

Philadelphia kromoszóma negatív MPN, Philadelphia pozitív MPN- CML, CLL

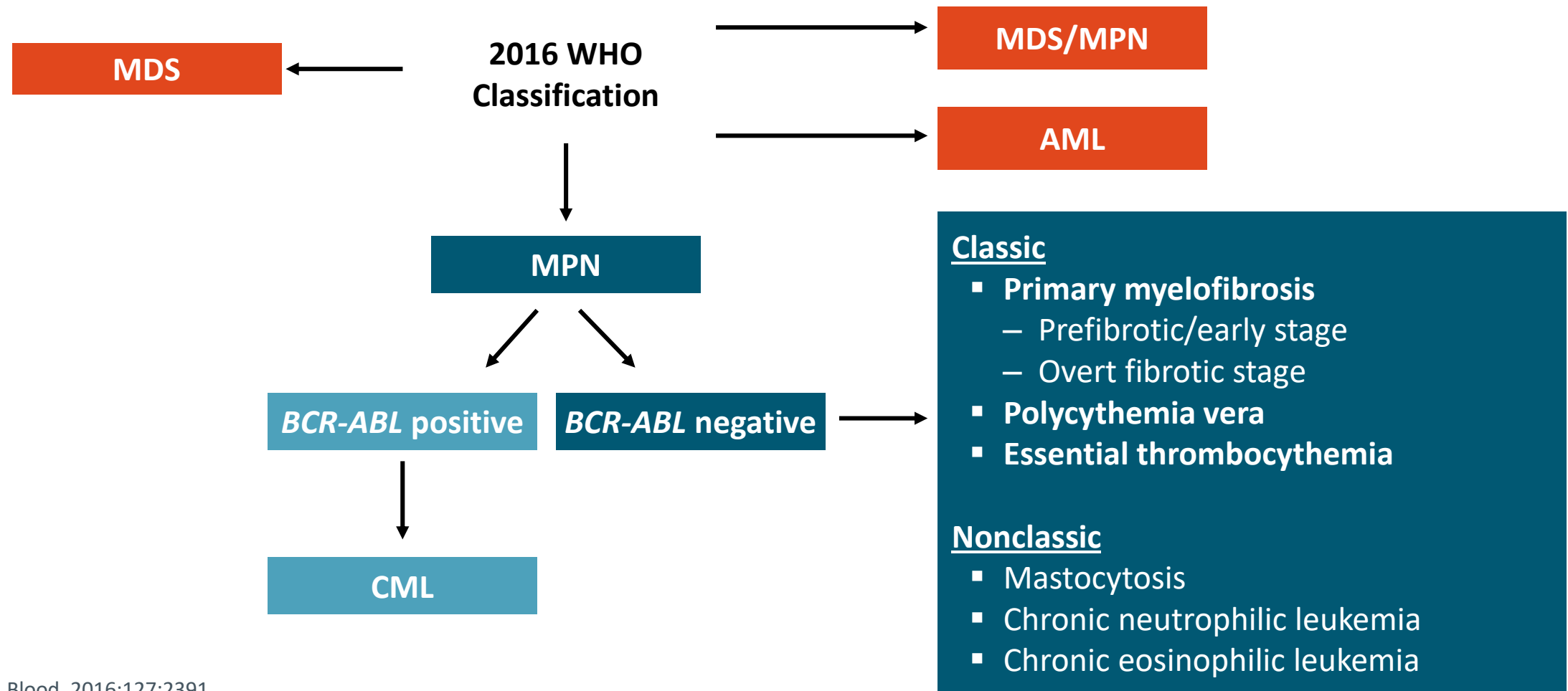
Belgyógyászati Szakvizsga Előkészítő Tanfolyam

2021.05.17-Június 11.

Pécs

On-line tanfolyam

Myeloid Malignancies



The WHO classification of myeloproliferative neoplasms (MPNs)

- -Chronic myeloid leukemia (BCR/ABL1+)
- -Chronic neutrophilic leukemia
- -Chronic eosinophilic leukemia, otherwise specified (NOS)
- -Essential thrombocythemia
- -Primary myelofibrosis (PMF)
 - PMF, prefibrotic early stage
 - PMF, overt fibrotic stage
- -Polycythemia vera
- -Myeloproliferative neoplasm, unclassifiable (MPN-u)

Közös jellemzőik

- Klonális megbetegedések
- Egy-egy sejtvonal proliferációja dominál
- A sejtek kiérnek (nincs dysplasia)
- Hepato-splenomegalia
- A kórlefolyás során transformálódhatnak acut leukemiába

MPN általános jellemzői

A haemopoieticus őssejt klonális, proliferatív daganata

Egy vagy több csontvelői sejtvonal proliferál

granulopoietikus

erythropoietikus

megakaryopoietikus

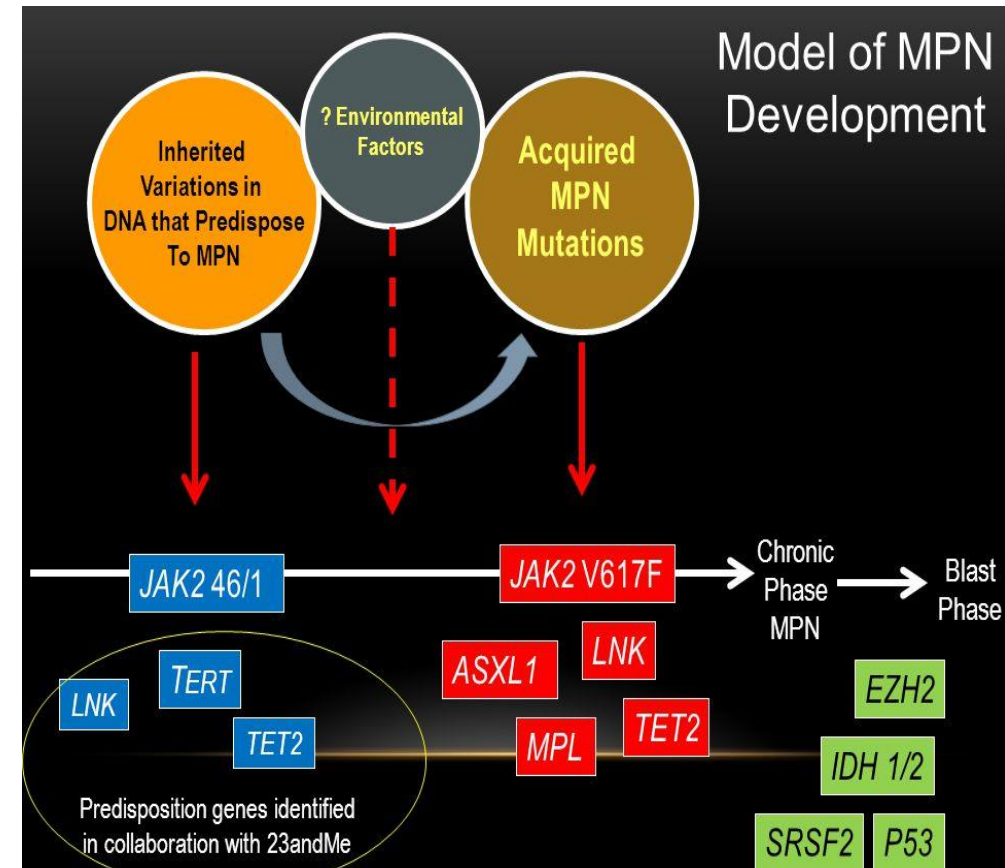
Végeredmény: a periférián érett, differenciált sejtek száma megnő

MPN további közös jellemzők

- rendszerint lassú progresszió, többéves kórlefolyás
 - a csontvelői blastok száma normális vagy csak kissé emelkedett, mindig $<20\%$
 - átmehet myelofibrosisba és/vagy akut myeloid leukaemiába
 - extramedullaris vérképzés és hepatosplenomegalia gyakori
 - jellegzetes genetikai eltérések
 - a JAK/STAT jelátvivő útvonal aktivált
-

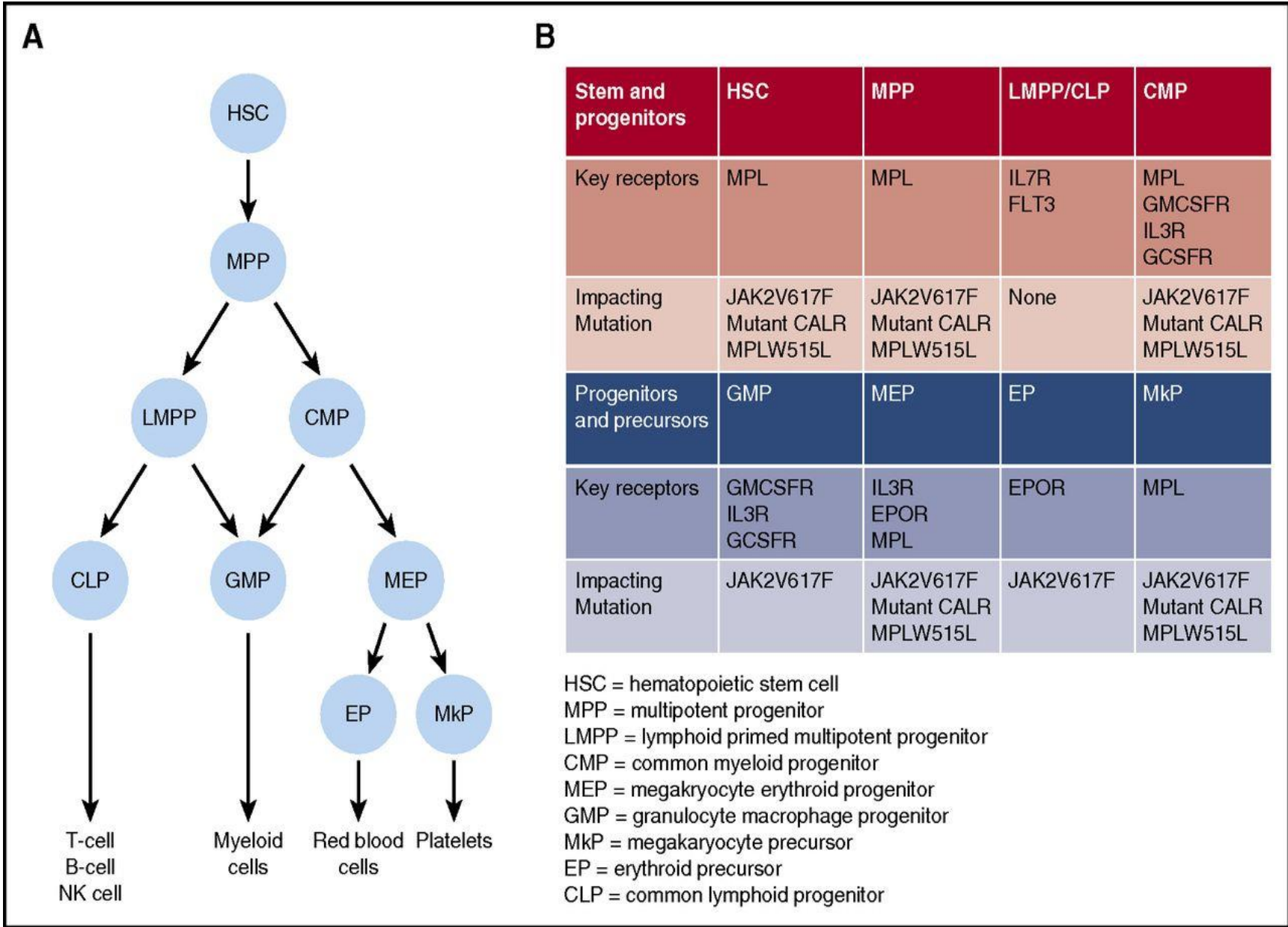
Jellemző molekuláris eltérések

- Polycythemia Vera (JAK2 V617F 95%)
- Chronicus Myeloid leukemia (Ph' chromosoma, *BCR-ABL* génátrendeződés)
- Essentialis Thrombocythemia (JAK2 V617F 50%, Calreticulin-9)
- Myelofibrosis (JAK2 V617F 50%)

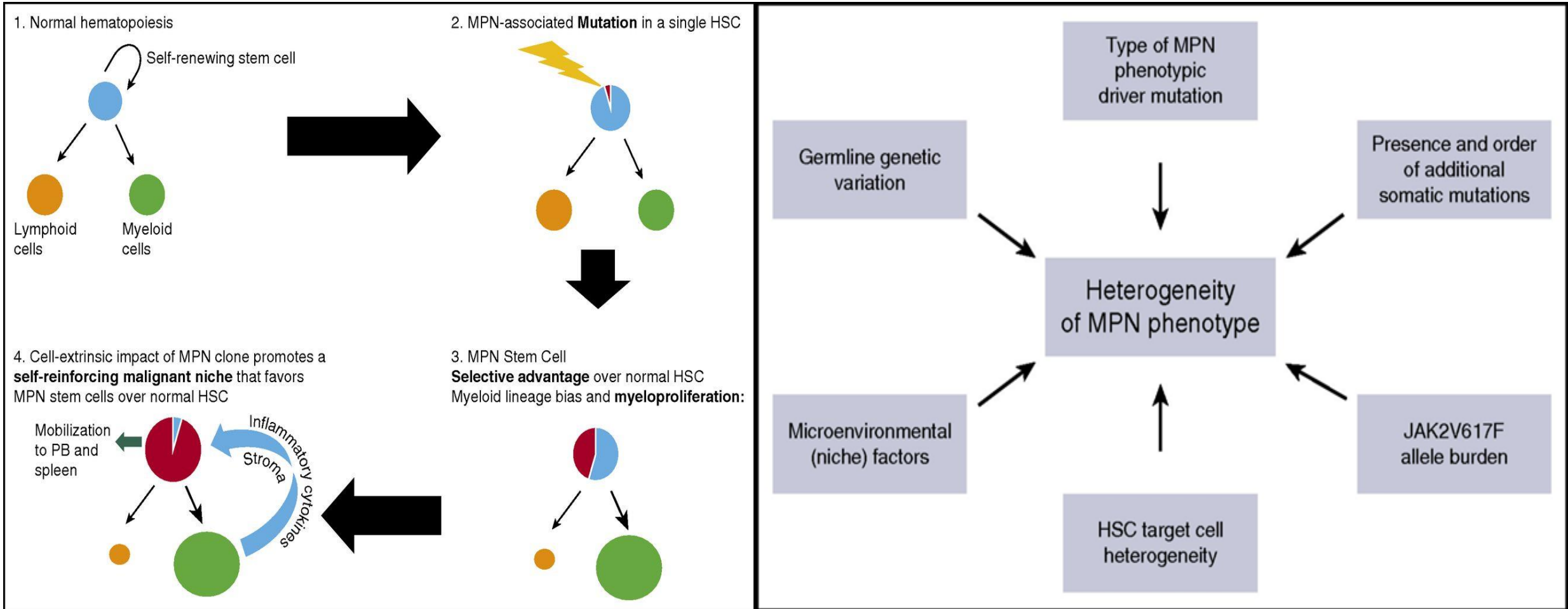


Stem Cells & Hematopoietic Differentiation

- Hematopoietic stem cells capable of **Self-renewal**
- Differentiation**
- Differentiation & proliferation controlled by molecular signals
- Contact with stromal cells in BM
- Growth factors



Myeloproliferative neoplasm stem cells



Mutations in epigenetic regulators and spliceosome genes

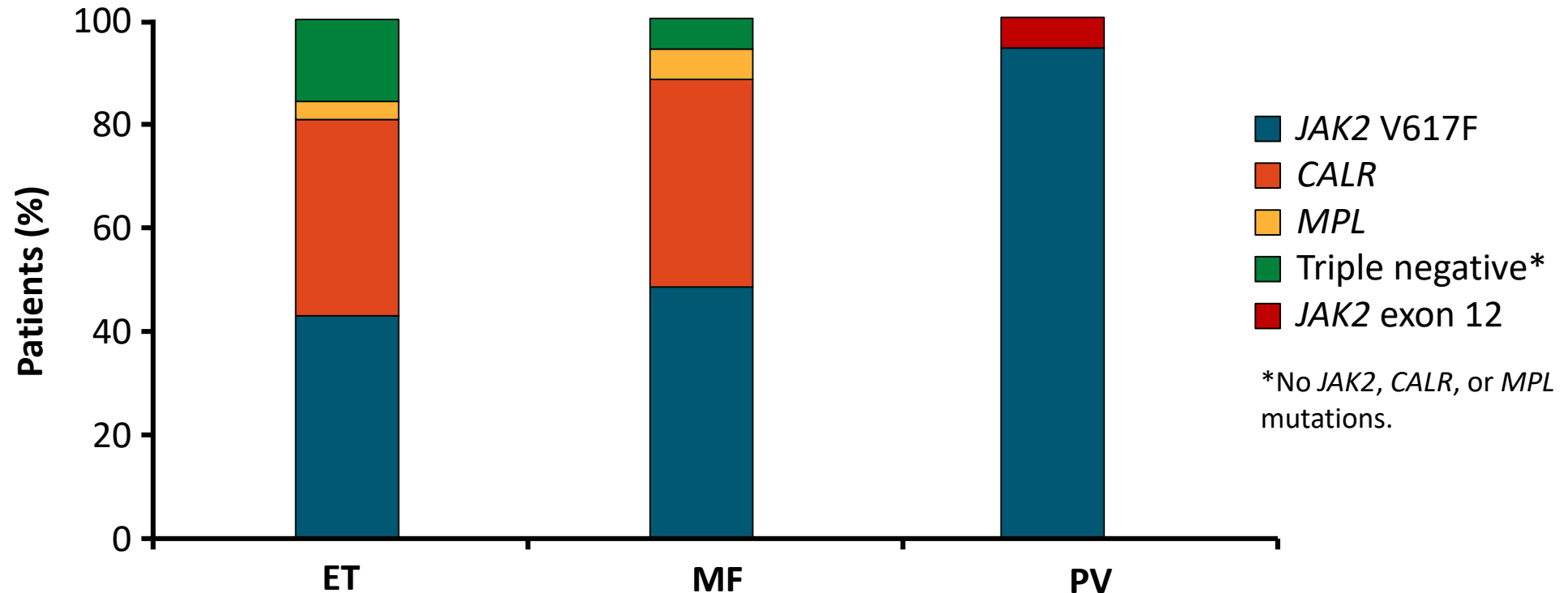
Gene	Chromosome location	PV (%)	ET (%)	M F (%)	Blast phase (%)
<i>TET2</i>	4q24	10-16	4-5	7-17	17-32
<i>IDH1/2</i>	2q33.3 / 15q26.1	2	1	4	9-22
<i>DNMT3A</i>	2p23	3-7	<1	2-15	14-17
<i>EZH2</i>	7q36.1	3	<1	7-13	---
<i>ASXL1</i>	20q11.1	2-7	0-3	13-32	18-33
<i>SRSF2</i>	17q25.1	---	---	≈15%	≈20%
<i>SF3B1</i>	2q33.1	---	---	7%	---
<i>CBL</i>	11q23.3	rare	rare	6%	---
<i>TP53</i>	17p13.1	---	---	4%	27%
<i>U2AF1</i>	21q22.3	---	---	16%	---

- Therefore, they are of no specific diagnostic value but indicate a myeloid malignancy

Vainchenker W et al, Blood. 2011; 18;118(7):1723-35; Vannucchi AM et al, Leukemia 2013; 27:1861-9.

Phenotype Driver Mutations Activating the JAK-STAT Pathway in MPNs

Driver Mutation Spectrum by Condition



- A very small percentage of PV patients may have *LNK* or *CALR* driver mutations
- Nondriver mutations mostly frequently occurring in MPNs: *TET2*, *ASXL1*, *DNMT3A*

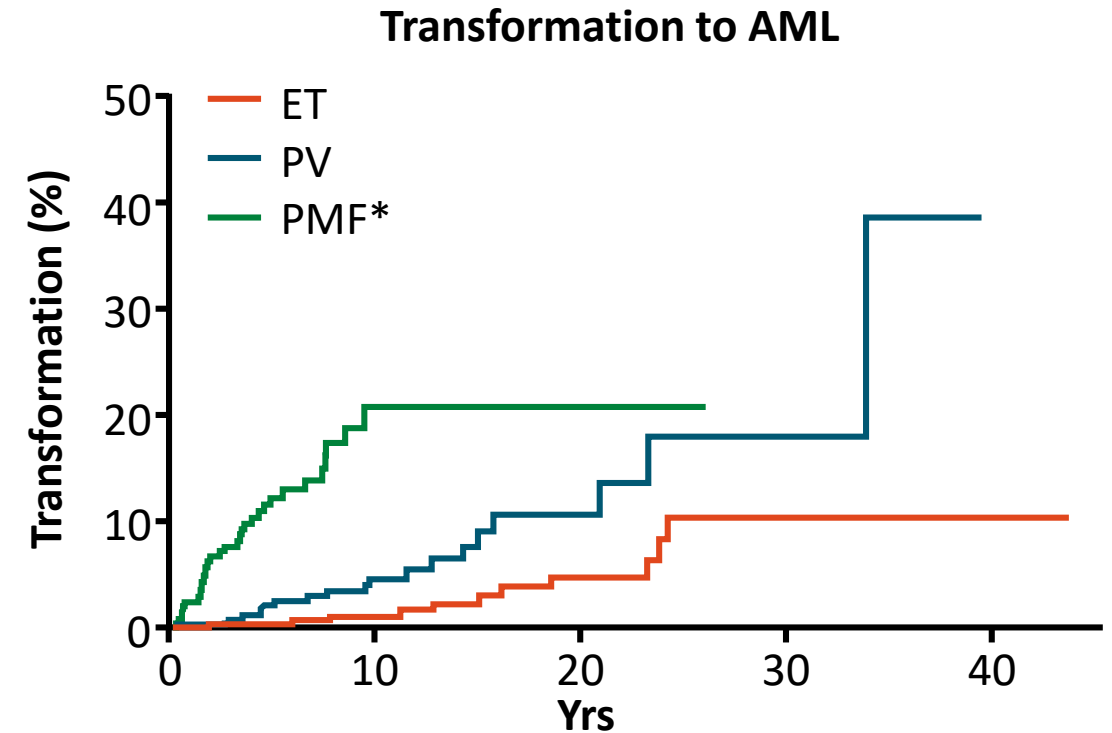
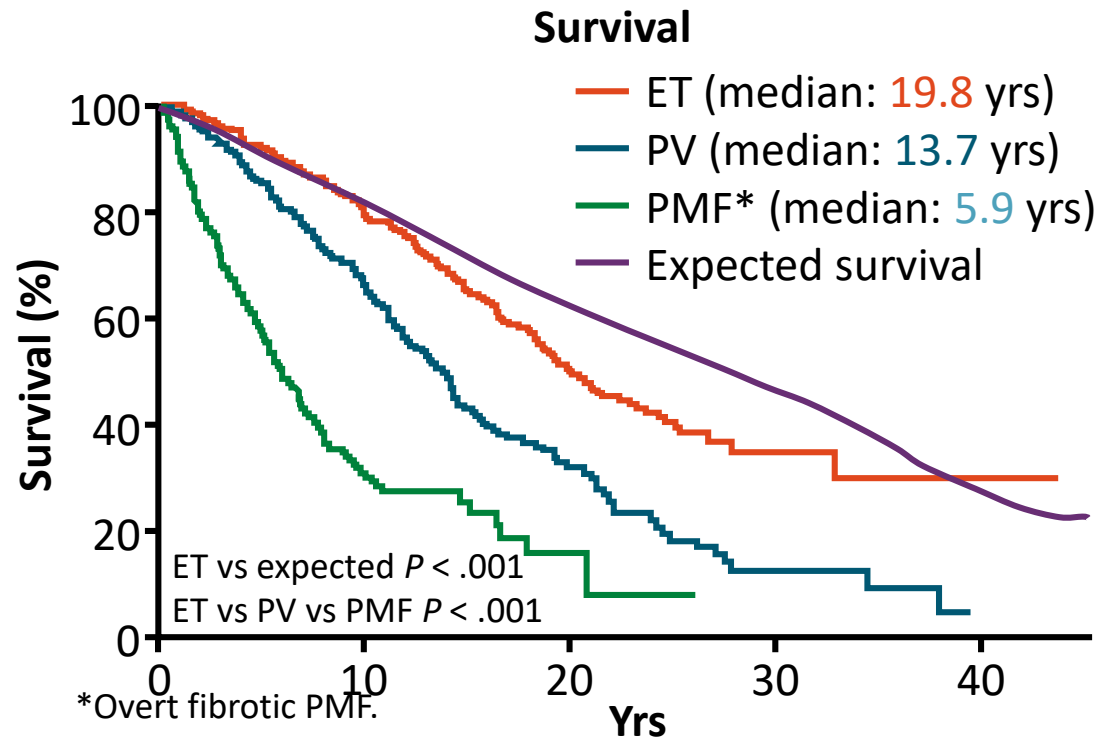
Grinfeld. Haematologica. 2017;102:7.



Slide credit: clinicaloptions.com

Survival and Disease Progression With PV, MF, and ET

- Although similarities exist in the molecular signature and presentation of PV, MF, and ET, important to distinguish among these conditions as prognosis and management can differ
- Assessment of survival and progression in patients with PV, MF, or ET at Mayo Clinic (N = 826)



WHO Diagnostic Criteria: MF

Primary MF Diagnosis

Requirement for diagnosis

- All 3 major criteria AND ≥ 1 minor criteria

Major criteria

1. Megakaryocytic proliferation and atypia, **without reticulin fibrosis > grade 1 (prefibrotic PMF)** or **with reticulin and/or collagen fibrosis grade 2/3 (overt fibrotic PMF)**
2. *JAK2*, *CALR*, or *MPL* mutation, presence of other clonal markers* OR absence of reactive MF
3. Not meeting WHO criteria for other myeloid malignancies

Minor criteria

- | | |
|--|--|
| 1. Anemia not attributed to a comorbid condition | 3. Palpable splenomegaly |
| 2. Leukocytosis $\geq 11 \times 10^9/L$ | 4. LDH increased above ULN |
| | 5. Leukoerythroblastosis (overt fibrotic PMF) |

*eg, *ASXL1*, *EZH2*, *TET2*, *IDH1/IDH2*, *SRSF2*, *SF3B1*.

Arber. Blood. 2016;127:2391.



Slide credit: clinicaloptions.com

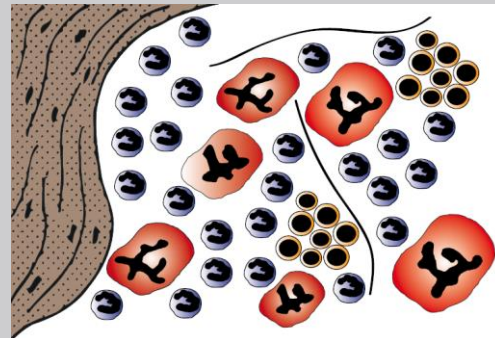
WHO Diagnostic Criteria: Prefibrotic PMF vs ET





ET Diagnosis
Requirement for diagnosis
<ul style="list-style-type: none"> All 4 major criteria OR first 3 major criteria and the minor criterion
Major criteria
<ol style="list-style-type: none"> Platelet count $\geq 450 \times 10^9/L$ Proliferation mainly of megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei; no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers Not meeting WHO criteria for other myeloid neoplasms Presence of <i>JAK2</i>, <i>CALR</i>, or <i>MPL</i> mutation
Minor criteria
<ol style="list-style-type: none"> Presence of a clonal marker or absence of evidence for reactive thrombocytosis

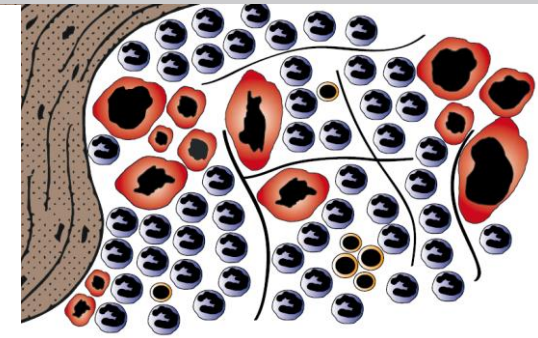
Prefibrotic PMF Diagnosis	
Requirement for diagnosis	
▪ All 3 major criteria AND ≥ 1 minor criteria	
Major criteria	
1.	Megakaryocytic proliferation and atypia, without reticulin fibrosis grade > 1, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis
2.	Not meeting WHO criteria for other myeloid neoplasms
3.	Presence of <i>JAK2</i> , <i>CALR</i> , or <i>MPL</i> mutation or, in the absence of these mutations, presence of another clonal marker*, or absence of minor reactive BM reticulin fibrosis [†]
Minor criteria [‡]	
1.	Anemia not attributed to a comorbid condition
2.	Leukocytosis ≥ 11 x 10 ⁹ /L
3.	Palpable splenomegaly
4.	LDH > ULN

ET vs Prefibrotic PMF: Morphologic Characteristics

Characteristic	ET	Prefibrotic PMF
Age-matched cellularity	<ul style="list-style-type: none"> No or slight increase 	<ul style="list-style-type: none"> Marked increase
Granulopoiesis/erythropoiesis	<ul style="list-style-type: none"> No significant increase 	<ul style="list-style-type: none"> Pronounced proliferation of granulopoiesis, reduction of erythroid precursors
Histology	<ul style="list-style-type: none"> Large/giant mature megakaryocytes <ul style="list-style-type: none"> Hyperlobulated or deeply folded nuclei Dispersed or loosely clustered in the marrow space 	<ul style="list-style-type: none"> Medium to giant megakaryocytes <ul style="list-style-type: none"> Hypolobulated, hyperchromatic, bulbous, or irregularly folded nuclei with aberrant nuclear/cytoplasmic ratio Dense or loose clustering and frequent endosteal translocation
Increase in reticulin fibers	<ul style="list-style-type: none"> None or minor 	<ul style="list-style-type: none"> None or not significant



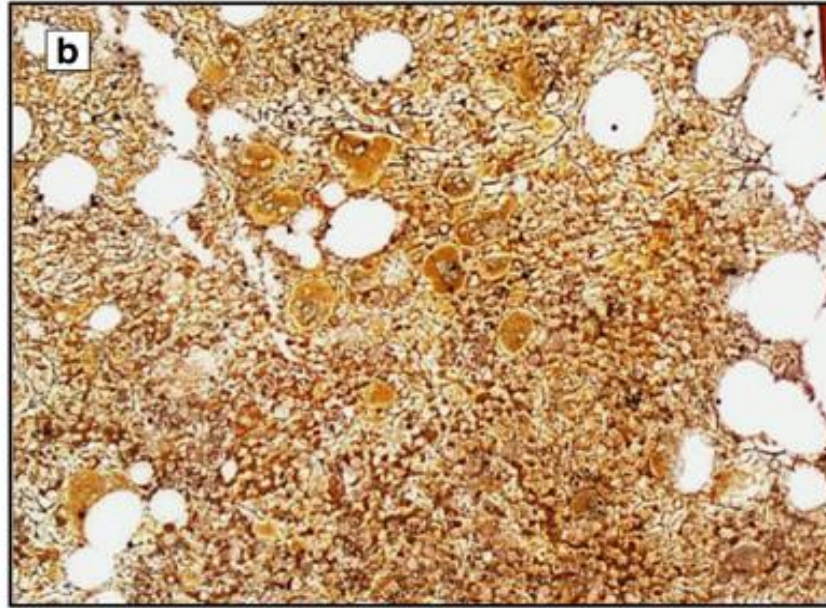
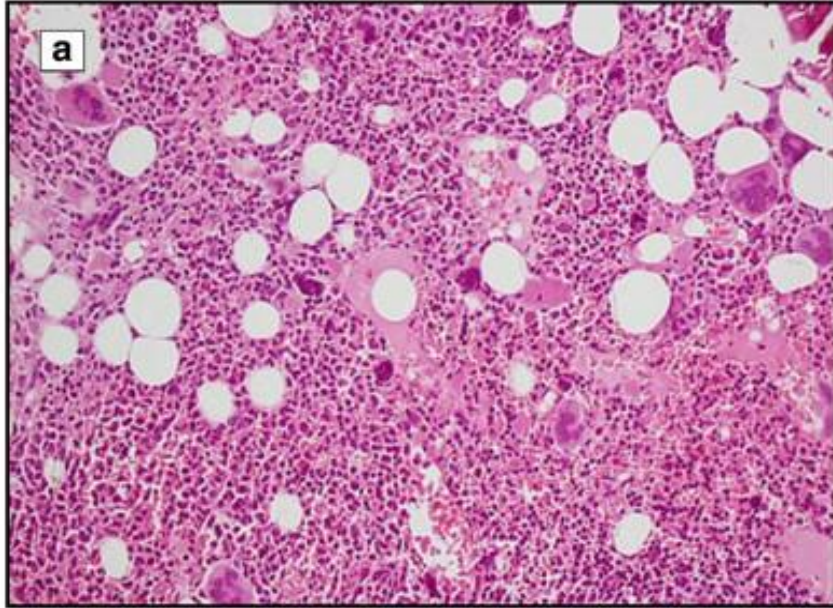
-  Megakaryopoiesis
-  Granulopoiesis
-  Erythropoiesis
-  Reticulin fibers



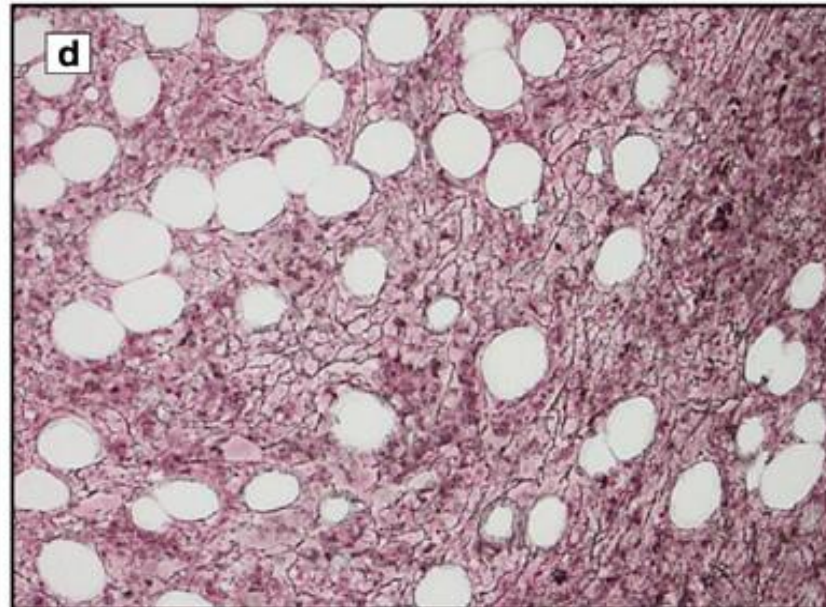
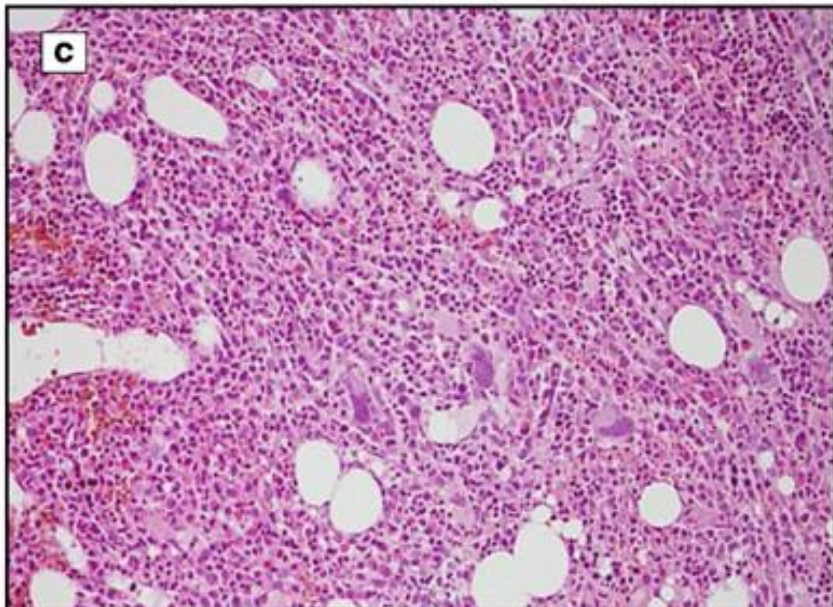
Semiquantitative Grading of MF

Hematoxylin-Eosin

Gomori

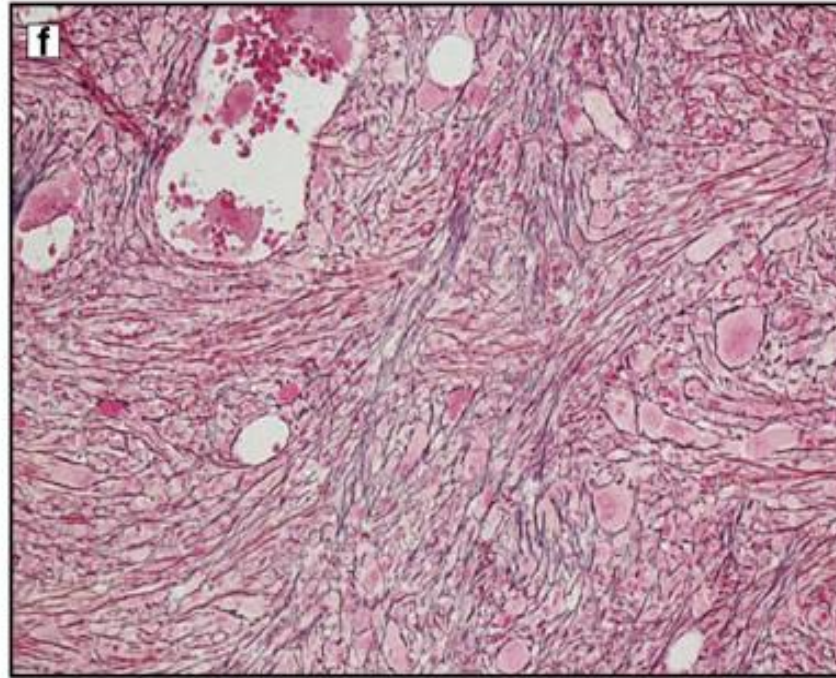
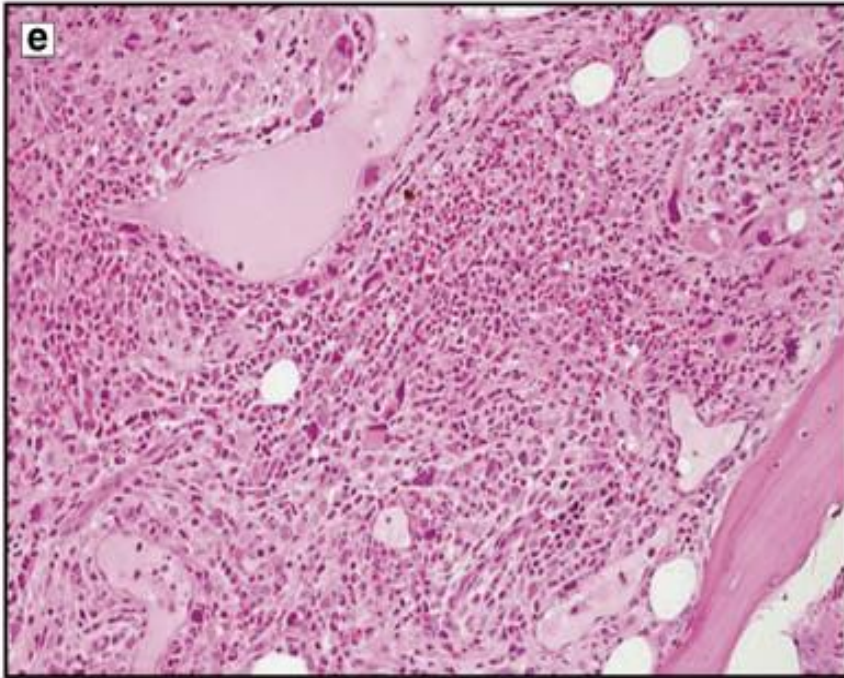


MF-0: Scattered linear reticulin with no intersections (cross-overs) corresponding to normal BM



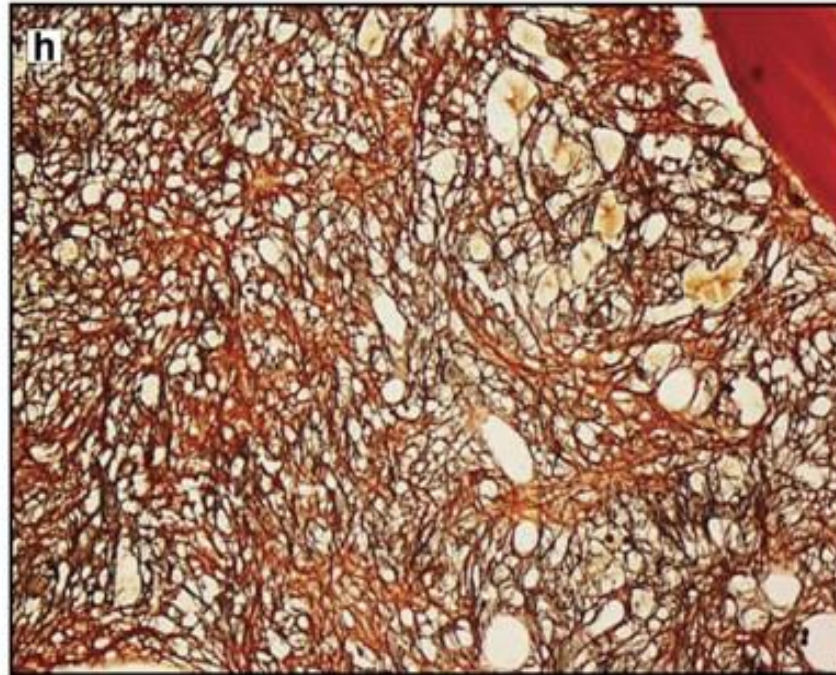
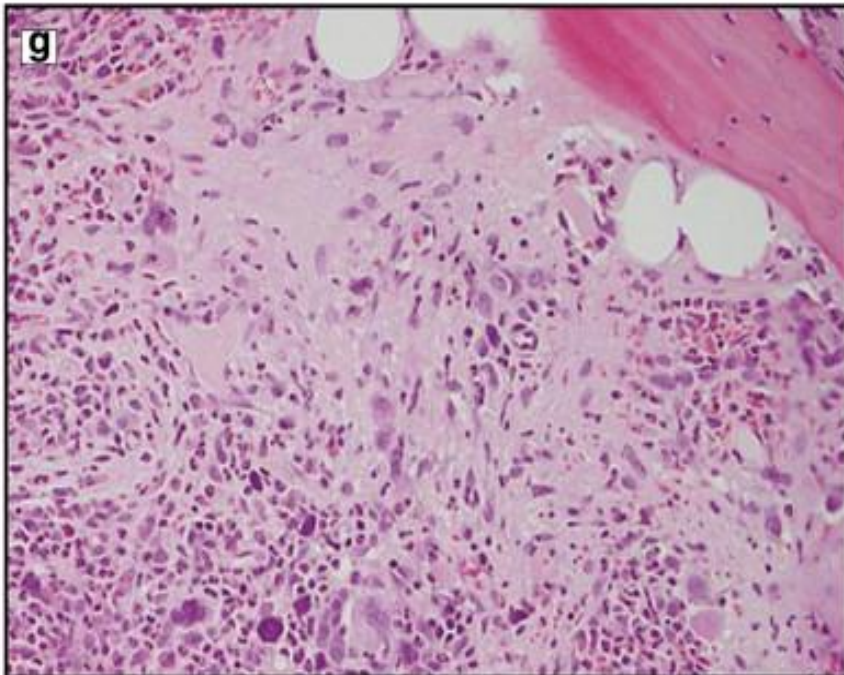
MF-1: Loose network of reticulin with many intersections, especially in perivascular areas

MF-2



MF-2: Diffuse and dense ↑ in reticulin with extensive intersections, occasionally with focal bundles of collagen and/or focal osteosclerosis.

MF-3



MF-3: Diffuse and dense ↑ in reticulin with extensive intersections and coarse bundles of collagen, often with osteosclerosis

Clinicohematologic-Based Prognostic Models of MF

Comparison of IPSS, DIPSS, and DIPSS-Plus^[1]

Parameter	IPSS	DIPSS	DIPSS-Plus
Age > 65 yrs	Yes (1 point)	Yes (1 point)	Yes*
Hb < 10 g/dL	Yes (1 point)	Yes (2 points)	Yes*
WBC > 25 x 10 ⁹ /L	Yes (1 point)	Yes (1 point)	Yes*
PB blasts ≥ 1%	Yes (1 point)	Yes (1 point)	Yes*
Constitutional symptoms	Yes (1 point)	Yes (1 point)	Yes*
Unfavorable karyotype	NA	NA	Yes (1 point)
RBC transfusion dependence	NA	NA	Yes (1 point)
Platelets < 100 x 10 ⁹ /L	NA	NA	Yes (1 point)
Can be used at any time point	No (only at diagnosis)	Yes	Yes

*0-3 points for each based on DIPSS risk categories; features not individually weighted.

Survival by Risk Group and Prognostic Model

Risk Group ▪ Points	Median OS, Yrs		
	IPSS ^[2]	DIPSS ^[3]	DIPSS-Plus ^[4]
Low ▪ 0	11.3	NR	15.0
Intermediate 1 ▪ IPSS/DIPSS-Plus: 1 ▪ DIPSS: 1-2	7.9	14.2	6.6
Intermediate 2 ▪ IPSS: 2 ▪ DIPSS: 3-4 ▪ DIPSS-Plus: 2-3	4.0	4.0	2.9
High ▪ IPSS: ≥ 3 ▪ DIPSS: ≥ 5 ▪ DIPSS-Plus: ≥ 4	2.3	1.5	1.3

1. Bose. Cancer. 2016;122:681. 2. Cervantes. Blood. 2009;113:2895. 3. Passamonti. Blood. 2010;115:1703. 4. Gangat. JCO. 2011;29:392.



Slide credit: clinicaloptions.com

Prognostic Impact of Driver and High Molecular Risk Nondriver Mutations in Primary MF

- Analysis of association between **driver mutations** and survival in patients with primary MF (N = 617)^[1]

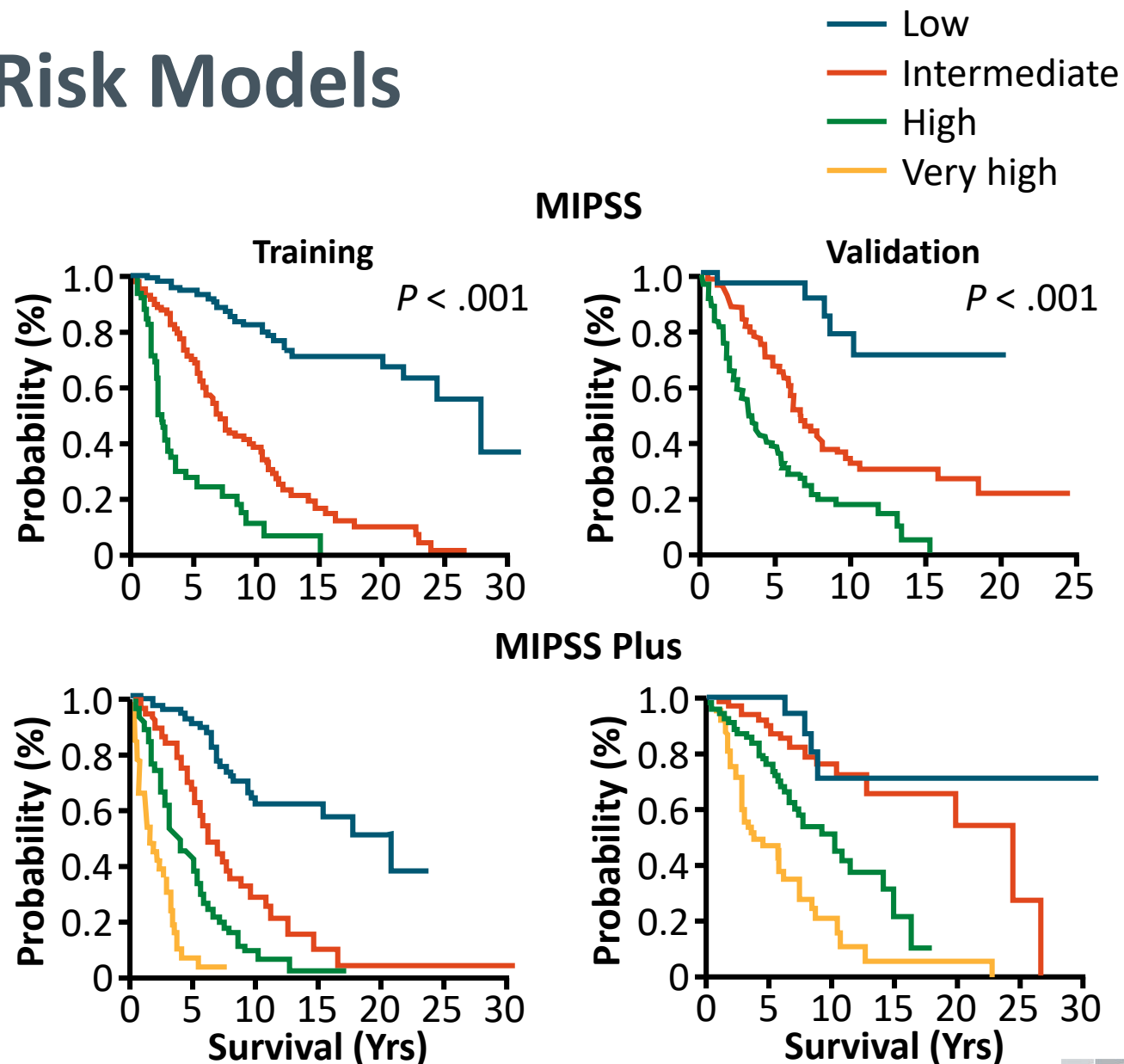
Driver Mutation	Patients, %	Median OS, Yrs
<i>CALR</i> mutated	22.7	17.7
<i>JAK2</i> mutated	64.7	9.2
<i>MPL</i> mutated	4.0	9.1
Triple negative	8.6	3.2

- Analysis of association between set of **nondriver mutations** (*IDH*, *EZH2*, *ASXL1*, *SRSF2*) and survival in patients with primary MF (N = 797)^[2]
 - Presence of mutations predicted decreased survival; ≥ 2 mutations predicted worst survival

MIPSS70/MIPSS70-Plus Risk Models

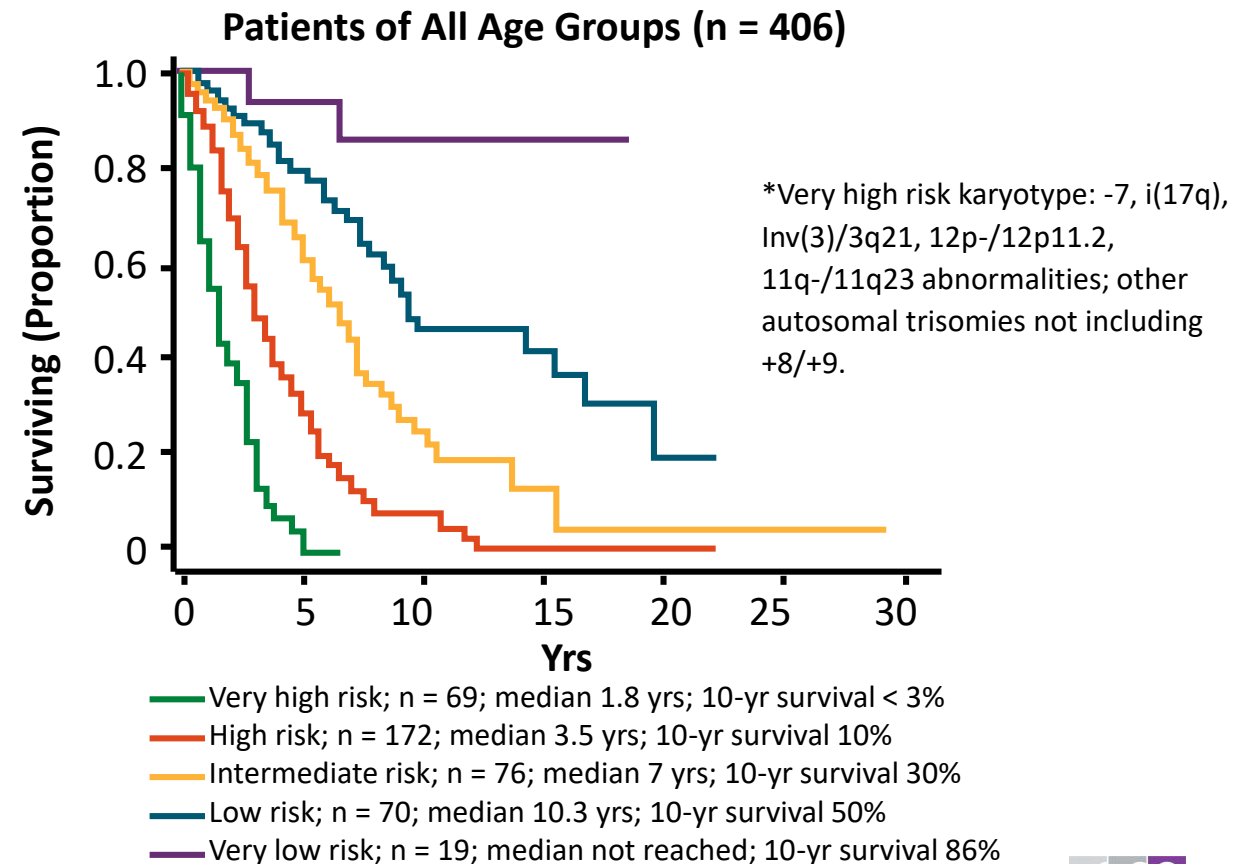
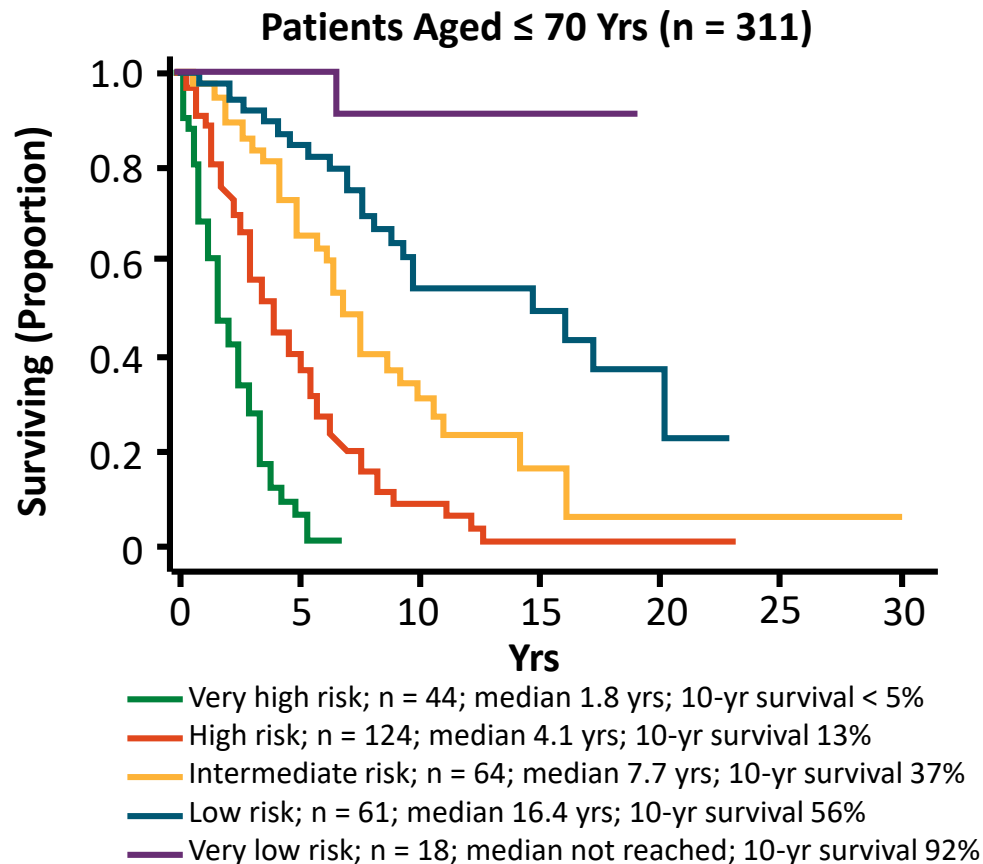
Variables	Rank
Hb < 100 g/L	1
WBC > 25 x 10 ⁹ /L	2
Platelets < 100 x 10 ⁹ /L	2
PB blasts ≥ 2%	1
Constitutional symptoms	1
Grade ≥ 2 BM fibrosis	1
Absence <i>CALR</i> type 1	1
HMR category*	1
≥ 2 HMR mutations	2

*HMR category, any mutation in *ASXL1*, *EZH2*, *SRSF2*, *IDH1/2*.

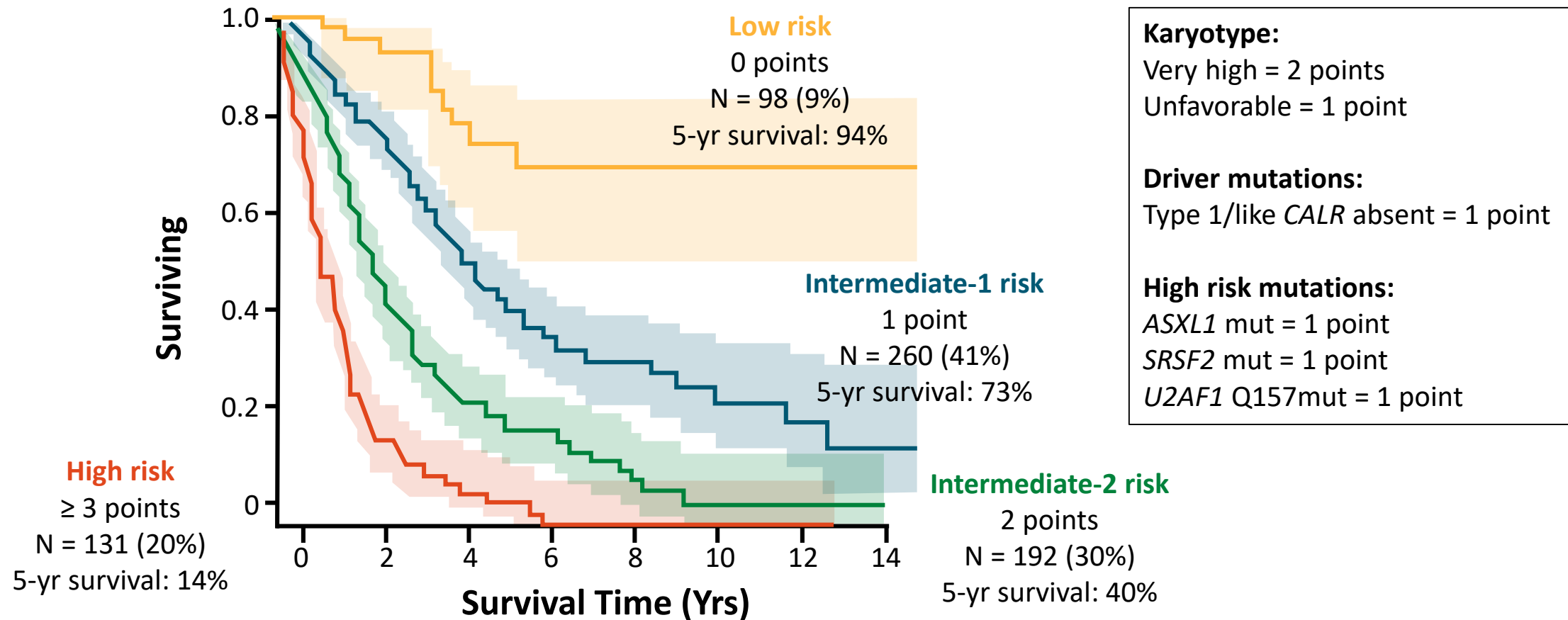


MIPSS70-Plus v2.0 Risk Model

- Also incorporates very high-risk karyotype,* U2AF1 Q157 mutation status, sex- and severity-adjusted Hb thresholds (vs MIPSS70-Plus) and defines 5 prognostic categories, from very low to very high risk



Genetically Inspired Prognostic Scoring System (GIPSS) for PMF



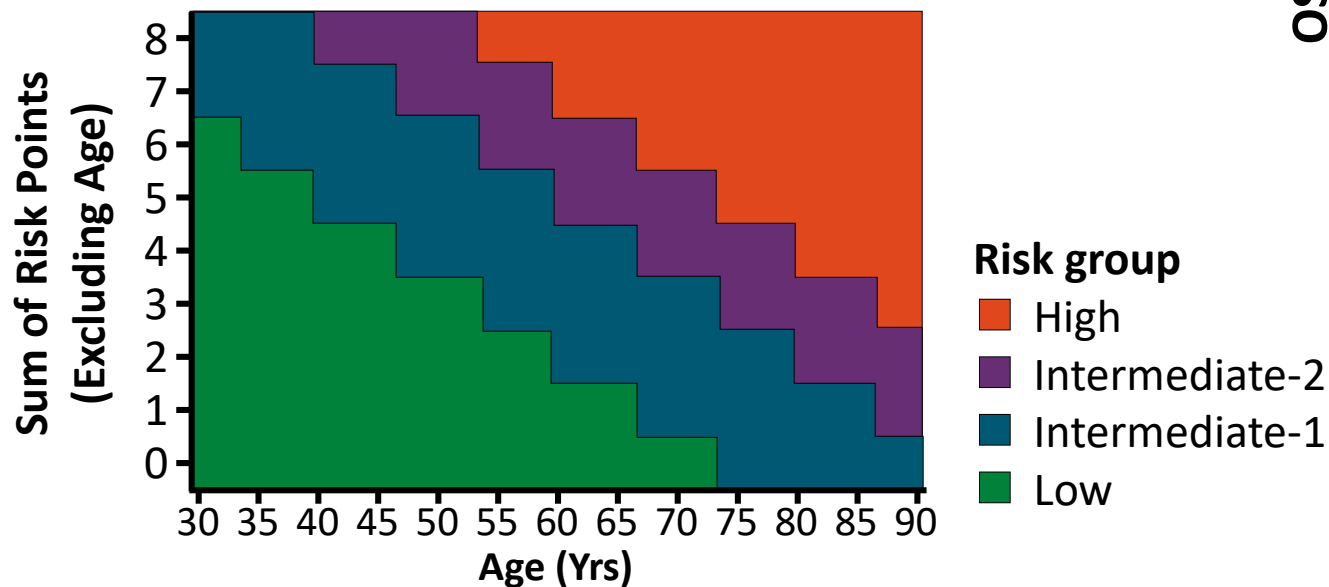
Tefferi. Leukemia. 2018;32:1631.



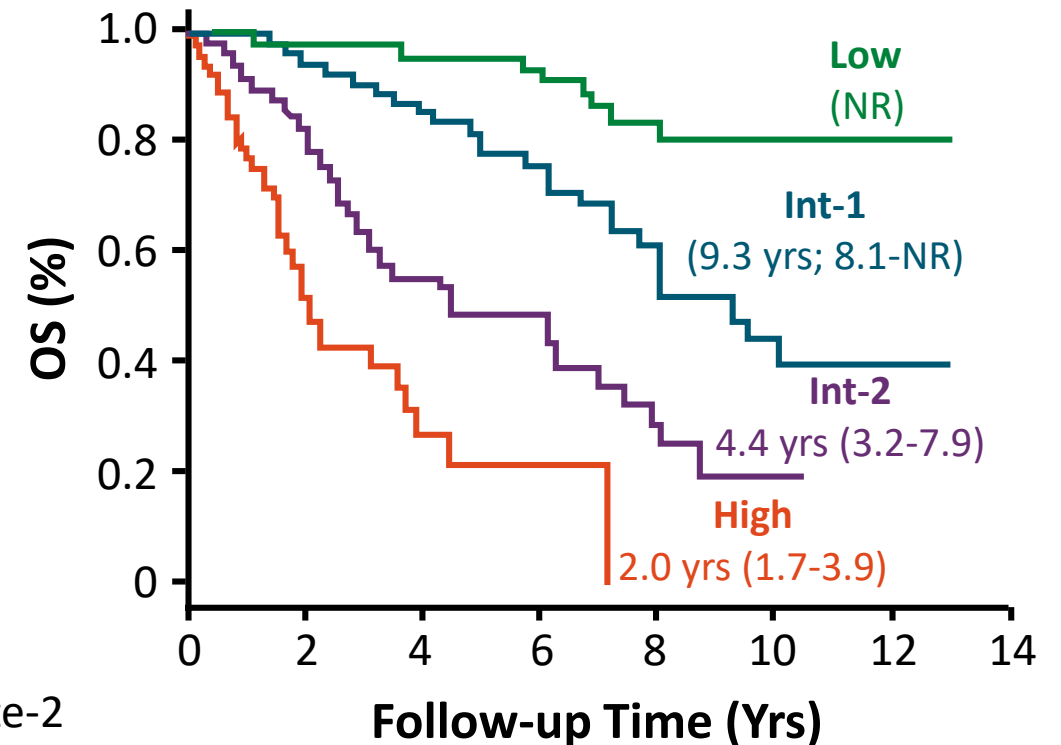
Slide credit: clinicaloptions.com

MYSEC-PM: Clinical-Molecular Prognostic Model for PET-MF and PPV-MF

Covariate	Points
Hb < 11 g/dL	2
Platelets < 150 x 10 ⁹ /L	1
PB blasts ≥ 3%	2
<i>CALR</i> wt	2
Const. symptoms	1



Passamonti. Leukemia. 2017;31:2726. <http://www.mysec-pm.eu>.



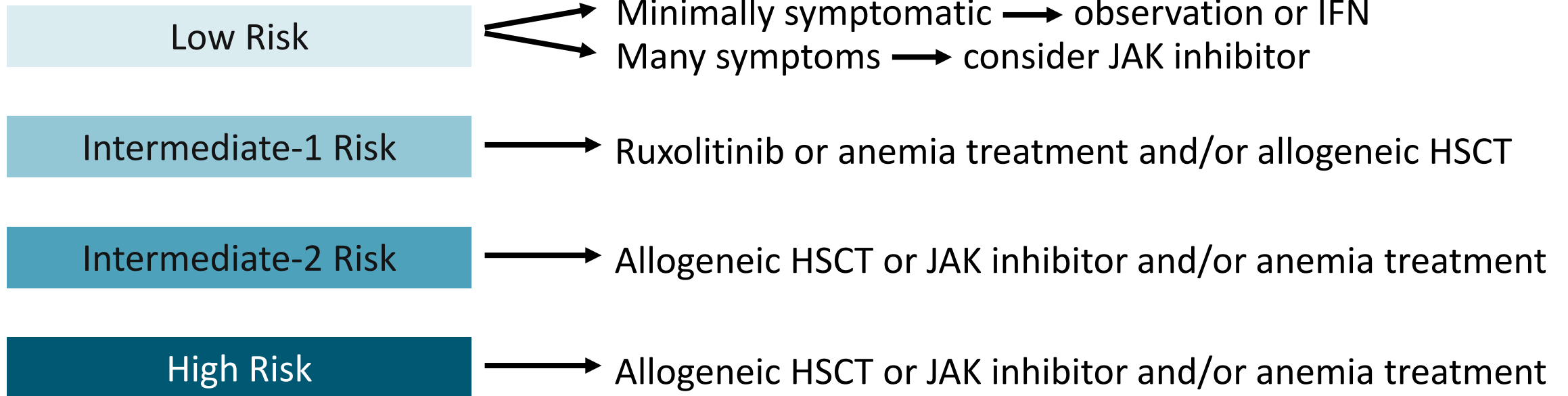
Slide credit: clinicaloptions.com

Ever-growing prognostic scores for MF - what should I use?

- Lille score
- International Prognostic Scoring system (IPSS)
- Dynamic IPSS (DIPSS)
- DIPSS plus
- MIPSS
- MIPSS70, MIPSS70-plus
- GIPSS



MF Treatment: Based on Risk and MF-Related Symptoms/Signs

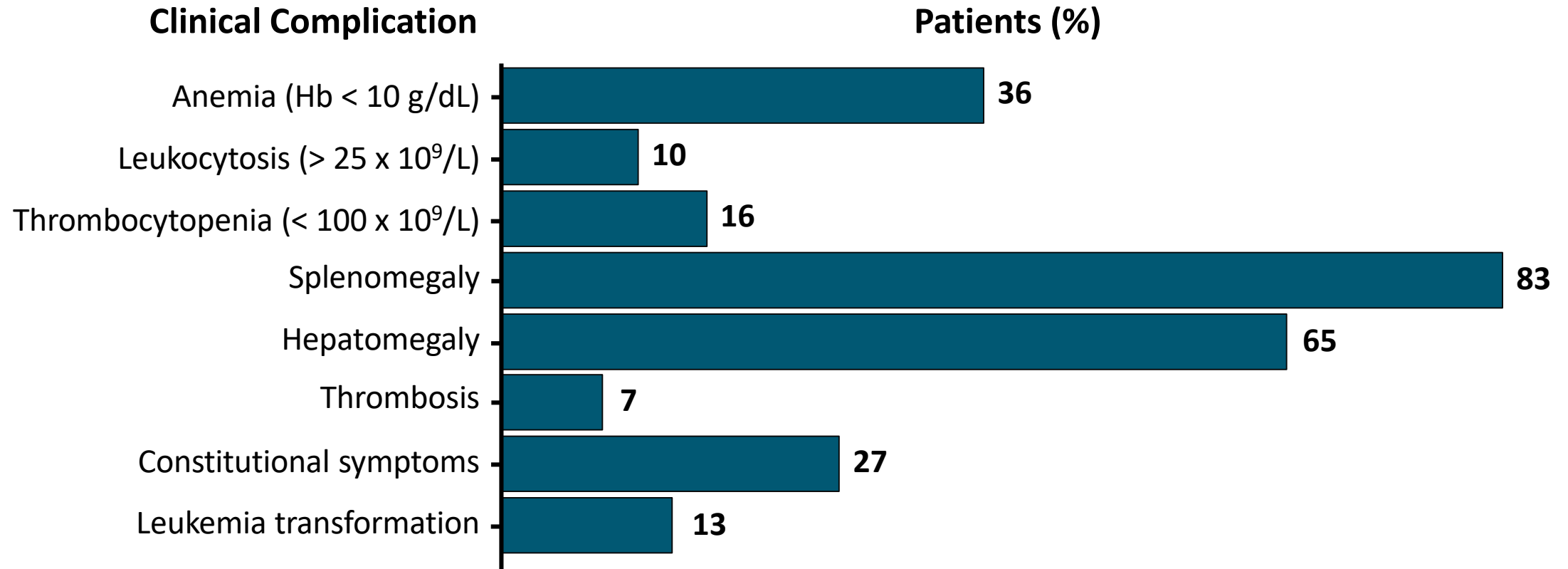


Mesa. Leuk Lymphoma. 2013;54:242. Geyer. Hematology Am Soc Hematol Educ Program. 2014;2014:277.



Slide credit: clinicaloptions.com

Main Clinical Complications in MF



- Common symptoms derived from complications: bone pain, pruritus (myeloproliferation), night sweats, weight loss, fever (constitutional), early satiety, abdominal discomfort (splenomegaly), fatigue, insomnia

Passamonti. Blood. 2010;115:1703. Barbui. Blood. 2010;115:778. Passamonti. Blood. 2010;116:2857. Scherber. Blood. 2011;118:401.



Needs-Oriented Therapy for MF

Clinical Issue		Treatments
Anemia	<ul style="list-style-type: none"> ▪ ESAs ▪ Corticosteroids ▪ Danazol 	<ul style="list-style-type: none"> ▪ Thalidomide, lenalidomide (IMiDs)
Symptomatic splenomegaly	<ul style="list-style-type: none"> ▪ Ruxolitinib, fedratinib ▪ Hydroxyurea 	<ul style="list-style-type: none"> ▪ Cladribine, IMiDs ▪ Splenectomy
Constitutional symptoms/QoL	<ul style="list-style-type: none"> ▪ Ruxolitinib, fedratinib ▪ Corticosteroids 	
Extramedullary hematopoiesis	<ul style="list-style-type: none"> ▪ Radiation therapy 	
Hyperproliferative (early) disease	<ul style="list-style-type: none"> ▪ Interferon 	
Risk of thrombosis	<ul style="list-style-type: none"> ▪ Low-dose aspirin 	
Accelerated/blastic phase	<ul style="list-style-type: none"> ▪ Hypomethylating agents 	
Improved survival	<ul style="list-style-type: none"> ▪ Allogeneic HSCT ▪ Ruxolitinib 	

Allogeneic HSCT for Patients With MF

- **Who:** consider HSCT in **younger patients whose survival is expected to be < 5 yrs** (int-2–risk/high-risk patients < 70 yrs of age but also int-1–risk patients < 65 yrs of age with refractory, transfusion-dependent anemia, circulating blasts >2%, adverse cytogenetics (as defined in the DIPSS+), triple negativity or *ASXL1* mutation^[1])
- **But:** **very few MF patients undergo HSCT**
 - Traditionally **limited to younger patients** < 60 yrs of age and those with HLA-identical sibling match (although now possible up to 75 yrs of age)
 - **High transplant-related mortality and morbidity** associated with transplantation due to acute and chronic GvHD^[1]
 - 1-yr NRM rate: 12% (completely matched donors) to 38% (mismatched)
 - 5-yr survival rate: 56% (matched sibling donors) to 34% (partially matched/ mismatched)

Tips for Using Ruxolitinib to Treat Patients With MF

- Effective regardless of patient's mutational profile (not specific for *JAK2* V617F mutation)
- **Starting dose selected based on platelet count**; anemia is **NOT** contraindication for use, can consider 10 mg BID x 12 weeks before escalating in anemic patients
- Development of anemia **DOES NOT** affect benefits of ruxolitinib
- Avoid abrupt interruption of ruxolitinib in patients responding well to therapy
 - Decision to stop ruxolitinib will depend on benefit and presence/absence of toxicity

Mesa. Int J Hematol. 2016;104:420. Ruxolitinib PI. Porpaczy. Blood. 2018;132:694.
Pemmaraju. Blood. 2019;133:2348. Cervantes. EHA 2019. Abstr PS1465..

Ruxolitinib Dosing Recommendations	
Starting dose	<i>Determined by platelet count:</i>
	▪ > 200 x 10 ⁹ /L: 20 mg BID PO
	▪ 100 to 200 x 10 ⁹ /L: 15 mg BID PO
	▪ 50 to < 100 x 10 ⁹ /L: 5 mg BID PO
Monitoring	Monitor CBC every 2-4 wks until doses stabilized, then as clinically indicated
Dose adjustment	Modify or interrupt dosing for thrombocytopenia

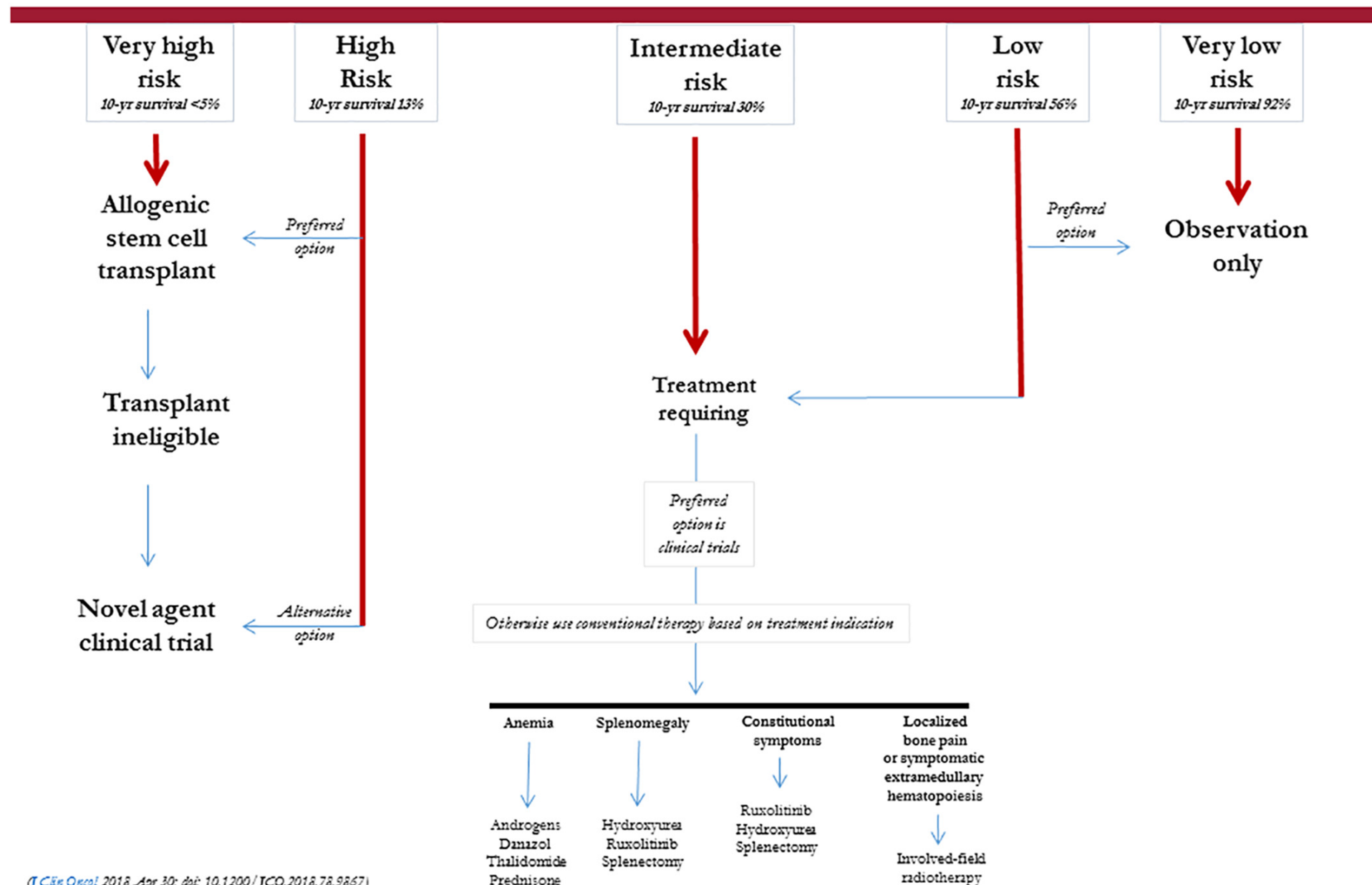
- Dose should be modified to the maximum tolerated when response not adequate, and treatment should be continued for ≥ 6 mos
- NHL risk appears unsubstantiated

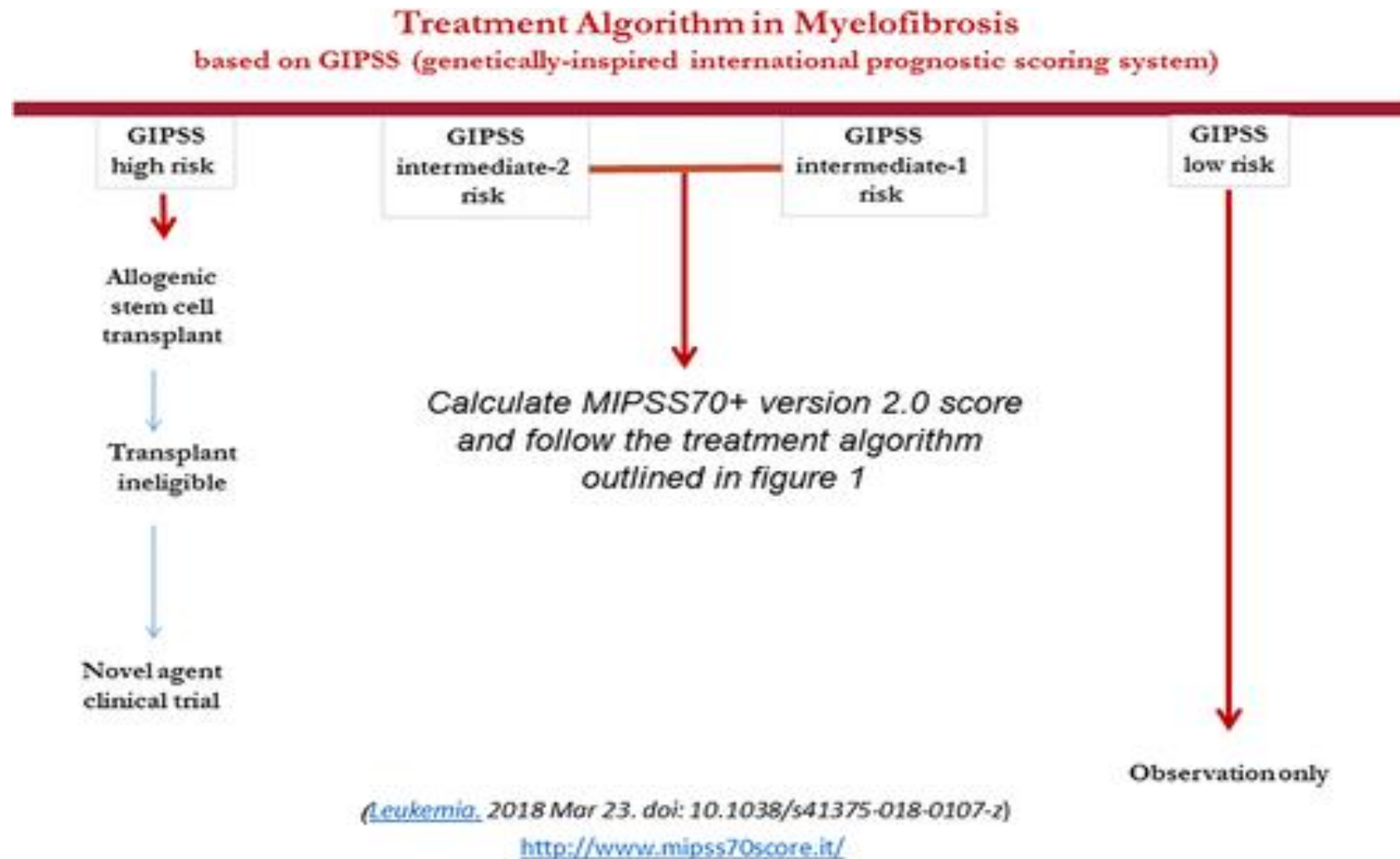
Fedratinib Indication in MF

- Approved by FDA in August 2019 for treatment of adults with intermediate-2–risk or high-risk primary or secondary MF
- Recommended dose 400 mg QD in patients with platelets $\geq 50 \times 10^9/L$
 - Reduce dose to 200 mg QD in patients receiving strong CYP3A inhibitors or if severe renal impairment
- Black box warning: Wernicke's encephalopathy (ataxia, AMS, ophthalmoplegia) occurred in 8/608 (1.3%) patients receiving fedratinib in trials
 - Measure and replace thiamine levels prior to treatment initiation
 - Do not start fedratinib in patients with thiamine deficiency

Treatment algorithm in myelofibrosis

based on risk stratification according to the mutation- and karyotype-enhanced international prognostic scoring system (MIPSS70+ version 2.0); see table 5 for risk variables and risk point allocations

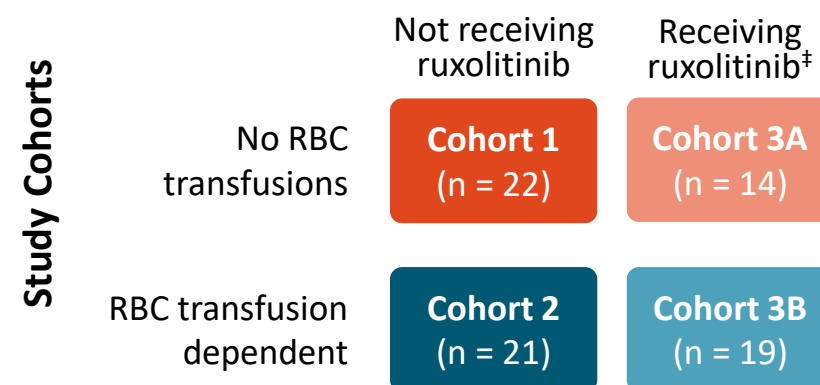




Luspatercept for Treating Anemia in MF

- Open-label, nonrandomized, multicohort phase II trial of **luspatercept** 1 mg/kg every 21 days for patients with primary or post-ET/post-PV MF and anemia (planned N = 100)

Parameter	RBC Transfusion Dependent	
	No RUX (Cohort 2; n = 21)	RUX (Cohort 3b; n = 19)
RBC transfusion-free ≥ 12 consecutive wks, n (%) [*]	2 (10)	6 (32)
<ul style="list-style-type: none"> Median duration of response, wks (range) 	32 (16-49)	39 (12-77)
≥ 50% reduction in RBC transfusion burden from BL, n (%)	8 (38)	10 (53)



Hb Increase ≥ 1.5 g/dL From BL for ≥ 12 Consecutive Wks [†]	No RBC Transfusions	
	No RUX (Cohort 1; n = 22)	RUX (Cohort 3a; n = 14)
Hb increase ≥ 1.5 g/dL at every assessment, n (%)	3 (14)	3 (21)
Mean Hb increase ≥ 1.5 g/dL, n (%)	4 (18)	9 (64)

^{*}Primary endpoint, [cohorts 2, 3b](#). [†]Primary endpoint, [cohorts 1, 3a](#). [‡]Stable dose for ≥ 16 wks at enrollment
Gerds. ASH 2019. Abstr 557.

Momelotinib for Patients With MF

- **Momelotinib**: JAK1/2 inhibitor with potential to improve anemia, possibly via suppression of hepcidin^[1]

Key Trial	Type	Key Findings
SIMPLIFY 2 ^[2]	Phase III RCT in MF previously treated with ruxolitinib (N = 156)	■ SVR ≥ 35% at Wk 24*: momelotinib, 7%; BAT, 6% (P = .90)
SIMPLIFY 1 ^[3]	Phase III RCT in JAKi-naïve patients with MF (N = 432)	■ SVR ≥ 35% at Wk 24*: momelotinib, 26.5%; ruxolitinib, 29% (noninferior)

- Ongoing double-blind, randomized **phase III MOMENTUM trial** (NCT04173494) of **momelotinib vs danazol** for **symptomatic patients with MF who have anemia** (Hb < 10 g/dL) and previous JAKi experience
 - Primary endpoint, symptom response; secondary endpoints, transfusion independence and spleen response)

*Primary endpoint(s).

1. Asshoff. Blood. 2017;129:1823. 2. Harrison. Lancet Haematol. 2018;5:e73. 3. Mesa. JCO. 2017;35:3844.



Slide credit: clinicaloptions.com

Pacritinib for Patients With MF

- **Pacritinib**: selective inhibitor of JAK2, JAK2 V617F, and FLT3

Key Trial	Type	Key Findings
PERSIST-1 ^[1]	Phase III RCT in higher-risk, JAKi-naïve MF with any degree of anemia/thrombocytopenia (N = 327)	▪ SVR ≥ 35% at Wk 24*: pacritinib, 19%; BAT (no JAK2i), 5% (P = .0003)
PERSIST-2 ^[2]	Phase III RCT in MF (prior JAKi allowed) with platelet count ≤ 100,000/μL (N = 311)	▪ SVR ≥ 35%*: pacritinib, 18%; BAT, 3% (incl RUX) (P = .001); TSS reduced ≥ 50%*: pacritinib, 25%; BAT, 14% (P = .08)
PAC203 ^[3]	Phase II dose-finding trial in higher-risk MF with previous ruxolitinib (N = 164)	▪ 200 mg BID dose most effective: SVR ≥ 35%, 9.3%; TSS reduced ≥ 50%, 7.4%

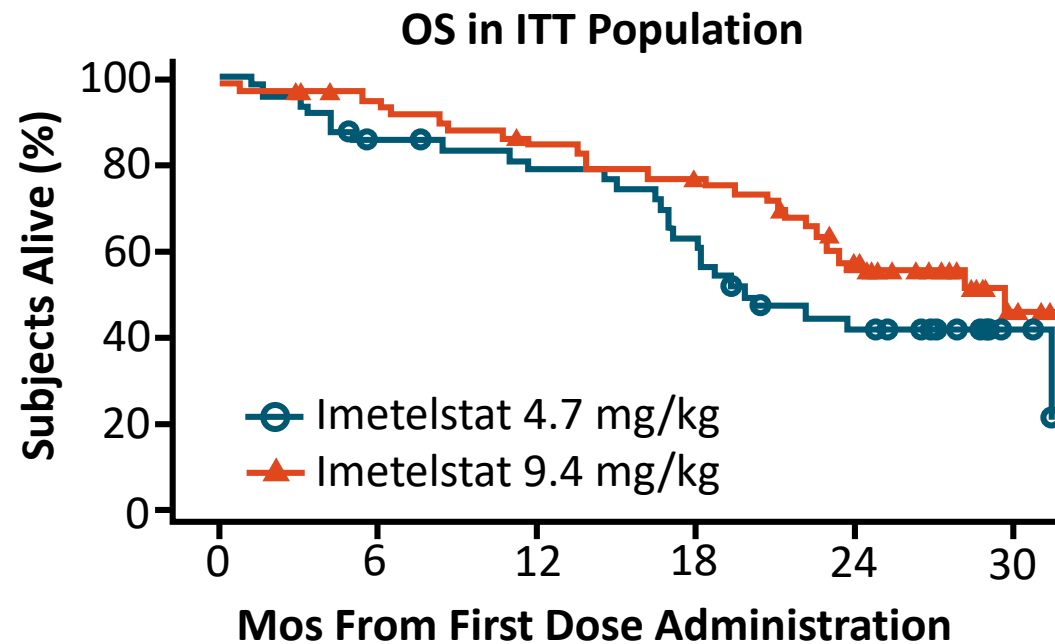
- Development of pacritinib put on hold by FDA in 2016 due to reports of patient deaths related to intracranial hemorrhage, cardiac failure, and cardiac arrest; **clinical hold removed in 2017**
- Ongoing randomized **phase III PACIFICA trial** of pacritinib vs physician's choice treatment for pts with limited (90 days)/no previous JAKi treatment and intermediate- or high-risk **MF and platelet count < 50,000/μL**^[4]
*Primary endpoint(s).

1. Mesa. Lancet Haematol. 2017;4:e225. 2. Mascarenhas. JAMA Oncol. 2018;4:652.
3. Gerds. ASH 2019. Abstr 667. 4. Harrison. ASH 2019. Abstr 4175.



Imetelstat for Patients With MF

- **Imetelstat:** 13-mer oligonucleotide that competitively inhibits telomerase (IC_{50} : 0.5-10 nM)
- IMbark/MYF2001: randomized phase II trial of imetelstat 4.7 mg/kg Q3W (n = 48) or imetelstat 9.4 mg/kg Q3W (n = 59)* for patients with relapsed/JAKi-refractory MF



- Median follow-up: 27.4 mos
- Median OS
 - 4.7 mg/kg: 19.9 mos (95% CI: 17.1-NE)
 - **9.4 mg/kg: 29.9 mos** (95% CI: 22.8-NE)
- In 9.4-mg/kg arm at Wk 24, 10% had SVR \geq 35%; 32% had \geq 50% symptom response

*After interim analysis, 4.7 mg/kg arm recruitment closed and dose escalation permitted.

Mascarenhas. ASH 2018. Abstr 685.



Slide credit: clinicaloptions.com

Evolution of WHO PV Diagnostic Criteria

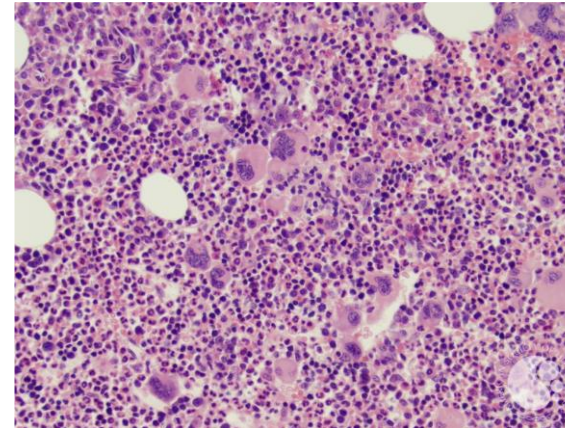
WHO 2008 ^[1]	WHO 2016 ^[2]
Requirement for diagnosis	
<ul style="list-style-type: none"> 2 major and 1 minor criteria OR first major and 2 minor criteria 	<ul style="list-style-type: none"> All 3 major criteria OR first 2 major criteria and the minor criterion
Major criteria	
<ol style="list-style-type: none"> Hb > 18.5 g/dL (men); > 16.5 g/dL (women) JAK2 V617F mutation or similar (JAK2 exon 12) 	<ol style="list-style-type: none"> Hb > 16.5 g/dL or Hct > 49% (men); Hb > 16.0 g/dL or Hct > 48% (women) BM biopsy showing hypercellularity, trilineage growth (panmyelosis) with erythroid, granulocytic, and pleomorphic, mature megakaryocytic proliferation JAK2 V617F or JAK2 exon 12 mutation
Minor criteria	
<ol style="list-style-type: none"> Subnormal serum EPO level BM trilineage proliferation Endogenous erythroid colony growth 	<ol style="list-style-type: none"> Subnormal serum EPO level

1. Thiele. Curr Hematol Malig Rep. 2009;4:33. 2. Arber. Blood. 2016;127:2391.

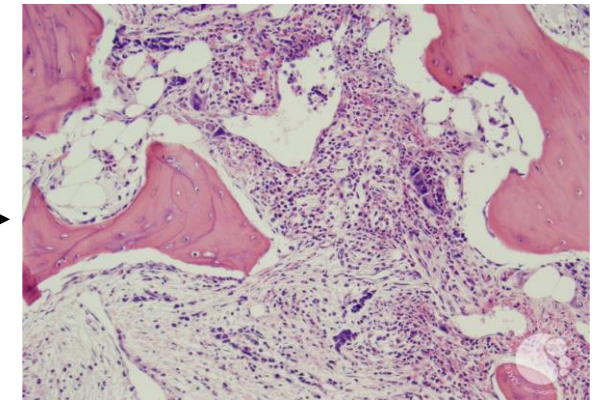
Bone Marrow Testing in PV Diagnosis

- **Bone marrow biopsy may not be required for diagnosis** if sustained Hb levels > 18.5 g/dL (men) or > 16.5 g/dL (women) where *JAK2* mutated and EPO suppressed^[1]
- **Biopsy may identify fibrosis at diagnosis**
 - Prevalence: 14% to 48% with grade 1 fibrosis at diagnosis; consequences include a higher rate of overt, fibrotic progression^[2,3]
- **Biopsy required to diagnose post-PV MF**^[4]
 - Progression prevalence: 5% to 19% at 15 yrs
 - Note that high-grade bone marrow fibrosis alone not enough to diagnose post-PV MF

PV



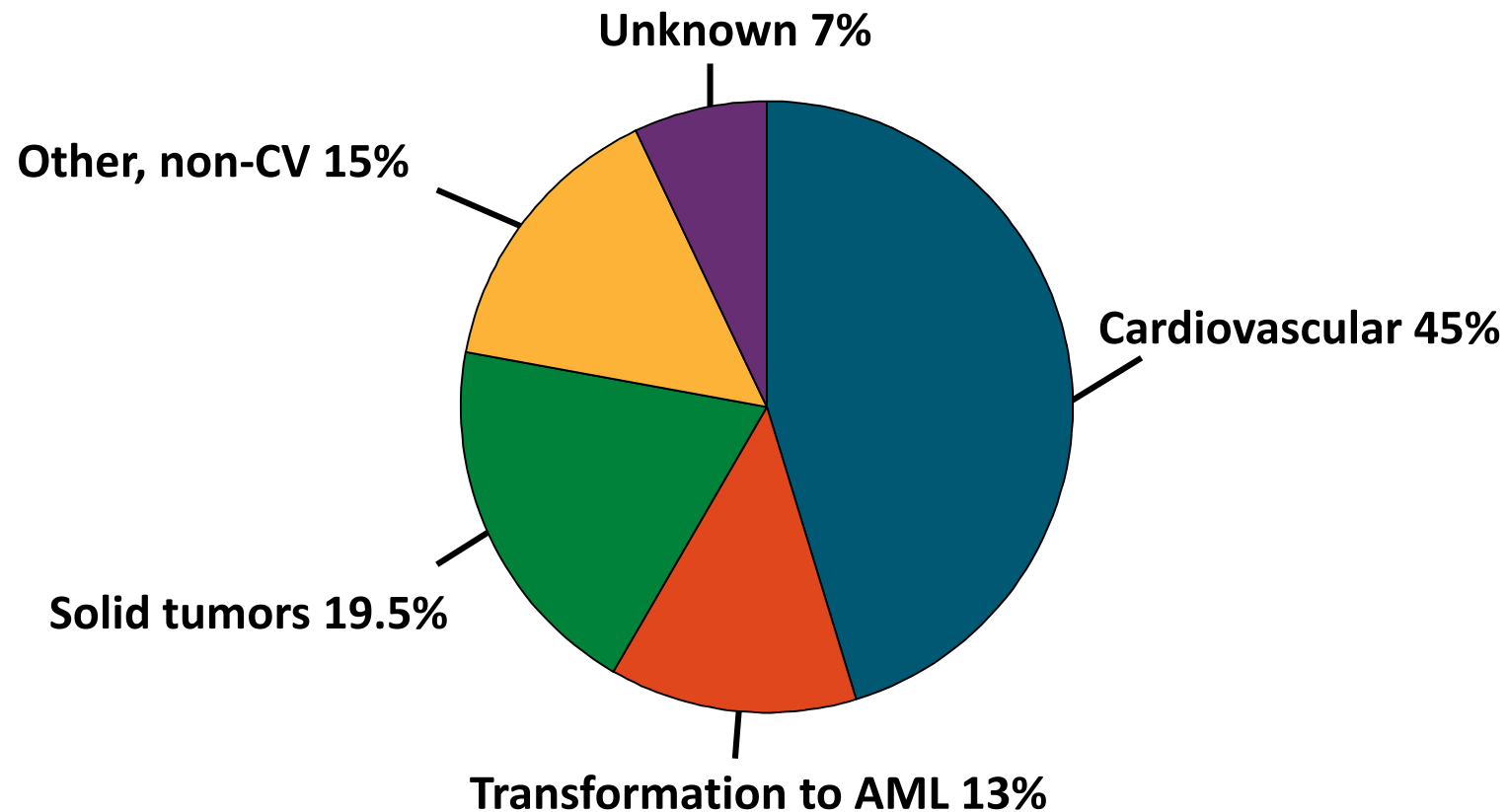
Post-PV MF



1. Arber. Blood. 2016;127:2391. 2. Barbui. Blood. 2012;119:2239. 3. Barraco. Blood Cancer J. 2017;7:e538. 4. Cerquozzi. Blood Cancer J. 2015;5:e366. These images were originally published in ASH Image Bank. Elizabeth L. Courville, MD. Polycythemia vera (PV), polycythemic phase, core biopsy 2; Post-polycythemic myelofibrosis, bone marrow core 1. ASH Image Bank. 2019; #00060162; #00060155. © the American Society of Hematology.

Thrombosis: A Major Cause of Mortality in PV

- Data from large prospective multicenter project in PV (ECLAP trial); 164 of 1638 patients deceased at time of analysis



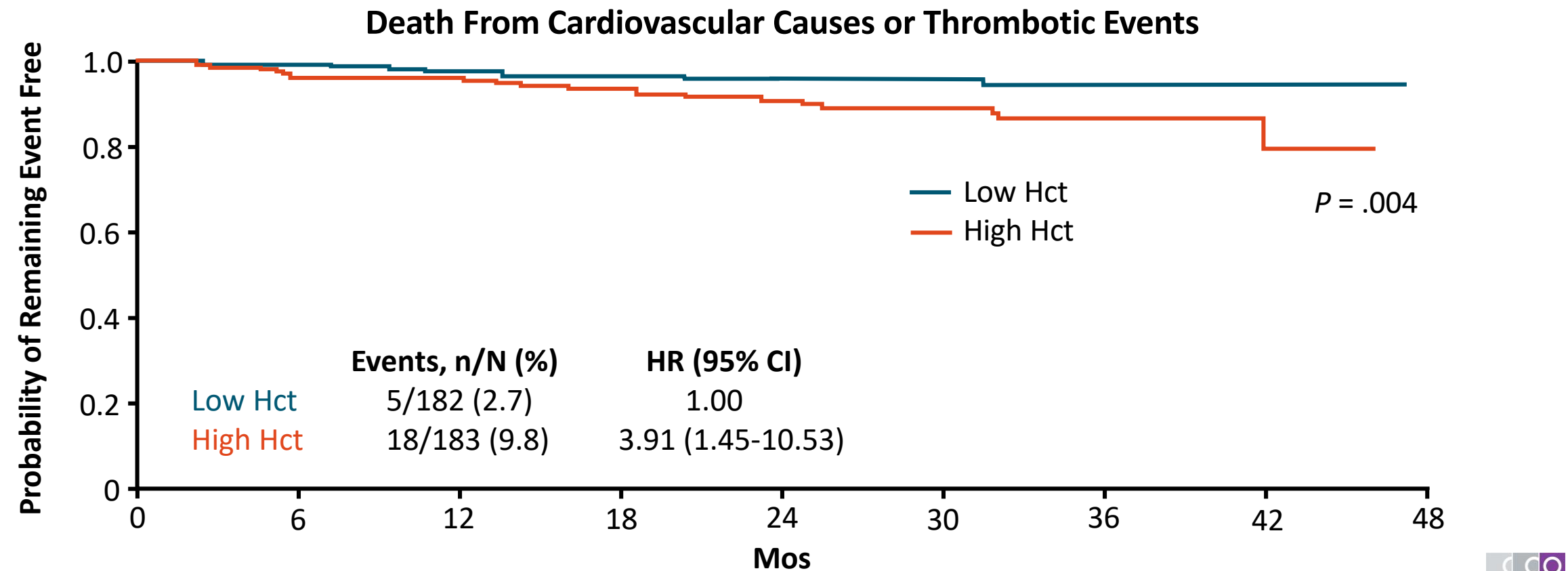
Thrombosis Risk–Adapted Management of ET and PV

Category	Characteristics	Treatment	
Low risk	Age ≤ 60 yrs AND no history of thrombosis	<ul style="list-style-type: none"> Therapeutic phlebotomy (goal Hct < 45%) in PV Aspirin 81 mg/day for ET/PV * Address CV modifiable risk factors for ET/PV 	
		<ul style="list-style-type: none"> All the above <i>AND</i> cytoreductive therapy 	
High risk	Age > 60 yrs <i>OR</i> history of thrombosis	Cytoreductive therapy	
		First line	Second line
		<ul style="list-style-type: none"> Hydroxyurea for ET/PV Anagrelide for ET PegIFN for ET/PV 	<ul style="list-style-type: none"> Ruxolitinib for PV PegIFN for ET/PV Busulfan (age > 70 yrs) for ET/PV

*ASA may not be needed for CALR-mutant ET patients ≤ 60 yrs AND no history of thrombosis.

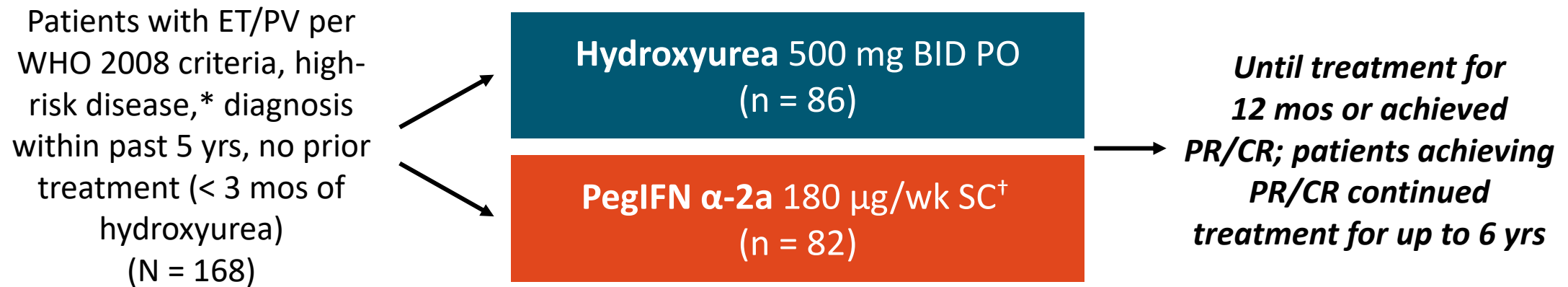
CYTO-PV: Death From CV or Thrombotic Events by Hematocrit Target

- Randomized, open-label phase III trial in which PV patients were treated to a **lower (< 45%)** or **higher (45% to 50%) Hct target** with ASA + phlebotomy ± cytoreductives (N = 365)



MPN-RC 112: First-line PegIFN vs HU for High-Risk PV and ET

- International, multicenter, randomized phase III study



- CR rate at 12 mos (primary endpoint): **hydroxyurea, 33%; pegIFN, 28%** ($P = .6$)

- ORR: **hydroxyurea, 69%; pegIFN, 81%**

*Any of following: age ≥ 60 yrs; thrombosis, erythromelalgia, or migraine (or hemorrhage for ET); symptomatic or significant (> 5 cm) splenomegaly, uncontrolled CV risk factor; for PV, platelets $> 1000 \times 10^9/L$; for ET, platelets $> 1500 \times 10^9/L$.

[†]Starting dose of 45 µg QW gradually increased to maximum dose of 180 µg QW.

Mascarenhas. ASH 2018. Abstr 577. Mascarenhas. ASH 2016. Abstr 479.



Slide credit: clinicaloptions.com

MPN-RC 112: Response

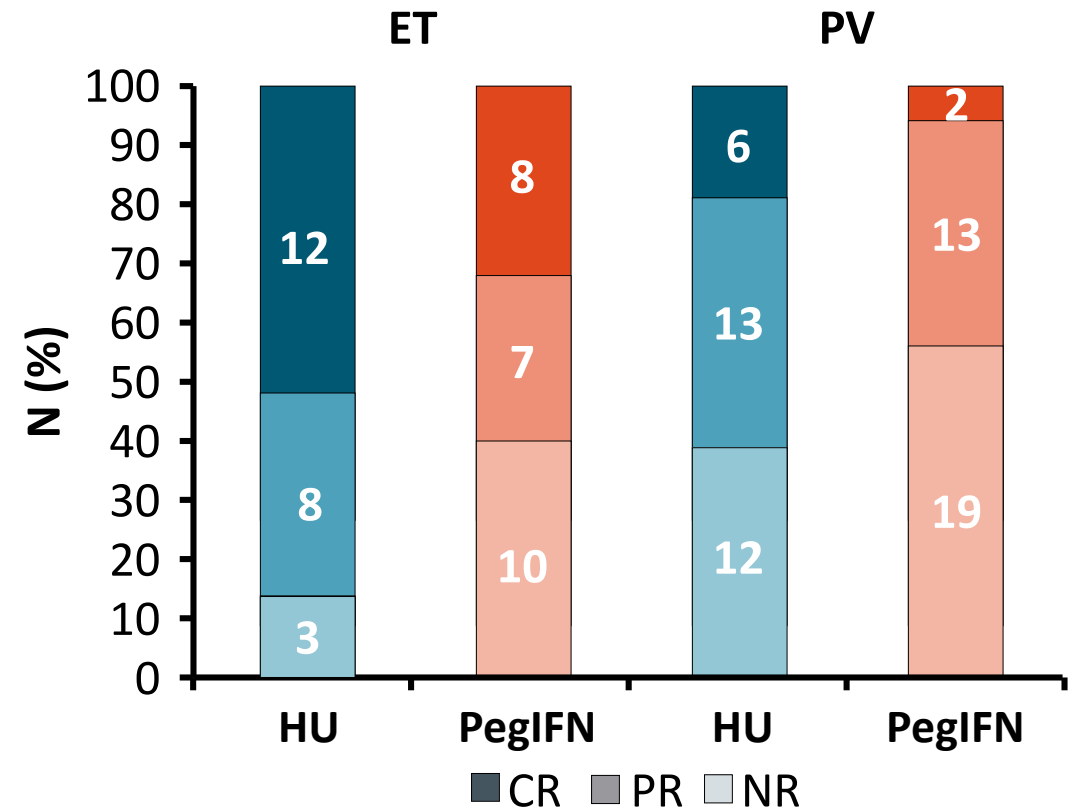
24-Mo Response Data

Response, n (%) [*]	HU (n = 54)			PegIFN (n = 52)			P Value (Total)
	ET	PV	Total	ET	PV	Total	
CR	6 (25)	5 (16.7)	11 (20.4)	9 (37.5)	7 (25)	15 (28.8)	.22
PR	2 (8)	9 (30)	11 (20.4)	5 (20.8)	10 (35.7)	16 (30.8)	.04
ORR	8/24 (33.3)	14/30 (46.7)	22/54 (40.7)	14/24 (58.3)	17/28 (60.7)	31/52 (59.6)	.22

*For all 106 patients eligible to receive treatment for 24 mos (due to study closure).

Mascarenhas. ASH 2018. Abstr 577.

Best Bone Marrow Response (n = 113)



CR, HU vs pegIFN: 18/54 (33%) vs 10/59 (17%), $P = .052$



Slide credit: clinicaloptions.com

MPN-RC 112: Nonhematologic Adverse Events

AE, n (%)*	HU (n = 80)		PegIFN (n = 82)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Fatigue	42 (53.0)	2 (2.6)	19 (23.2)	5 (6.1)
Pain	20 (25.0)	3 (3.9)	30 (36.6)	2 (2.4)
Headache	10 (12.5)		18 (21.9)	3 (3.7)
Diarrhea	8 (10.0)	1 (1.3)	14 (17.1)	
Cough	9 (11.3)		11 (13.4)	
Flu-like symptoms	2 (2.5)		18 (21.9)	2 (2.4)
Pruritus	4 (5.0)		13 (15.9)	2 (2.4)
Nausea	6 (7.5)		13 (15.9)	
Arthralgia	6 (7.5)	1 (1.3)	11 (13.4)	
Dizziness	8 (10.0)		8 (9.8)	

*Nonhematologic any grade AEs occurring in > 10%.

AE, n (%)*	HU (n = 80)		PegIFN (n = 82)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Upper respiratory Infection	5 (5.3)		11 (13.4)	
AST increased	3 (3.8)	1 (1.3)	10 (12.2)	2 (2.4)
Dyspnea	4 (5.0)		9 (11.0)	2 (2.4)
Abdominal pain	3 (3.8)		11 (13.4)	
Blurred vision	4 (5.0)		9 (11.0)	
Constipation	9 (11.3)		4 (4.9)	
Peripheral sensory neuropathy	3 (3.8)	1 (1.3)	9 (11.0)	
Depression	2 (2.5)		10 (12.2)	
Hypertension		2 (2.6)	3 (3.7)	6 (7.3)
Mucositis	8 (10.0)	1 (1.3)	1 (1.2)	

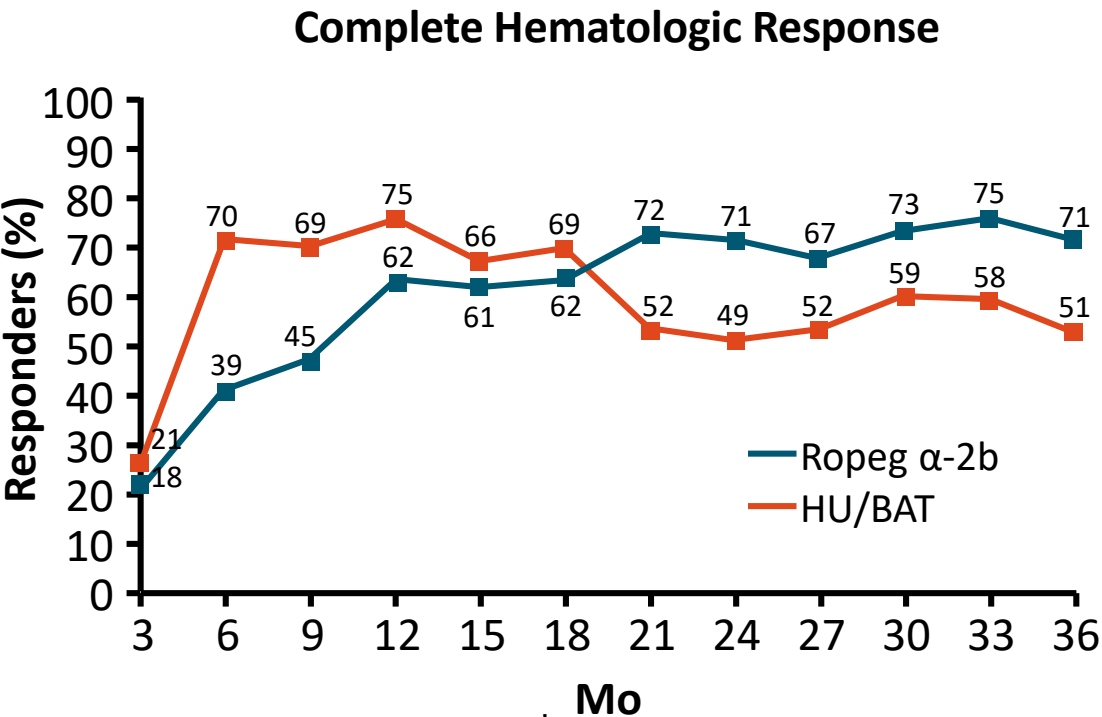
Mascarenhas. ASH 2018. Abstr 577.



Slide credit: clinicaloptions.com

PROUD-PV/CONTI-PV: Ropeginterferon α-2b for Patients With PV

- Randomized phase III study of **ropeginterferon α-2b** vs **HU*** for cytoreductive-naïve or previously HU-treated patients[†] with PV (N = 254)



Study Mo	Responder, n/N (%)		P Value	RR (95% CI)
	Ropeg α-2b (n = 95)	HU/BAT (n = 76)		
12 (EOT in PR)	59/95 (62.1)	57/76 (75.0)	.1201	0.85 (0.70-1.04)
24	67/95 (70.5)	33/67 (49.3)	.0111	1.42 (1.08-1.87)
36	67/95 (70.5)	38/74 (51.4)	.0122	1.38 (1.07-1.79)

*After 12 mos, could switch to BAT. [†]Could not have HU resistance.
Gisslinger. ASH 2018. Abstr 579.

IFN for First-line PV Treatment

Parameter		Considerations
Patients in whom IFN may be considered		<ul style="list-style-type: none">▪ Preserved performance status and limited comorbidities▪ Earlier in disease course▪ Modest splenomegaly modest▪ No additional non-<i>JAK2</i> mutations (?)
Limitations		<ul style="list-style-type: none">▪ Potential for short-term negative impact on QoL▪ Tolerable in the long term?
Impact of use	Early	<ul style="list-style-type: none">▪ Blood count control▪ Address splenomegaly, when modest▪ Reduction in thrombosis risk
	Late	<ul style="list-style-type: none">▪ Anticlonal activity▪ Potential for regression of histologic changes, delayed transformation

Current Treatment Recommendations in Polycythemia Vera



Phlebotomy to hematocrit <45% in both males and females

+

Once-daily low-dose aspirin (40-100 mg)

Low-risk Disease

- No history of thrombosis
- Age ≤60 years

*Inadequate control of microvascular symptoms
or
Presence of cardiovascular risk factors
or
Presence of leukocytosis*

Consider
twice-daily
aspirin

High-risk disease

- History of thrombosis or
- Age >60 years

Add hydroxyurea (500 mg BID starting dose)

*Arterial
thrombosis
history*

Consider
twice-daily
aspirin

*Venous
thrombosis
history*

Add
systemic
anticoagulation

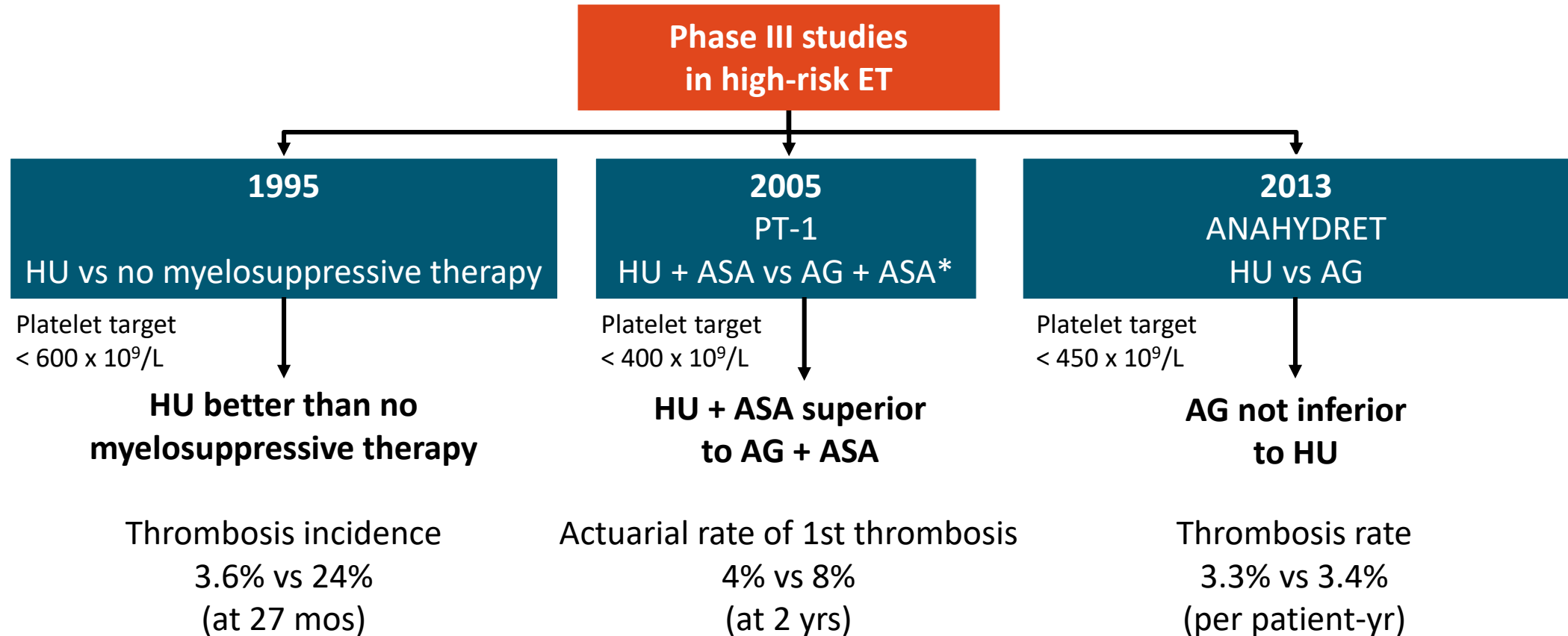
Hydroxyurea
intolerant or
resistant

Pegylated IFN- α
(younger patients)

Busulfan
(older patients)

Ruxolitinib
(Failing treatment with above drugs)

Prospective Randomized Clinical Trials in ET



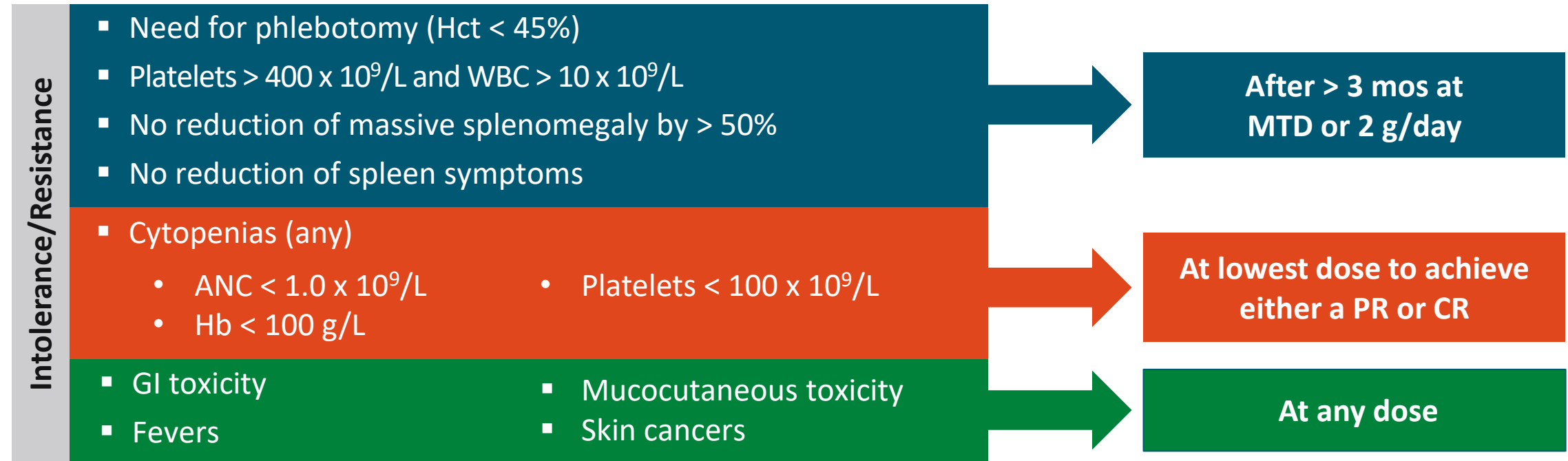
*Composite primary endpoint: arterial or venous thrombosis, serious hemorrhage, or death from vascular causes.

Cortelazzo. NEJM. 1995;332:1132. Harrison. NEJM. 2005;353:33. Gisslinger. Blood. 2013;121:1720.



Slide credit: clinicaloptions.com

HU Resistance and Intolerance: ELN Criteria



- Prevalence of HU resistance/intolerance: up to 25%
- Among individual criteria, development of cytopenia at the lowest required HU dose associated with increased risk of MF/AML progression and death
- Uncontrolled PV symptoms can be a trigger to re-evaluate therapeutic strategy

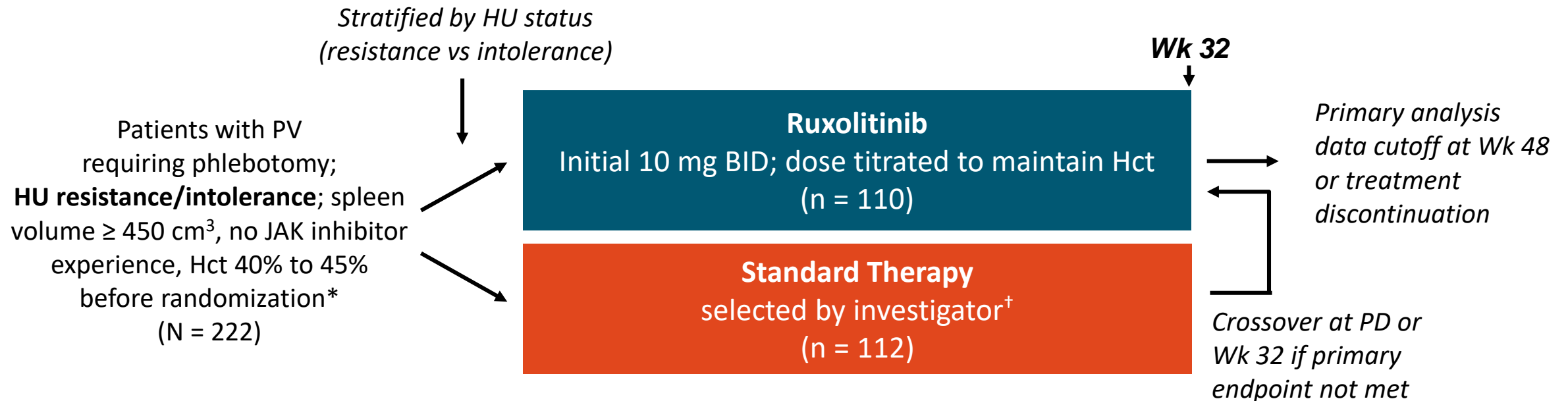
Barosi. Br J Haematol. 2010;148:961. Griesshammer. Ann Hematol. 2015;94:901. Alvarez-Larrán. Br J Haematol. 2016;172:786.



Slide credit: clinicaloptions.com

RESPONSE: Ruxolitinib vs Standard Therapy in Patients With PV and HU Resistance/Intolerance

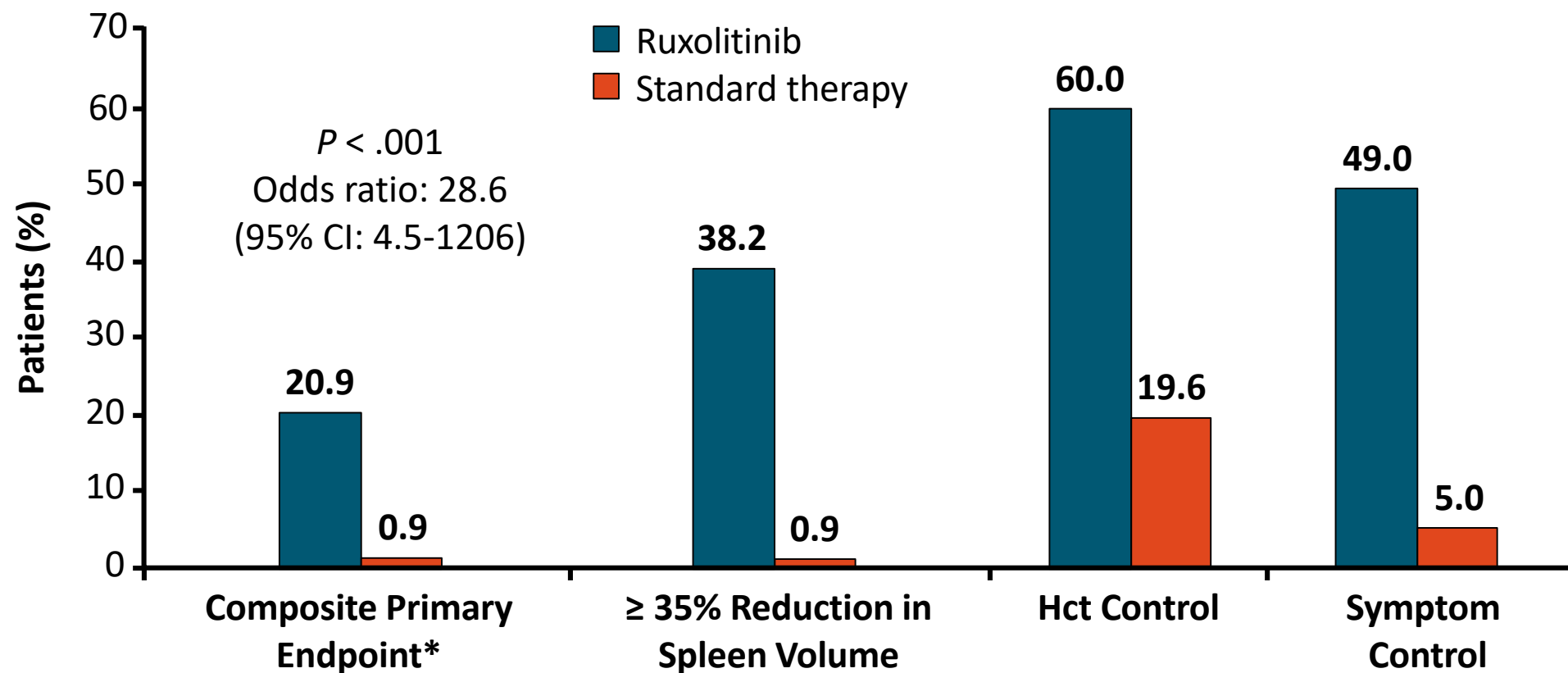
- International, multicenter, randomized, open-label phase III study
 - **Ruxolitinib:** JAK 1 and 2 inhibitor



All patients received low-dose ASA.

*Patients with Hct < 40% or > 50% entered Hct control period prior to randomization. [†]Excluding ³²P, busulfan, and chlorambucil.

RESPONSE: Key Efficacy Findings at Wk 32



*Proportion with Hct control + spleen volume reduction ≥ 35%.

- Complete hematologic response also significantly improved with ruxolitinib vs standard therapy (23.6% vs 8.9%; $P = .003$)

Vannucchi. NEJM. 2015;372:426.



Slide credit: clinicaloptions.com

RESPONSE: 256-Wk Follow-up Data

- For patients randomized to **ruxolitinib** (n = 110)
 - Median exposure: 255 wks
 - Remained on or completed treatment: 66%
 - For patients achieving response at 32 wks (n = 25), KM estimate of maintaining response for 224 wks:
 - Primary endpoint*: 0.74
 - Hct control: 0.73
 - Spleen reduction: 0.72

*Proportion with Hct control + spleen volume reduction $\geq 35\%$.

Kiladjian. ASH 2018. Abstr 1753.

Events/100 PY	Ruxolitinib (n = 110)
Thromboembolic events	1.2
Grade 3/4 thrombocytopenia	1.2
Zoster	4.7
Nonmelanoma skin cancer	5.1
Increased weight	6.1



Slide credit: clinicaloptions.com

RESPONSE-2: Ruxolitinib vs Best Available Therapy in Patients Without Splenomegaly

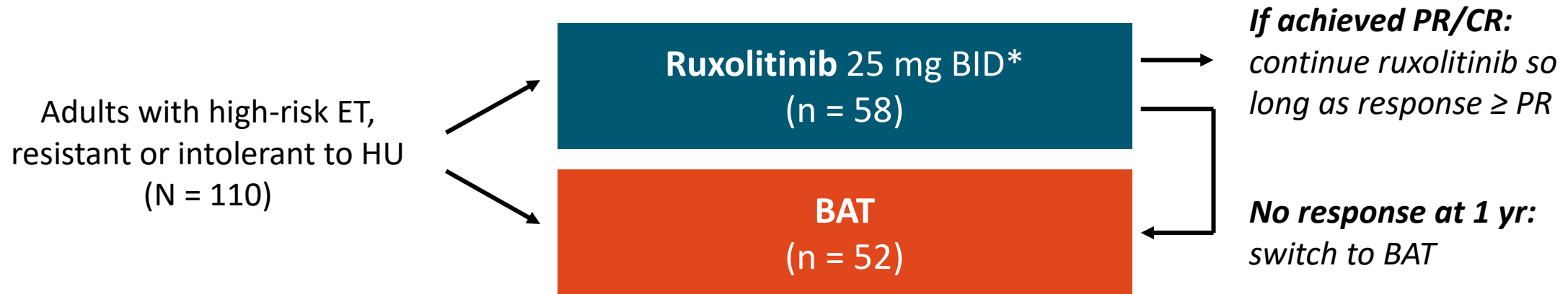
- Multicenter, randomized, open-label phase IIIb study in which patients with HU-resistant/intolerant PV who required phlebotomy and had **no splenomegaly** were treated with **ruxolitinib** or **best available therapy** (N = 149)

Outcome, Wk 28	Ruxolitinib (n = 74)	BAT (n = 75)	P Value
Hct control,* n (%)	46 (62)	14 (19)	< .0001
Complete hematologic response, n (%)	17 (23)	4 (5)	.0019
Complete resolution in symptoms, n/N [†] (%)	17/34 (50)	2/26 (8)	NR
■ ≥ 50% reduction in MPN-SAF TSS, n/N (%)	29/64 (45)	5/22 (23)	NR

*Primary endpoint. [†]Patients with baseline MPN-SAF TSS of ≥ 20.

MAJIC-ET: Ruxolitinib vs BAT in Patients With ET Resistant or Intolerant to HU

- Randomized, open-label phase II study



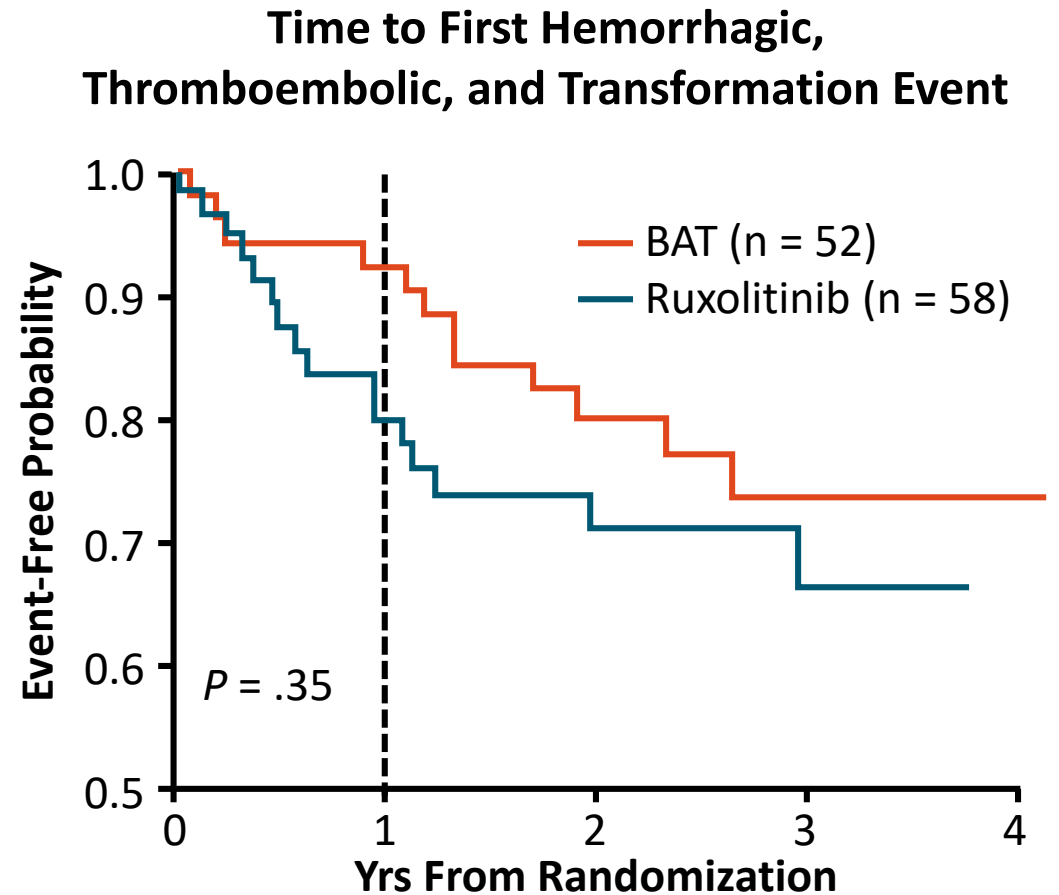
*If platelets 100-200 x 10⁹/L, ruxolitinib dosed at 20 mg BID.

- Baseline: resistant to HU, 48.2%; intolerant to HU, 51.8%; both, 22.7%
- Primary endpoint: CR rate within 1 yr of treatment (ELN criteria)
- Secondary endpoints: PR rate within 1 yr of treatment, DoR, ORR, histologic response, molecular response, hemorrhagic and thromboembolic events, disease transformation, OS, PFS, QoL, disease symptom burden, safety

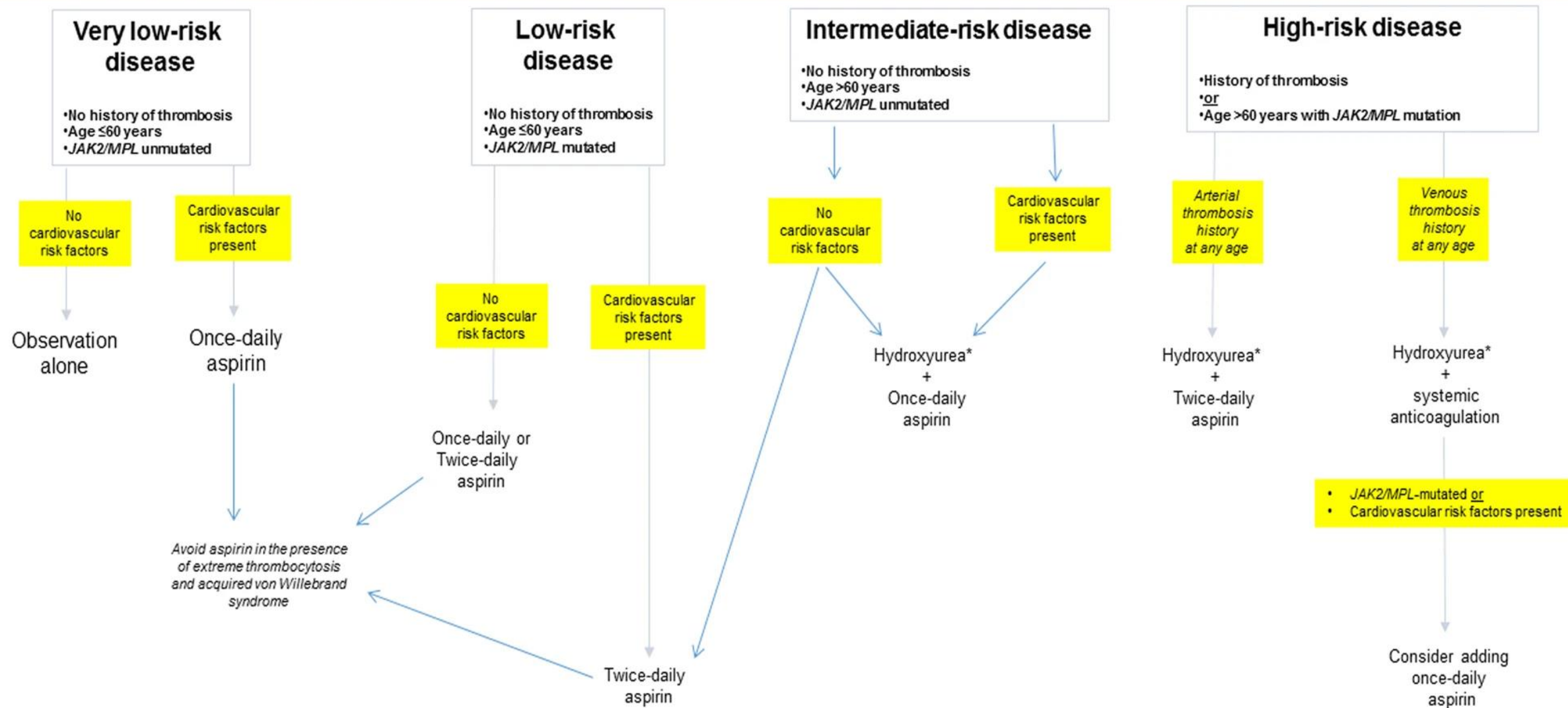
MAJIC-ET: No Difference in Outcomes With Ruxolitinib vs BAT in ET

- No difference in CR, PR within first yr of treatment
 - CR: ruxolitinib, 46.6%; BAT, 44.2% ($P = .40$)
- Rates of thrombosis, hemorrhage, or transformation not different between arms at 2 yrs
- More grade 3/4 anemia, thrombocytopenia, and grade 3 infections with ruxolitinib vs BAT
- More d/c with ruxolitinib vs BAT (60% vs 19%)
- Some molecular responses in ruxolitinib-treated patients with *JAK2* V617F or *CALR* positivity
- Better improvement of some disease-related symptoms with ruxolitinib

Harrison. Blood. 2017;130:1889.



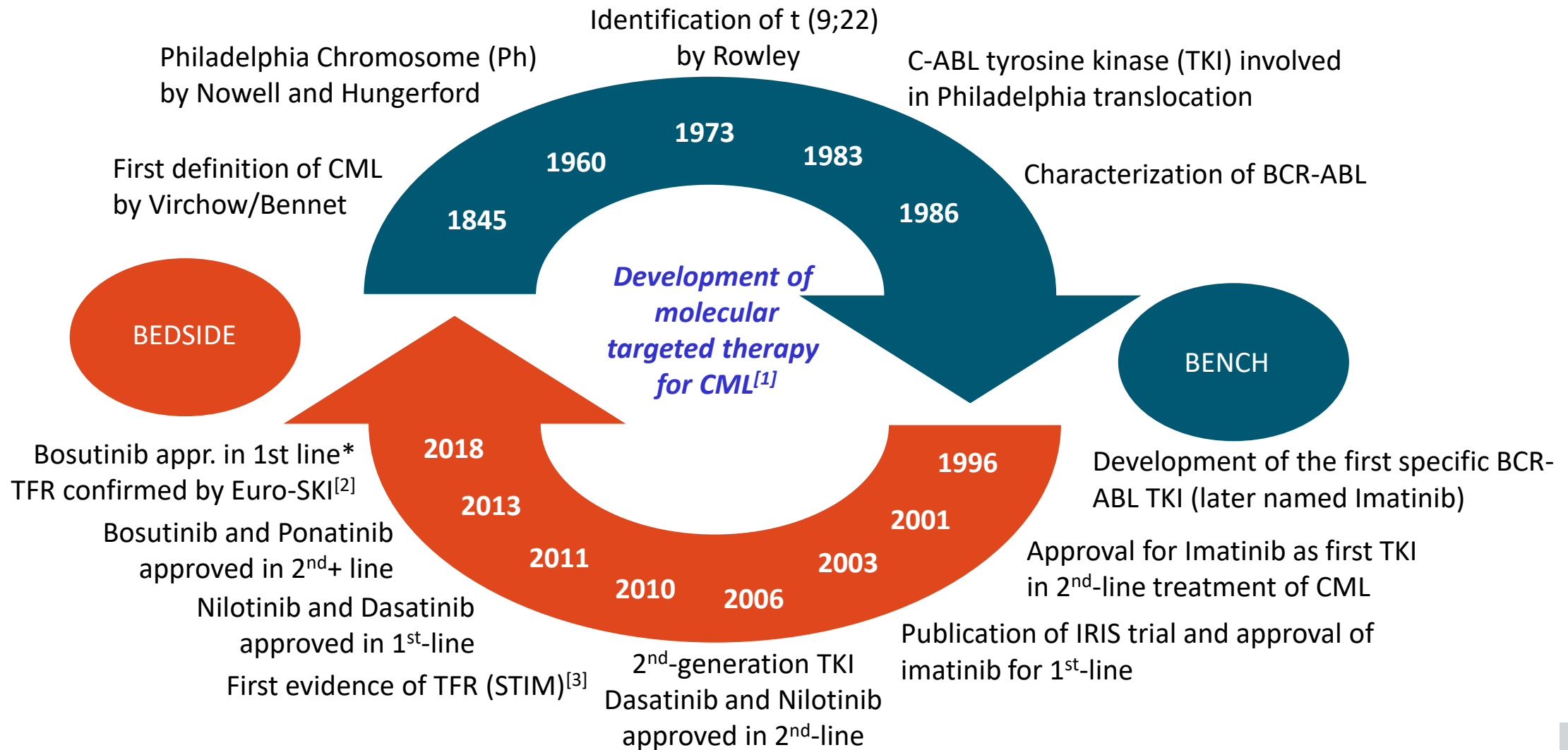
Current Treatment Algorithm in Essential Thrombocythemia



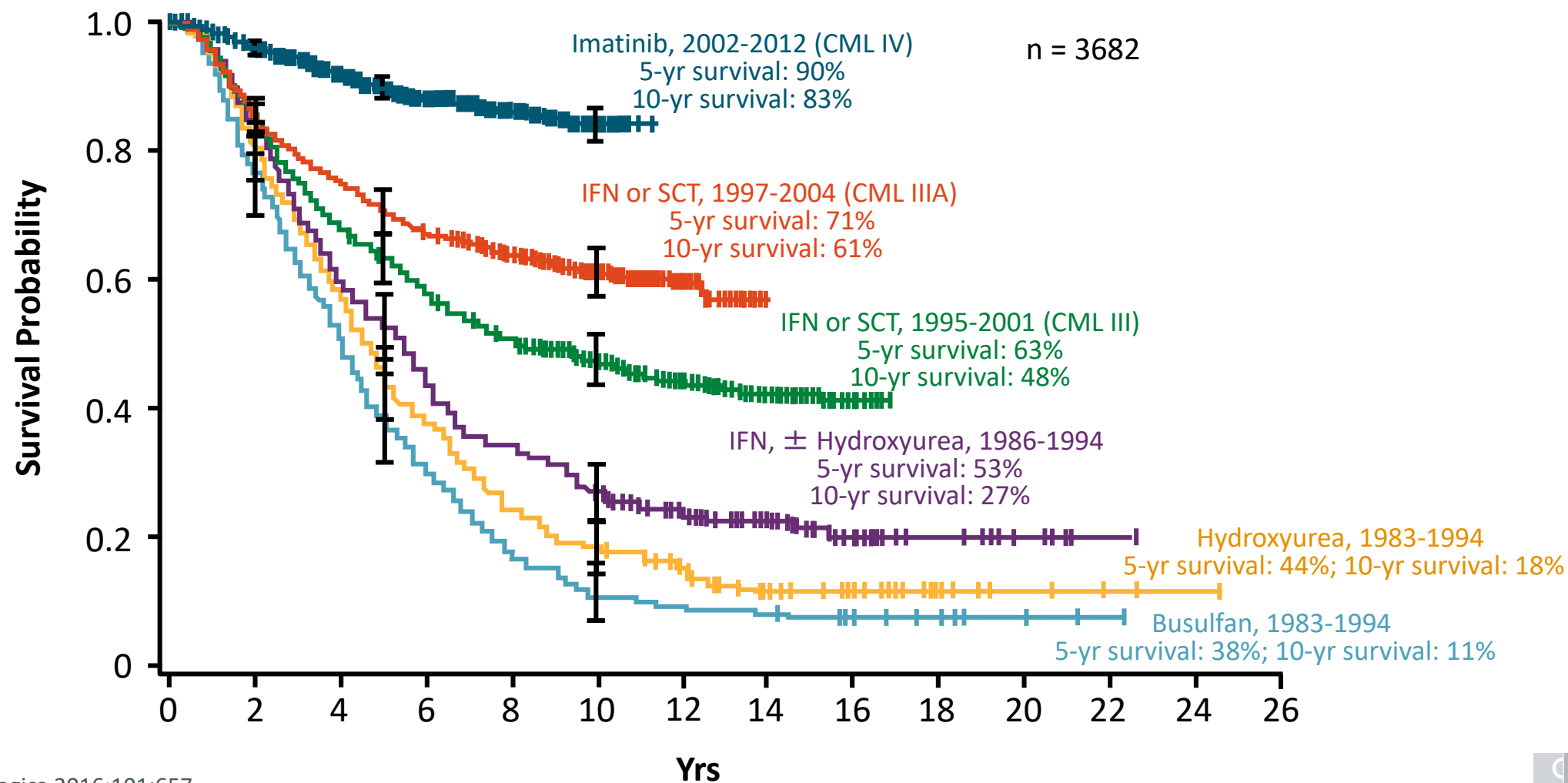
*Second-line treatment in hydroxyurea intolerant or refractory patients is pegylated IFN- α or busulfan

Ayalew Tefferi Tiziano Barbui
<https://doi.org/10.1002/ajh.25303>

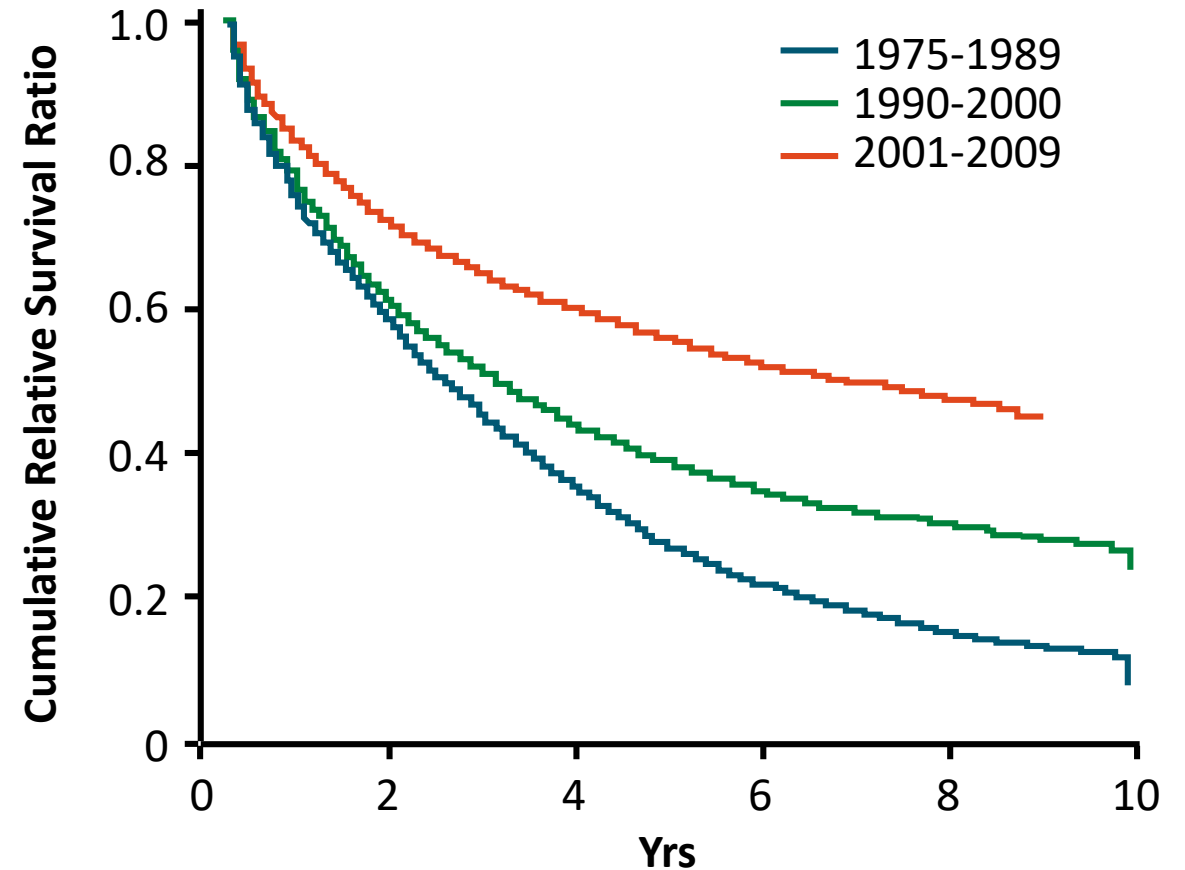
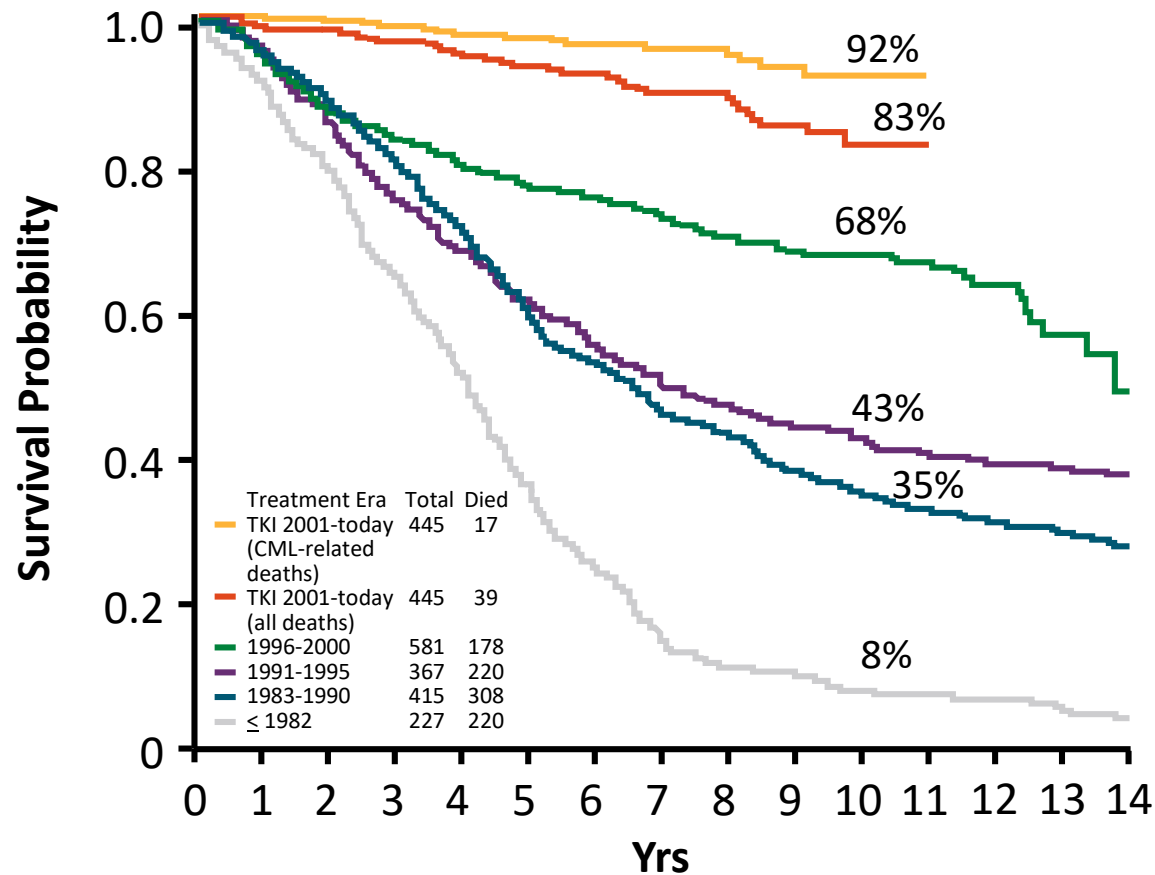
Chronic Myeloid Leukemia (CML): A Model Disease in Oncology



Survival With CML Over Time: The German CML-Study Group Experience



CML Survival by Era: MDACC vs SEER

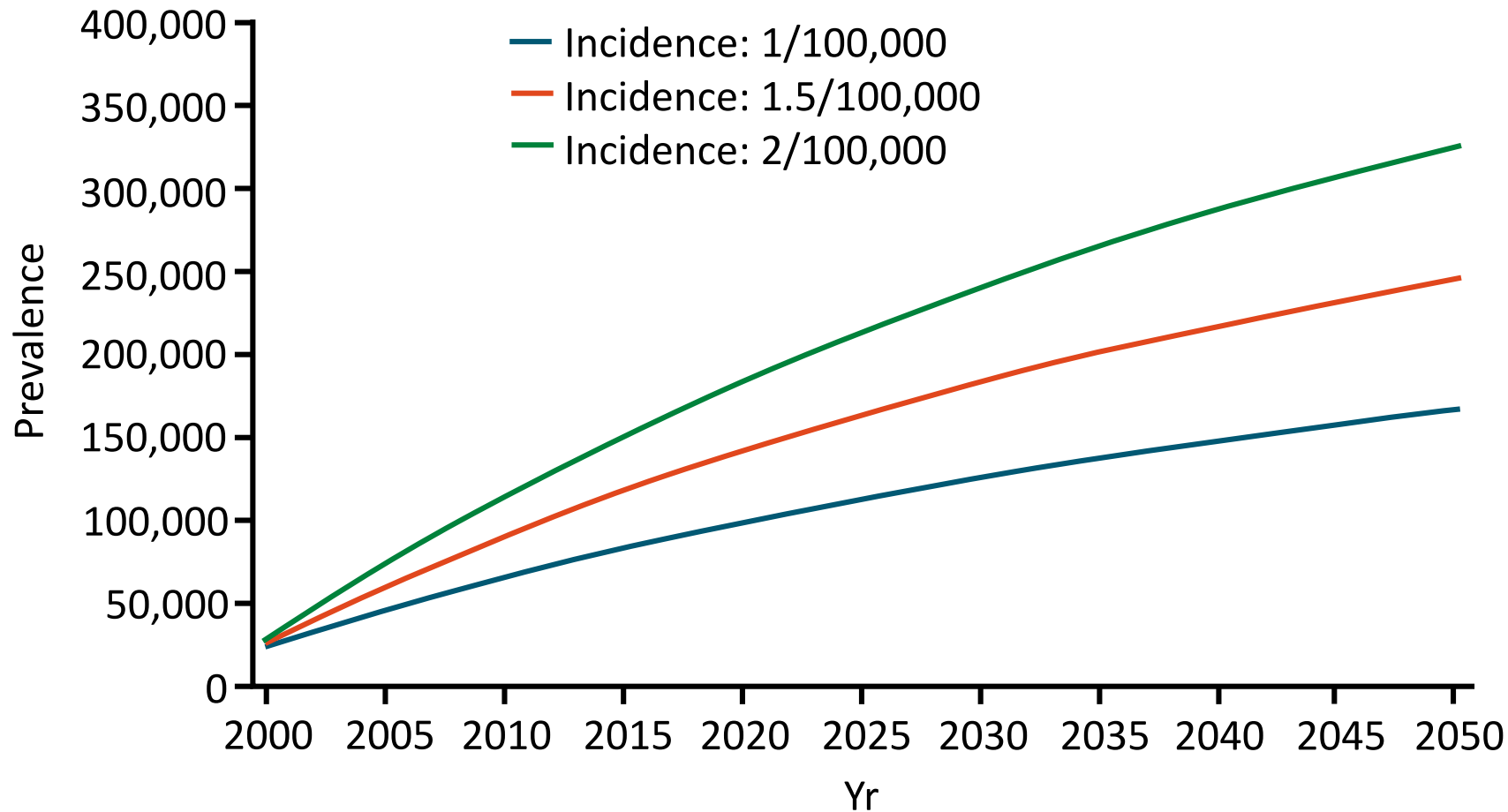


Kantarjian. Chronic Myeloid Leukemia, In: Harrison's Principles of Internal Medicine. 2014. Chen. Leuk Lymphoma. 2013;54:1411.



Slide credit: clinicaloptions.com

Expected Prevalence of CML in Europe in 2050



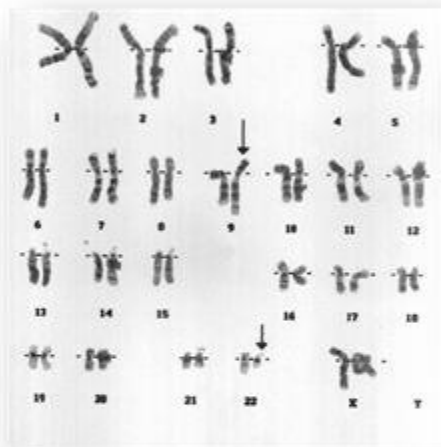
Assumptions: Population 500 million, mortality 2% per yr, incidence constant.

Courtesy of J. Hasford, IBE, Munich.



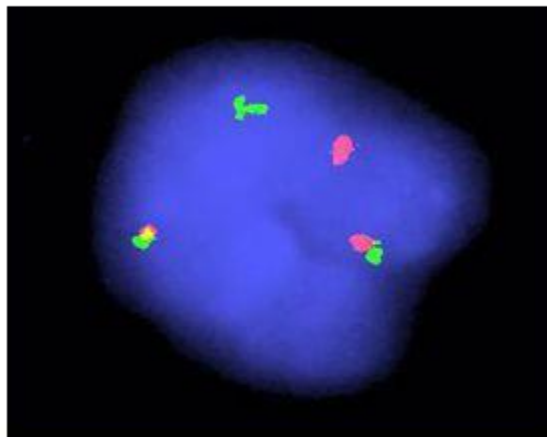
Slide credit: clinicaloptions.com

Options for Establishing the Diagnosis of CML



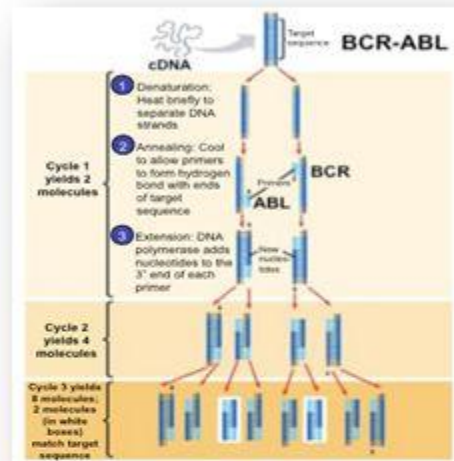
Karyotyping

Requires BM aspirate for optimal metaphases
Allows for evaluation of CE as well ACA in Ph-clones
Occasionally, cryptic and complex translocation events may result in the missed identification of t(9;22)



FISH

Can be done with interphase cells
Allows for the identification of potential duplications of the Ph chromosome
Allows for the identification of the loss of der(9) chromosome
Allows for the identification of cryptic translocations involving BCR-ABL that can be missed on karyotypes
Fails to identify CE or ACA



qRT-PCR

Can quantify the amount of disease
Allows for the identification of cryptic translocations involving BCR-ABL
Many primers sets only detect the p190 and/or p210 translocation and may miss p230 or alternative translocations
Requires consistent use of the same laboratory give different control genes
Fails to identify CE or ACA

The History of CML Is Long, the Kinase Inhibitor Era Short

1845 1865 1879 1903 1953 1965 1968 1983 2001 2006 2012 2016

First description of CML

Fowler's solution - 1% arsenic trioxide



1845:
John Hughes
Bennett reported a
"Case of
Hypertrophy of the
Spleen and Liver in
which Death Took
Place from
Suppuration of the
Blood" in the
Edinburgh Medical
Journal

Staining methods for blood

Radiotherapy

Busulfan



1960:
Nowell & Hungerford
describe the
Philadelphia
Chromosome



1973:
Janet Rowley
describes the
9:22 translocation

Hydroxyurea

Bone Marrow Transplant

Interferon

Imatinib

**Dasatinib,
Nilotinib**

Bosutinib

Ponatinib

Generic Imatinib



1999: After seminal
preclinical work first
clinical trials commence
with STI571 (imatinib)

IRIS: The Largest Phase III CML Study to Date

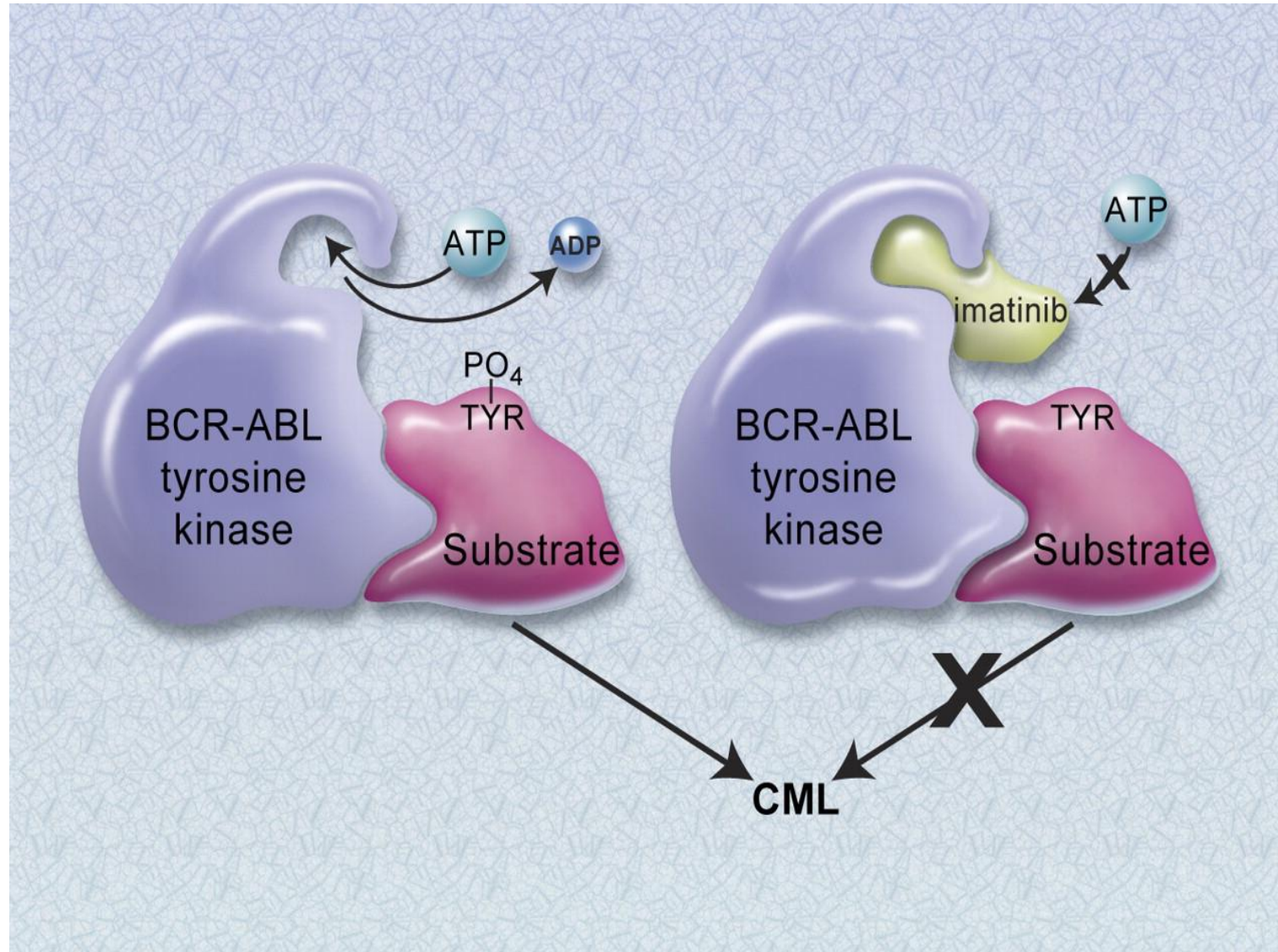
1106 patients enrolled from June 2000 to January 2001



S = screening.
R = randomization.

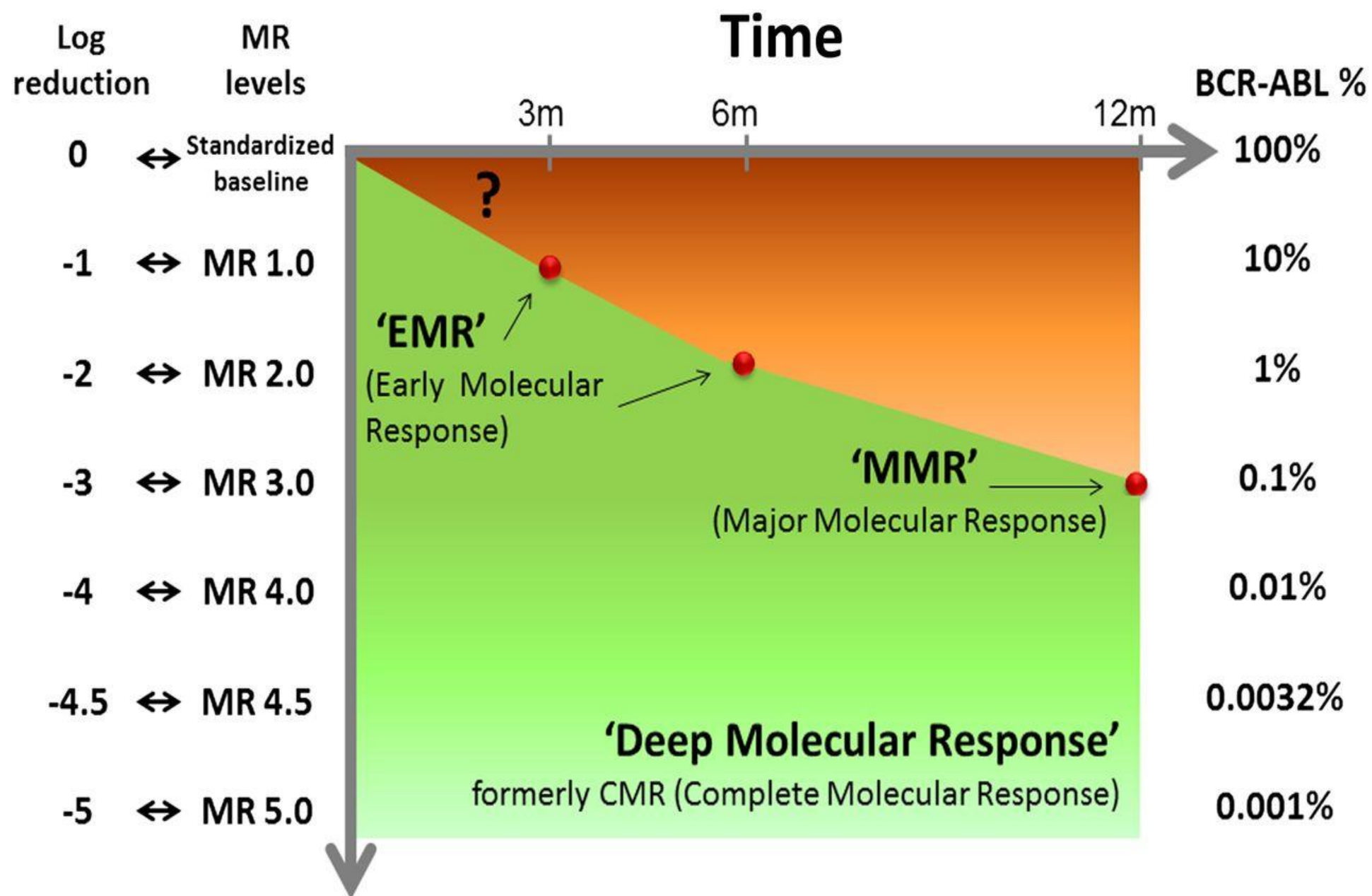
*Independent Data Monitoring Board recommended protocol amendment.

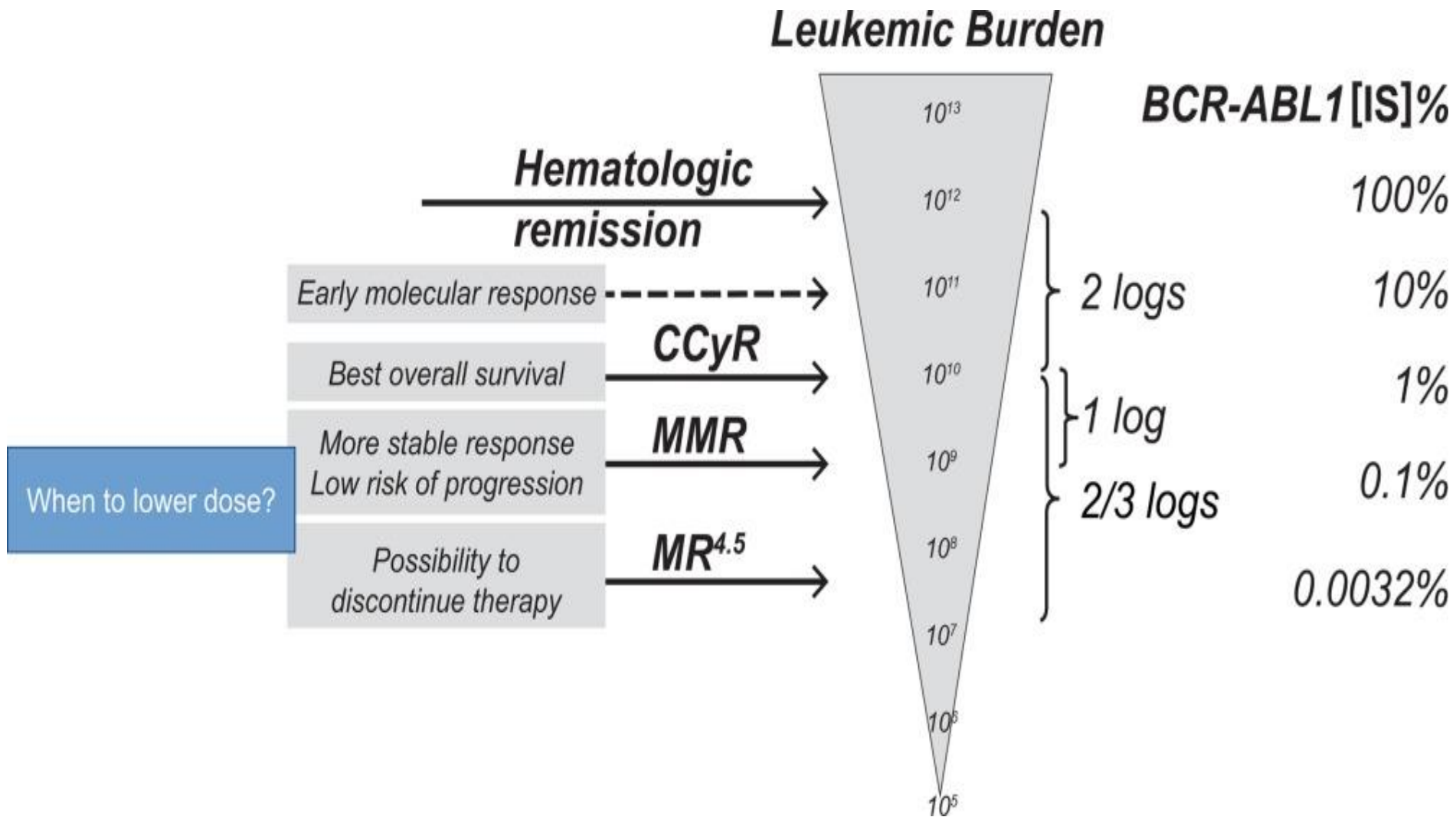
Mechanism of action of imatinib.



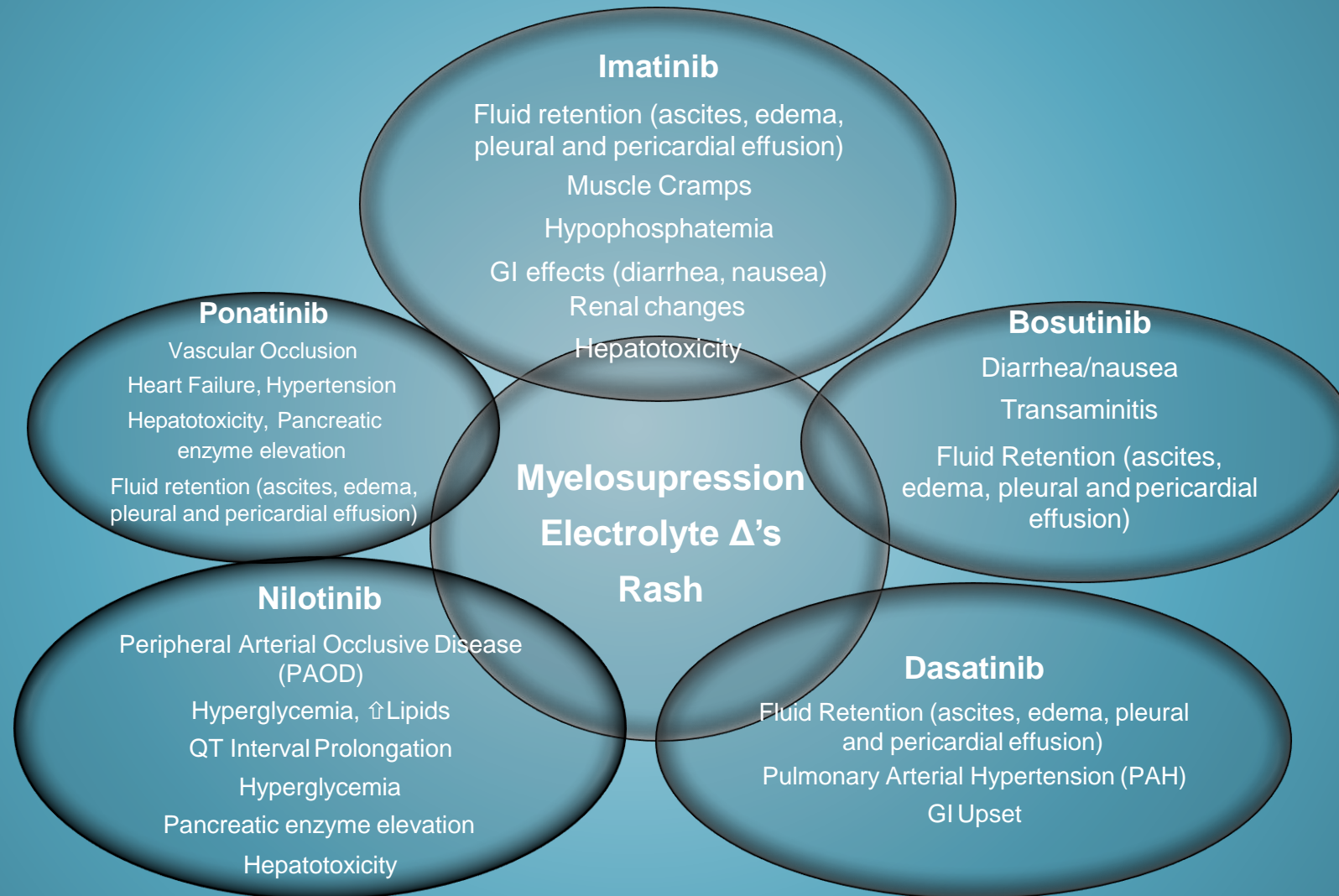
Defining Response

Type of Response		Definition
CHR	Complete Hematologic Response	Normal differential, WBC, platelets \leq ULN
MCyR	Major Cytogenetic Response	0-35% Ph+ marrow metaphases
CCyR	Complete Cytogenetic Response	0% Ph+ marrow metaphases
MMR	Major Molecular Response	BCR-ABL/ABL \leq 0.1% (International Scale)
CMR	Complete Molecular Response	Undetectable BCR-ABL (test of sensitivity \geq 4.5 logs)

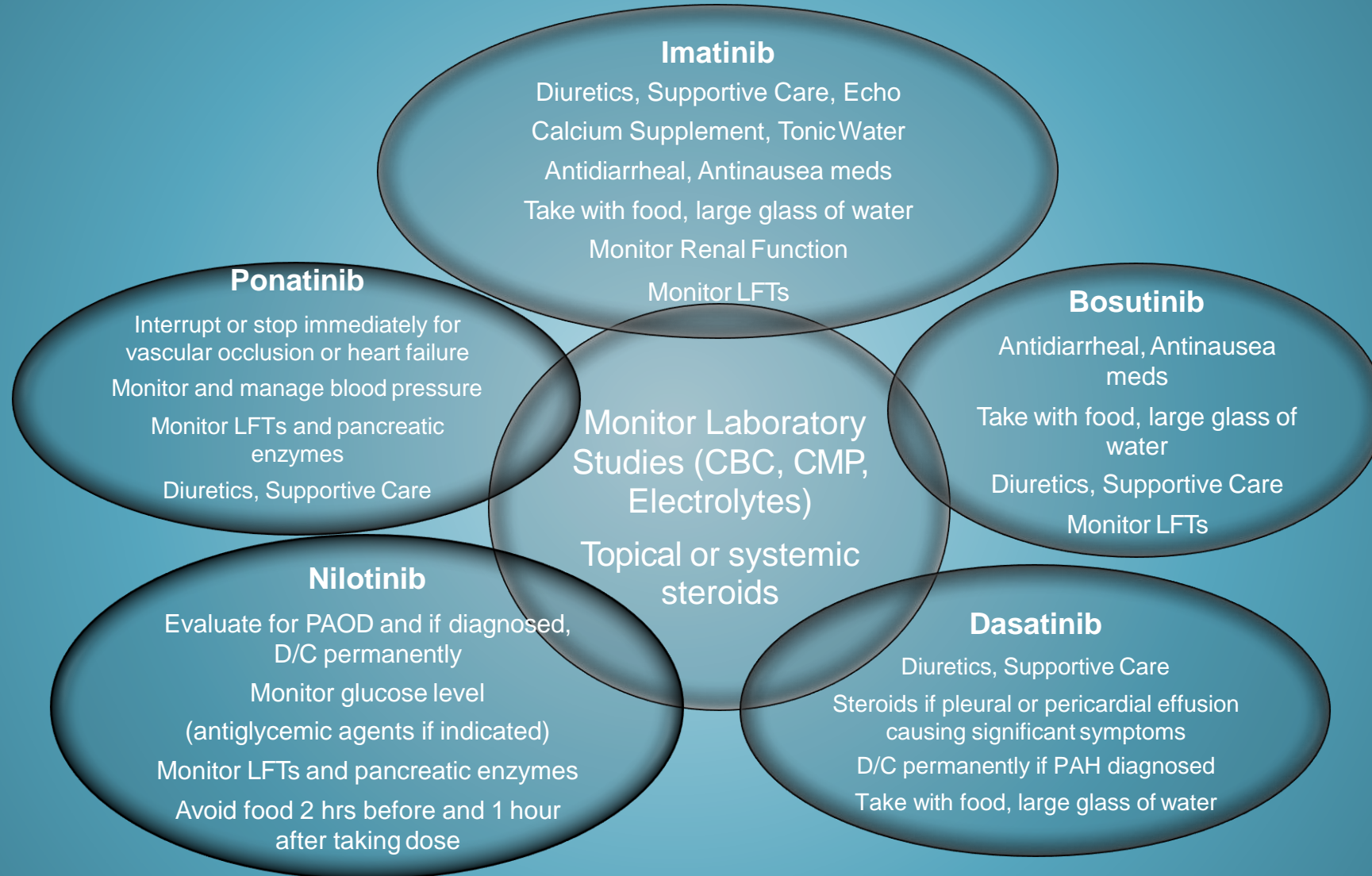




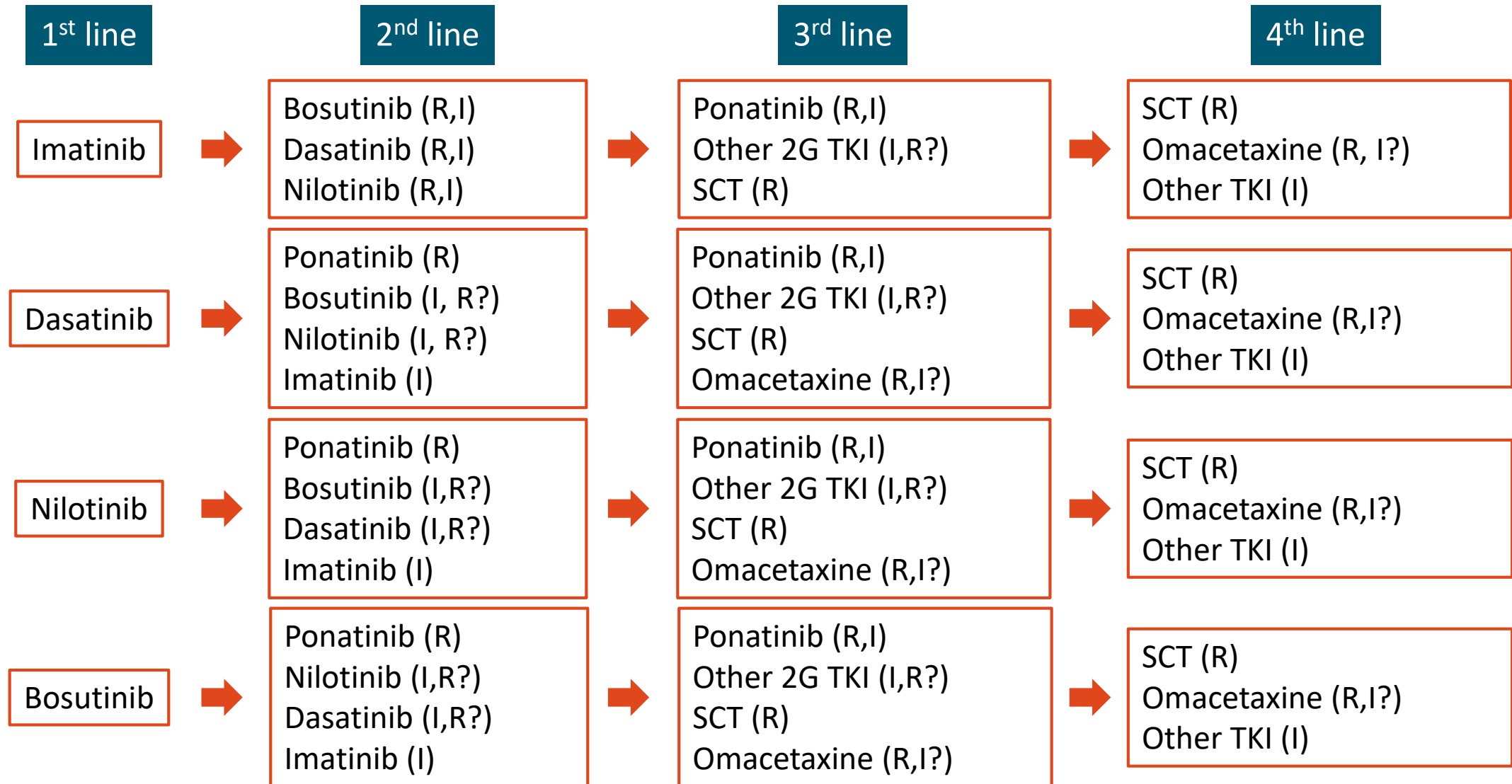
The Spectrum of CML TKI Toxicities



Interventions to Manage Toxicities



Selection of Therapy After TKI Failure



2nd Generation TKI in CML CP Post-Imatinib Resistance

Response, %	Dasatinib [†]	Nilotinib [‡]	Bosutinib
Follow-up (mo)	>24	>24	>24
CHR	89	77	86
MCyR	59	56	58
CCyR	44	41	46
24 mo PFS*	80%	64%	76%
24 mo OS*	91%	87%	88%

†7-yr MMR 46%, PFS 42%, OS 65%; discontinued 78%

‡4-yr PFS 57%, OS 78%; discontinued 70%

*All patients (resistant + intolerant)

Shah. Haematologica. 2010;95:232. Shah. Am J Hematol. 2016;91:869. Kantarjian. Blood. 2011;117:1141. Giles. Leukemia. 2013;27:107. Cortes. Blood. 2011;118:4567. Gambacorti-Passerini. Am J Hematol. 2014;89:732.



Slide credit: clinicaloptions.com

A Unique Spectrum of Adverse Events Has Been Reported For Each TKI Used to Treat CML

- Profiles of clinically overt recurrent non-haematologic AEs in pts with CML treated with BCR-ABL1–targeting TKIs

Adverse event	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib
Facial oedema	++	+/-	+/-	+/-	-
Peripheral oedema	+	+/-	+	+/-	-
Pleural effusion	-	-	++	-	-
Pericardial effusion	-	-	+/-	-	-
Constipation	+	+	-	-	+
Diarrhoea	++	+	+	++	-
Viral reactivation	-	-	+/-	-	-
Major bleeding	+/-	-	+/-	-	-
Arterial occlusive disease	-*	++	+/-*	+/-*	++
Venous thrombosis	-	-	-	-	+/-
Pulmonary hypertension	-	-	+/-	-	-
Skin rash	+	++	+	+	++
Muscle cramps or myalgia	++	+	+	+/-	+
Increase in fasting glucose	+	++	-	-	-
Increase in lipase or amylase	+	+	-	-	+

*Clinically overt arterial occlusive events have been reported in a few patients receiving imatinib, dasatinib, or bosutinib.

++, Reported in >20% of patients in at least 2 different studies; +, Reported in >5% of patients in at least 2 different studies;

+/-, Reported in 1%–5% in at least 1 study; -, Reported in <1%.



Challenges in the Treatment of CML in 2020

- Background: Most patients with newly diagnosed CML are assumed to have a normal life expectancy
- Challenges:
 - Offering the perspective of a **treatment-free remission** (cure?) to as many patients as possible
 - Prevention of and (in case it happens) improved treatment of:
 - **Disease progression** to AP/BC and
 - Development of **resistance** to TKI
 - Improvement of **tolerability** and **adherence** to TKI
 - **Eradication of leukemic stem cells** as a continued source of relapse/disease progression

Evolution of Targeted First-line Therapy of CML: A Simplified View

	BCR-ABL	c-KIT	PDGF-R	SRC	LYN	FGFR1	DDR1
Imatinib (2001)	1 x T315I						
2 nd generation							
Nilotinib (2006)	30 x T315I						
Dasatinib (2006)	325 x T315I						
Bosutinib (2013)	100 x T315I						
DEGREE OF INHIBITION +++ (+) resistant							

Rationale behind compound

**Proof of principle,
role model of TKIs**

**Modulation of
resistance**

**Escalation to
synergistic pathways**

**De-escalation of “off-
target” kinases**

ELN Recommendations 2020

	Optimal	Warnings	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	BCR-ABL1 $\leq 10\%$	BCR-ABL1 $> 10\%$	BCR-ABL1 $> 10\%$ if confirmed within 1-3 months
6 months	BCR-ABL1 $\leq 1\%$	BCR-ABL1 $> 1\% - 10\%$	BCR-ABL1 $> 10\%$
12 months	BCR-ABL1 $\leq 0.1\%$	BCR-ABL1 $> 0.1\% - 1\%$	BCR-ABL1 $> 1\%$
Then, at any time	BCR-ABL1 $\leq 0.1\%$	BCR-ABL1 $> 0.1\% - 1\%$ Loss of $\leq 0.1\%$ (MMR) ^a	BCR-ABL1 $> 1\%$, resistance mutations, high-risk ACA

Change

^a Loss of MMR (BCR-ABL1 $> 0.1\%$) indicates failure after TFR

Hochhaus. Leukemia 2020;34:966.



Slide credit: clinicaloptions.com

ELN Recommendations 2020

Wait and monitor closely! Carefully considered for continuation or change, depending on patients' characteristics, comorbidities, and tolerance

	Optimal	Warnings	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	BCR-ABL1 $\leq 10\%$	BCR-ABL1 $> 10\%$	BCR-ABL1 $> 10\%$ if confirmed within 1-3 months
6 months	BCR-ABL1 $\leq 1\%$	BCR-ABL1 $> 1\% - 10\%$	BCR-ABL1 $> 10\%$
12 months	BCR-ABL1 $\leq 0.1\%$	BCR-ABL1 $> 0.1\% - 1\%$	BCR-ABL1 $> 1\%$
Then, at any time	BCR-ABL1 $\leq 0.1\%$	BCR-ABL1 $> 0.1\% - 1\%$ Loss of $\leq 0.1\%$ (MMR) ^a	BCR-ABL1 $> 1\%$, resistance mutations, high-risk ACA

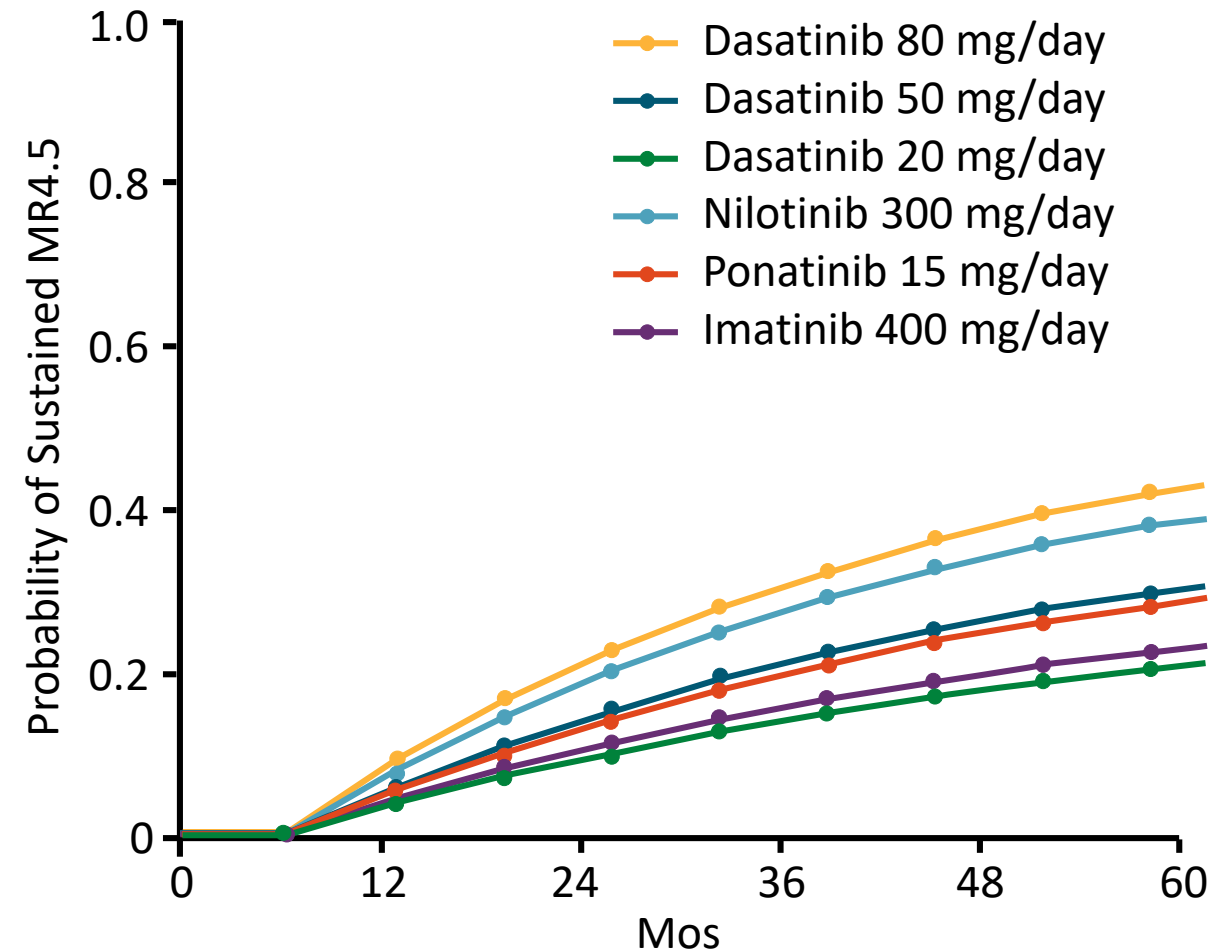
^a Loss of MMR (BCR-ABL1 $> 0.1\%$) indicates failure after TFR.

Considering the Next Treatment Option

- What is available (other TKI? Donor for SCT?, etc.)
- What is the expected efficacy (realistic probability of response compared to expectations)
- What is the local experience (e.g., SCT results)
- What is safe (co-morbidities, known safety)
- What are the patient's goals (QoL, TFR, etc)

Dynamic Personalized Assessment in Patients With CML-CP

- 646 patients enrolled on frontline TKI trials
 - 10,623 clinical visits to verify dose
 - 8319 PCR for BCR-ABL
- Multivariate joint modeling with multiple longitudinal measurements for dynamic personalized assessment with combination of Cox proportional hazard model with generalized linear mixed models
- Bayesian approach with Markov Chain Monte Carlo method
- Dose and BCR-ABL/ABL ratio considered as time-dependent covariates
- The dose of each TKI was handled as numeric value to accommodate treatment effect of dose reductions and change of TKI



Sasaki. ASH 2018. Abstr 3026.

New TKIs Under Development

TKI	Features	Current status
Asciminib (ABL-001)	Allosteric inhibitor	<ul style="list-style-type: none">Completed phase 1, single agent and combination^[1,2]Pivotal phase 3 third-line vs bosutinib^[3]
Radotinib	2 nd generation	<ul style="list-style-type: none">Approved in South Korea 1st and 2nd linePending studies elsewhere^[4]
PF-114	Ponatinib analog, not binding VEGFR	<ul style="list-style-type: none">Phase 1 completed^[5]Starting phase 2^[6]
HQP1351	Active against T315I	<ul style="list-style-type: none">Phase 1 completed^[7]
K0706	No activity vs T315I	<ul style="list-style-type: none">Phase 1 completed^[8]

1. Hughes. NEJM. 2019;381:2315. 2. Rea. ASH 2018. Abstr 792. 3. NCT03106779. 4. NCT03459534. 5. Turkina. ASH 2018. Abstr 790. 6. NCT02885766. 7. Jiang. ASH 2018. Abstr 791. 8. Cortes. ASH 2019. Abstr 4158.



Slide credit: clinicaloptions.com

Indications for allo-SCT in CML in 2020

- -Chronic phase
 - Failure of first-line TKI and predicted poor response to second-line TKI
 - Failure to respond to first- and second-line TKIs
 - Presence of T315I mutation and/or failure to respond to ponatinib
 - Presence of repeated grade 4 cytopenias in response to treatment with different TKIs despite appropriate dose reduction and cytokine support
- -Advanced phase
 - TKI naïve
 - TKI naïve with suboptimal response to TKI
 - TKI resistant
- -Blast phase
 - Acquisition of second CP after TKI or chemotherapy salvage

Conclusions

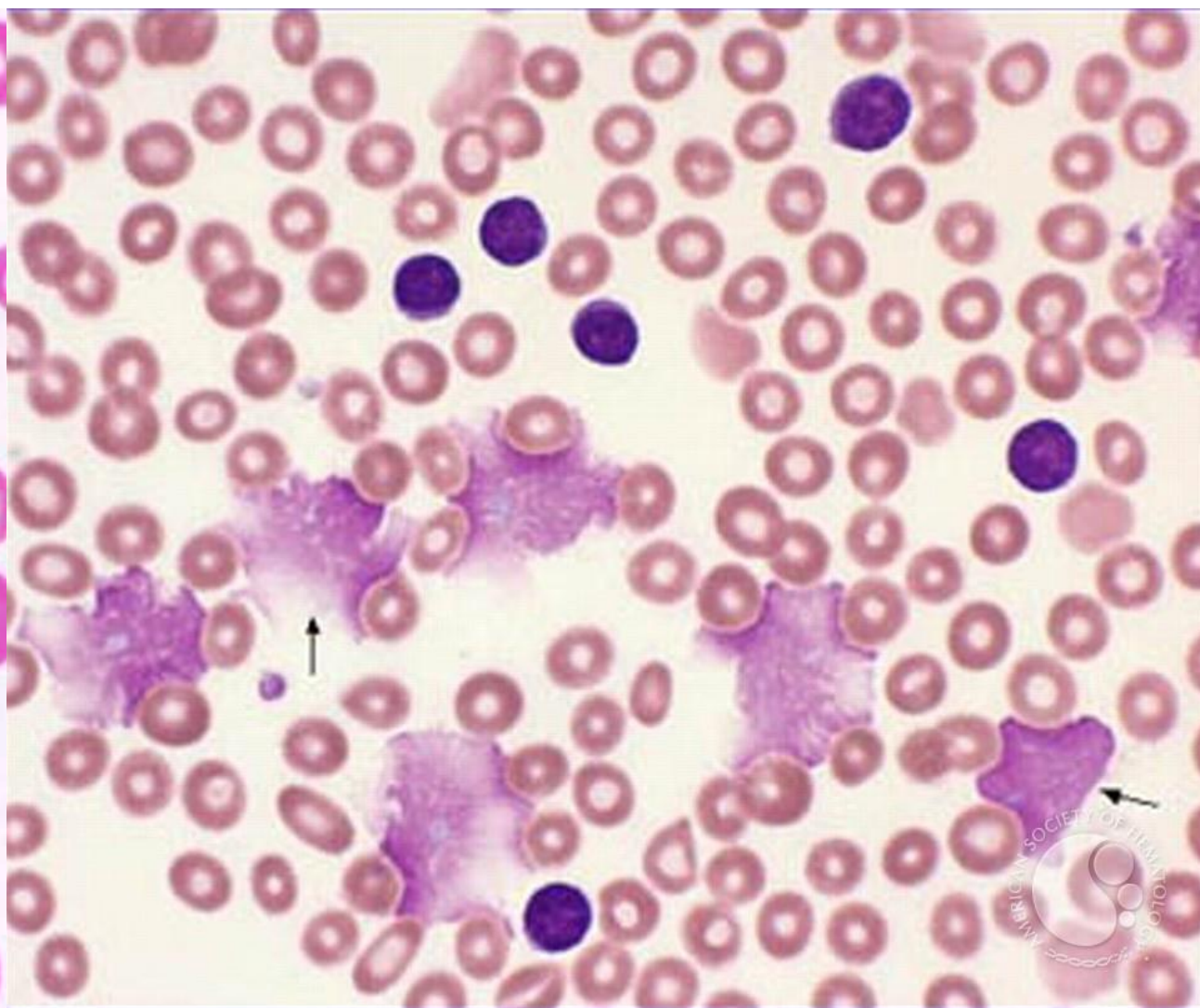
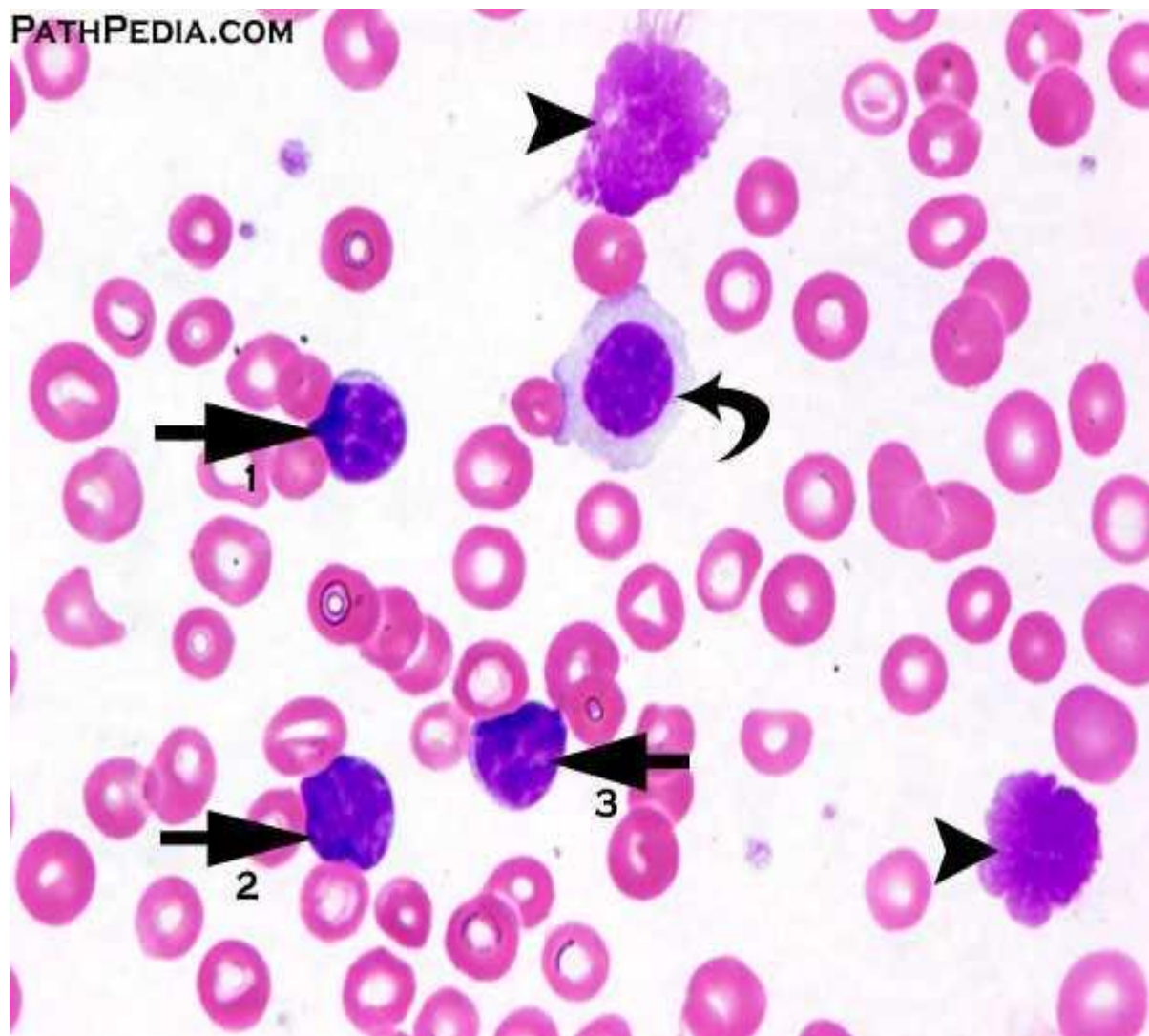
- -TKI therapy can help patients with CML achieve a normal life expectancy.
 - -Although the use of TKIs has generated great advancements in treatment options, some challenges nonetheless remain, including drug resistance, risk for relapse, and toxicities. -Tailoring treatment decisions based on patient characteristics and disease profiles is essential to achieving optimal outcomes.
 - -Carefully observing a patient's response to the selected treatment can help eliminate relapse and resistance.
 - -Optimum patient–provider communication may assist with monitoring for and managing AEs, in addition to potentially curtailing the likelihood of nonadherence.
 - -As the TKI treatment armamentarium continues to evolve, the emphasis will focus on overcoming resistance and reducing toxicities.
-

A Final Word

- Being PCR+ is not failure (and no reason to change)
- Change at 3 months only in clinical trials
- Change only if you have something better (not just something else)
- Do not be afraid of diarrhea
- Do not be afraid of ponatinib
- Do not be afraid of SCT (but be mindful)
- Do not be intolerant with AEs

CLL

- The most prevalent type of adult leukemia
 - Median age of diagnosis of CLL is ~ 72 yrs, with only 10% of patients younger than 50 yrs of age
 - More common in men than women (2:1 ratio)
 - Environmental predisposition uncertain, although Vietnam veterans with Agent Orange exposure warrant “service-connected status”
 - Genetic predisposition present, with ~ 10% of patients having a first-generation relative with CLL
-



CLL/SLL: Background

- More than 21,000 estimated new cases in 2020 in the United States^[1]
 - 7% of all NHL are CLL/SLL
 - Most common type of leukemia in adults (37%)
- Median age at diagnosis: 70 yrs^[2]
- SLL & CLL considered the same B-cell malignancy^[3]
 - CLL: > 5000 clonal lymphocytes in peripheral blood
 - CLL cells coexpress the surface antigen CD5 together with the B-cell antigens CD19, CD20, and CD23. A panel of CD19, CD5, CD20, CD23, κ and λ is usually sufficient to establish the diagnosis. In borderline cases, markers such as CD43, CD79b, CD81, CD200, CD10, or ROR1 may help to refine the diagnosis.
 - SLL: presence of lymphadenopathy and/or splenomegaly and < 5000 clonal lymphocytes in peripheral blood
- Historical 5-yr survival: 66% (range: few mos to normal life span)^[4]
 - Recent (2009-2015) 5-yr survival: 85%^[2]

CLL Statistics at a glance

■ Estimated New Cases in 2020	21,040
■ % of All New Cancer Cases	1.2%
■ Estimated Deaths in 2020	4,060
■ % of All Cancer Deaths	0.7%
■ 5-Year Relative Survival: 86.1%	(2010–2016)

What are the clinical symptoms?

- Often none!
 - Non-specific (drenching night sweats, fever, fatigue, weight loss)
 - Related to lymph node and spleen enlargement
 - Related to bone marrow involvement (cytopenia)
 - Infections
 - Skin involvement
 - High lymphocyte count does NOT cause symptoms!
-

Baseline Evaluation of Patients with CLL

Diagnostic test	General practice	Clinical trial
Tests to establish the diagnosis		
Complete blood count and differential count	Always	Always
Immunophenotyping of peripheral blood lymphocytes	Always	Always
Assessment prior to treatment		
History and physical, performance status	Always	Always
Complete blood count and differential count	Always	Always
Marrow aspirate and biopsy	When clinically indicated (unclear cytopenia)	Desirable
Serum chemistry, serum immunoglobulin, and direct antiglobulin test	Always	Always
Chest radiograph	Always	Always
Infectious disease status	Always	Always
Additional tests prior to treatment		
Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), add(12) in peripheral blood lymphocytes	Always	Always
Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation)	NGI*	Desirable
<i>TP53</i> mutation	Always	Always
IGHV mutational status	Always	Always
Serum β_2 -microglobulin	Desirable	Always
CT scan of chest, abdomen, and pelvis	NGI	Desirable
MRI, PET scans	NGI	NGI
Abdominal ultrasound**	Possible	NGI

*General practice is defined as the use of accepted treatment options for a CLL patient not

Rai and Binet staging

Table 1. Rai classification system*

Stage	Description	Median survival (months)	Risk status (Modified Rai)
0	Lymphocytosis, lymphocytes in blood >15,000/mcL and >40% lymphocytes in the bone marrow	140	Low
I	Stage 0 with enlarged node(s)	100	Intermediate
II	Stage 0–I with splenomegaly, hepatomegaly, or both	70	Intermediate
III	Stage 0–II with hemoglobin <11.0 g/dL or hematocrit <33%	20	High
IV	Stage 0–III with platelets <100,000/mcL	20	High

* Adapted from the 2008 NCI guidelines; BC Cancer Agency 2008 guidelines.^{3,4}

System	Clinical features	Median survival, y
Rai stage (simplified 3-stage)		
0 (low risk)	Lymphocytosis in blood and marrow only	> 10
I and II (intermediate risk)	Lymphadenopathy, splenomegaly +/- hepatomegaly	7
III and IV (high risk)	Anemia, thrombocytopenia	0.75-4
Binet group		
A	Fewer than 3 areas of lymphadenopathy; no anemia or thrombocytopenia	12
B	More than 3 involved node areas; no anemia or thrombocytopenia	7
C	Hemoglobin < 100 g/L platelets < 100 × 10 ⁹ g/L	2-4

CLL-IPI score

CLL- IPI Prognostic Model

- 1) TP53 status (no abnormalities v/s del[17p] or TP53 mutation or both)
- 2) IGHV mutational status (mutated v/s unmutated)
- 3) Serum β 2-microglobulin concentration (≤ 3.5 mg/L v/s > 3.5 mg/L)
- 4) Clinical stage (Binet A or Rai 0 v/s Binet B–C or Rai I–IV)
- 5) Age (≤ 65 years v/s > 65 years)

Risk Group	CLL-IPI risk score
Low-risk	0-1
Intermediate-risk	2-3
High-risk	4-6
Very High-risk	7-10

CLL-IPI : How to implement

Risk Group	CLL-IPI risk score	Management
Low-risk	0-1	Do not touch : watch-and-wait approach
Intermediate-risk	2-3	Do not treat (except when the patient is symptomatic)
High-risk	4-6	Treat (except when the patient is asymptomatic)
Very High-risk	7-10	Treat in experimental protocol or with non-cytotoxic drugs if possible (no chemotherapy or chemo-immunotherapy)

Prognostic factor

Points

Del17p on FISH or <i>TP53</i> mutation	4
Unmutated <i>IGHV</i> genes	2
Serum β 2 microglobulin > 3.5 mg/L	2
Rai stage I–IV	1
Age > 65 years	1

Cumulative CLL-IPI score

Risk category

5-year TFS^a

0–1	Low risk	78%
2–3	Intermediate risk	54%
4–6	High risk	32%
7–10	Very high risk	0%

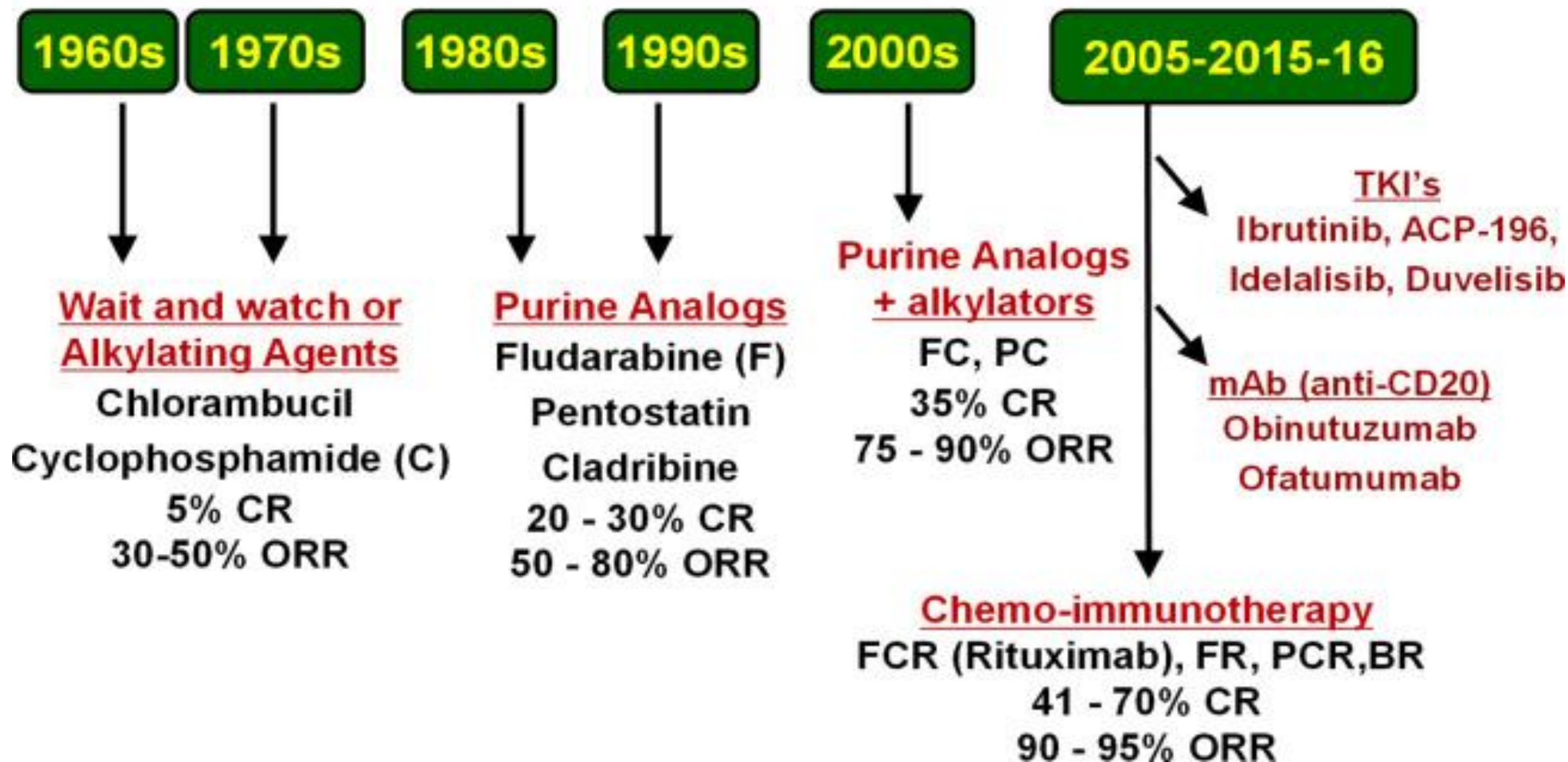
FISH fluorescence in situ hybridization, *IGHV* immunoglobulin heavy chain gene, *TFS* treatment-free survival

^aFor the Mayo validation cohort

Risk categories according to the revised high-risk CLL concept.

Refractoriness to	TP53 abnormality present (del17p/TP53 ^{mut})	High risk Category
CIT only	yes	I – CIT-resistant (BTKi- and BCL2i-sensitive)
CIT + BTKi or CIT + BCL2i or BTKi + BCL2i (+/- CIT)	yes or no	II – CIT- and PI-resistant (BTKi- and/or BCL2i-refractory)

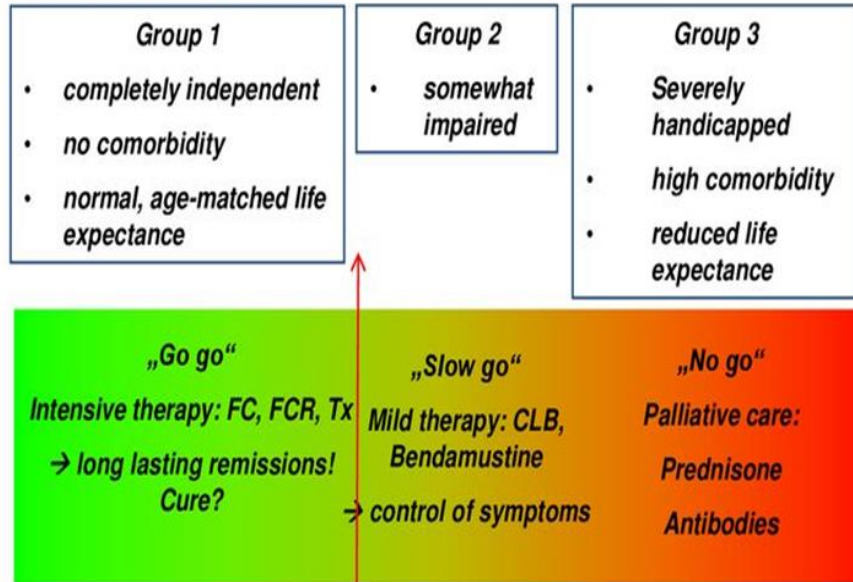
Progress in the treatment of CLL



**Recommendations
Regarding Indications for
Treatment in CLL**

	General practice	Clinical trial
Treat with Rai stage 0	NGI*	RQ
Treat with Binet stage A	NGI*	RQ
Treat with Binet stage B or Rai stage I or Rai stage II	Possible*	Possible*
Treat with Binet stage C or Rai stage III or Rai stage IV**	Yes	Yes
Treatment of active/progressive disease	Yes	Yes
Treat without active/progressive disease	No	RQ

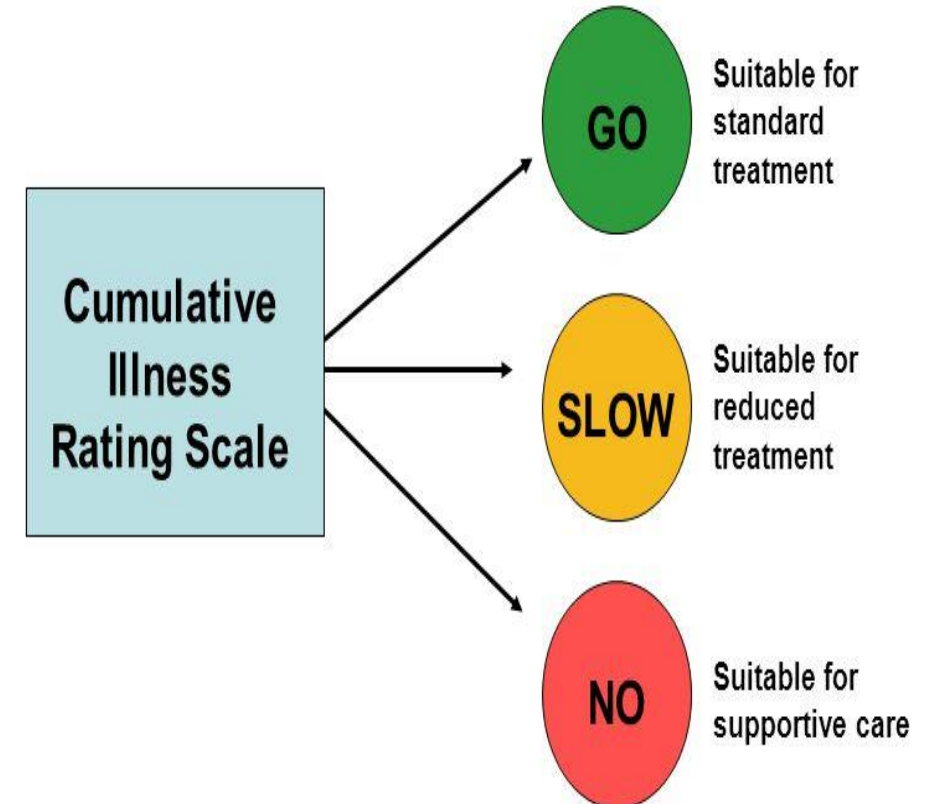
CLL Comprehensive Geriatric Assessment (CGA)



CIRS > 6



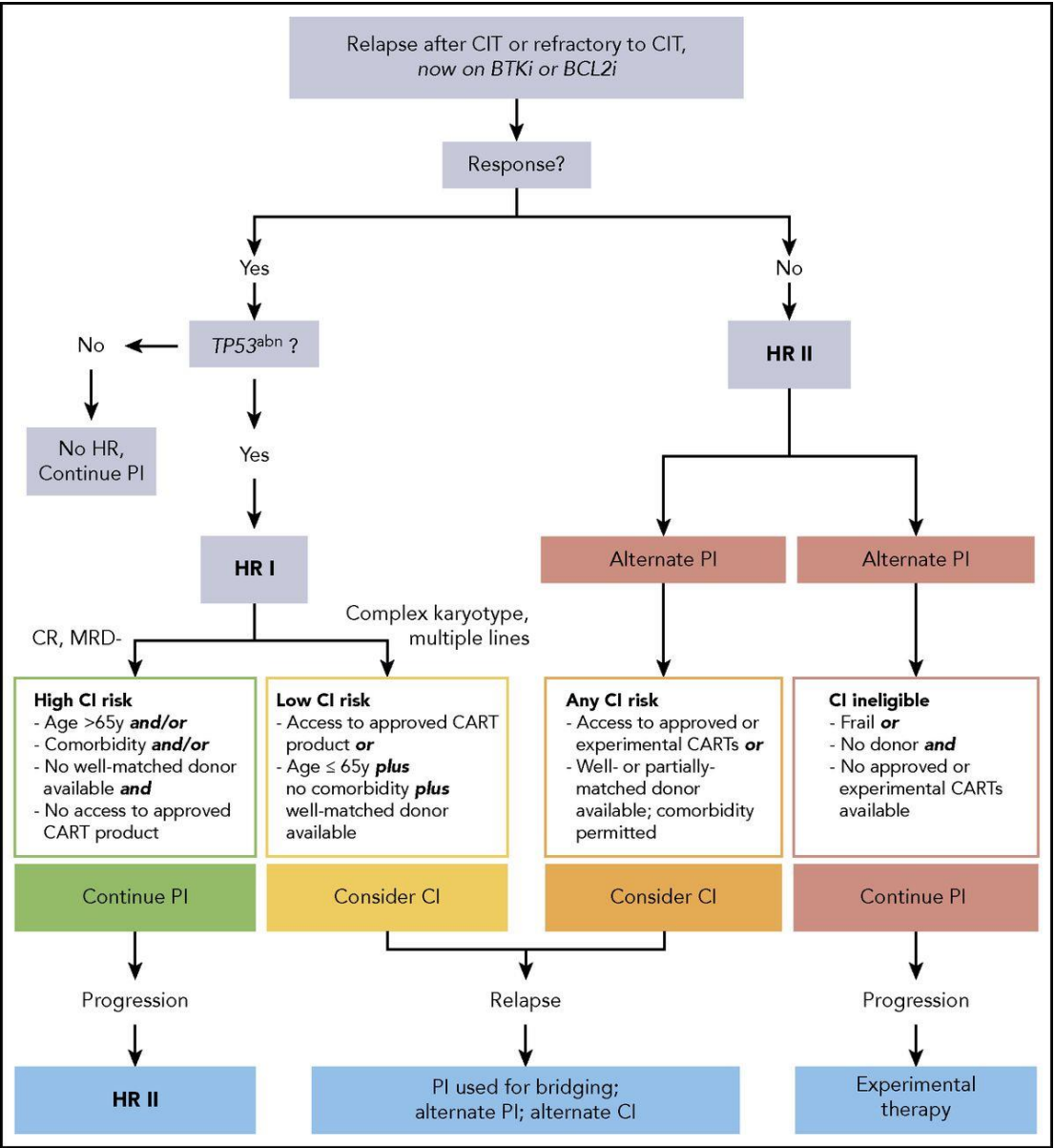
Classification of Patients by a Comprehensive Geriatric Assessment (CGA)



Adapted from Michael Hallek

Gribben JG. *Blood* 2009;114:3359-60; Balducci L, Extermann M. *Oncologist* 2000;5:224-37.

Decision tree for therapy of chemoimmunotherapy-resistant untransformed CLL according to the revised high-risk concept. *Additional factors to be taken into account when considering cellular therapy.



Peter Dreger et al. Blood 2018;132:892-902

CLL first line treatment (updated June 2019)

Stage	del(17p) or p53mut	Fitness	IGVH	Therapy
Binet A-B, Rai 0-II, inactive disease	Irrelevant	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III-IV	Yes	Irrelevant	Irrelevant	Ibrutinib or Venetoclax + Obinutuzumab or Idelalisib + Rituximab (if contraindications for ibrutinib)*
	No	Go go	M	FCR (BR above 65 years) or ibrutinib*
			U	Ibrutinib or FCR (BR above 65 years)*
		Slow go	M	Venetoclax + Obinutuzumab or Chlorambucil + Obinutuzumab or Ibrutinib*
			U	Venetoclax + Obinutuzumab or Ibrutinib or Chlorambucil + Obinutuzumab*

* Consider and discuss with patient: long-term vs fixed (6-12 m) duration therapy, lack of convincing evidence of overall survival differences, specific side effects of each therapeutic option (myelosuppression, infections, secondary malignancies for CIT; cardiac toxicity, bleeding and autoimmune disease for Ibru; TLS and infections for Ven-Obi; autoimmune disease (diarrhea) and opportunistic infections for Idelalisib).

CLL first line treatment

Stage	Fitness	del(17p) p53mut	Therapy
Binet A-B, Rai 0-II, inactive	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III-IV	Go go	No	FCR (BR above 65 years?)
		Yes	Ibrutinib, Idelalisib+Rituximab (Allogeneic SCT)
	Slow go	No	Chlorambucil + Obinutuzumab (GA-101) or + Rituximab or + Ofatumumab or Ibrutinib
		Yes	Ibrutinib, Alemtuzumab, HD Rituximab or Ofatumumab

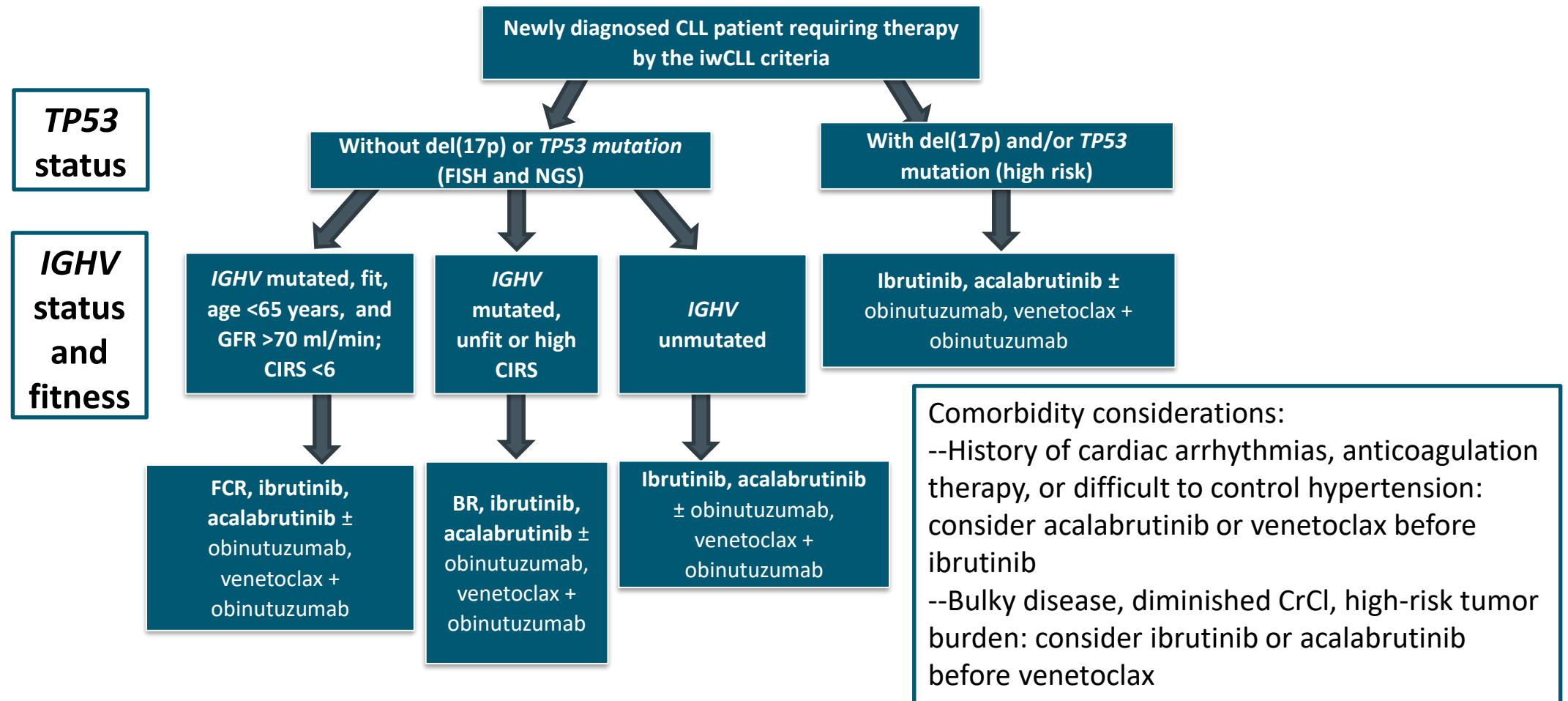
CLL second line treatment

Response to 1L Therapy	Fitness	Therapy
Refractory or progress within 3 years	Go go	Change therapy to one of the following options: Ibrutinib, Idelalisib + R, FA, FCR (after BR), Venetoclax, A-Dex, Lenalidomide (+ R), BR (after FCR). Discuss consolidation with allogeneic SCT.
	Slow go	Change therapy to one of the following options: Ibrutinib, Idelalisib + R, Venetoclax, A, FCR-lite, BR, Lenalidomide (+R), Ofatumumab, HD R
Progress after 3 years	All	Repeat first-line therapy

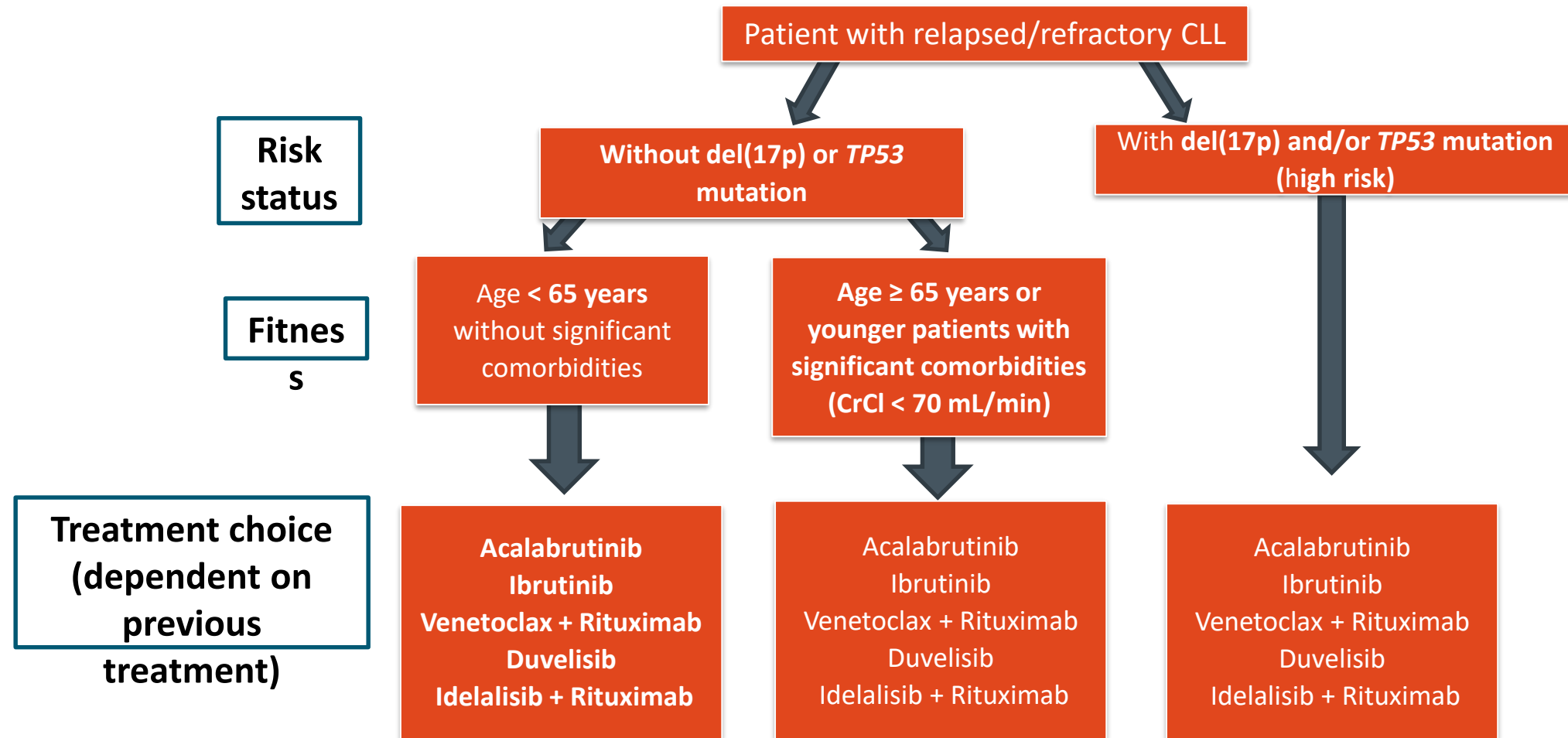
CLL 2L treatment June 2019

Response to 1L Therapy	Fitness	Therapy
Refractory or progress within 3 years	Go go	Change to one of the following options: Ibrutinib, Idelalisib+R, Venetoclax+Rituximab, FCR or BR, Lenalidomide (+R), Alemtuzumab+Dexamethasone, Fludarabine+Alemtuzumab. Discuss consolidation with allogeneic SCT.
	Slow go	Change to one of the following options: Ibrutinib, Idelalisib + R, Venetoclax +Rituximab, Alemtuzumab+Dexamethasone, FCR-lite, BR, Lenalidomide (+R), High-dose rituximab.
Progress after 3 years	All	Repetition of 1L therapy is possible.

Treatment Algorithm for Newly Diagnosed CLL

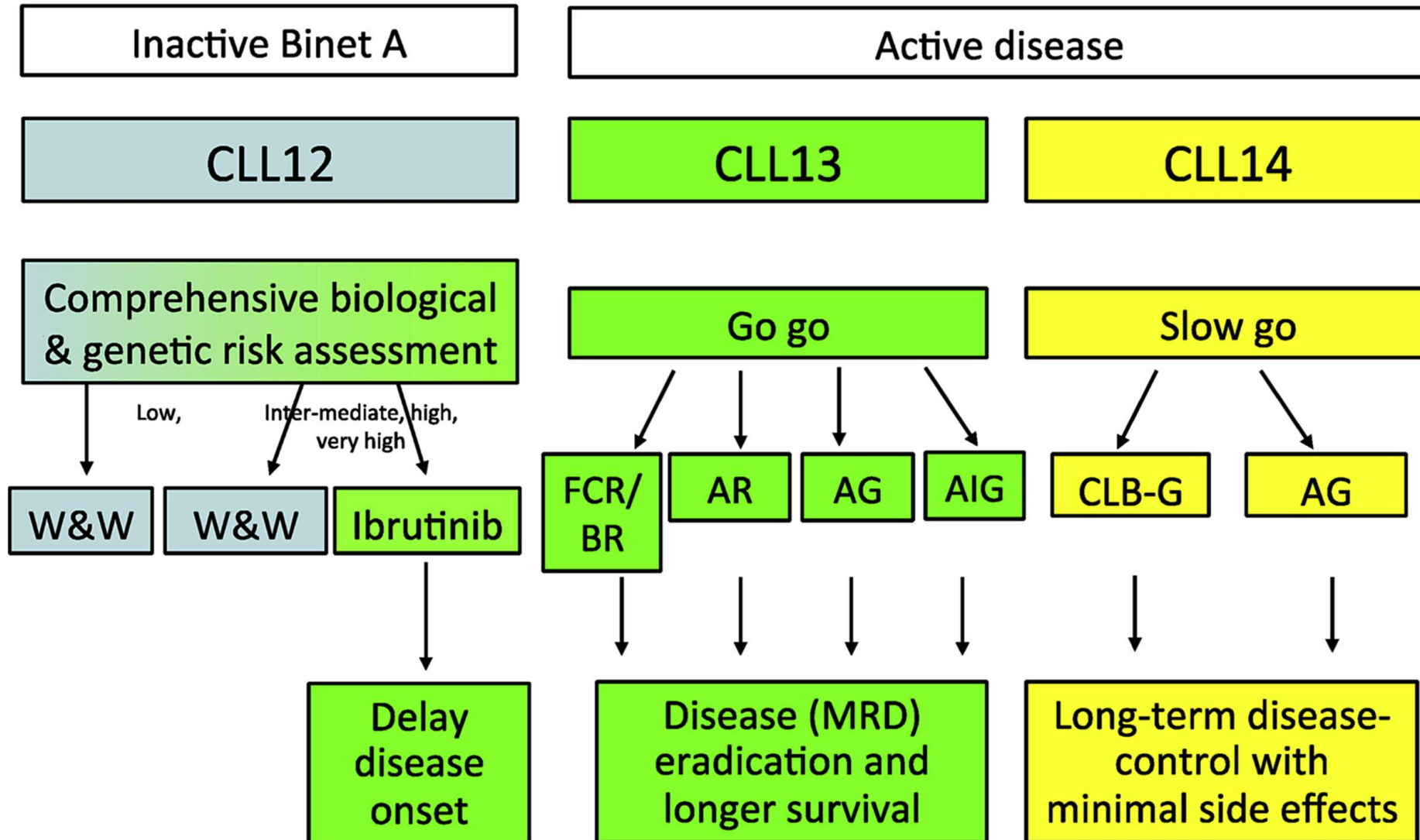


Treatment Algorithm for Relapsed/Refractory CLL

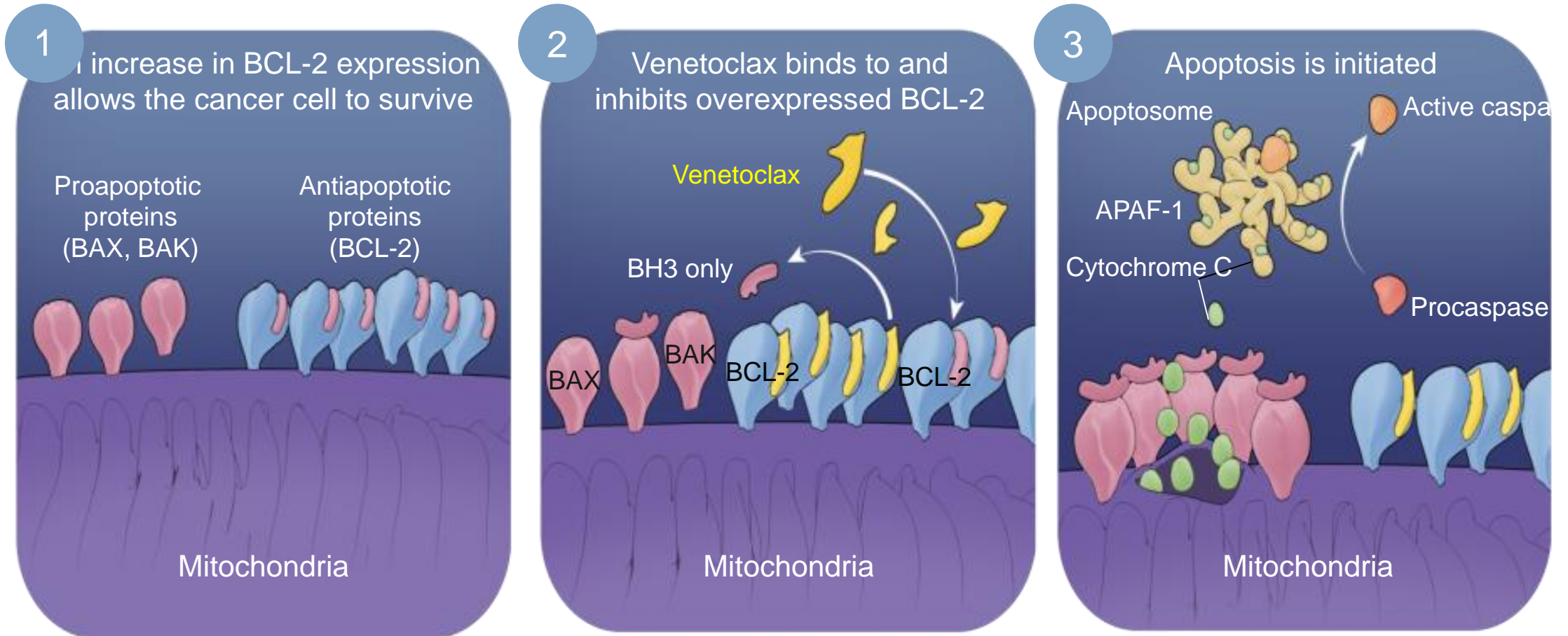


Fourth Generation of GCLLSG Trials

Risk, Stage and Fitness Adapted, Using Targeted Agents



Venetoclax: Mechanism of Action

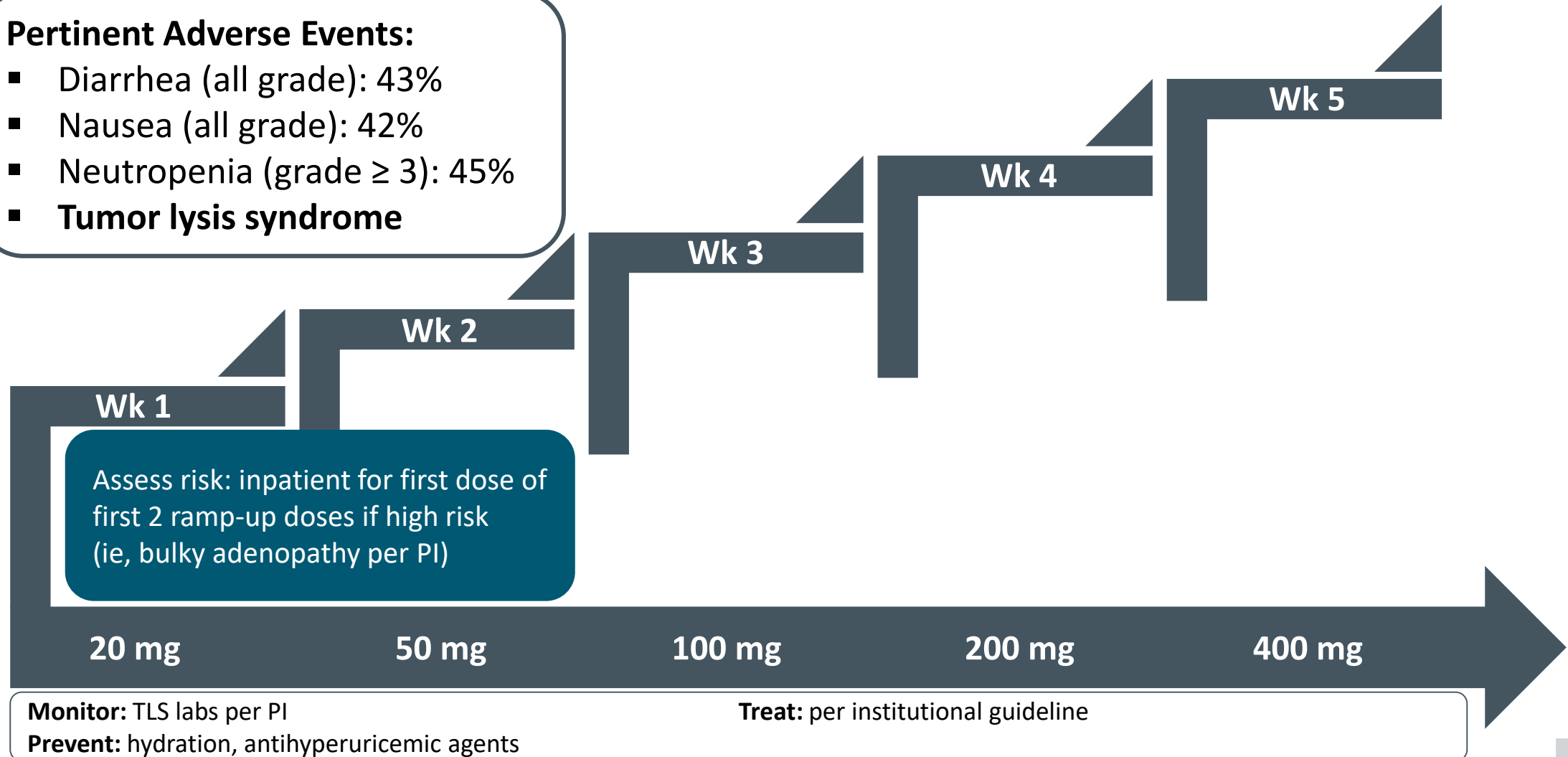


Kumar S, et al. ASCO 2015. Abstract 8576. Reproduced with permission.

Venetoclax: Adverse Events and Management

Pertinent Adverse Events:

- Diarrhea (all grade): 43%
- Nausea (all grade): 42%
- Neutropenia (grade ≥ 3): 45%
- **Tumor lysis syndrome**



Venetoclax: TLS Management

Tumor Lysis Syndrome

1

Assess Risk

TLS Risk	Disease Characteristics
Low risk	No bulky adenopathy ALC < 25 x 10 ⁹ /L
Intermediate risk	Bulky adenopathy: ≥ 5 cm and < 10 cm or ALC: ≥ 25 x 10 ⁹ /L
High risk	Bulky adenopathy: ≥ 10 cm or bulky adenopathy: ≥ 5 cm and ALC ≥ 25 x 10 ⁹ /L
Additional factors to consider: baseline uric acid, LDH, potassium, phosphorous, SCr, calcium	

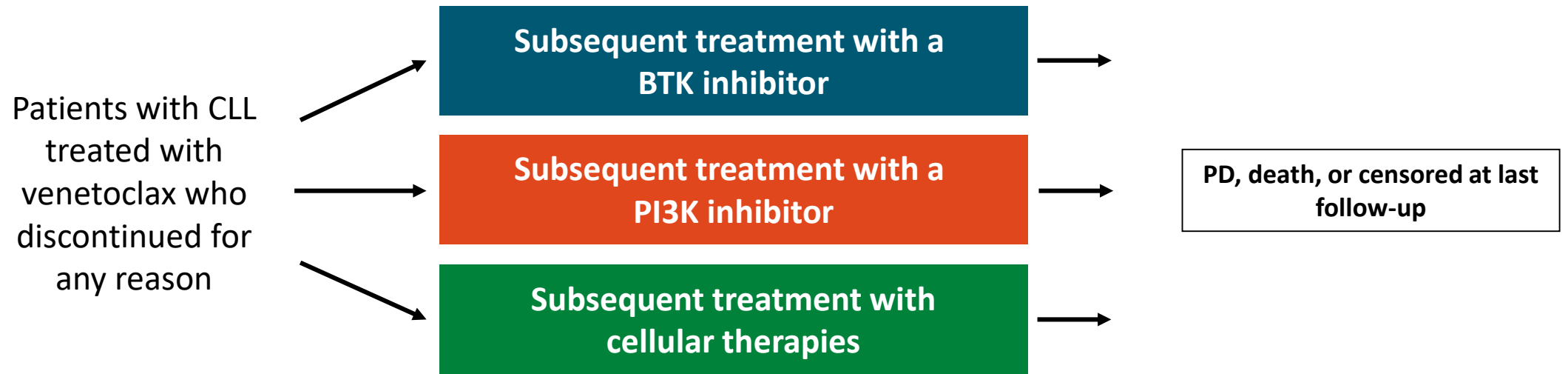
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Management

TLS Risk	Management Plan
Low risk	Outpatient: <ul style="list-style-type: none"> Oral hydration (1.5-2.0 L/day) and allopurinol Lab monitoring: predose, 6-8 hrs, 24 hrs at first dose of 20 mg and 50 mg and then predose at subsequent ramp-up doses
Intermediate risk	Outpatient: <ul style="list-style-type: none"> Oral hydration (1.5-2.0 L/day), IV (PRN), and allopurinol Lab monitoring: predose, 6-8 hrs, 24 hrs at first dose of 20 mg and 50 mg and then predose at subsequent ramp-up doses if creatinine clearance < 80 mL/min, consider inpatient admission for first 2 dose escalations
High risk	Inpatient for first dose of first 2 ramp-up doses: <ul style="list-style-type: none"> Oral hydrations and IV as tolerated Allopurinol (consider rasburicase based on baseline uric acid)

Sequencing of CLL Therapy: Study Design

- Multicenter, international retrospective cohort study to assess subsequent treatment response after venetoclax



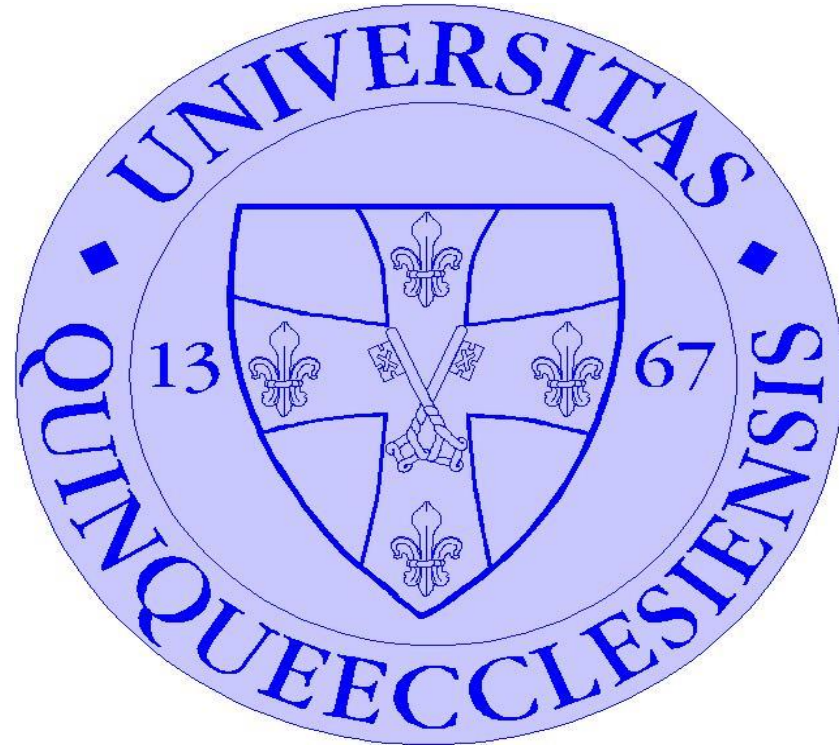
- Primary endpoints: ORR, PFS after treatment following venetoclax discontinuation
 - PFS: time from post-venetoclax tx to PD, death, or censored at last follow-up
 - PFS2: PFS from start of venetoclax therapy to progression on ibrutinib, death, or censored on last follow-up

Sequencing of CLL Therapy: Investigator Conclusions

- Response to CLL therapy following use of venetoclax varied by prior treatment and cause of venetoclax discontinuation
- BTKi resulted in high ORR and durable remissions in BTKi-naïve patients
- Alternative BTKi active in BTKi-intolerant patients
- BTKi not effective in BTKi-resistant patients
- PI3Ki not effective in PI3Ki-naïve patients, indicating potential cross-resistance
- AlloSCT effective following treatment with venetoclax and second novel agent
- Data suggest support for use of venetoclax earlier in CLL course
- Findings may inform clinical practice and clinical trials needed to inform sequencing of new therapies

Conclusions

- Novel targeted agents are eclipsing chemoimmunotherapy both in patients with newly diagnosed and relapsed CLL
 - Initial therapy options include acalabrutinib ± obinutuzumab, ibrutinib, and venetoclax + obinutuzumab
 - Therapy options for relapsed CLL include acalabrutinib, ibrutinib, venetoclax + rituximab, duvelisib, and idelalisib + rituximab
 - Ongoing investigation is exploring novel agents and multitargeted combination regimens with the goal of MRD eradication
 - CAR T-cells are showing early promise as a potential future option for high-risk relapsed/refractory disease
-



Köszönöm a megtisztelő figyelmet
