Myeloproliferative Neoplasm

GP Perspective

Dr James Liang
Consultant Haematologist
Middlemore Hospital

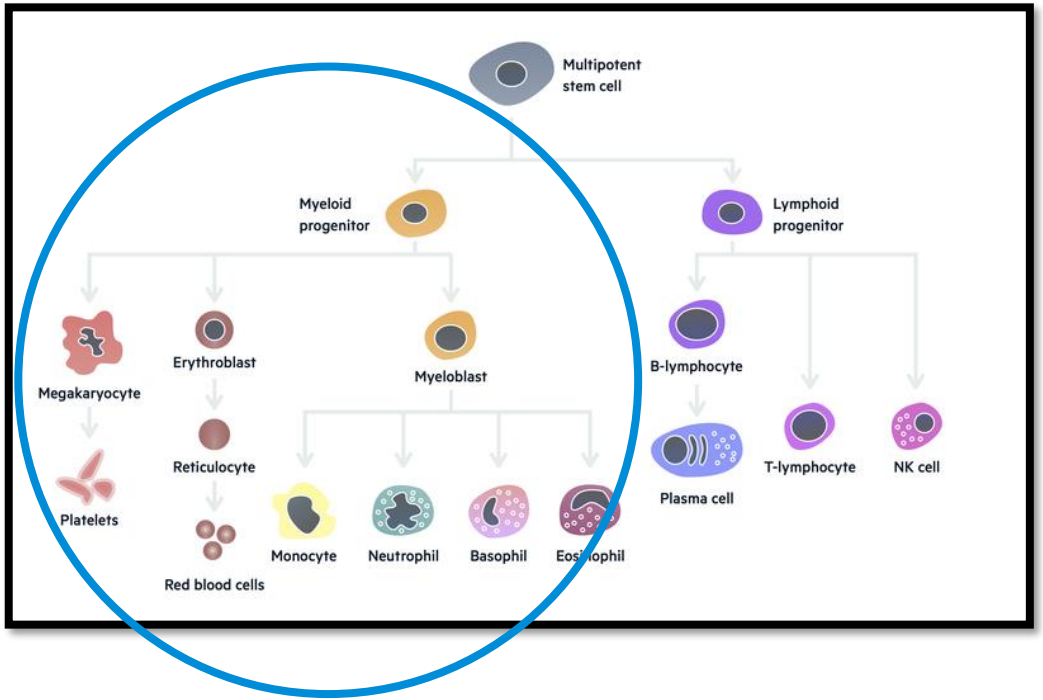
Date:

MPN

- Myeloproliferative Neoplasms (WHO 2016/2017)
  1) Chronic myeloid leukaemia, *BCR-ABL1* – positive
  2) Chronic neutrophilic leukaemia
  3) Polycythaemia vera (PV)
  4) Primary myelofibrosis (PMF)
  5) Essential thrombocythaemia (ET)
  6) Chronic eosinophilic leukaemia, NOS
  7) ~~Mastocytosis~~
  7) Myeloproliferative neoplasm, unclassifiable

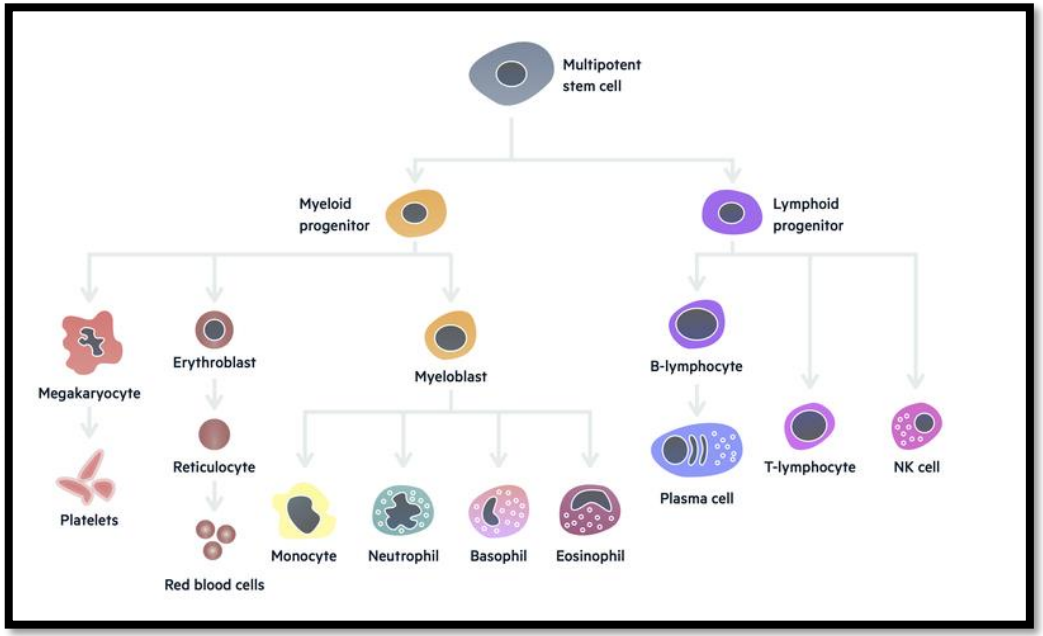
Introduction

- Clonal disorder of stem or early progenitor cell
  - Excessive **maturation** of myeloid cells
  - Associated with "**Driver**" mutation
  - Tendency to progress to acute leukaemia or myelofibrosis



Introduction

- CML
  - Predominantly affect the WBC and the platelets
    - **Basophilia** & Eosinophilia
- PMF
  - Predominantly affect the WBC, platelets and microenvironment (fibrosis)
    - **Red cell show teardrop**
    - **Leucoerythroblastic**
- PV
  - Predominantly affect RBC but **all 3 lineages** can be involved
    - Polycythaemia but with time progress to "**panmyelosis"**
- ET
  - Only affect the platelets
    - **Isolated "persistent" thrombocytosis >450**



CML 101

- Epidemiology
  - Incidence
    - 1 ~2 cases per 100,000/year
      - 15 to 20% of adult “leukaemias”
    - Median age ~50
    - Slight male predominance
    - Risk factor
      - Ionizing radiation
    - ?Family pre-disposition
      - Association with chromosome 6 and 17

- Symptoms and Signs
  - Fatigue/malaise ~33%
  - “B” symptoms (constitutional)
    - Weight loss
    - Excessive sweating
  - Bone pain
  - Gout

  - Abdominal fullness ~15%
    - Splenomegaly (50 – 75%)
    - Early satiety
    - LUQ or L shoulder tip pain

  - Bleeding (20%)
    - Acquired von Willebrand disease

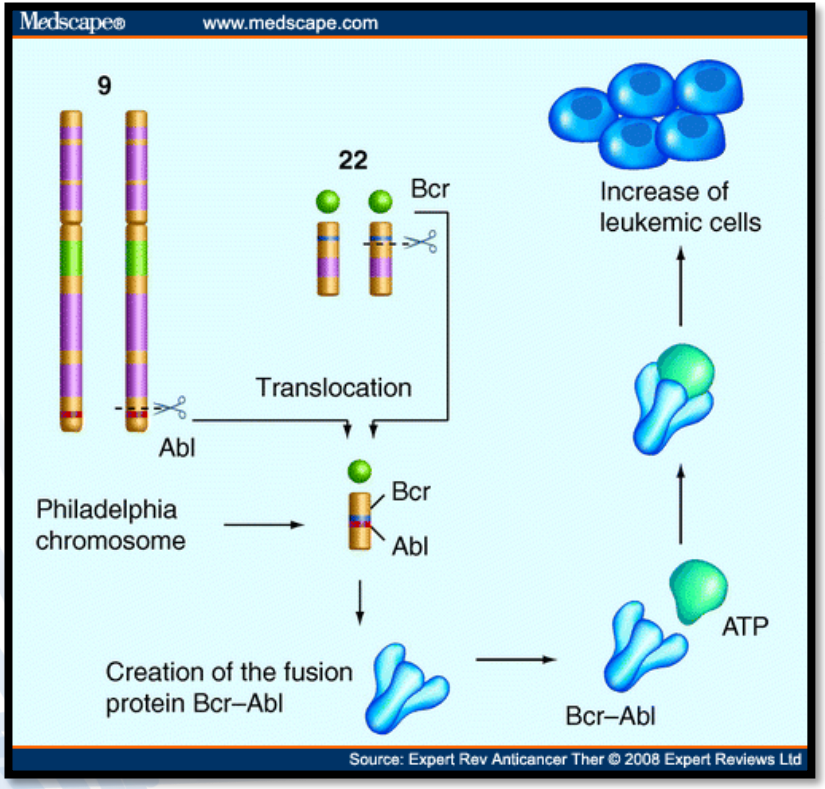
Laboratory Findings

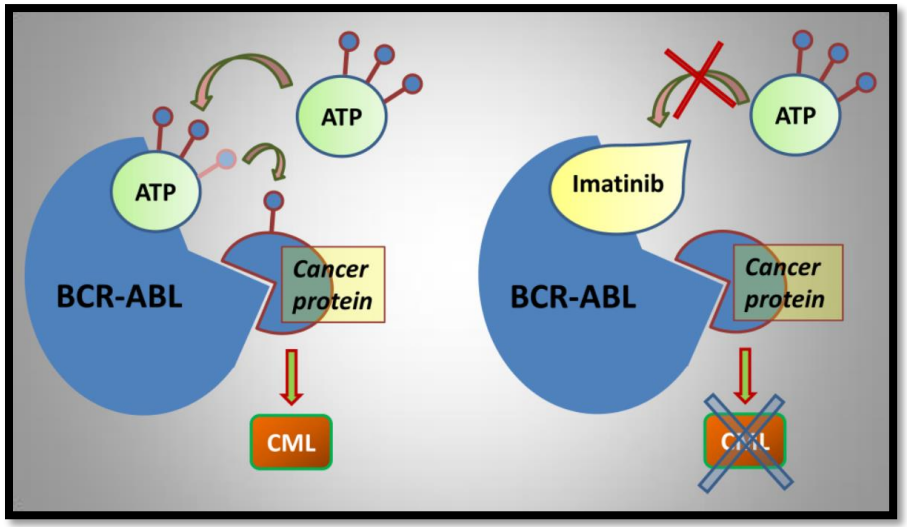
- FBC/CBC

		Ref. Range
Haemoglobin	96	(115 – 155)
Platelets	785	(150 – 400)
WBC	205.2	(4.0 – 11.0)
Blasts	2.1	
Promyelocytes	6.2	
Myelocytes	15.4	
Metamyelocytes	10.2	
Neutrophils	142.7	(1.90 – 7.50)
Lymphocytes	6.16	(1.00 – 4.00)
Monocytes	2.05	(0.20 – 1.00)
Eosinophils	10.2	(<0.51)
Basophils	10.2	(0.00 – 0.20)

- Key findings
  - Increased white cell and platelet
    - Majority of the cells are normal looking neutrophils
      - No or minimal dysplasia
    - Blasts <20%
    - “Twin peak”
      - Myelocytes and neutrophils
    - Basophilia
      - >3% then think “CML”

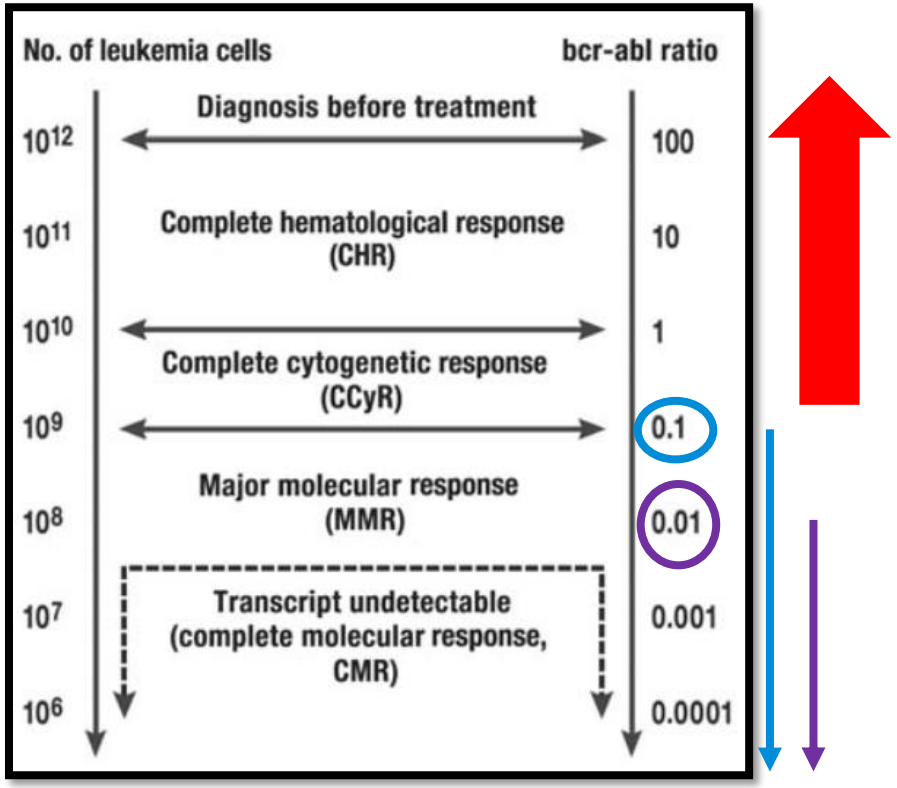
Poster Child of Targeted Therapy





Tyrosine Kinase Inhibitor

- Outcomes
  - 80-90% response
  - Medication compliance >90% is critical
    - Think of HIV
    - Remember
      - TKI is suppressing the clone but does not remove the proto-oncogene
    - **Once progressed median OS is 10.5 months**
  - Side effects
    - Cross inhibition of other tyrosine kinases
      - Oedema/Pleural effusion
      - Pancreatitis
      - Increase risk of cardiovascular disease
- Treatment Free Remission (TFR)
  - 50/50 in highly selected patient



CLASSICAL MPN

Presentation

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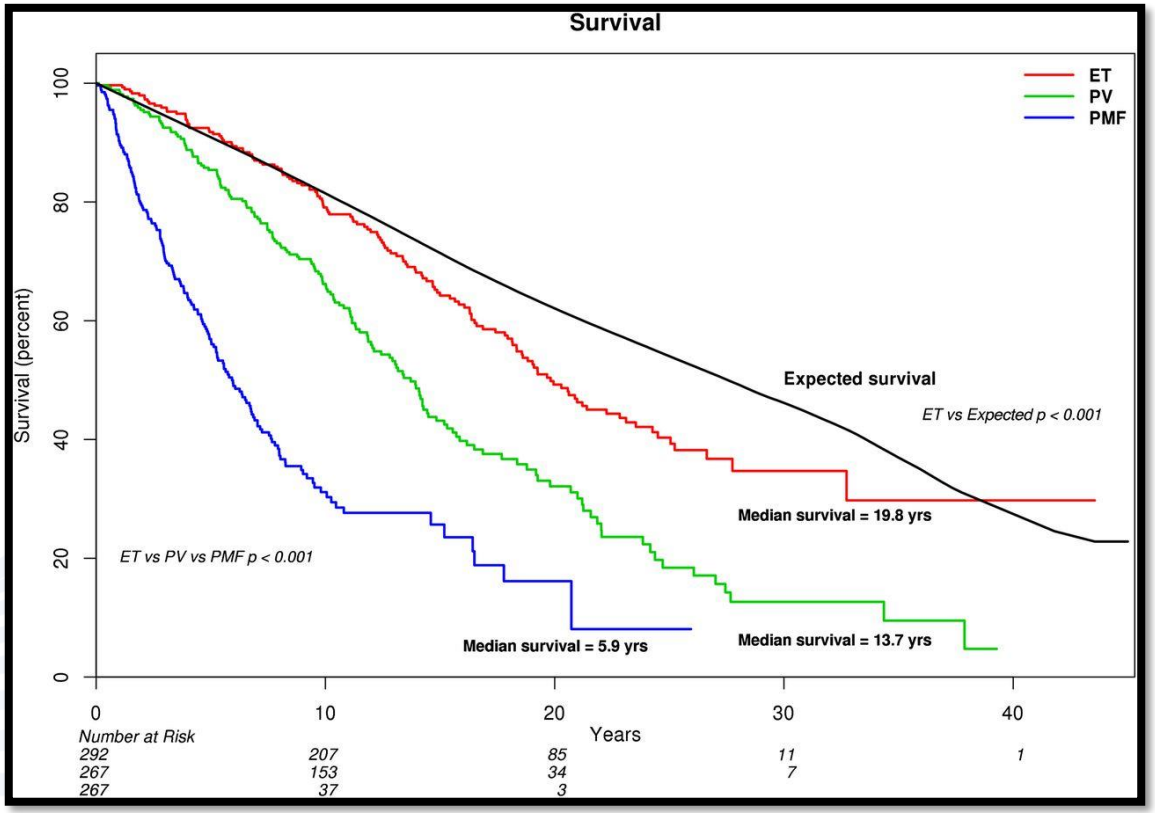
	PV	ET	MF
Epidemiology			
• Incidence (/100000)	2	2.5	1.5
• Gender (M:F)	2:1	1:2	1:1
• Median Age	60	60	67
- <40	10%	20%	5-10%
Manifestation			
• Thrombosis (/100 patient years)	5.5	1~3	2
- At diagnosis	23%	9-22%	13.2%
• Bleeding			
- At diagnosis	4%	3-37%	---
• Constitutional Symptoms	+/-	+/-	+++
• Splenomegaly	36%	35%	>90%

* Pruritis, erythromelalgia, vasomotor symptoms …etc.

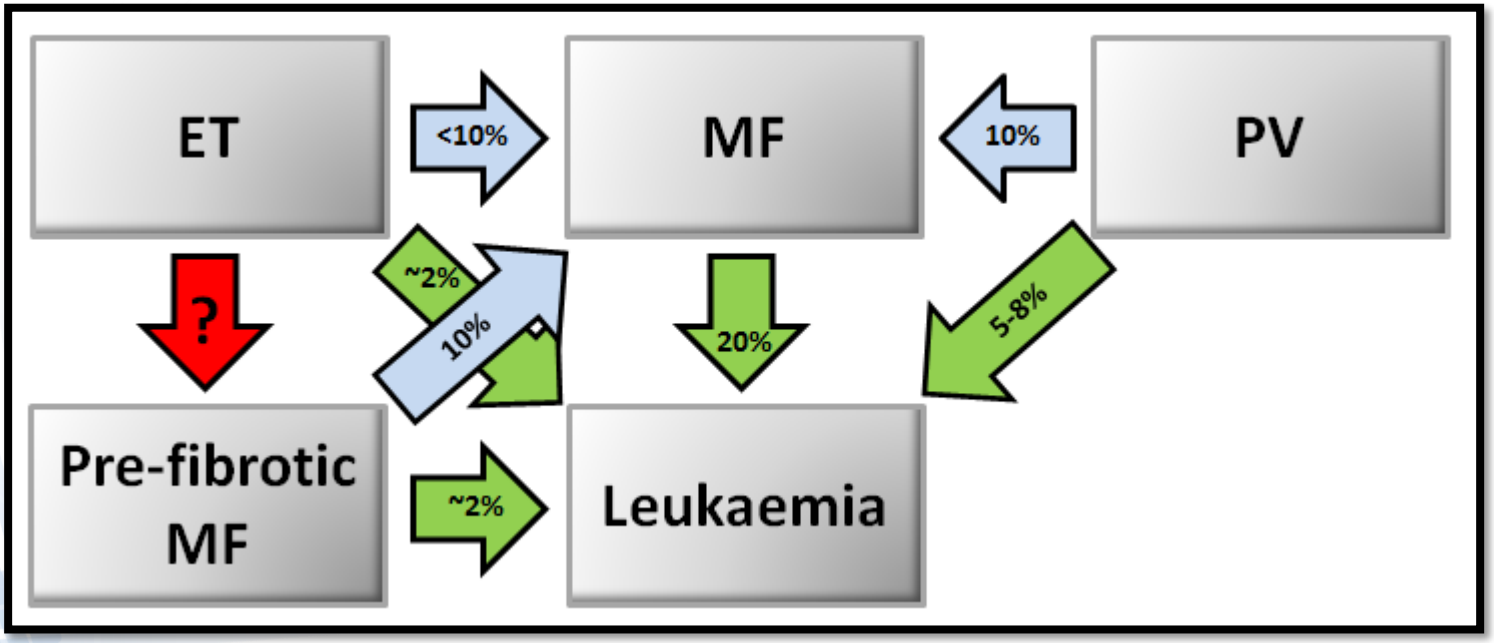
Prognosis

Tefferi et al. *Blood*. 2014 (124): 2507



Transformation

Rate of fibrotic and leukaemic transformation over 10 years



Laboratory Findings - PV

		Ref. Range
Haemoglobin	163	(115 – 155)
RBC	6.34	(3.60 – 5.60)
HCT	0.48	(0.40 – 0.46)
MCV	78	(80 – 99)
MCH	25.8	(27.0 – 33.0)
Platelets	420	(150 – 400)
WBC	8.9	(4.0 – 11.0)
Neutrophils	6.3	(1.90 – 7.50)
Lymphocytes	1.9	(1.00 – 4.00)
Monocytes	0.26	(0.20 – 1.00)
Eosinophils	0.3	(<0.51)
Basophils	0.22	(0.00 – 0.20)
Ferritin	10	(20 – 170)

- Typical Findings
  - Persistent and progressive polycythaemia
    - **With time may develop "panmyelosis"**
  - Occasionally "iron deficiency" indices
  - Blood film relatively unhelpful

Laboratory Findings - ET

		Ref. Range
Haemoglobin	150	(115 – 155)
RBC	5.22	(3.60 – 5.60)
HCT	0.46	(0.40 – 0.46)
MCV	88	(80 – 99)
MCH	28.7	(27.0 – 33.0)
Platelets	702	(150 – 400)
WBC	8.1	(4.0 – 11.0)
Neutrophils	5.8	(1.90 – 7.50)
Lymphocytes	1.9	(1.00 – 4.00)
Monocytes	0.2	(0.20 – 1.00)
Eosinophils	0.1	(<0.51)
Basophils	0.1	(0.00 – 0.20)

Laboratory Findings - ET

	2009	2011	2014	2016	2019	Now	Ref. Range
Haemoglobin	140	143	141	148	151	150	(115 – 155)
RBC		4.80	4.87	5.40	5.3	5.22	(3.60 – 5.60)
HCT	0.43	0.45	0.42	0.47	0.47	0.46	(0.40 – 0.46)
MCV	89	90	87	87	89	88	(80 – 99)
MCH	29	29.4	29.0	27.4	28.5	28.7	(27.0 – 33.0)
Platelets	446	426	571	482	640	702	(150 – 400)
WBC	10.7	8.3	12.4	9.5	11.9	8.1	(4.0 – 11.0)
Neutrophils	7.0	5.2	8.8	6.1	7.8	5.8	(1.90 – 7.50)
Lymphocytes	2.6	2.2	2.3	2.4	2.7	1.9	(1.00 – 4.00)
Monocytes	0.9	0.6	0.8	0.6	0.7	0.2	(0.20 – 1.00)
Eosinophils	0.2	0.3	0.5	0.4	0.6	0.1	(<0.51)
Basophils	<0.1	<0.1	<0.1	<0.1	0.1	0.1	(0.00 – 0.20)

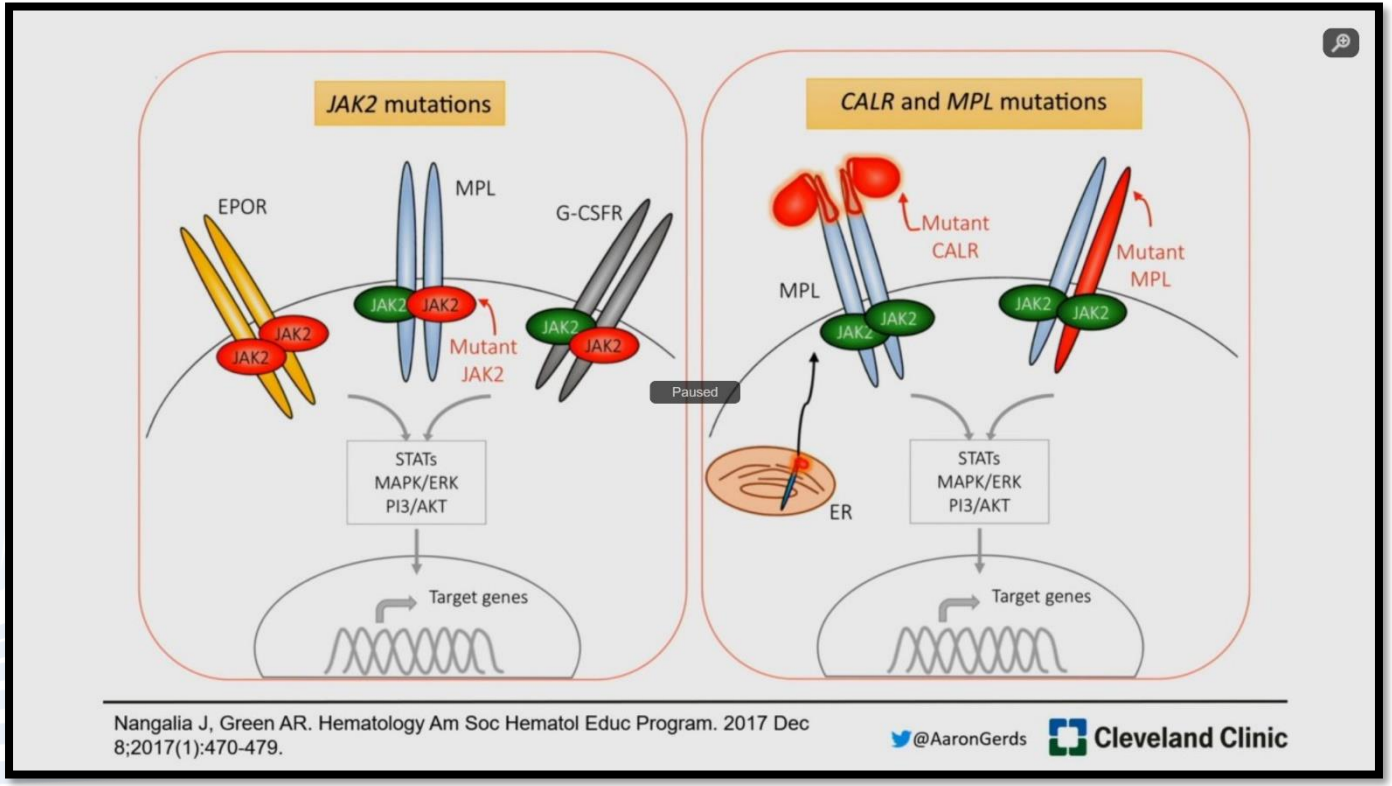
- Blood film - **increased variation in platelet size and granulation.**

Laboratory Findings - MF

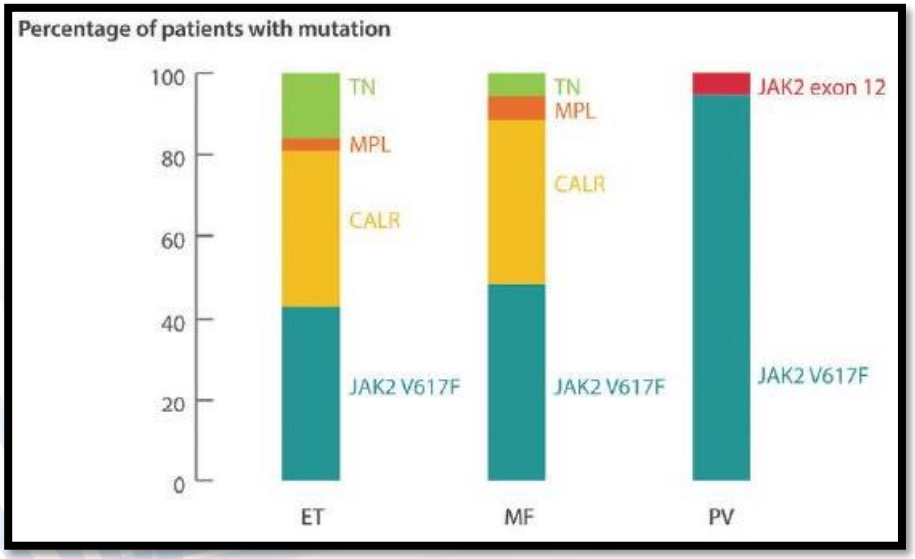
		Ref. Range
Haemoglobin	149	(130 – 175)
RBC	4.89	(4.30 – 6.0)
HCT	0.46	(0.40 – 0.52)
MCV	94	(80 – 99)
MCH	30.5	(27.0 – 33.0)
Platelets	512	(150 – 400)
WBC	16.4	(4.0 – 11.0)
Myelocytes	0.2	
Neutrophils	13.4	(1.90 – 7.50)
Lymphocytes	1.5	(1.00 – 4.00)
Monocytes	0.6	(0.20 – 1.00)
Eosinophils	0.5	(<0.51)
Basophils	0.2	(0.00 – 0.20)
Nucleated Red Cells	0.2	

- Typical Findings
  - Anaemia (normocytic normochromic)
  - Increased platelet and WBC
  - Blood film very important
    - Leucoerythroblastic blood film
      - Nucleated red cell & immature granulocyte
      - Rare blasts can be seen
    - Teardrop red cells
    - Variable platelet size and granulation

Driver Mutations



Molecular Investigations



Grinfeld J, et al. Haematologica. 2017;102:7-17

- PV
  - **JAK2 V617F** +/- exon 12
  - **Serum erythropoietin**
- ET/MF
  - **BCR-ABL1**
  - **JAK2 V617F** if negative then proceed to **CALR and MPL** mutation

Goals of Treatment

Specialist

- Prevent comorbidity
  - Thrombosis
    - Aspirin
    - Venesection (PV)
    - Cytoreductive therapy
      - Hydroxyurea
      - Novel therapy
- Curative in selected cases
  - Allogeneic stem cell transplant
    - Fit and young patient with advanced MF or transformed AML

GP

- Prevent comorbidity
  - Lifestyle modification
  - Aggressive vascular modification
    - 6 monthly vascular RF assessment
- Avoid iron replacement in PV
- Psychosocial support

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Vision to Cure. Mission to Care.

Every Day

LBC provides individualised support to over 50 patients or family members

Every Week

LBC distributes over 36 financial assistance vouchers

Every Year

LBC actively supports over 4,000 patients and their whānau

Every Year

LBC holds over 220 education and support groups

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- Psychosocial support
- Education
- Practical Assistance
- Advocacy
- Research

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What Your Haematology Patients Need To Know:

1. **Patients can self-refer to Leukaemia & Blood Cancer New Zealand (LBC) by visiting their website: www.leukaemia.org.nz**

2. **You can contact LBC for disease-specific booklets and receive other resources that help patients and loved ones living with blood cancers and related blood disorders.**

3. **Patients can receive phone calls, emails and personalized visits from LBC support staff**

Summary

- MPN is prevalent in our community
  - Rare “cancer” with long survival
- Diagnosis is often delayed
  - Asymptomatic
  - CBC/FBC trend is very important
- Primary care play a critical role in disease management
  - Vascular risk factor modification
  - Avoid iron replacement in PV
    - Inform haematology service
  - Psychosocial support
    - Leukaemic Blood Cancer NZ

COUNTIES MANUKAU HEALTH