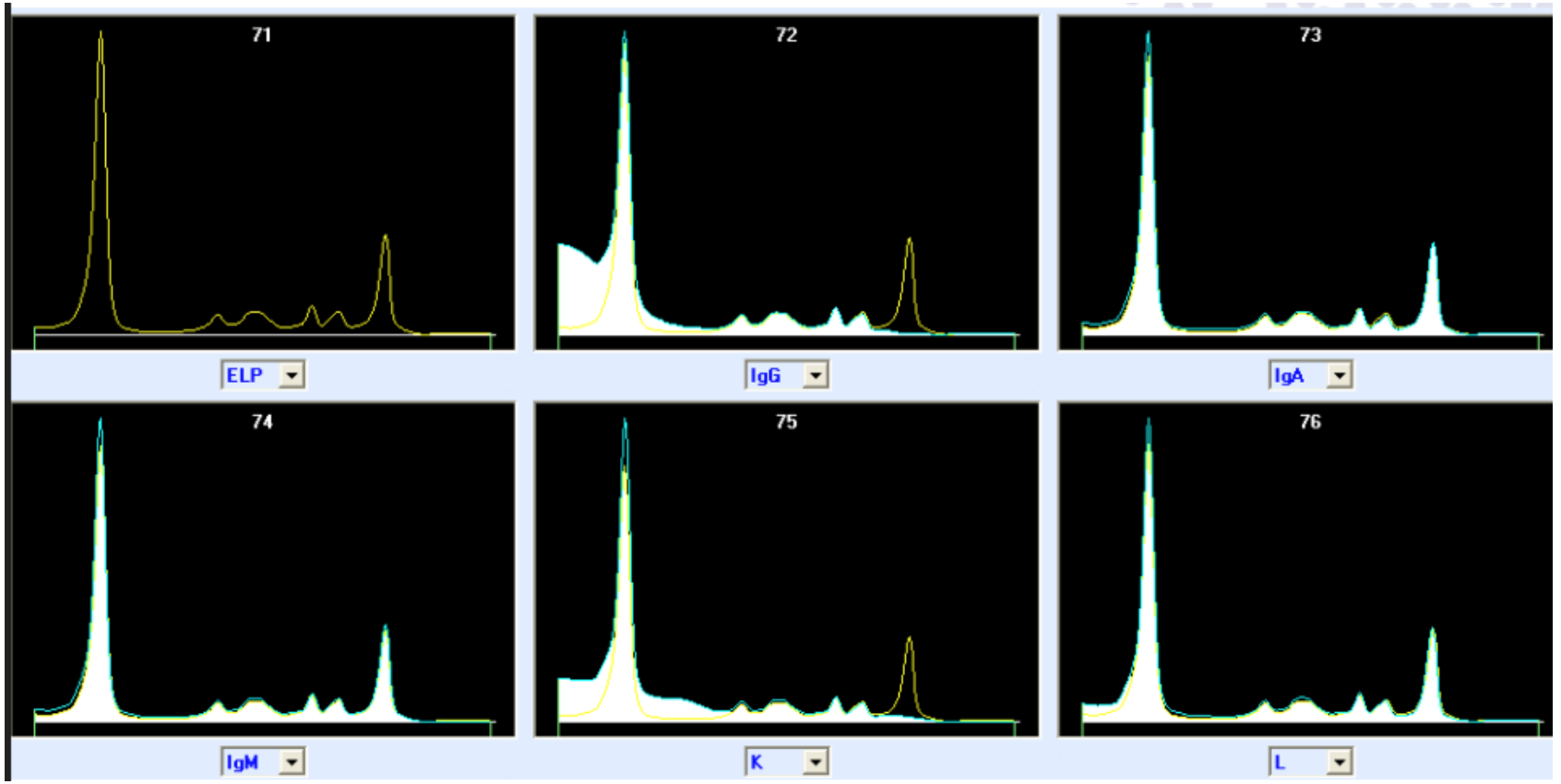
- Main utility is the detection of paraproteins (monoclonal immunoglobulin)
- Useful for Myeloma/MGUS screening and monitoring.



- Albumin
- Alpha-1: alpha-1 antitrypsin, alpha-1-acid glycoprotein (orosomucoid)
- Alpha-2: alpha-2 macroglobulin, haptoglobin
- Beta-1: transferrin, hemopexin
- Beta-2: C3 and C4 complement, IgA
- Gamma: IgG, IgM, Ig A, IgD, IgE, CRP

Immunofixation and Immunosubtraction





MGUS/SM/Myeloma

NICE guideline [NG12] Suspected cancer: recognition and referral (2017) https://www.nice.org.uk/guidance/ng12
NICE guideline [NG35] Myeloma: diagnosis and management (2018) https://www.nice.org.uk/guidance/ng35

Asymptomatic

- MGUS (Monoclonal Gammopathy of Undetermined Significance)
- Smoldering myeloma

Malignant

- Multiple myeloma
- Waldenström macroglobulinemia
- Solitary plasmacytoma
- Other lymphoproliferative syndromes

Prevalence

Myeloma Type	Prevalence
IgG	50 – 60% of cases
IgA	20%
IgM	1%
IgD	1-2%
IgE	<0.1%
Light chain only	15%
Non secretory	3-5%

Patient Case

- 57-year-old male presented to GP with anaemia, SOB, weight loss and cough. Normal CXR and no localising factors on examination.
- All correct tests performed for Myeloma screen ->
  - Full blood count
  - Adjusted/corrected serum calcium
  - Serum creatinine
  - Plasma viscosity or ESR*
  - Serum protein electrophoresis (to check for a paraprotein)
  - sFLC assay (or urine BJP if sFLC is unavailable)**
  - Serum immunoglobulins (IgG, IgA, and IgM)

Patient Case – Routine Chem/Haem

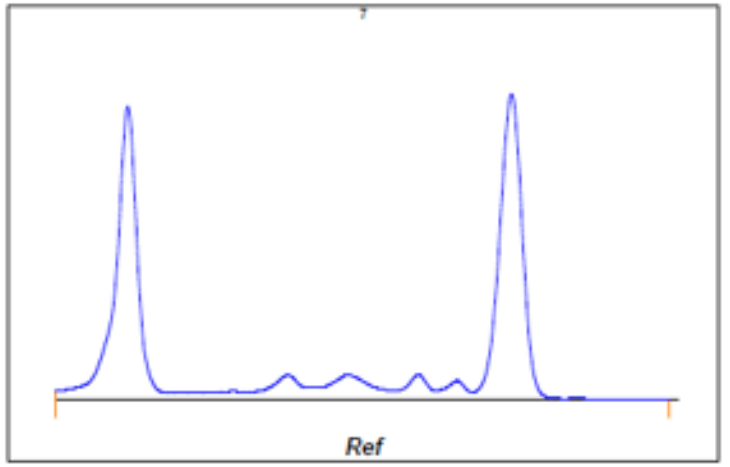
- Full blood count → Rbc – 2.16 (4.50 – 5.50); Hb – 70 (130 – 170)
- Adjusted/corrected serum calcium → Adjusted Calcium – 3.09 (2.20 – 2.60)
- Serum creatinine → Urea – 12.5 (1.7 – 7.1); Creatinine – 131 (59 – 104)
- Plasma viscosity or ESR* → ESR – 121 (0 – 12)

Patient Case - Electrophoresis, SFLC, Igs

- IgG – 2.5 (6 – 16)
- IgA – <0.07 (0.8 – 4)
- IgM – <0.05 (0.5 – 2)

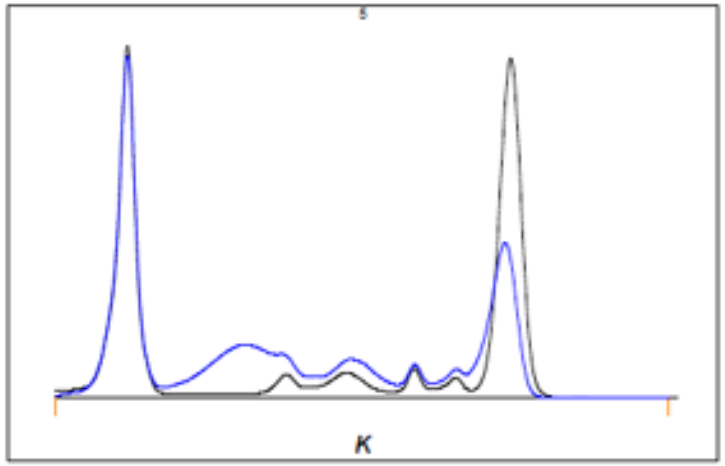
- Paraprotein band in gamma region – 46.4 g/L

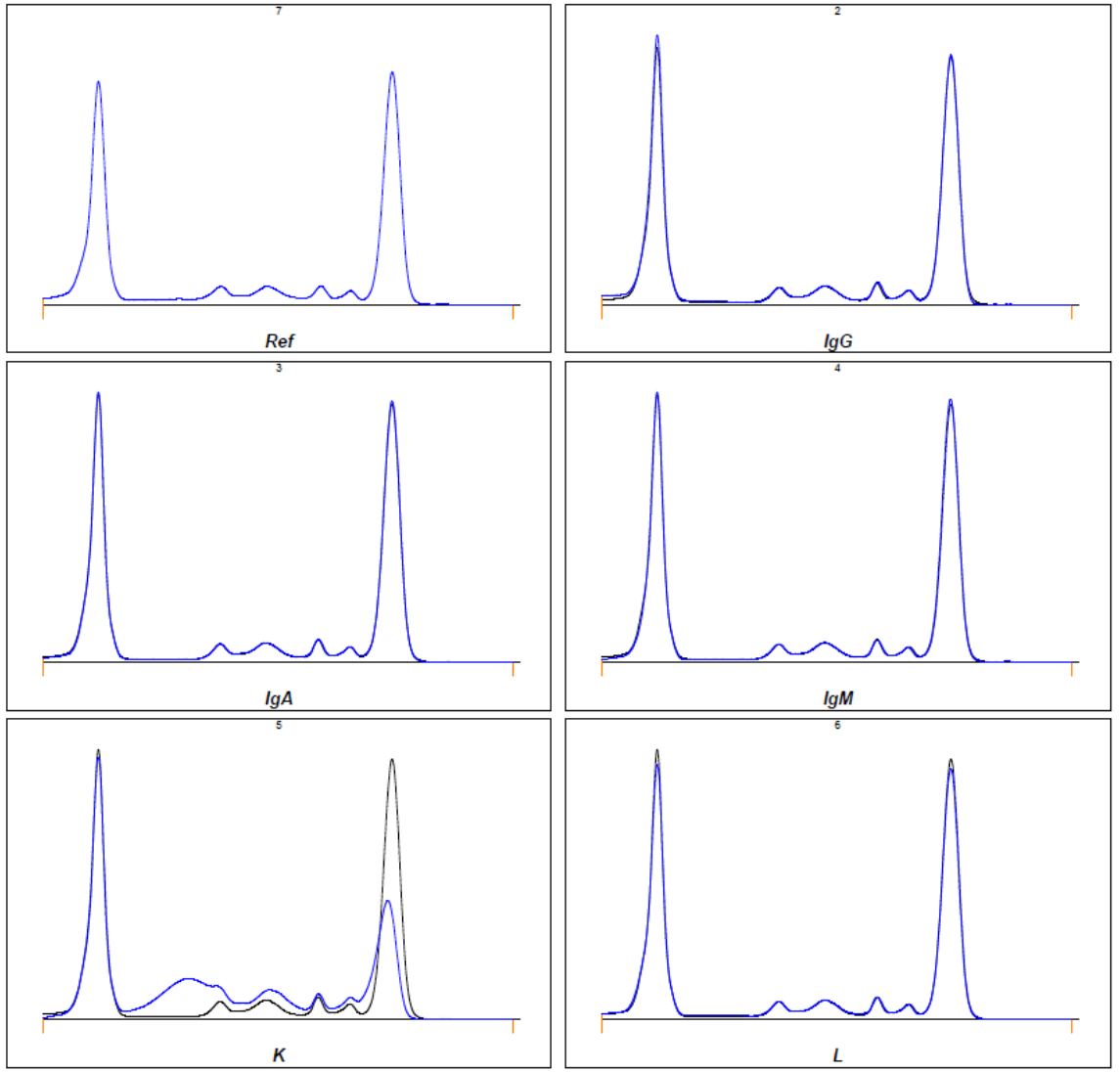
- Free kappa – 460.4 (3.3 – 19.4)
- Free lambda – <1.4 (5.7 – 26.3)
- Ratio – 328.86 (0.26 – 1.65)



Patient Case – Electrophoresis follow up

- Serum immunosubtraction – Clear kappa free light chain but no heavy chain (G,A,M).

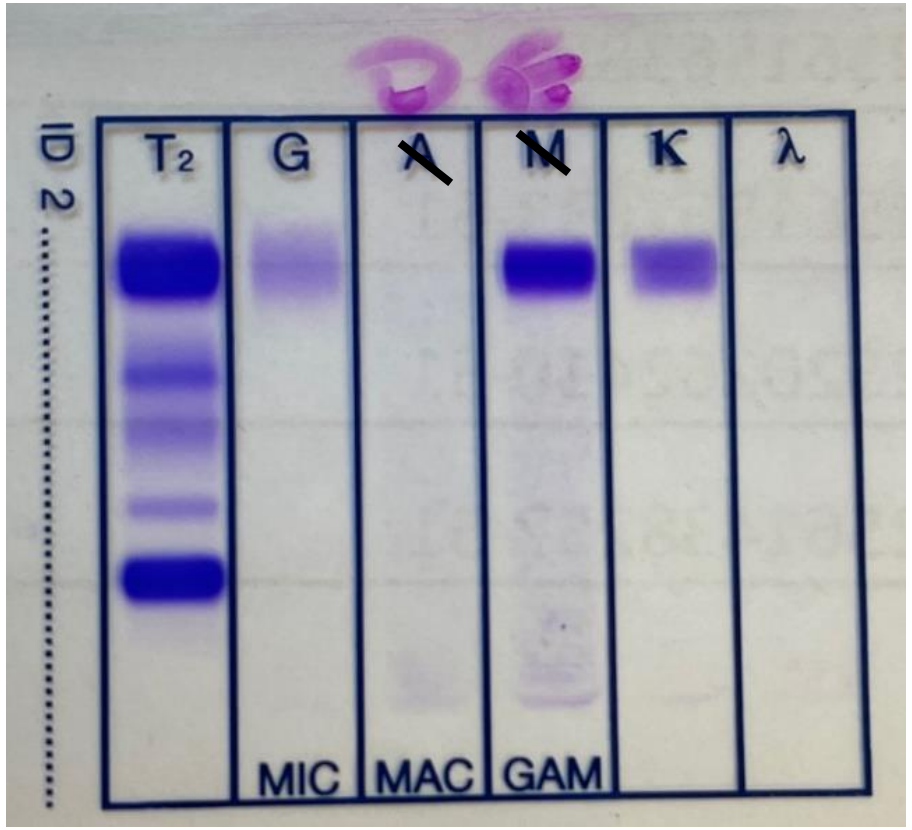




Patient Case – Electrophoresis follow up

2.5 All newly identified free light chain monoclonal proteins via serum immunofixation have IgD/IgE immunofixation performed

Reflexed IgD and IgE Immunofixation…



Large IgE kappa paraprotein.

Diagnosis – IgE Myeloma

- HODS Report:

Markedly hypercellular, particulate bone marrow aspirate with reduced trilineage haemopoiesis and **70% plasma cells**. Features in keeping with myeloma

Table 1. Diagnostic criteria for active myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and one or more of the following **myeloma-defining events:**

- Ca — HyperCalcaemia: >2.75 mmol/L serum calcium or >0.25 mmol/L higher than the upper limit of normal ✓
- Renal insufficiency: serum creatinine >177 µmol/L or creatinine clearance <40 ml/min ✓
- Anaemia: haemoglobin <100 g/L or >20 g/L below lower limit of normal ✓
- Bone lesions: ≥1 osteolytic lesion on X-ray, CT or PET/CT (>5 mm in size)

- Sixty percent or greater (≥60%) clonal plasma cells in bone marrow ✓
- Ratio of abnormal Light chains/normal light chains ≥100, provided the involved light chain is >100 mg/L ✓
- >1 focal lesion on MRI (>5 mm in size)

IgE myeloma details

- Severe and fast clinical course, Very poor prognosis
- Male predominant
- Patients present earlier in life
- Often present with evidence of end organ damage
- Higher risk of progression to plasma cell leukaemia
- Higher risk of developing AL amyloidosis
- If well enough, these patients are candidates for autologous PBSC transplant.

OPTIMUM/MUK-9 – A high risk Myeloma Trial

Up to 6, 3- week cycles of:

Cyclophosphamide

Bortezomib

Lenalidomide

Daratumumab

Dexamethasone

Stem cell transplant

Stem cells harvested at hospital.

High dose chemotherapy (melphalan)

Transplant stem cells via drip.

Consolidation 1 – Up to 6, 4-week cycles of:

Bortezomib

Lenalidomide

Daratumumab

Dexamethasone

Consolidation 2 – Up to 12 4-week cycles of:

Bortezomib

Lenalidomide

Daratumumab

Maintenance treatment – Continue until Myeloma worsens:

lenalidomide

daratumumab

Sponsor

University of Leeds

Collaborators

- Myeloma UK
- Celgene
- Janssen, LP

Investigators

- Principal Investigator: Martin Kaiser, University of Leeds

MUK-9b – A high risk Myeloma Trial

Up to 6, 3- week cycles of:

Cyclophosphamide

Bortezomib

Lenalidomide

Daratumumab

Dexamethasone

Stem cell transplant

Stem cells harvested at hospital.

High dose chemotherapy (melphalan)

Transplant stem cells via drip.

- 3 cycles prior to transplant which reduced paraprotein from 46 g/L to 1.6 g/L.
- Excellent response so decided to go ahead with transplant work-up.
- Patient bone marrow stimulated to increase volume of PBSC.

Full blood count:

Wbc	38.5 H	10^9/L	(4.0-10.0)			
Rbc	4.41 L	10^{12}/L	(4.50-5.50)			
Hb	130	g/L	(130-170)			
Hct	0.393 L		(0.400-0.500)			
MCV	89	fL	(83-101)			
MCH	29.4	pg	(27.0-32.0)			
MCHC	330	g/L	(315-345)			
Platelets	186	10^9/L	(150-410)	PDW	15.6	fL
MPV	9.5	fL	(5.0-20.0)			
Neutrophils	32.51 H	10^9/L	(2.00-7.00)	Neutrophils.	84.43	%
Lymphocytes	1.42	10^9/L	(1.00-3.00)	Lymphocytes.	3.69	%
Monocytes	2.84 H	10^9/L	(0.20-1.00)	Monocytes.	7.38	%
Eosinophils	0.16	10^9/L	(0.02-0.50)	Eosinophils.	0.41	%
Basophils	0.16 H	10^9/L	(0.00-0.10)	Basophils.	0.41	%
Metamyelocytes	0.95	10^9/L		Metamyelocytes.	2.46	%
Myelocytes	0.47	10^9/L		Myelocytes.	1.23	%
NRBC	0.00	10^9/L				
RDW	12.9	%CV	(10.0-16.0)			

Immature Granulocytes	3.55	%	PCT	1.8 L

Film Blood film examined.

Diff Manual film

Manual differential count performed.
Neutrophil leucocytosis.
Neutrophils show left shift.
Monocytosis.

Up to 6, 3- week cycles of:

Cyclophosphamide

Bortezomib

Lenalidomide

Daratumumab

Dexamethasone

Stem cell transplant

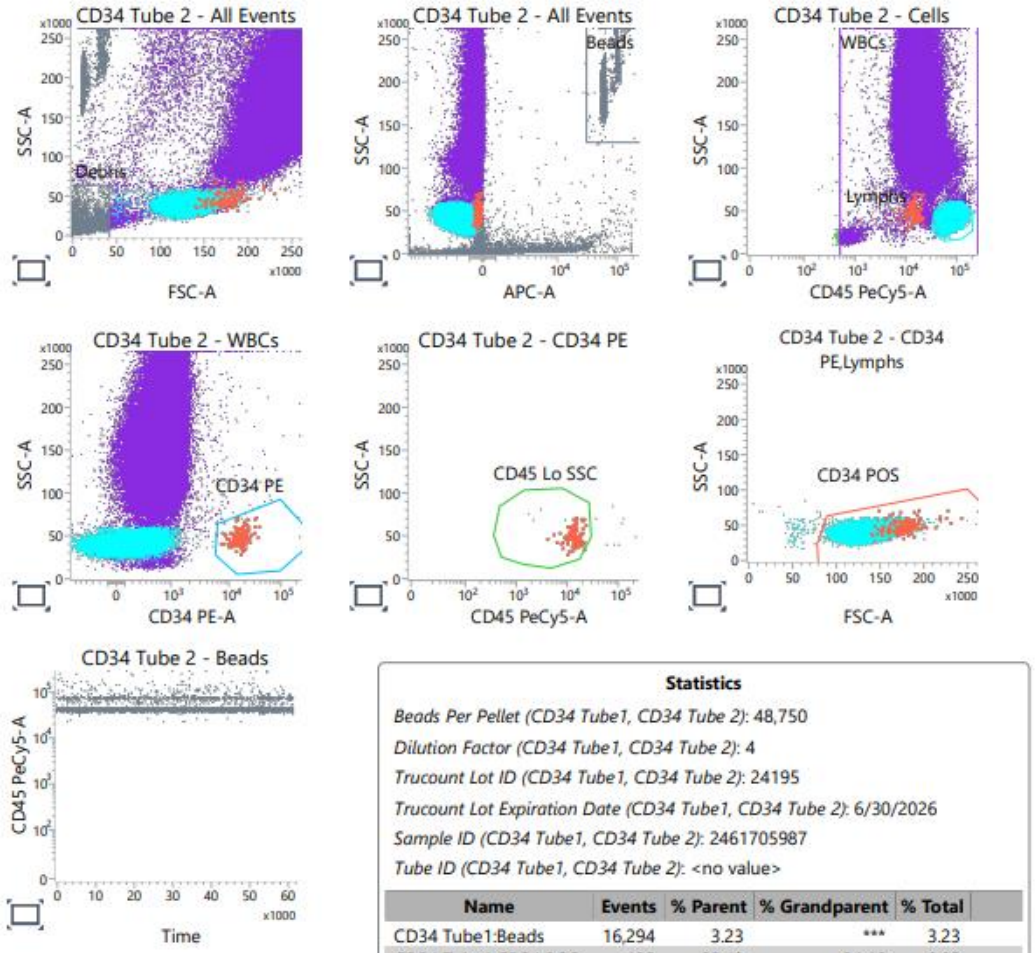
Stem cells harvested at hospital.

High dose chemotherapy (melphalan)

Transplant stem cells via drip.

CD34+ Stem Cell Assay

Cytometer SN: R654587000194 | Assay: CD34 NNUH Version 2 UD | Trucount Lot ID: 24195
Operator: Ewan Jones | Sample ID: 2461705987 | Beads Per Pellet: 48,750



Statistics

Beads Per Pellet (CD34 Tube1, CD34 Tube 2): 48,750

Dilution Factor (CD34 Tube1, CD34 Tube 2): 4

Trucount Lot ID (CD34 Tube1, CD34 Tube 2): 24195

Trucount Lot Expiration Date (CD34 Tube1, CD34 Tube 2): 6/30/2026

Sample ID (CD34 Tube1, CD34 Tube 2): 2461705987

Tube ID (CD34 Tube1, CD34 Tube 2): <no value>

Name	Events	% Parent	% Grandparent	% Total
CD34 Tube1:Beads	16,294	3.23	***	3.23
CD34 Tube1:CD34 POS	125	95.42	84.46	0.02
CD34 Tube 2:Beads	14,451	3.25	***	3.25
CD34 Tube 2:CD34 POS	125	96.15	90.58	0.03

RESULTS

CD34 Duplicate tube QC check <10% = Fail

Absolute CD34 Count Tube1 = 14.96 /uL

Absolute CD34 Count Tube 2 = 16.87 /uL

Average CD34 Count between Tubes 1 and 2 = 15.91 /uL

CD34+ Stem Cell Results

06/11/2018

PERIPHERAL BLOOD STEM CELLS

WBC (CD34)	38.5	10^9/L
WBC (CORRECTED)	38.5	10^9/L
NUCLEATED RBC	0.0	10^9/L
RBC	4.4	10^{12}/L
Hb	130	g/L
PLT	186.0	10^9/L
GRANULOCYTES	88.9	%
LYMPHOCYTES	3.7	%
MONOCYTES	7.4	%
MONONUCLEAR CELLS (L+M)	11.1	%
GRANULOCYTES	34.3	10^9/L
LYMPHOCYTES	1.4	10^9/L
MONOCYTES	2.8	10^9/L
MONONUCLEAR CELLS (L+M)	4.2	10^9/L
CD34	23	/uL

07/11/2018

PERIPHERAL BLOOD STEM CELLS

WBC (CD34)	45.4	10^9/L
WBC (CORRECTED)	45.4	10^9/L
NUCLEATED RBC	0.0	10^9/L
RBC	4.5	10^{12}/L
Hb	134	g/L
PLT	125.0	10^9/L
GRANULOCYTES	81.2	%
LYMPHOCYTES	3.4	%
MONOCYTES	10.3	%
MONONUCLEAR CELLS (L+M)	13.7	%
GRANULOCYTES	36.9	10^9/L
LYMPHOCYTES	1.5	10^9/L
MONOCYTES	4.7	10^9/L
MONONUCLEAR CELLS (L+M)	6.2	10^9/L
CD34	31	/uL

MUK-9b – 100 Days post transplant

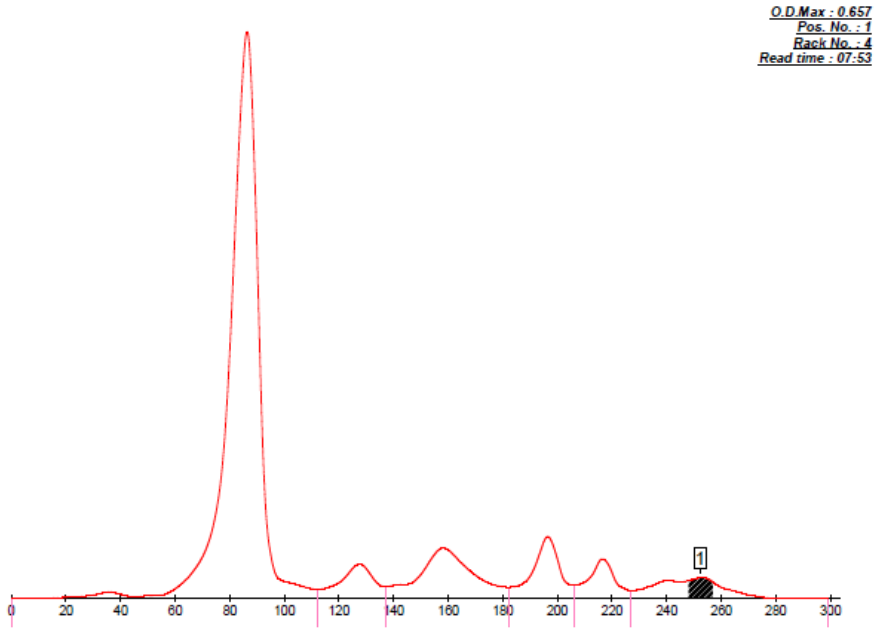
Consolidation 1 – Up to 6, 4-week cycles of:
Bortezomib
Lenalidomide
Daratumumab
Dexamethasone

Consolidation 2 – Up to 12 4-week cycles of:
Bortezomib
Lenalidomide
Daratumumab

HODS Report
Bone Marrow (BM) Aspirate Morphology
•Normocellular bone marrow aspirate
•Active trilineage haematopoiesis
•**1% plasma cells**

Flow Cytometry
•Total events counted: 207,733
•Flow cytometry of this haemodilute and partially clotted bone marrow aspirate **did not identify a plasma cell population** using the gating strategy CD38/CD138/weak CD45.
•Recommendation: correlate with aspirate/trephine morphology.

Bone Marrow (BM) Trephine Morphology
•Normocellular marrow with **<1% plasma cells**, consistent with remission.



Paraprotein remained undetectable throughout consolidation phase!

MUK-9b – Latest update

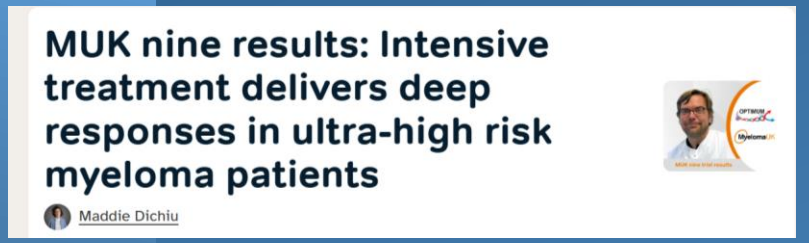
Maintenance treatment – Continue until Myeloma worsens:

lenalidomide

daratumumab

- Last correspondence from April 2025, 7 years on from transplant.
- Remained on Maintenance phase of trial for many years, now had 50+ cycles of treatment.
- Latest bloods:
  Hb 149 g/L Wbc 4.9 x10^9/L Neuts 1.75 x10^9/L Plts 224 x10^9/L
  ParaP not detected g/L C.Ca 2.28 mmol/l Creat 95 µmol/l k/l 0.68.

Results from MUK9 trial



Trial characteristics	Results (n=107)
Median Age	60 (35-78)
Sex	59.8% male
Inclusion criteria	92% by central tumour molecular analysis 8% Plasma cell leukaemia
Median follow-up	22.2 months
ISS stage at baseline	Stage I – 22.4% Stage II – 37.4% Stage II – 26.2% Missing data – 14.0%
Early mortality	2 patients died during induction
Treatment response – End of induction	ORR: 94%, CR: 22%, VGPR: 58%, PR: 15%, PD: 1%, timepoint not reached: 5%.
Treatment response – D100 Post ASCT	ORR: 83%, CR: 47%, VGPR: 32%, PR: 5%, PD: 7%, timepoint not reached: 10%.
MRD status – End of Induction	MRD-negative: 41% MRD-positive: 40% No sample available: 19%
MRD status – D100 Post-ASCT	MRD-negative: 64% MRD-positive: 14% No sample available: 22%
Response in PCL – D100 Post-ASCT	CR: 22%, VGPR: 22%, PR: 22%, PD: 22%, timepoint not reached: 12%.