Association of Physician Assistants in Oncology

Making Sense of Molecular Mutations in Hematologic Malignancies

MATTHEW ULRICKSON, MD

CHIEF, SECTION OF HEMATOLOGY

BANNER MD ANDERSON CANCER CENTER

AUGUST 25, 2022

Banner MD Anderson Cancer Center
Making Cancer History®

Disclosures

- Advisory Board/Consultant – Gilead, Bristol Meyers Squib, Stemline

Banner MD Anderson Cancer Center
Making Cancer History®

Learning Objectives

1. Discuss common mutations used to diagnose hematologic malignancies
2. Describe mutations useful in risk-stratification
3. Understand targetable mutations and approved medications

Banner MD Anderson Cancer Center
Making Cancer History®

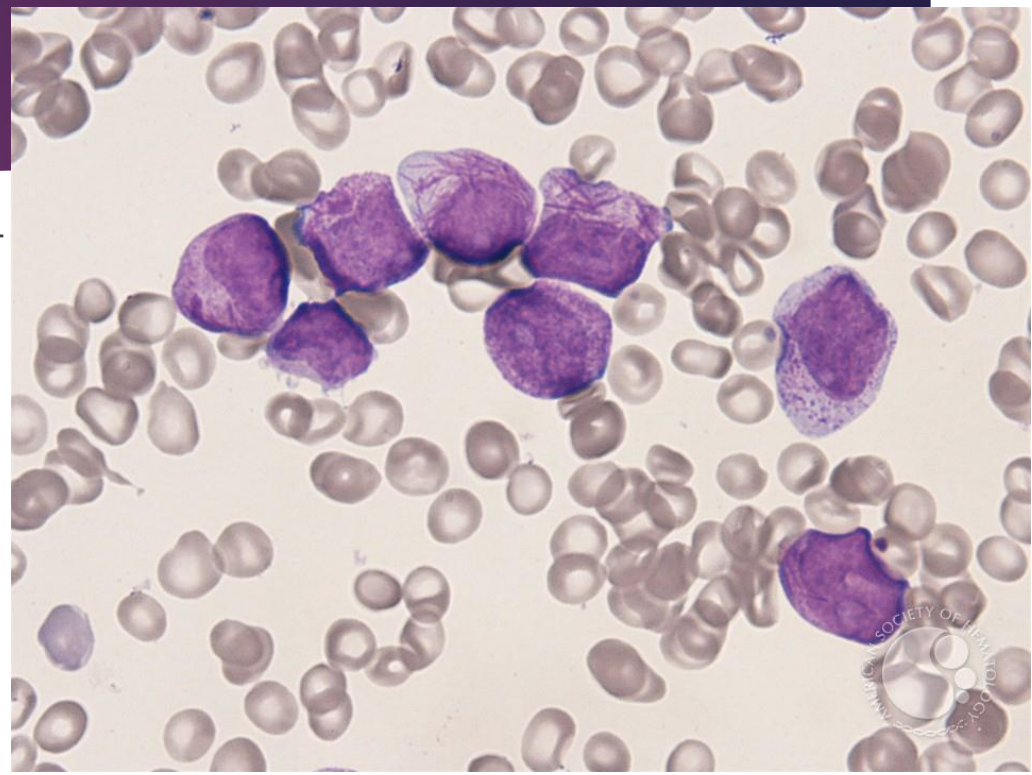
Mutations in hematology

- Diagnosis
- Prognosis
- Response (MRD)
- Target
- Noise (CHIP)

Banner MD Anderson Cancer Center
Making Cancer History®

Case 1

- 44yo woman presents to the ED with bleeding gums and a non-blanching erythematous rash on her lower extremities. Labs as follow:
- CBC: WBC 1.9>7.2<5
- INR 2.6 PTT 48 Fibrinogen 93
- Peripheral smear is below.



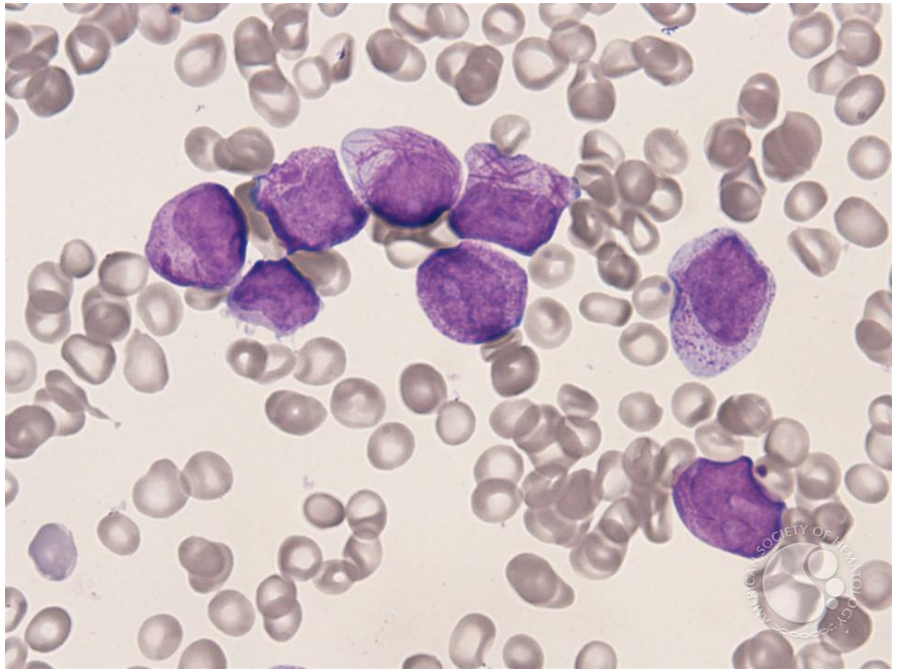
Marco Gambassi ASH image #5910

- Which of the following mutations is most likely in the WBCs?
  - A. BCR/ABL
  - B. JAK2
  - C. BCL2
  - D. PML/RARA
  - E. TP53

Banner MD Anderson Cancer Center
Making Cancer History®

Case 1

- 44yo woman presents to the ED with bleeding gums and a non-blanching erythematous rash. Labs as follow:
- CBC: WBC 1.9>7.2<5
- INR 2.6 PTT 48 Fibrinogen 93
- Peripheral smear is below.



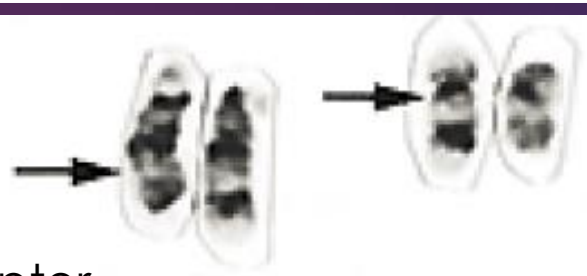
- Which of the following mutations is most likely in the WBCs?
  - A. BCR/ABL
  - B. JAK2
  - C. BCL2
  - D. PML/RARA
  - E. TP53

Banner MD Anderson Cancer Center
Making Cancer History®

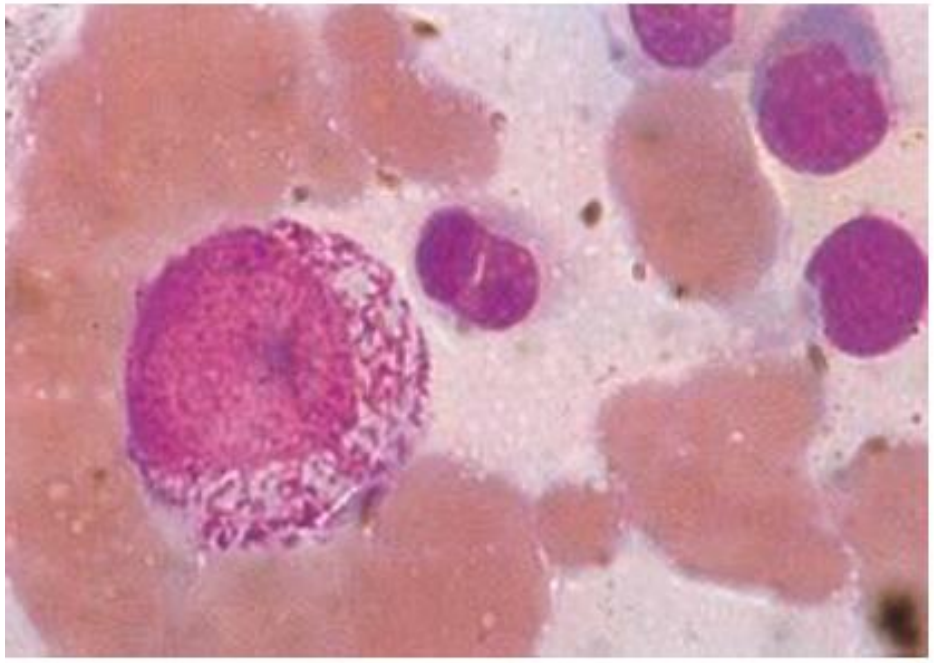
APL

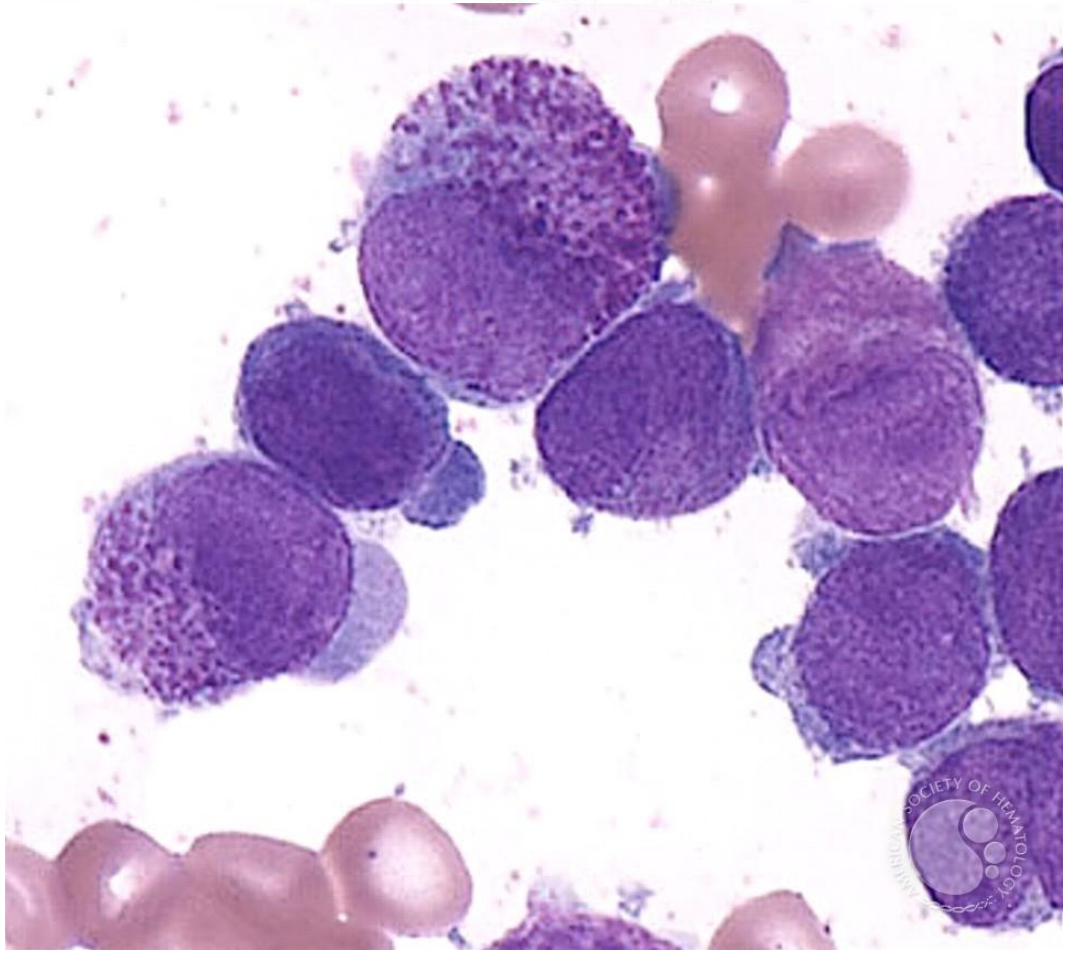
PML/RARA

Promyelocytic Leukemia – Retinoic Acid Receptor



t(15;17)(q22;q12)





Banner MD Anderson Cancer Center
Making Cancer History®

Aggressive early care for APL

- Early mortality (within days of diagnosis) ~5-10%
  - Bleeding
  - Bleeding
  - Intracranial bleeding
- Start ATRA as soon as suspected
  - If wrong, no harm done (as long as HCG negative)
  - Do not wait for testing results to start but send t(15;17)

- Long-term cure rate >95% (Low/Int risk)
  - ATRA/Arsenic (Lo-Coco NEJM 2013)
- Aggressive blood product transfusion to decrease bleeding risk
- Monitor for differentiation syndrome (elevated WBC, fever, effusions, etc)

ATRA = All trans retinoic acid

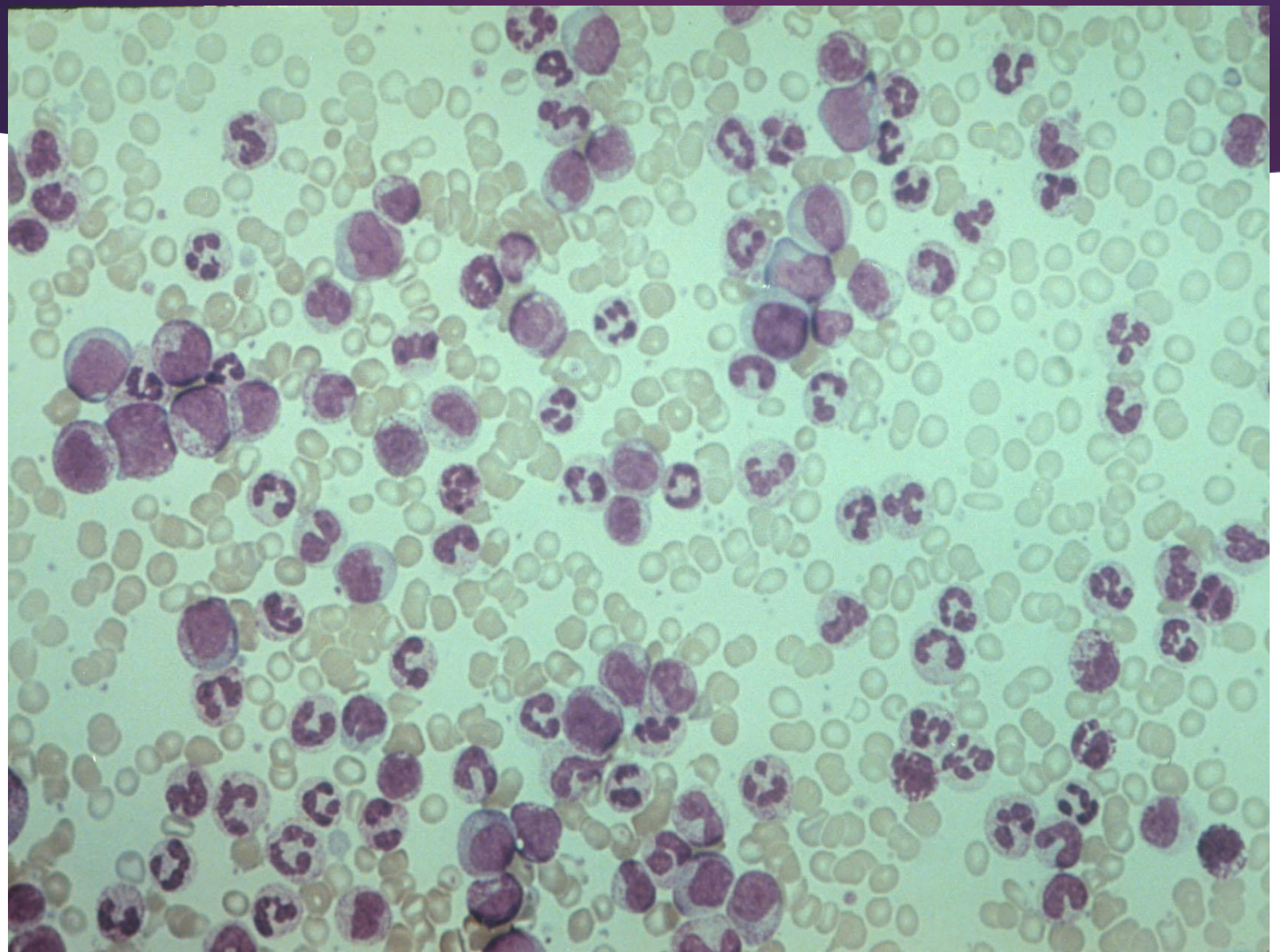
Banner MD Anderson Cancer Center
Making Cancer History®

56yo admitted with abdominal pain and leukocytosis (Case 2)

- 3 months of gradually increasing abdominal pain, L>R
- Temp 100.8°F HR 110bpm
- Abdomen TTP in the LUQ, spleen palpable 8cm below the costal margin

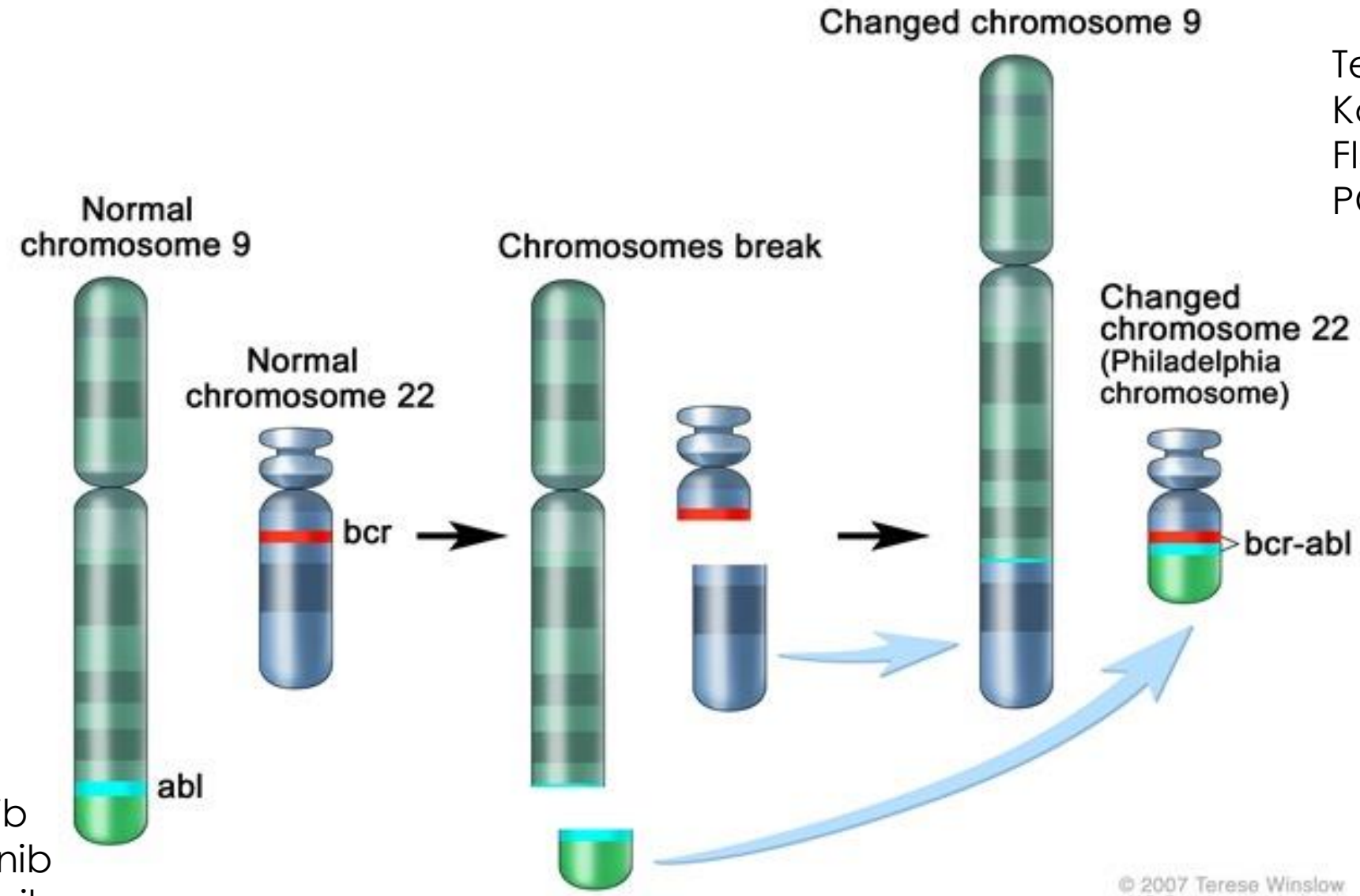
Banner MD Anderson Cancer Center
Making Cancer History®

What is the most likely mutation?

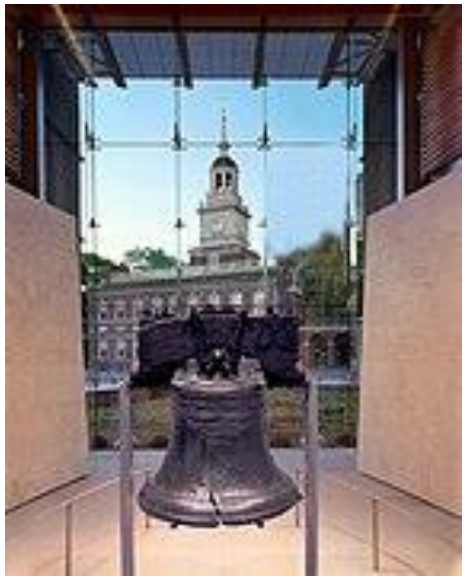


Banner MD Anderson Cancer Center
Making Cancer History®

CML: BCR/ABL1 fusion gene, the result of a genomic rearrangement



Testing:
Karyotype
FISH
PCR



National park service image

Imatinib
Dasatinib
Ponatinib
Bosutinib The 'TKIs'

Banner MD Anderson Cancer Center
Making Cancer History®

Case 3

- 32yo resident presents with sore throat and fever
- Cervical adenopathy is present on exam

- CBC: 35>35%<35k

Banner MD Anderson Cancer Center
Making Cancer History®

Peripheral Smear

Blast

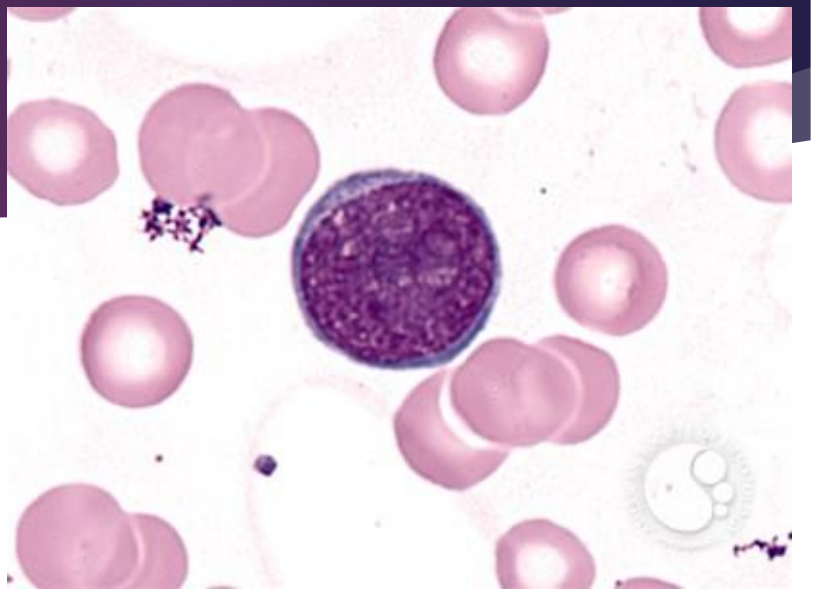


Image courtesy of Peter Maslak

- 92% Blasts
- 4% Lymphocytes
- 4% Neutrophils

- Flow cytometry showed these blasts to be positive for CD19, CD20, and TdT consistent with lymphoblasts.
- Which of the following mutations is most common in this disease?
  - A. CRLF2
  - B. BCR/ABL
  - C. CBFB/MYH
  - D. IGH/MYC
  - E. EZH2

Banner MD Anderson Cancer Center
Making Cancer History®

Peripheral Smear

- 92% Blasts
- 4% Lymphocytes
- 4% Neutrophils

- Flow cytometry showed these blasts to be positive for CD19, CD20, TdT consistent with lymphoblasts.
- Which of the following mutations is most commons in his presentation?
  - A. CRLF2
  - B. BCR/ABL
  - C. CBFB/MYH
  - D. IGH/MYC
  - E. EZH2

B
CML
R
ALL
B
L

Blast

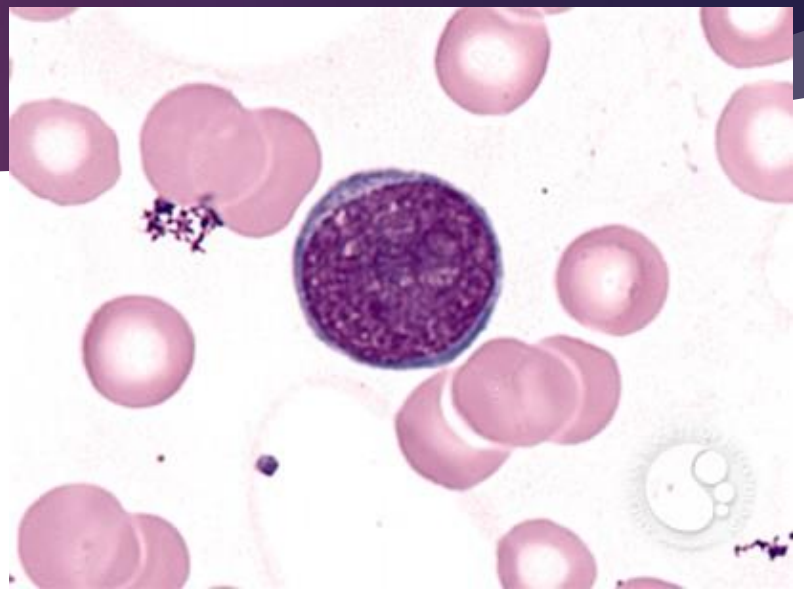


Image courtesy of Peter Maslak

He is diagnosed with Ph+ ALL

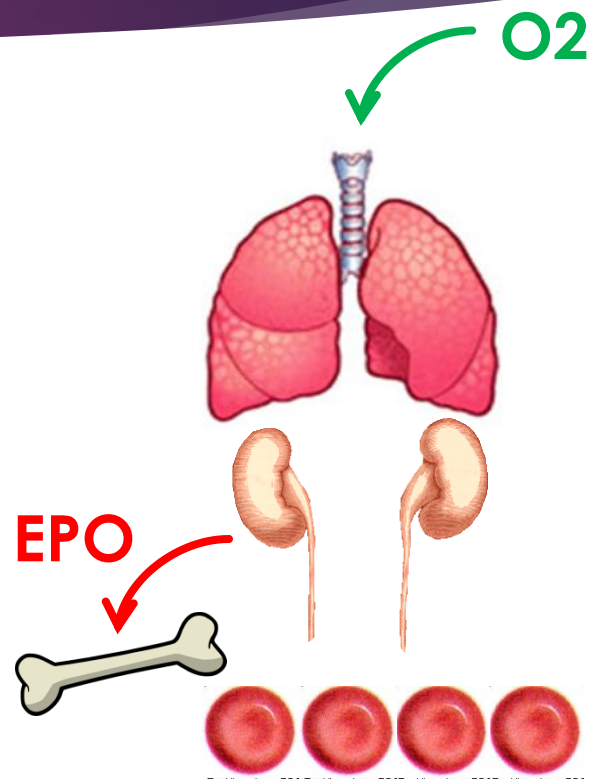
- BCR/ABL can be targeted with TKIs such as ponatinib, dasatinib, imatinib, etc just like CML

Case 4 - Presentation

- 65yo woman is referred for 'abnormal labs'
- Nonsmoker, no OSA, no history of pulmonary disease. She does not live at altitude.
- She reports pruritis but no other symptoms
- O2 saturation 98% RA
- Hb = 19 Hct = 57%
- WBC 19k Plt 440k

You recommend checking for which of the following mutations?

A. TP53
B. IDH2
C. FLT3
D. JAK2
E. COVID



Banner MD Anderson Cancer Center
Making Cancer History®

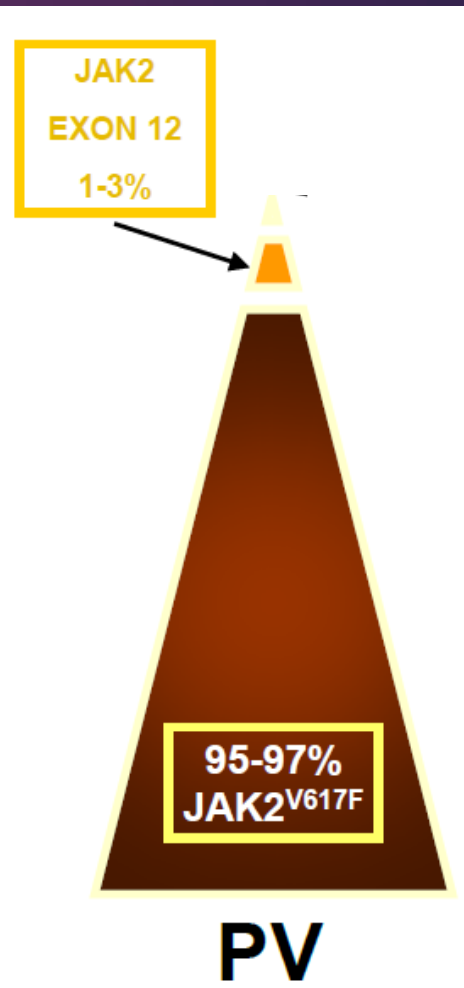
Case 4 – Diagnostics: Polycythemia Vera

- EPO = 5 (2-18)
- JAK2 V617F mutation positive

- (Potential causes of secondary polycythemia include altitude, lung disease/hypoxia, renal cell carcinoma and hepatocellular carcinom as well as testosterone/anabolic steroid use or exogenous EPO)

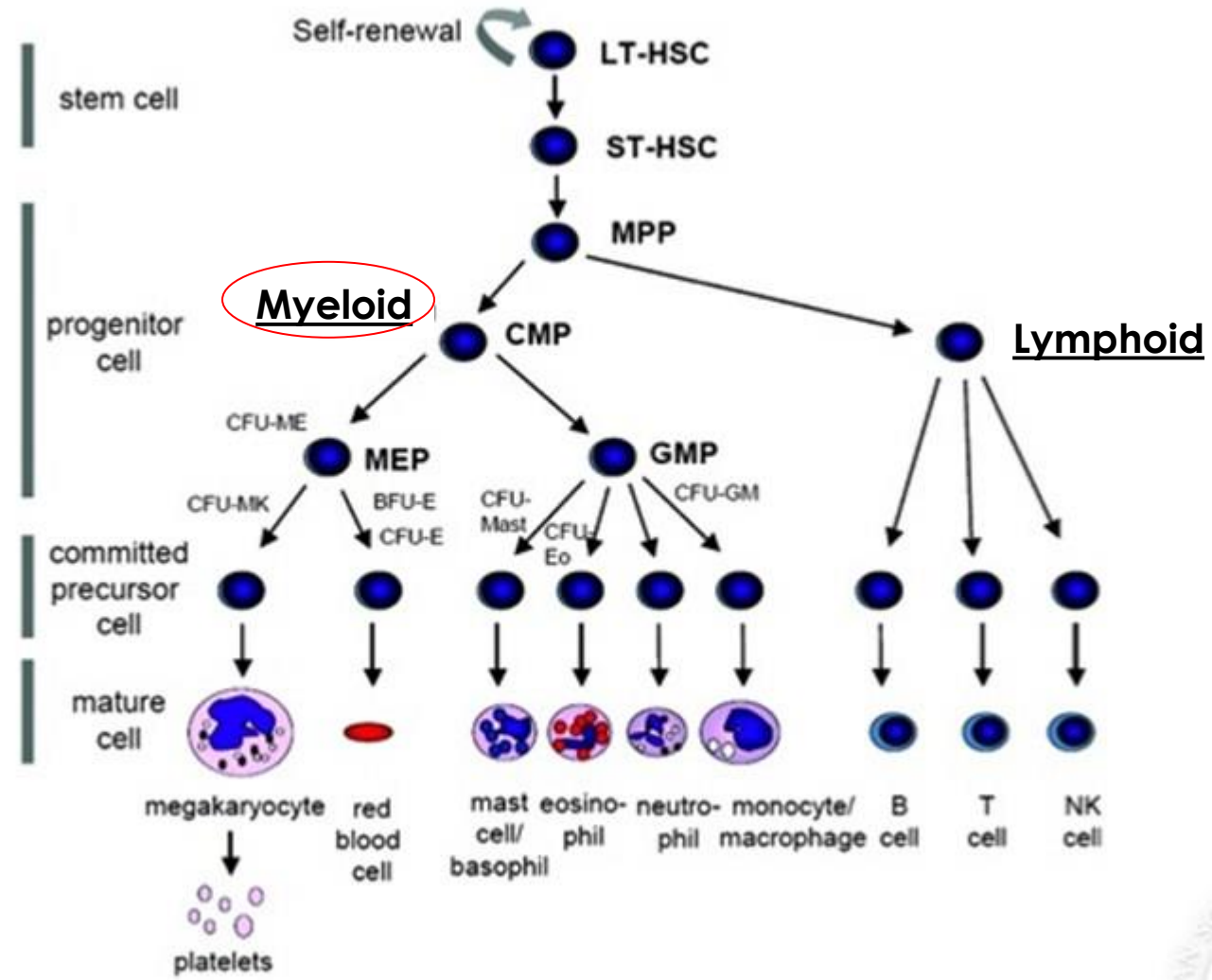
JAK2= Janus Kinase

Rome 1517



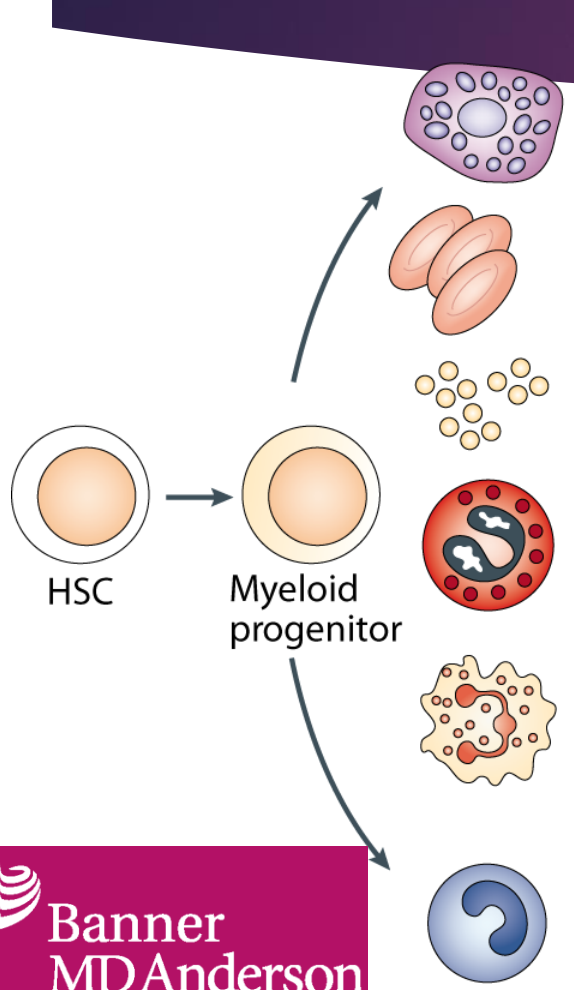
Banner MD Anderson Cancer Center
Making Cancer History®

Figure 12-3 Classical hierarchal map of hematopoietic development



Cantor, A. B. et al. ASH-SAP 2010;2010:331-372

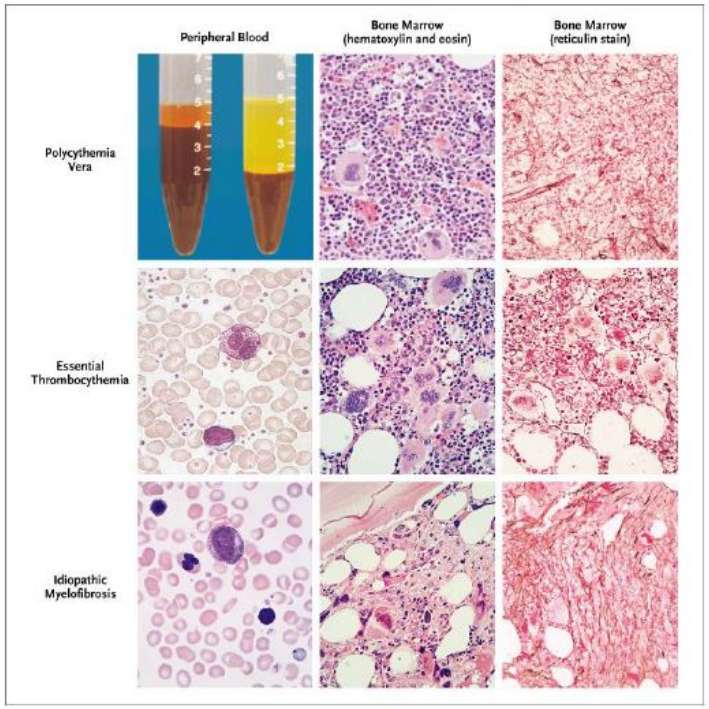
Myeloproliferative Neoplasms (MPN)



		MPD	Activating mutation
Mast cell	→	Systemic mastocytosis	KITD816V FIP1L1-PDGFRA
Red blood cells	→	Polycythemia vera	JAK2
Platelets	→	Essential thrombocytosis	JAK2, CALR, MPL
Eosinophils	→	Chronic eosinophilic leukemia	FIP1L1-PDGFRA
Neutrophils	→	Chronic myeloid leukemia	BCR-ABL
		Chronic myelomonocytic leukemia	TEL-PDGFRB BCR-PDGFRA TEL-JAK2 other fusion TKs
Monocytes	→	Primary myelofibrosis	JAK2, CALR MPL

Nature Reviews | Cancer

Lab Features of PV, ET, and MF



Campbell P and Green A. *N Engl J Med* 2006;355:2452-2466

Banner MD Anderson Cancer Center
Making Cancer History®

Case 4 – Treatment: Back to the Future

- Goal Hct is <45% (better than <50% in randomized trial by Marchioli et al. *NEJM* 2013 368:22)
  - Phlebotomy
  - Hydroxyurea
- ASA

Ancient Greek Painting

Photograph from the Burns Archive 1860

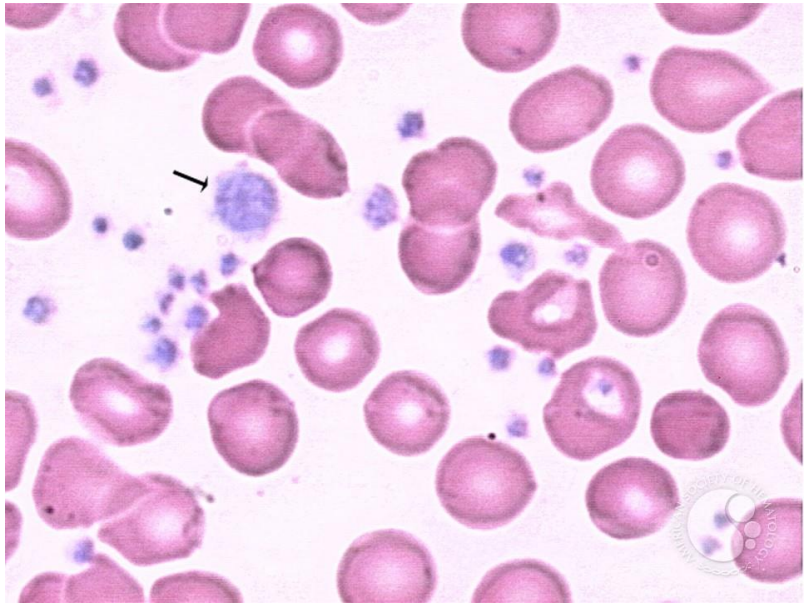
Banner MD Anderson Cancer Center
Making Cancer History®

Case 5 - Presentation

- 55yo man presents with fatigue, and abnormal labs prior to upcoming hernia surgery.
- He has no active infections. He has no organomegaly. His hernia is easily reducible without associated erythema or tenderness.
- CBC: 27>45%<750
- N65%, L25%, M8%, E2%

Which of the following is the best next diagnostic test?

A. EPO
B. BCR/ABL
C. Ferritin
D. Cdiff toxin
E. PML/RARA



Peter Maslak

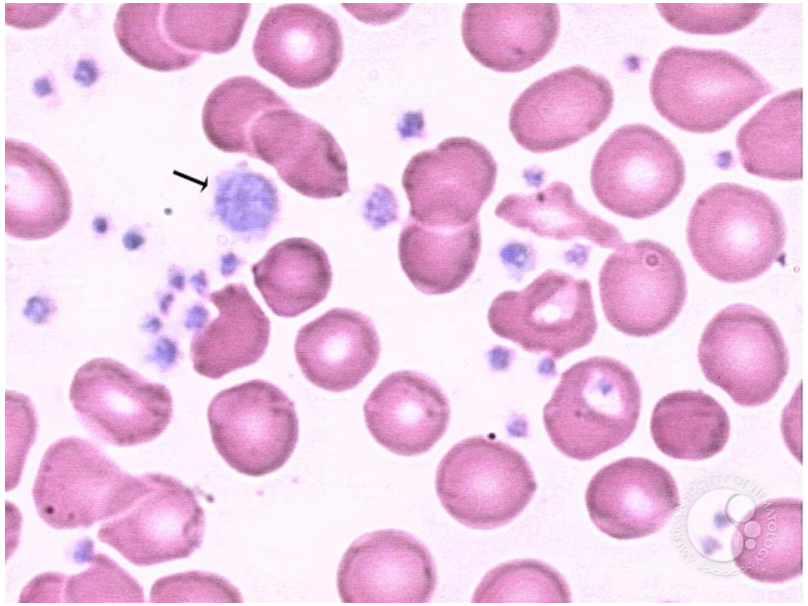
Banner MD Anderson Cancer Center
Making Cancer History®

Case 5 - Presentation

- 55yo man presents with fatigue, and abnormal labs prior to upcoming hernia surgery.
- He has no active infections. He has no organomegaly. His hernia is easily reducible without associated erythema or tenderness.
- CBC: 27>45%<750
- N65%, L25%, M8%, E2%

Which of the following is the best next diagnostic test?

A. EPO
B. BCR/ABL
C. Ferritin
D. Cdiff toxin
E. PML/RARA



Peter Maslak

Banner MD Anderson Cancer Center
Making Cancer History®

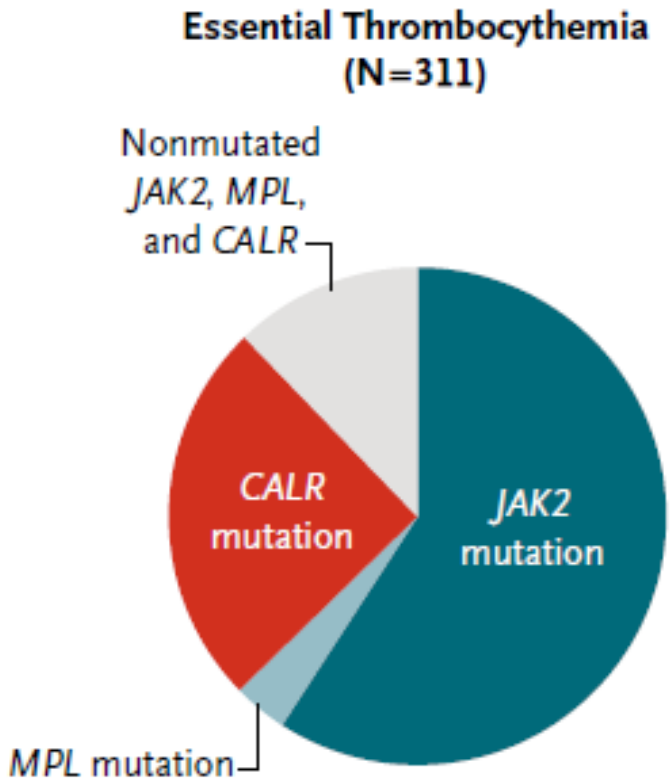
Case 5 – Calreticulin (CALR) the 'other' mutation

- JAK2 V617F mutation negative
- BCR/ABL negative
- CALR positive
- Bone Marrow - increased megakaryocytes, some are increased in size but not abnormal. No increase in fibrosis.

- Diagnosis of Essential Thrombocythemia

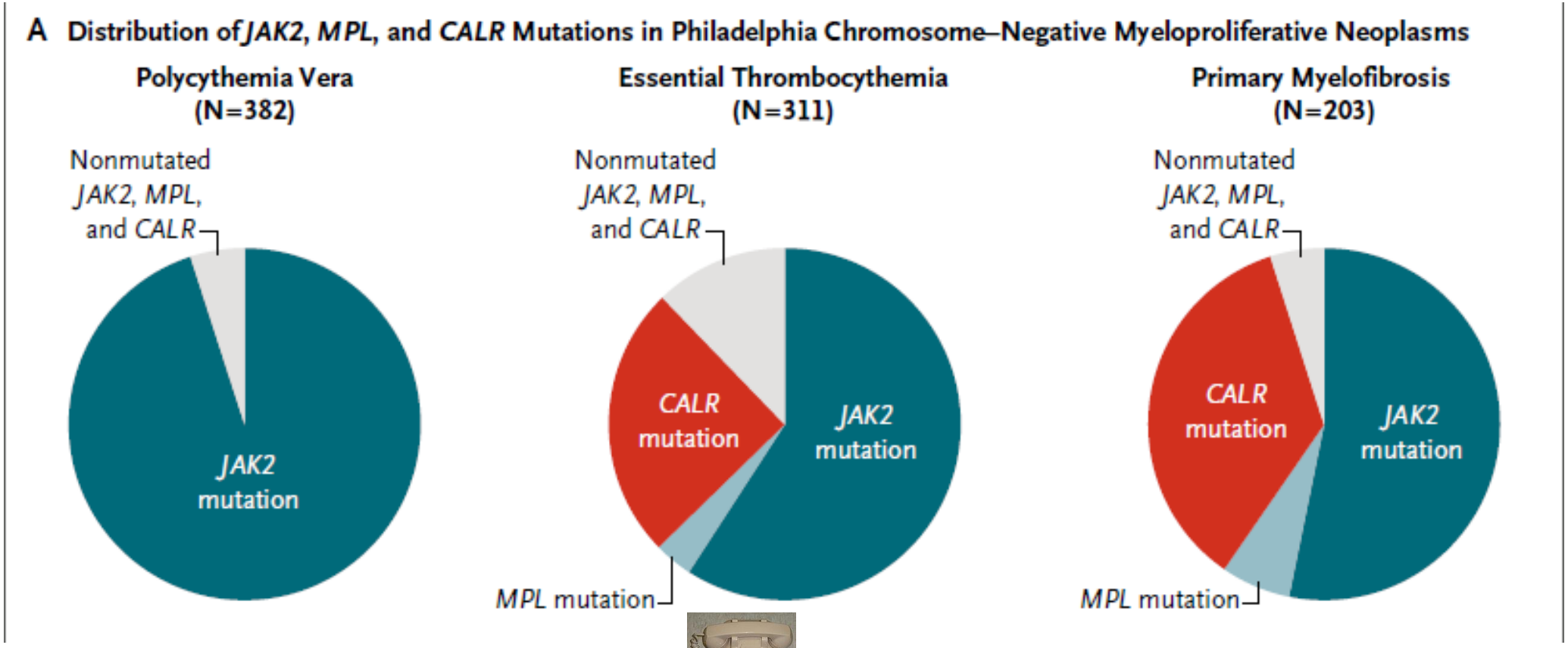
→ Exclusion of CML with negative BCR/ABL is a requirement for MPN diagnosis!

(CML can present with thrombocytosis)



Banner MD Anderson Cancer Center
Making Cancer History®

Calreticulin in ET and MF (not PV)



Dante Aleghieri

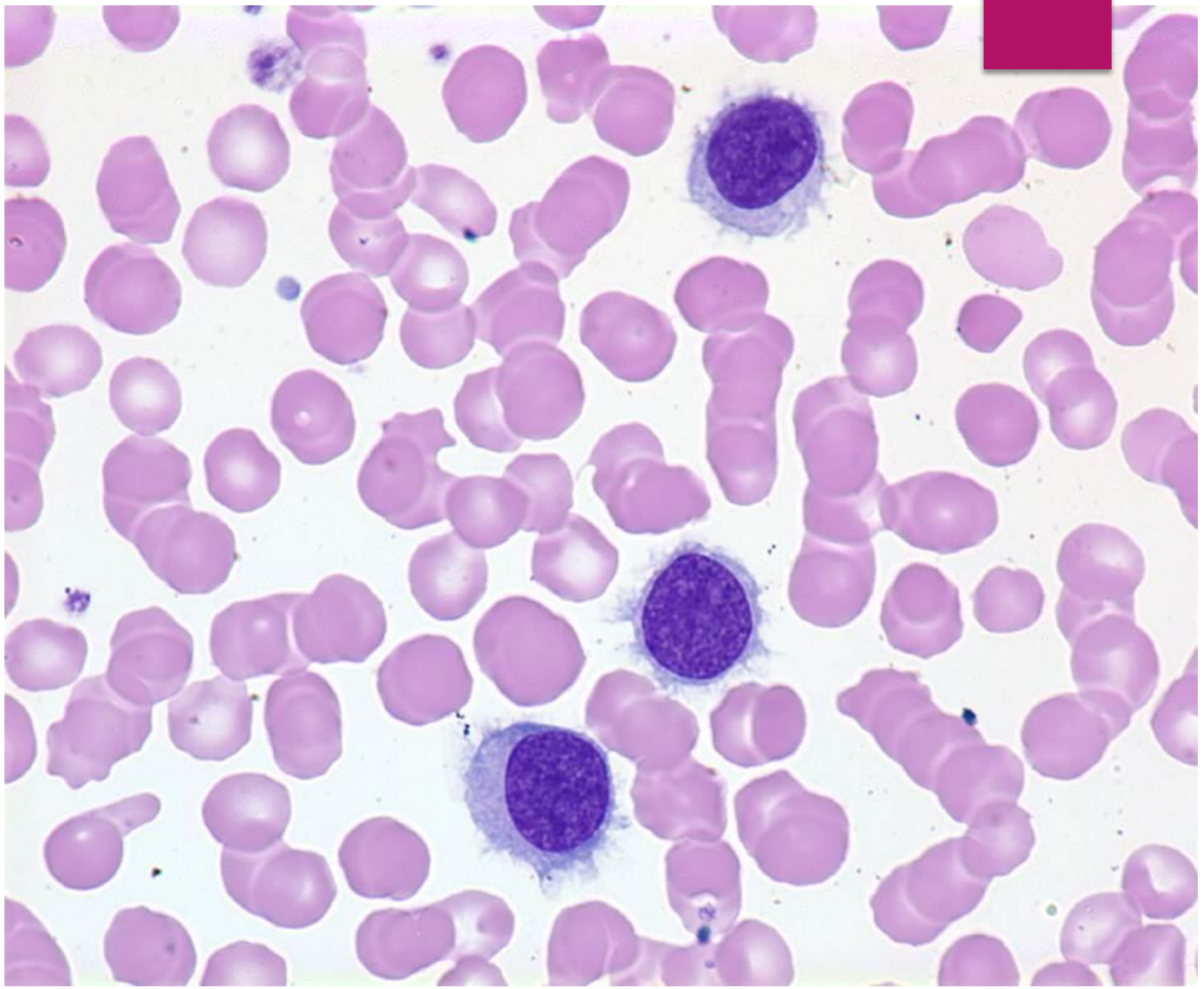
Remember: CALR, phone home ET

Klampfl NEJM 2013

Case 6

- 54yo man presents with pancytopenia.
- CBC 1.8>10.1<88
- Splenomegaly present on exam
- Peripheral smear is shown

- What mutation is most likely to be found?



Peter Maslak. ASH Image #4234

Hairy Cell Leukemia

- BRAF V600E mutation identified in ~100% of patients with typical hairy cell leukemia; not usual in other lymphoproliferative disorders[1]
- BRAF inhibitors (vemurafenib) with activity in hairy cell leukemia[2,3]

1. Arcaini, L., et al., The BRAF V600E mutation in hairy cell leukemia and other mature B-cell neoplasms. Blood, 2012. ***119****(1): p. 188-91.*

2. Follows, G.A., et al., Rapid response of biallelic BRAF V600E mutated hairy cell leukaemia to low dose vemurafenib. Br J Haematol, 2013. ***161****(1): p. 150-3.*

3. Dietrich, S., et al., BRAF inhibition in refractory hairy-cell leukemia. N Engl J Med, 2012. ***366****(21): p. 2038-40.*

Banner MD Anderson Cancer Center
Making Cancer History®

Hairy Cell Leukemia

- **BRAF V600E mutation**
  identified in ~100% of patients with typical hairy cell leukemia; not usual in other lymphoproliferative disorders[1]
- BRAF inhibitors (vemurafenib) with activity in hairy cell leukemia[2,3]

Hairy = BRAf

*1. Arcaini, L., et al., The BRAF V600E mutation in hairy cell leukemia and other mature B-cell neoplasms. Blood, 2012. **119**(1): p. 188-91.*

*2. Follows, G.A., et al., Rapid response of biallelic BRAF V600E mutated hairy cell leukaemia to low dose vemurafenib. Br J Haematol, 2013. **161**(1): p. 150-3.*

*3. Dietrich, S., et al., BRAF inhibition in refractory hairy-cell leukemia. N Engl J Med, 2012. **366**(21): p. 2038-40.*

Banner MD Anderson Cancer Center
Making Cancer History®

Many other common mutations in diagnosis

- Chronic Neutrophilic Leukemia (CNL) = CSF3R
- Myelofibrosis = JAK2 (50%) or CALR or MPL (or triple negative)
- Lymphoplasmacytic lymphoma/Waldenströms = MYD88, CXCR4
- Systemic mastocytosis = KIT D816V
- MDS with ringed sideroblasts and MDS/MPN with RS-T = SF3B1
- CMML = 80% with SRSF2, TET2 and/or ASXL1

Mighty Mouse

Banner MD Anderson Cancer Center
Making Cancer History®

Adapted from Bannon et al. *Int J Mol Sci* 2016.

Germline mutations with predisposition to hematologic malignancy

Syndrome	Gene	Inheritance	Heme Malignancy	Other Characteristics
Familial platelet disorder with propensity to myeloid malignancy	RUNX1	AD	MDS/AML/T-ALL	Thrombocytopenia, bleeding, aspirin-like platelet dysfunction
Thrombocytopenia 2	ANKRD26	AD	MDS/AML	Thrombocytopenia, bleeding
Thrombocytopenia 5	ETV6	AD	MDS/AML, CMML, B-cell ALL, MM, AA	
Famililal AML with mutated CEBPA	CEBPA	AD	AML	None
Familial AML with mutated DDX41	DDX41	AD	MDS/AML, CMML	None; AML remains avg age at dx
GATA2 Deficiency	GATA2	AD	MDS/AML, CMML	None or neutropenia, monocytopenia (MonoMAC)
Myeloid neoplasms with duplications of *ATG2B* and *GSKIP*	*ATG2B, GSKIP*	AD	AML, ET, CMML, myelofibrosis, CML, aCML	None
Telomere Biology Disorders (dyskeratosis congenita)	*TERC, TERT* Telomere length <1%	AD, AR	MDS/AML, AA	Macrocytosis, hypocellular bone marrow, squamous cell carcinomas, chemo/XRT toxicity
Familial aplastic anemia with *SRP72* mutation	SRP72	AD	MDS, AA	None
Fanconi Anemia	Multiple (complementation groups) *FANCA> FANC> FANCG> BRCA2> BRIP1* DEB or MMC assay – abnormal	AR	MDS/AML, AA	Short stature, café au lait macules, skeletal malformations, microcephaly Squamous cell carcinomas, chemo/XRT toxicity
Familial B-cell ALL	PAX5	AD	ALL	None
Germline SH2B3 mutation	SH2B3	AR	ALL	None
Li-Fraumeni Syndrome	TP53	AD	Familial ALL (hypodiploid)	Young-onset solid tumors(breast, brain)
Familial CLL	POT1	AD	CLL	Solid Tumors (brain, melanoma)

Banner MD Anderson Cancer Center
Making Cancer History®

Adapted from Bannon et al. *Int J Mol Sci* 2016.

Germline mutations with predisposition to hematologic malignancy

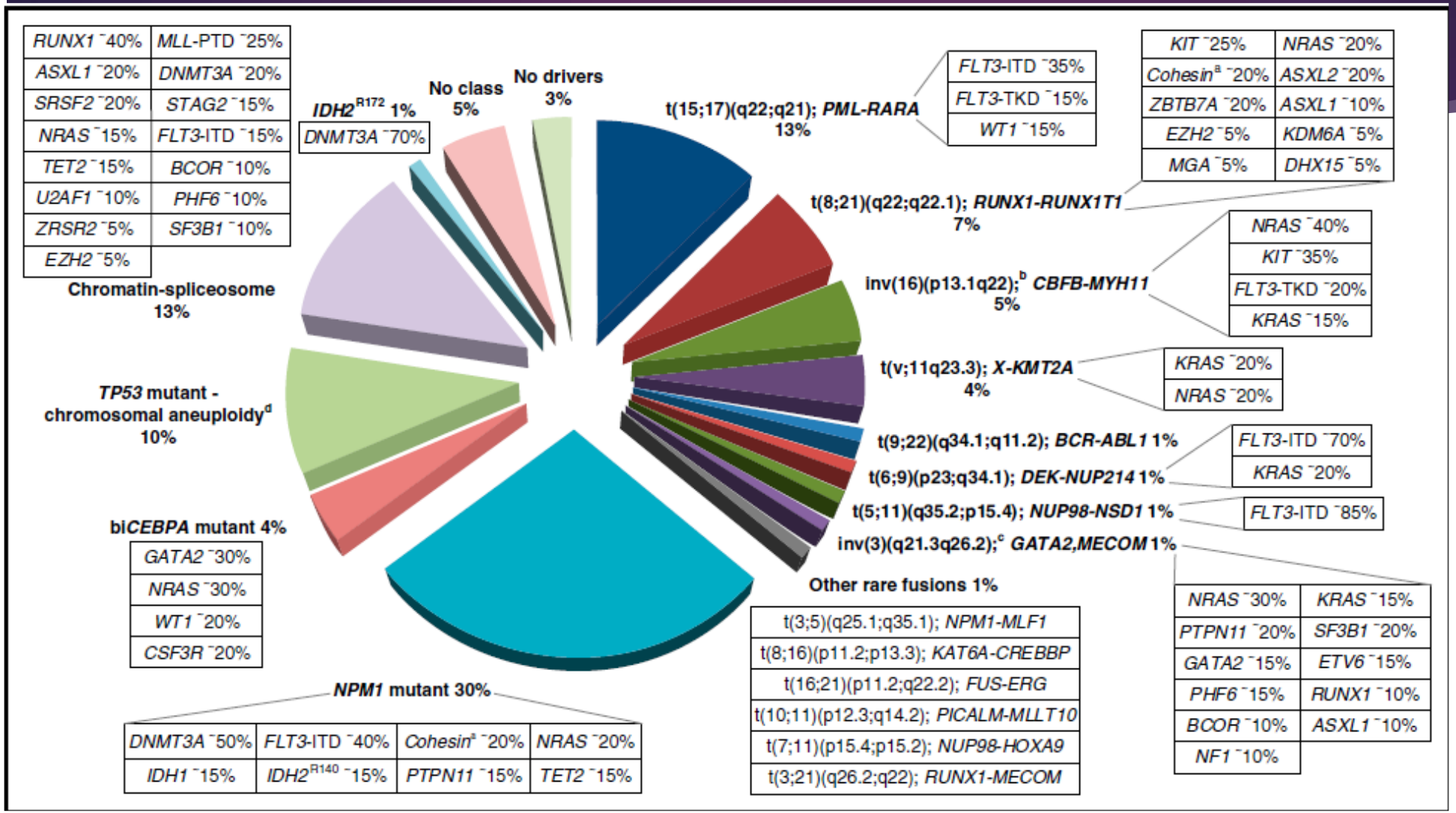
Syndrome	Gene	Inheritance	Heme Malignancy	Other Characteristics
Familial platelet disorder with propensity to myeloid malignanc	RUNX1	AD	MDS/AML/T-ALL	Thrombocytopenia, bleeding, aspirin-like
Thrombocytopenic				eeding
Thrombocytopenic				
Familiial AML with mutated CEBPA				
Familial AML with mutated DDX41				g age at dx
GATA2 Deficiency				monocytopenia
Myeloid neoplasms with duplications o *ATG2B* and *GSKIP*				
Telomere Biology Disorders (dyskeratosis congenita)	<1%			llular bone marrow, squamous cell carcinomas, chemo/XRT toxicity
Familial aplastic anemia with *SRP72* mutation	SRP72	AD	MDS, AA	None

Consider if VAF is ~50% at diagnosis, and especially if still ~50% without increase in blasts

Banner MD Anderson Cancer Center
Making Cancer History®

Mutations and risk-stratification in hematology

Expanding Genetic Landscape of AML



Optimal treatment of AML requires cytogenetic and molecular data

Dohner et al. Blood 2017. 129:424.

ICC of Myeloid Neoplasms: AML

- **Acute promyelocytic leukemia (APL) with t(15;17)(q24.1;q21.2)/*PML*::*RARA* ≥10%**
- **APL with other *RARA* rearrangements* ≥10%**
- **AML with t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1* ≥10%**
- **AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11* ≥10%**
- **AML with t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A* ≥10%**
- **AML with other *KMT2A* rearrangements** ≥10%**
- **AML with t(6;9)(p22.3;q34.1)/*DEK*::*NUP214* ≥10%**
- **AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*; *MECOM*(*EVI1*) ≥10%**
- **AML with other *MECOM* rearrangements*** ≥10%**
- **AML with other rare recurring translocations (see Supplemental Table 5) ≥10%**
- **AML with t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*‡ ≥20%**
- **AML with mutated *NPM1* ≥10%**
- **AML with in-frame bZIP *CEBPA* mutations ≥10%**
- **AML and MDS/AML with mutated *TP53*† 10-19% (MDS/AML) and ≥20% (AML)**
- **AML and MDS/AML with myelodysplasia-related gene mutations 10-19% (MDS/AML) and ≥20% (AML)**
  - Defined by mutations in *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*
- **AML with myelodysplasia-related cytogenetic abnormalities 10-19% (MDS/AML) and ≥20% (AML)**
  - Defined by detecting a complex karyotype (≥3 unrelated clonal chromosomal abnormalities in the absence of other class-defining recurring genetic abnormalities), del(5q)/t(5q)/add(5q), -7/del(7q), +8, del(12p)/t(12p)/add(12p), i(17q), -17/add(17p) or del(17p), del(20q), and/or idic(X)(q13) clonal abnormalities
- **AML not otherwise specified (NOS) 10-19% (MDS/AML) and ≥20% (AML)**
- **Myeloid Sarcoma**

Mutations and karyotype likely matter more than number of blasts

Bacher U, et al. Prognosis in patients with MDS or AML and bone marrow blasts between 10% and 30% is not associated with blast counts but depends on cytogenetic and molecular genetic characteristics. Leukemia. 2011 Aug;25(8):1361-4. doi: 10.1038/leu.2011.80.

Arber DA,et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemia: Integrating Morphological, Clinical, and Genomic Data. Blood. 2022 Jun 29:blood.2022015850. doi: 10.1182/blood.2022015850.

Prognosis: European Leukemia Net

Favorable: t(8;21), inv(16) – the CBF
NPM1 and biallelic CEBPA

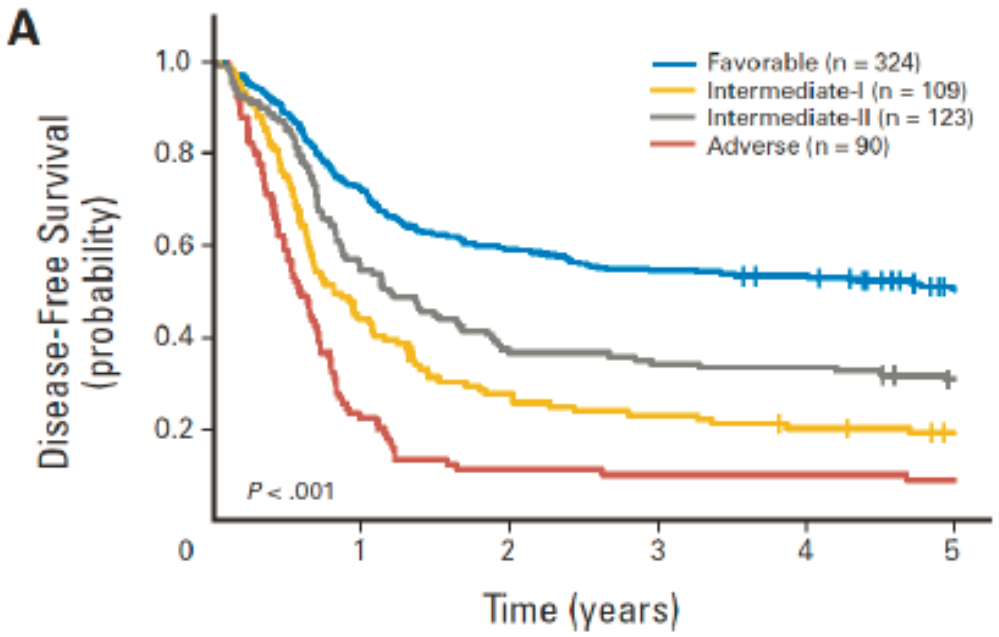


Table 1. European LeukemiaNet Standardized Reporting System for Correlation of Cytogenetic and Molecular Genetic Data in AML With Clinical Data[12]

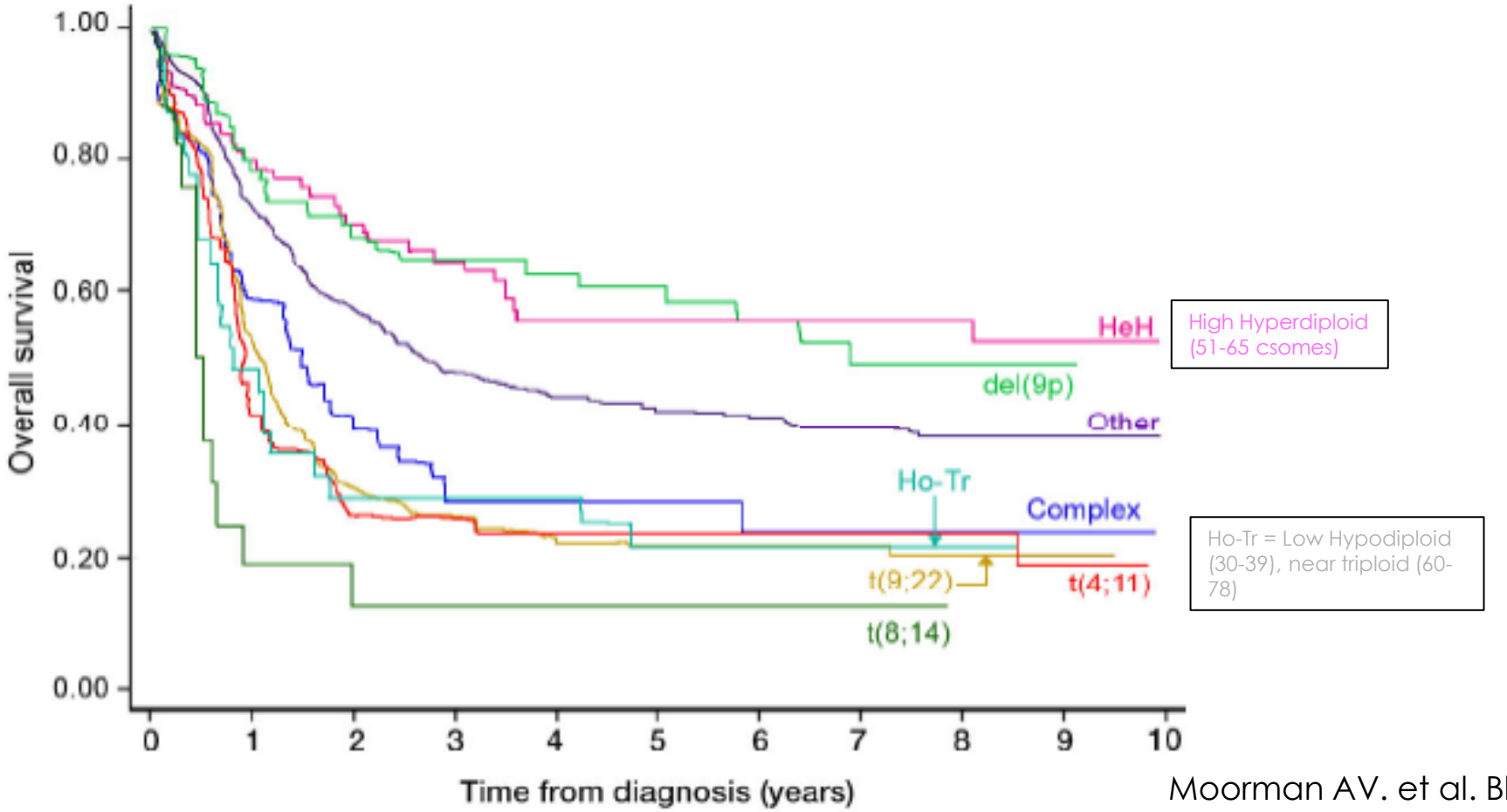
Genetic Group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD (normal karyotype)
	Mutated *CEBPA* (normal karyotype)
Intermediate-I	Mutated *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL*
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
	t(6;9)(p23;q34); *DEK-NUP214*
	t(v;11)(v;q23); *MLL* rearranged
	–5 or del(5q)
	–7
	abnl(17p)
	Complex karyotype*

Abbreviations: AML, acute myeloid leukemia; ITD, internal tandem duplication.
*Complex karyotype is defined as three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions: t(8;21), inv(16) or t(16;16), t(15;17), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3).

Mrózek K, et al. J Clin Oncol. 2012 Dec 20;30(36):4515-23. doi: 10.1200/JCO.2012.43.4738.

Banner MD Anderson Cancer Center
Making Cancer History®

Survival by Cytogenetic Subgroup in ALL: MRC UKALL XII/ECOG 2993



High Hyperdiploid (51-65 csomes)

Ho-Tr = Low Hypodiploid (30-39), near triploid (60-78)

Moorman AV. et al. Blood 2007. 109:3189

Banner MD Anderson Cancer Center
Making Cancer History®

Not quite Philly

- ‘Ph-like’ ALL (25% of AYA ALL)
  - Cytokine receptor-like factor 2 (***CRLF2***) gene (most common at 35-75% of Ph-Like)
  - V-abl Abelson murine leukemia (*ABL*)
  - Viral oncogene homolog gene-class fusions (*ABL1*, *ABL2*, *CSF1R*, *PDGFRB*, *PDGFRA*),
  - Janus kinase 2 (*JAK2*) gene,
  - Erythropoietin receptor (*EPOR*) gene rearrangements, JAK/STAT-activating aberrations,
  - Ras pathway mutations (*KRAS*, *NRAS*, *NF1*, *PTPN11*),
  - other fusions (*NTRK3*, *PTK2B*, *BLNK, FLT3*)

Rocky, in Philly – does a lot of **CRL**s

Ph-Like: More likely to have MRD and require Allo SCT

Płotka A, Lewandowski K. BCR/ABL1-Like Acute Lymphoblastic Leukemia: From Diagnostic Approaches to Molecularly Targeted Therapy. Acta Haematol. 2022;145(2):122-131. doi: 10.1159/000519782.

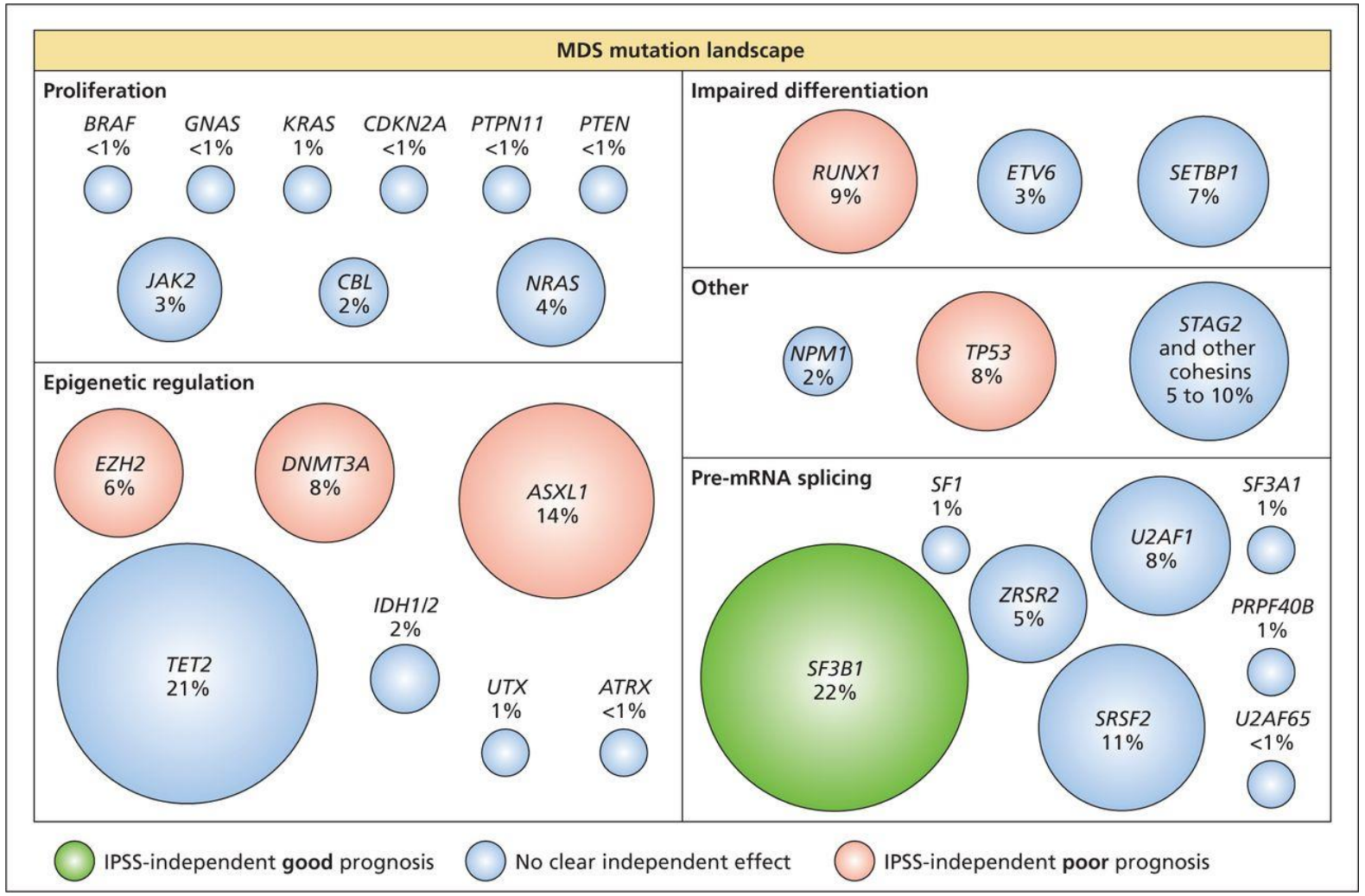
MDS and Molecular Risk

Adverse:
ASXL1
EZH2
RUNX1
ETV6
TP53
CBL

A lot of gray!!!

Richardson DR, DeZern AE. Hematology Am Soc Hematol Educ Program. 2021 Dec 10;2021(1):435-438. doi: 10.1182/hematology.2021000320.

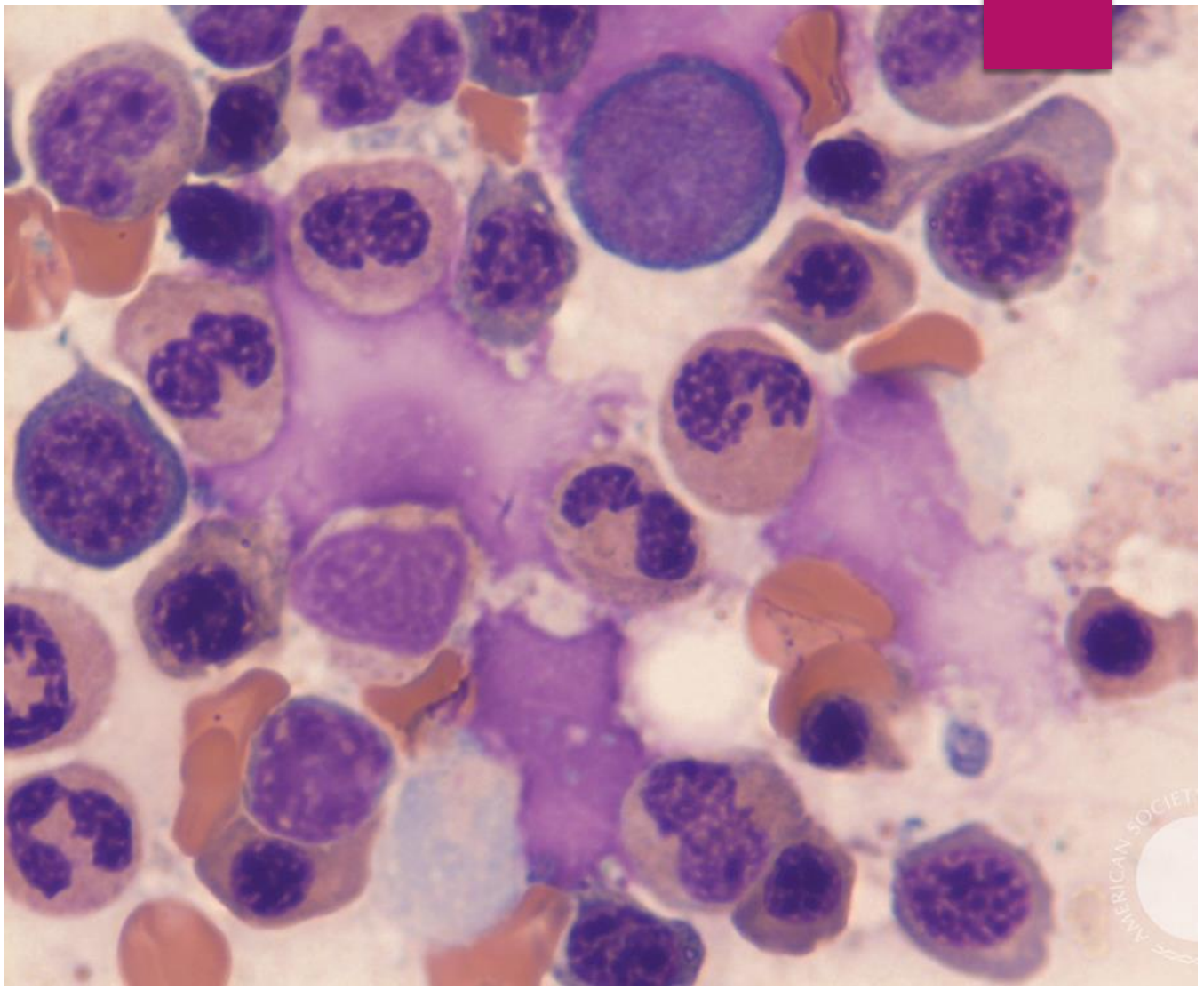
Recurrent somatic mutations in MDS, including approximate frequency of the most common recurrent somatic mutations in MDS and their prognostic significance.



Phillip Scheinberg et al. ASH 2016;2016:489-520

Morphology Still Matters!

- MDS changes in marrow with a mutation: Risk stratify
- Mutations without MDS changes: CCUS/CHIP
- Cytopenias without mutations or MDS changes: ICUS



ASH #61623

What about MRD?

Nazaré, Portugal

Level of evidence
IV
V
IV

Summary of European Leukemia Network Molecular MRD Recommendations

- MRD assessment should reach a level of detection (LOD) of 10^{-3} or lower (first pull on marrow is optimal)
- Leukemia-specific PCRs (NPM1, PML/RARa, CBF/MYH are preferred over less-specific (WT1, EVI1)
- If NGS is used for MRD, emerging variants not present at diagnosis should be reported only if significantly above background noise

Log Reduction	Percent Reduction	Exponent
1 Log	90% (10% left)	10^{-1}
2 Log	99% (1% left)	10^{-2}
3 Log	99.9% (0.1% left)	10^{-3}
4 Log	99.99% (0.01% left)	10^{-4}

Heuser Blood 2021. 138(26): 2753-2767.

Summary of European Leukemia Network Molecular MRD Recommendations

	Level of evidence
MRD assessment should reach a level of detection (LOD) of 10^{-3} or lower (first pull on marrow is optimal)	IV
Leukemia-specific PCRs (NPM1, PML/RARa, CBF/MYH are preferred over less-specific (WT1, EVI1)	V
If NGS is used for MRD, emerging variants not present at diagnosis should be reported only if significantly above background noise	IV

- Using NGS as MRD, consider all mutations as potential MRD markers except:
  - Germline mutations (~50%) should not be used — IV-V
  - DTA mutations (DNMT3A, TET2, ASXL1) should be excluded as CHIP related (NEJM 2018; 378:1189-1199) — V
  - Signaling pathway mutations (FLT3, KIT, KRAS, NRAS): low negative predictive value
  - Patients treated with targeted agents (FLT3i, IDHi) should include the target and other mutations present at baseline

Heuser Blood 2021. 138(26): 2753-2767.

Quant PCR in AML

- NPM1 mutated AML
- Send PCR in peripheral blood after 2 cycles of chemotherapy (Ivey et al. NEJM 2016)
- Send PCR from marrow at end of consolidation
- Send from marrow or blood regularly during follow up (q3m in marrow, q6weeks PB) x 2 years

- CBF AML (inv 16 = CBF/mYH PCR)
- Send from PB after 2 cycles
- Send BM at end of consolidation
- PB every 4-6 weeks x 2 years after consolidation

3 log reduction after 1st consolidation cycle
Jourdan et al. Blood 2013. 121:2213

Aim for 007!

- APL
- Most important MRD end point is end of consolidation (often send between cycles 3 and 4 of ATO)
- End of induction marrow PCR may not reflect disease burden**

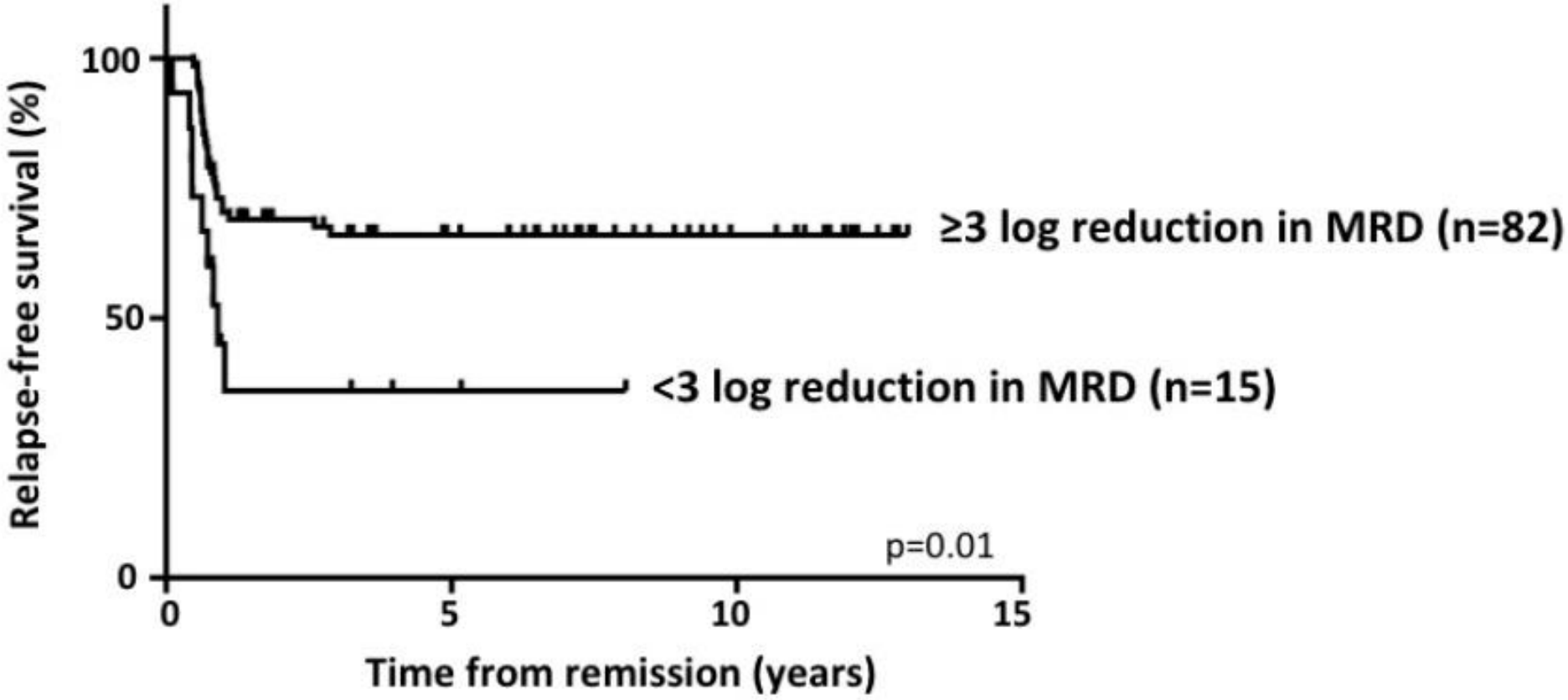
Heuser Blood 2021. 138(26): 2753-2767.

MRD monitoring of AML

- Measure depth of response from initial therapy
- Risk stratify to direct use of consolidative Allo SCT
- Monitoring during maintenance/post SCT and end of therapy to predict relapse
- Use the most sensitive test
- Run MRD on first tube pulled from marrow

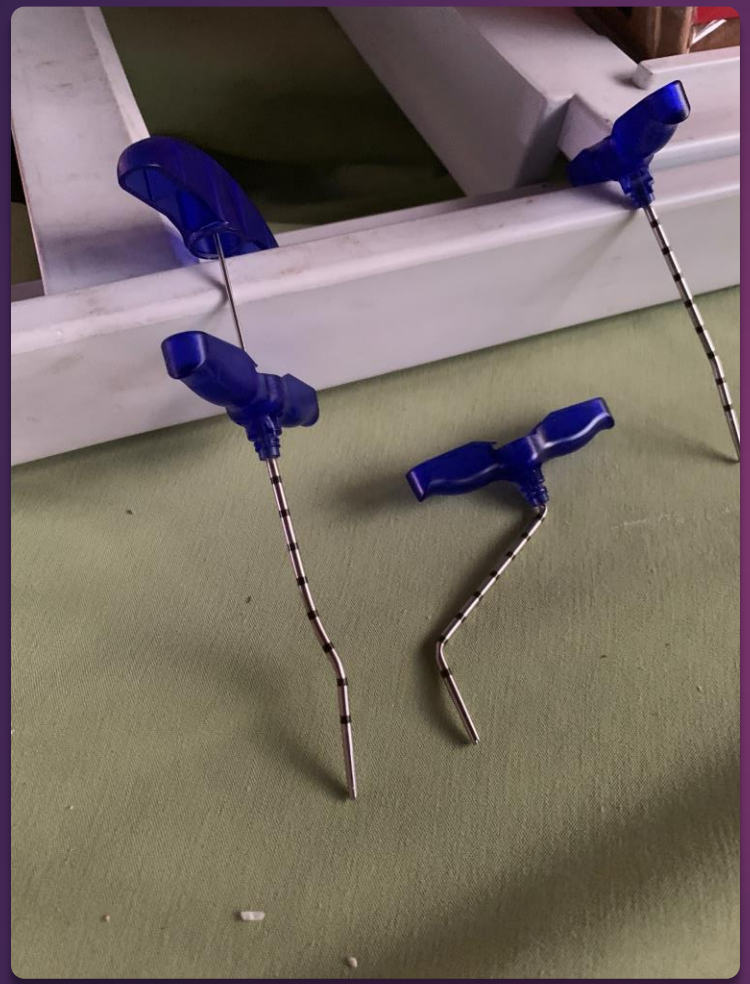
End of treatment MRD predicts risk of relapse

t(8;21) or inv16
PCR for RUNX or CBFB



Higher risk of relapse in patients who did not achieve ≥3 log reduction in MRD transcripts at end of chemotherapy (60.0% vs 32.9%, p=0.046)

Puckrin et al. Abstract #113090



How can we improve treatment as a result of mutation identification?

Banner MD Anderson Cancer Center
Making Cancer History®

On target Mutations help optimally treat AML

- Current targeted medicines available:
  - FLT3 + = midostaurin, gilteritinib
  - IDH2 + = enasidenib
  - IDH1 + = ivosidenib
  - Many others in clinical trials
    - Magrolimab (?TP53)
    - Menin Inhibitors (KMT2A rear and NPM1)
    - MDM2 inhibitor

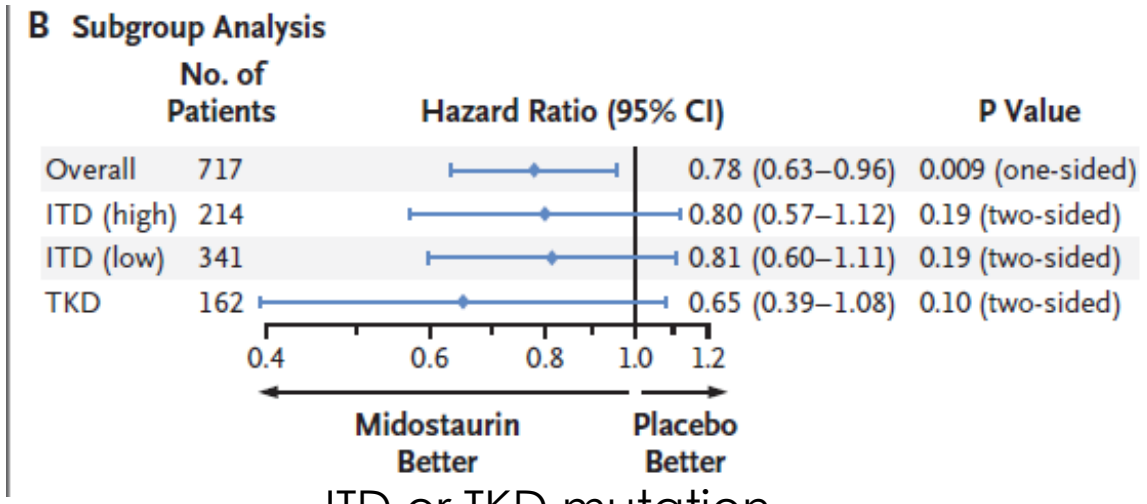
Stein, EM et al. *Blood.* 2017 Aug 10;130(6):722-731. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia.
Stone, RM et al. *N Engl J Med.* 2017 Aug 3;377(5):454-464.
Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation.

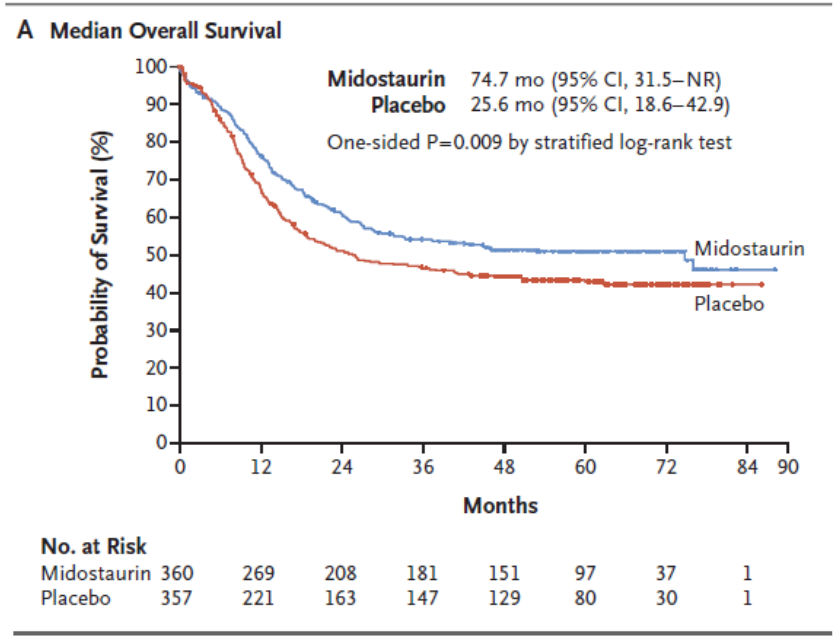
FLT3 and Midostaurin in AML

Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a *FLT3* Mutation

R.M. Stone, S.J. Mandrekar, B.L. Sanford, K. Laumann, S. Geyer, C.D. Bloomfield, C. Thiede, T.W. Prior, K. Döhner, G. Marcucci, F. Lo-Coco, R.B. Klisovic, A. Wei, J. Sierra, M.A. Sanz, J.M. Brandwein, T. de Witte, D. Niederwieser, F.R. Appelbaum, B.C. Medeiros, M.S. Tallman, J. Krauter, R.F. Schlenk, A. Ganser, H. Serve, G. Ehninger, S. Amadori, R.A. Larson, and H. Döhner

FLT3 in 20-30% of pts with AML





ITD or TKD mutation

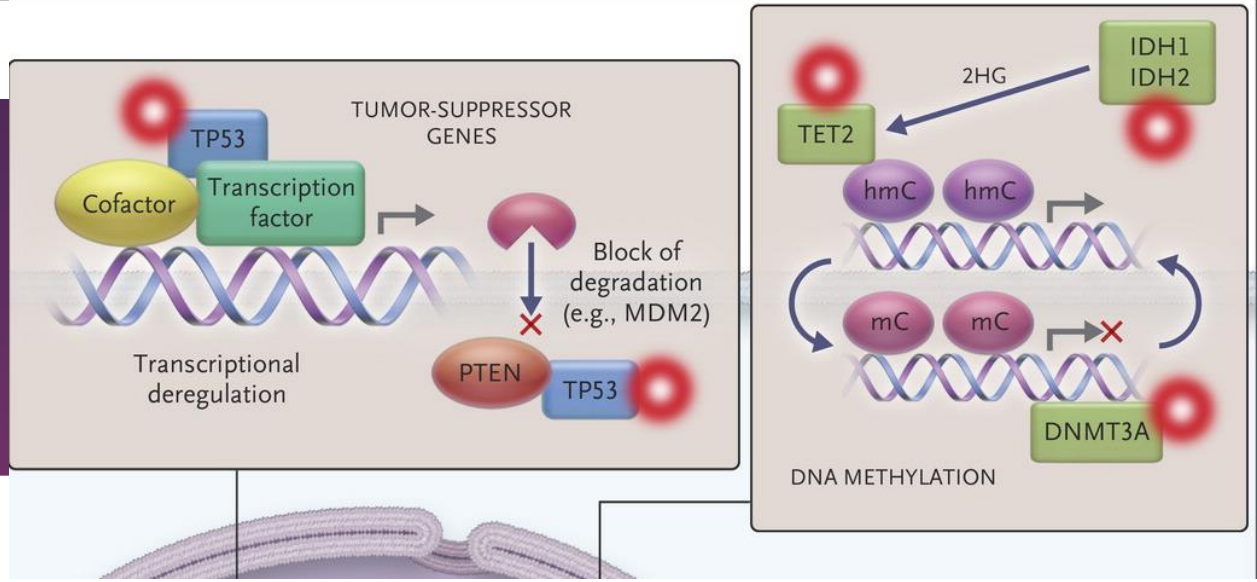
213/360 (59%) Underwent transplantation

196/357 (55%) Underwent transplantation

Of randomized pts, 50-60% were transplanted in both groups

Stone et al. NEJM 2017. 377:454

IDH (isocitrate dehydrogenase)



Dohner et al. *NEJM* 2015

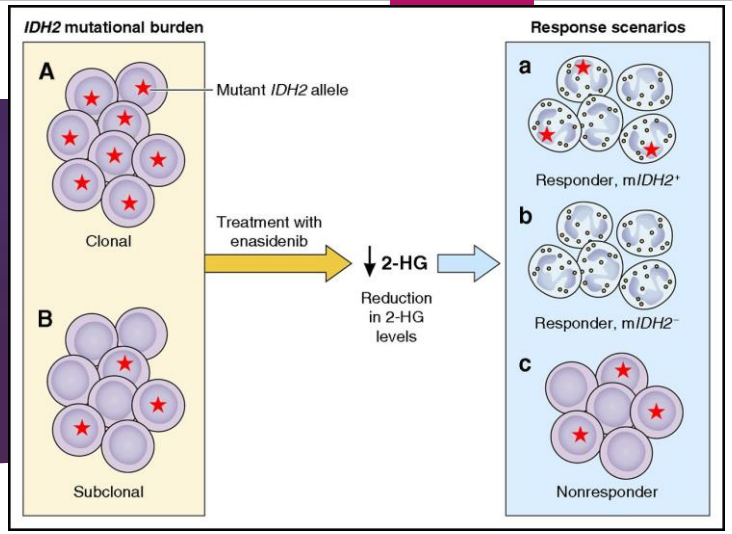
- IDH2 mutation (R140) increases with age
- IDH2 mutations in 12% of AML (more in pts with normal karyotype)
- 10% with mutation in IDH1
- Can be seen in combination with NPM1 (except IDH2^{R172})
- IDH1 and IDH2 may identify patients likely to respond to Bcl2 inhibition

- R140 and R172 are positions within the active enzymatic site
  - Cause synthesis of **2-hydroxyglutarate** (leads to histone hypermethylation) – 'neomorphic activity' (alpha-ketoglutarate reduced to **R-2-HG**)
  - R-2-HG leads to <u>differentiation arrest</u> of hematopoietic cells

Marisakastner

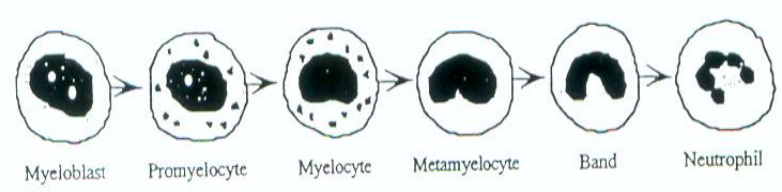
The Krebs cycle!

Enasidenib (AG-221)



Wouters, B. *Blood* 2017

- Phase I/II study; Relapsed/refractory AML
- N= 176, ≥18yo (Median 67yo (19-100yo); 43% normal karyotype
  - 53% with ≥2 prior therapies
- 100mg PO daily (reduces 2-HG by >90% in serum) as monotherapy
  - 2-HG levels are not predictive of response, however
- ORR 40.3%, median response duration 5.8 months
  - ~50% achieved CR (Median OS 19m after CR)
- Efficacy is via differentiation of myeloblasts – not cytotoxicity



Adverse Event (Gd 3/4)	N pts	% pts
Hyperbilirubinemia	13	8
IDH differentiation syndrome	11	7
Anemia	10	7
Thrombocytopenia	8	5
TLS	5	3
Anorexia	3	2
Leukocytosis	2	1
Fatigue	2	1

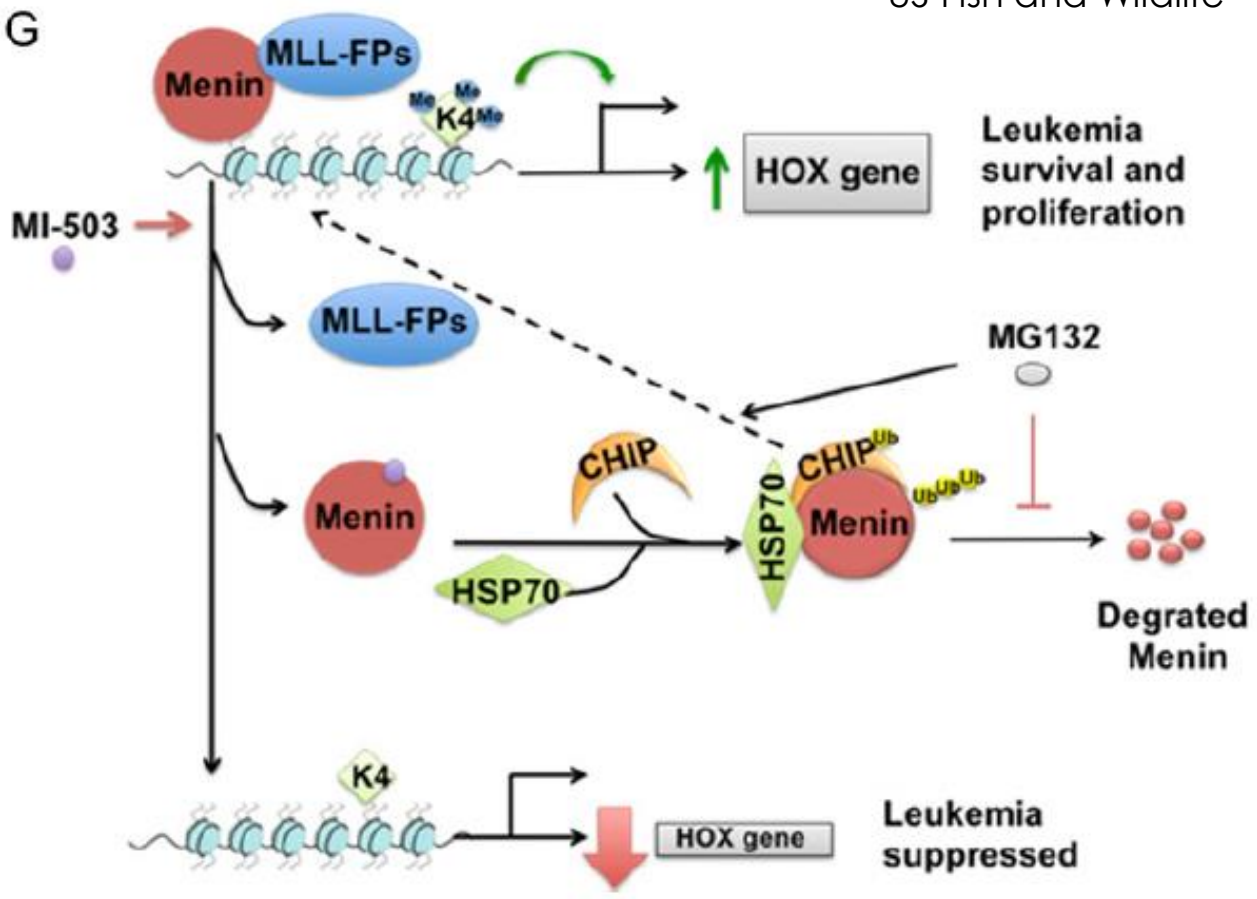
Ivosidenib (AG-120) is an IDH1 mutant inhibitor

Stein, EM et al. *Blood* 2017. Epub

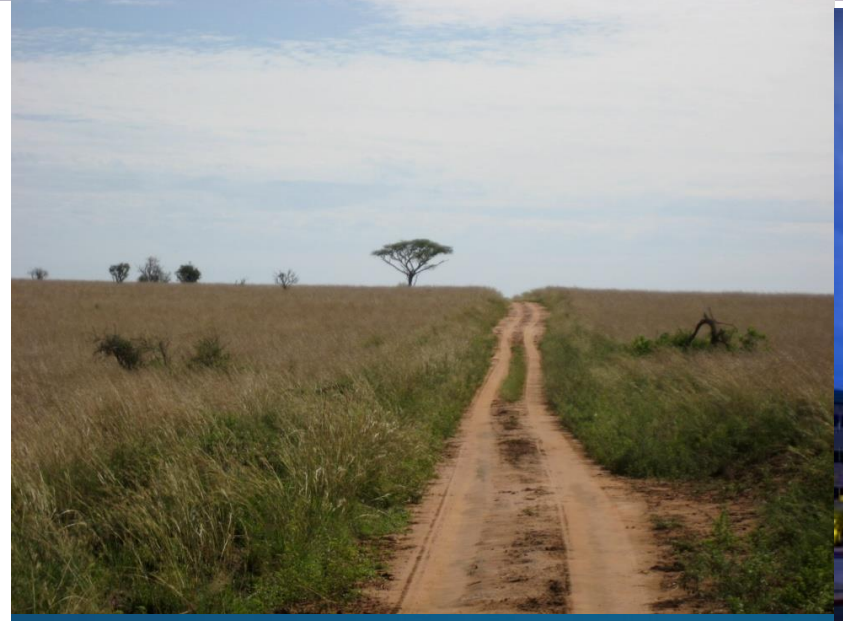
HOX-boxing leukemia cells, by Menin

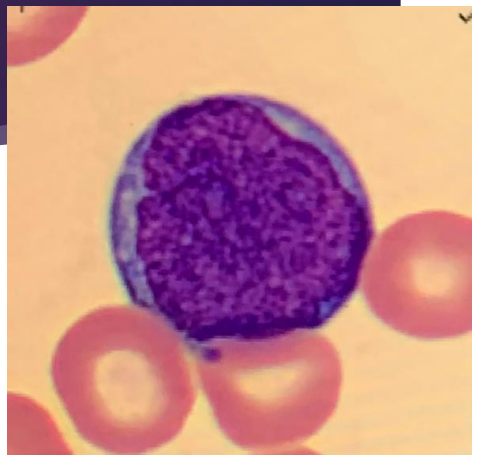
US Fish and Wildlife

- MLL translocations lead to fusions (MLL-FP) with >10 partner genes leading to chemoresistant features.
- The chimeric proteins form complexes that upregulate HOX and MEIS1 genes (that are leukemogenic)
- Menin is a key member of the complex and localizes it to the chromatin.
- NPM1 mutations lead to dysregulation of the interaction between wtMLL and menin.
- At BMDACC menin inhibitor trial open and enrolling
  - Differentiation syndrome seen



Wu Y et al. Disruption of the menin-MLL interaction triggers menin protein degradation via ubiquitin-proteasome pathway. Am J Cancer Res 2019. 9(8):1682-1694





Questions?

Matthew.Ulrickson@bannerhealth.com
@MattUlricksonMD