Multidisciplinary Approaches to Cancer Symposium

Myelodysplastic Syndrome and Myeloproliferative Neoplasm: Molecular Markers & Management with Novel Drugs

Subheading: Novel Agents in MPNs

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Disclosures

- Consultant for GSK, Karyopharm, PharmaEssentia, & Sobi;
- Grant/Research Support from Incyte

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of Fludarabine, Melphalan, Hypomethylating Agents, Selinexor, INCA 33989, Janssen Vaccine, Imetalstat will be addressed.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

Myeloproliferative neoplasms (MPN)

- Phenotypically diverse group that are stem cell-derived clonal disorders charactered initially by slow, progressive myeloid proliferation
- Classified according to molecular drivers: BCR/ABL+ in CML, BCR/ABL- in classical MPN (PV, ET, and MF)
- Driver mutations within stem cells and myeloid progenitors provide cytokine-independent or -hypersensitive proliferative signals leading to the overproduction of myeloid cells
- MPN share several clinical and lab features
  - Cytosis
  - Pronounced constitutional symptom burden
  - Organomegaly due to extramedullary hematopoeisis
  - Progressive marrow fibrosis
  - Thrombotic complications
  - Bone marrow failure and risk for AML

MPN Classification

ICC 2022	WHO 2022
Chronic myeloid leukemia	Chronic myeloid leukaemia
Polycythemia Vera	Polycythemia Vera
Essential thrombocythemia	Essential thrombocythaemia
Primary myelofibrosis **Early/Prefibrotic PMF** **Overt PMF**	**Primary myelofibrosis**
Chronic neutrophilic leukemia	Chronic neutrophilic leukaemia
Chronic eosinophilic leukemia, not otherwise specified	Chronic eosinophilic leukaemia
	Juvenile myelomonocytic leukaemia
MPN, unclassifiable	Myeloproliferative neoplasm, not otherwise specified

Khoury, J.D., *et al.* The 5th edition of the WHO Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. *Leukemia* **36**, 1703–1719 (2022)
Arber DA et al., ICC of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. *Blood* 2022; 140 (11): 1200–1228.

Myelofibrosis

- Annual incidence of MF is 0.2-0.5 cases per 100,000
- Median age at diagnosis at 65 years (70% after 60 years of age)
- Subtypes
  - Prefibrotic MF
  - Primary
  - MF Evolved from ET and PV
    - Post-ET MF
    - Post-PV MF

Myelofibrosis Diagnostic Criteria

Primary myelofibrosis (Overtly fibrotic stage) (*Diagnosis requires meeting all 3 major criteria and one minor criterion*)	**Primary myelofibrosis (Pre-fibrotic/early stage) (*Diagnosis requires meeting all 3 major criteria and one minor criterion*)**
Major criteria: 1. Megakaryocyte proliferation and atypia,[a] accompanied by ≥grade 2 reticulin/collagen fibrosis[b] 2. Presence of *JAK2*, *CALR* or *MPL* mutations, or presence of other clonal markers, or absence of evidence for reactive bone marrow fibrosis 3. Not meeting ICC criteria for other myeloid neoplasms	***Major criteria***: 1. Megakaryocyte proliferation and atypia,[a] accompanied by ≤grade 1 reticulin/collagen fibrosis, granulocyte proliferation/ decreased erythropoiesis 2. Presence of *JAK2*, *CALR* or *MPL* mutations, or presence of other clonal markers, or absence of evidence for reactive bone marrow fibrosis 3. Not meeting ICC criteria for other myeloid neoplasms
Minor criteria: *Anemia not otherwise explained* *Leukocytosis ≥11 × 10^9/L* *Palpable splenomegaly* *Increased serum lactate dehydrogenase* *A leukoerythroblastic blood smear*	***Minor criteria***: *Anemia not otherwise explained* *Leukocytosis ≥11 × 10^9/L* *Palpable splenomegaly* *Increased serum lactate dehydrogenase*

Tefferi: PMF. 2023 update. Am J Hematol; 2023;1-23

Secondary Myelofibrosis

Post-polycythemia vera myelofibrosis (post-PV MF)	Post-essential thrombocythemia myelofibrosis (post-ET MF)
Required: 4. Prior documentation of ICC[a]-defined PV 5. Bone marrow fibrosis grade ≥2[b]	***Required***: 1. Prior documentation of ICC[a]-defined ET 2. Bone marrow fibrosis grade ≥2[b]
Additional criteria (***two required***) *Anemia or loss of phlebotomy requirement* *A leukoerythroblastic blood smear* *Increasing splenomegaly* *Development of constitutional symptoms*	***Additional criteria*** (***two required***) *Anemia and ≥2 g/dl decrease in hemoglobin level* *A leukoerythroblastic blood smear* *Increasing splenomegaly* *Development of constitutional symptoms* *Increased serum lactate dehydrogenase*

Tefferi: PMF. 2023 update. Am J Hematol; 2023;1-23

Primary Myelofibrosis: Risk Stratification

Models	Variables	Risk categories					
		Very low	Low	Intermediate-1	Intermediate-2	High	Very high
IPSS[d] *International* *Prognostic* *Scoring* *System*	Age >65 years (1 point) Constitutional symptoms[a] (1 point) Hemoglobin <10 g/dl (1 point) Leukocytes >25 × 10(9)/L (1 point) Circulating blasts ≥1% (1 point)	NA	(0 points) 11.3 years	(1 point) 7.9 years	(2 points) 4 years	(≥3 points) 2.3 years	NA
DIPSS[e] *Dynamic* *International* *Prognostic* *Scoring* *System*	Age >65 years (1 point) Constitutional symptoms (1 point) Hemoglobin <10 g/dl (2 points) Leukocytes >25 × 10(9)/L (1 point) Circulating blasts ≥1% (1 point)	NA	(0 points) Not reached	(1–2 points) 14.2 years	(3–4 points) 4 years	(5–6 points) 1.5 years	NA
DIPSS-plus[e]	Age > 65 years (1 point) Constitutional symptoms[a] (1 point) Hemoglobin <10 g/dl (1 point) Leukocytes >25 × 10(9)/L (1 point) Circulating blasts ≥1% (1 point) Unfavorable karyotype[h] (1 point) Platelet count <100 × 10(9)/L (1 point) Transfusion needs (1 point)	NA	(0 points) 15.4 years	(1 point) 6.5 years	(2–3 points) 2.9 years	(≥4 points) 1.3 years	NA

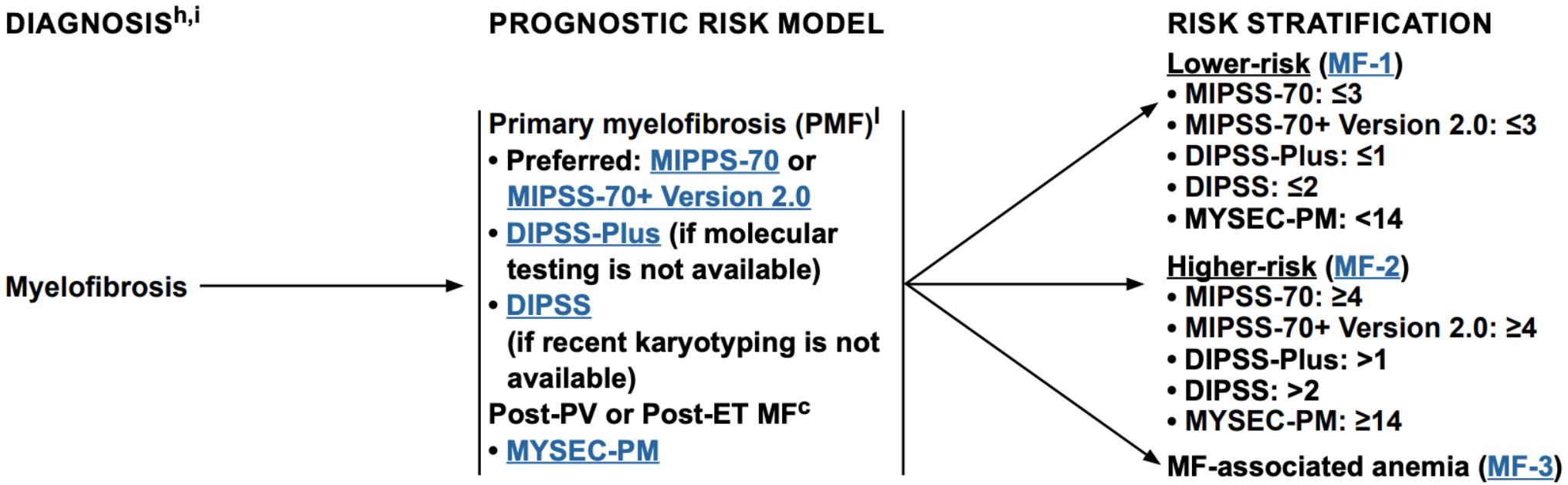
Tefferi: PMF. 2023 update. Am J Hematol; 2023;1-23

Primary Myelofibrosis: Risk Stratification

Models	Variables	Risk categories					
		Very low	Low	Intermediate-1	Intermediate-2	High	Very high
MIPSS70[d] *Mutation-enhanced International Prognostic Scoring System (Age ≤ 70 years)*	≥2 HMR mutations[b] (2 points) Leukocytes >25 × 10^9/L (2 points) Platelets <100 × 10^9/L (2 points) Hemoglobin <10 g/dl (1 point) Circulating blasts ≥2% (1 point) BM fibrosis grade ≥2 (1 point) Constitutional symptoms[a] (1 point) Type 1/like *CALR* absent (1 point) One HMR mutation[b] (1 point)	NA	(0–1 point) Not reached	(2–4 points) 6.3 years		(≥5 points) 3.1 years	NA
MIPSS70 + v2[e]	Very high-risk karyotype[f] (4 points) Unfavorable karyotype[g] (3 points) ≥2 HMR mutations[c] (3 points) One HMR mutation[c] (2 points) Type 1/like *CALR* absent (2 points) Constitutional symptoms[a] (2 points) Severe anemia[i] (2 points) Moderate anemia[j] (1 point) Circulating blasts ≥2% (1 point)	(0 points) Not reached	(1–2 points) 16.4 years	(3–4 points) 7.7 years		(5–8 points) 4.1 years	(≥9 points) 1.8 years
GIPSS[e] *Genetics-inspired International Prognostic Scoring System*	Very high-risk karyotype[f] (2 points) Unfavorable karyotype[g] (1 point) *ASXL1* mutation (1 point) *SRSF2* mutation (1 point) *U2AF1*Q157 mutation (1 point) Type 1/like *CALR* absent (1 point)	NA	(0 points) 26.4 years	(1 point) 8 years	(2 points) 4.2 years	(≥3 points) 2 years	NA

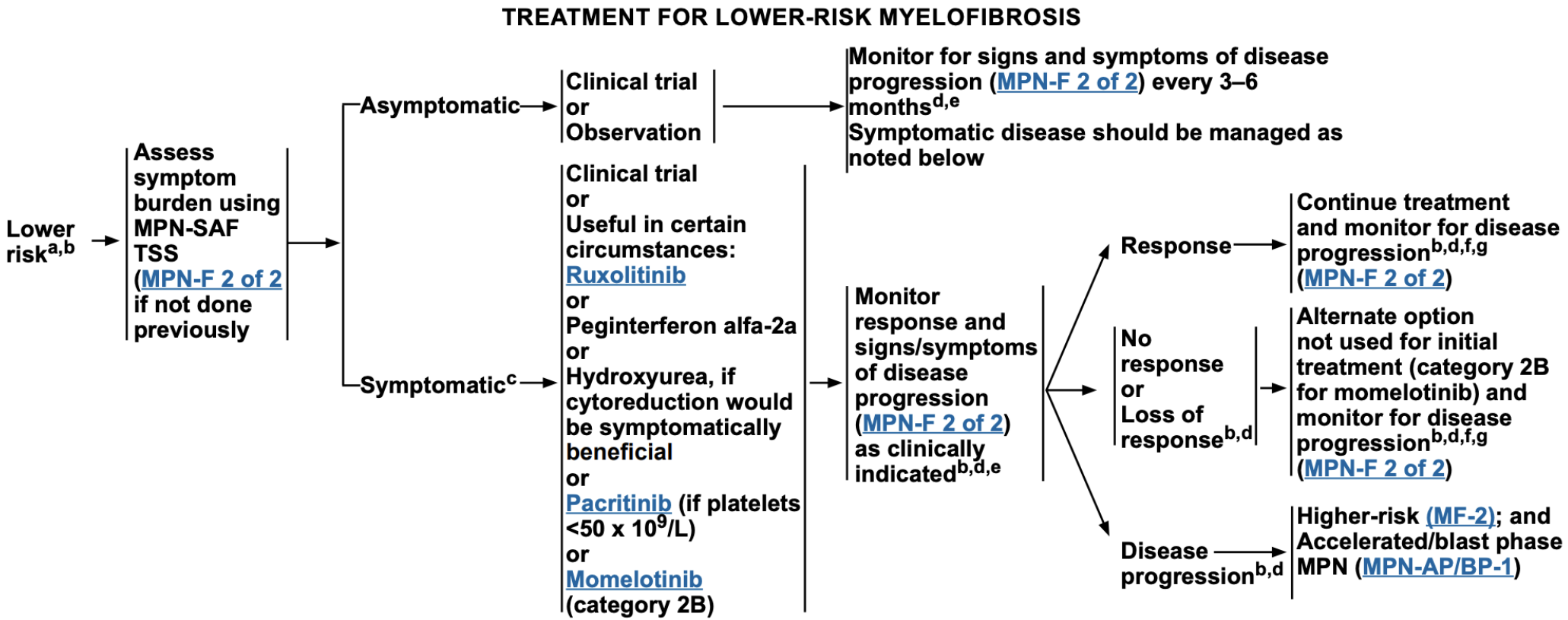
Tefferi: PMF. 2023 update. Am J Hematol; 2023;1-23

Treatment: Risk and Symptom based approach



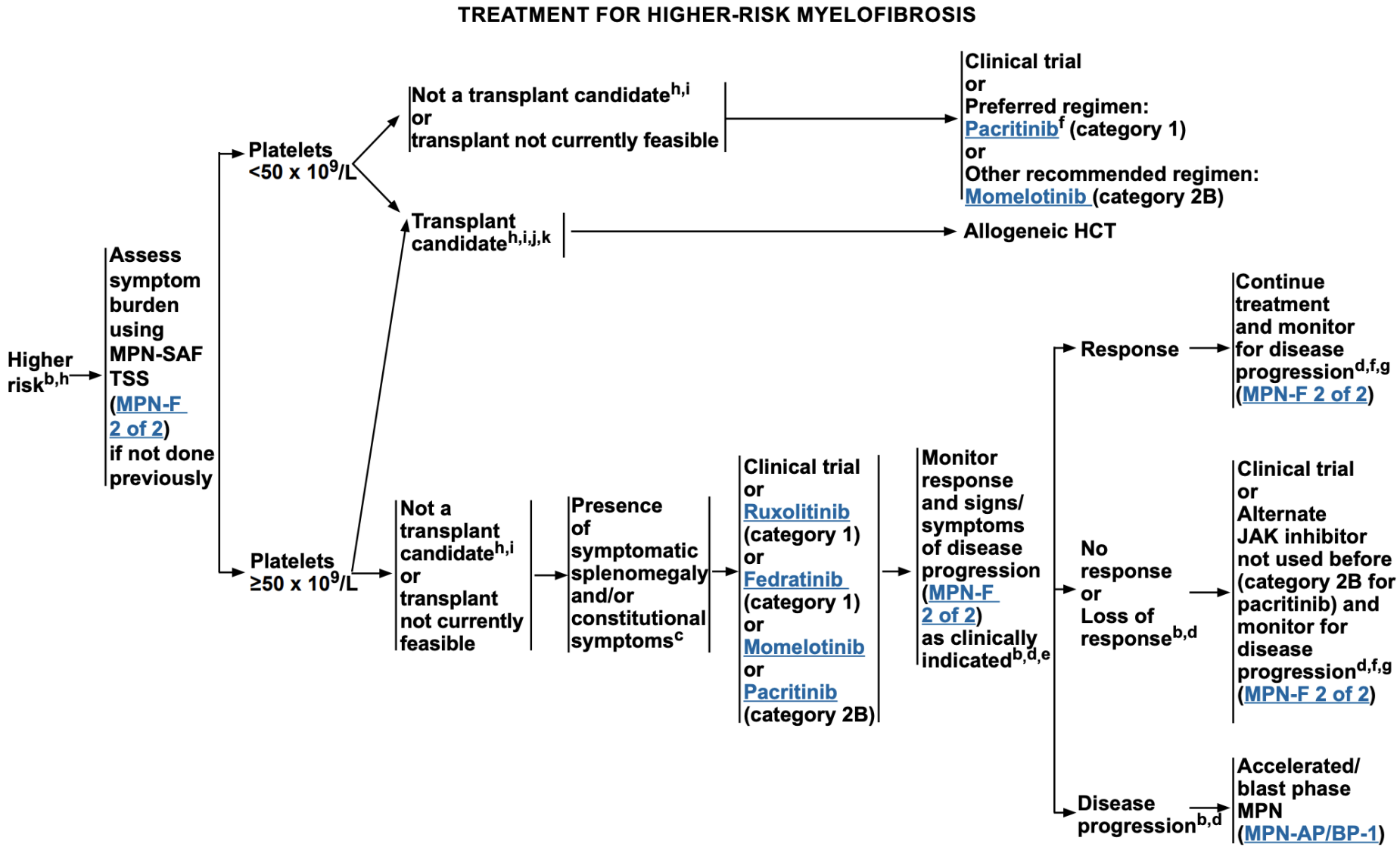
NCCN Guidelines v1.2024

Treatment: Risk and Symptom based approach



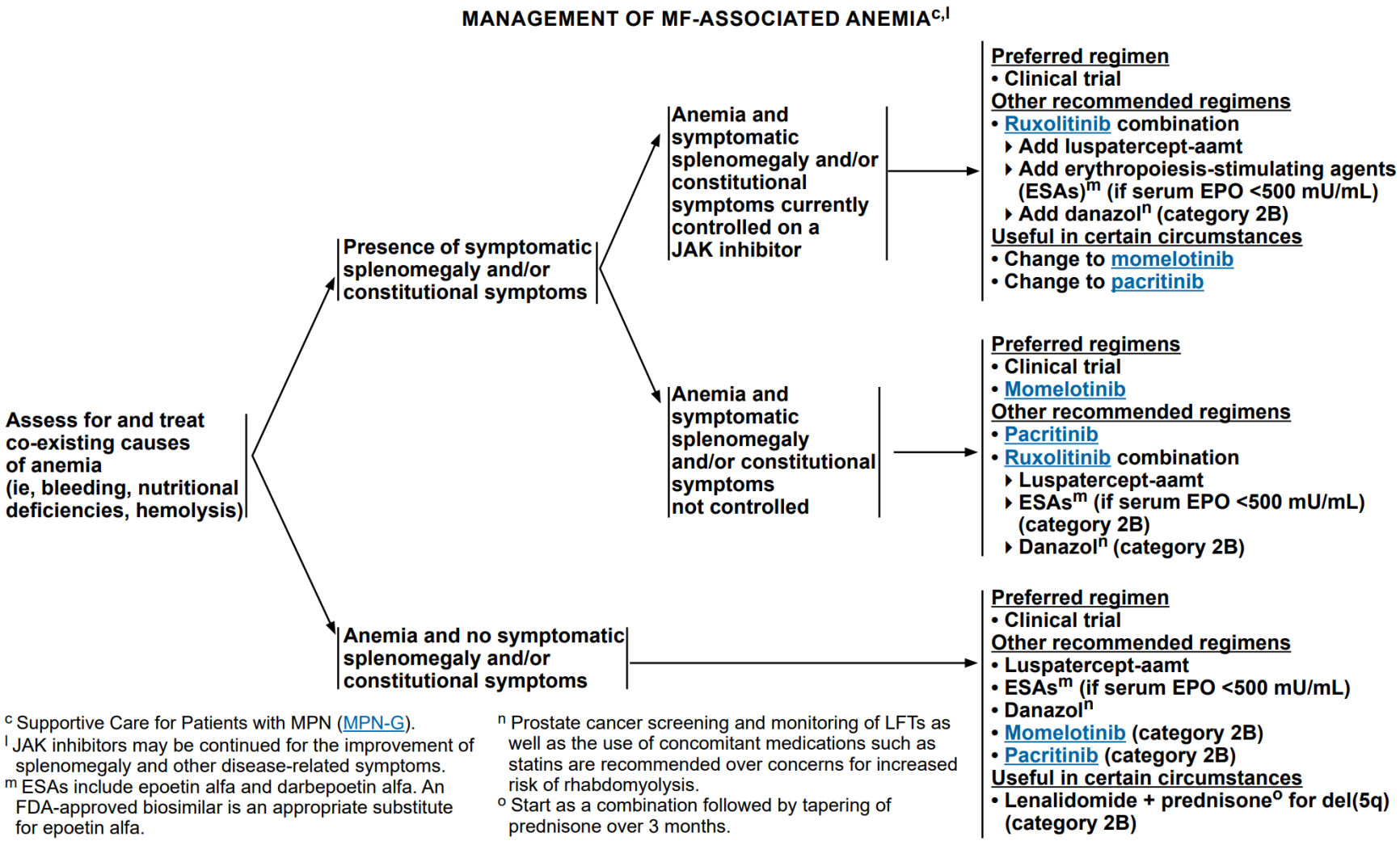
NCCN Guidelines v1.2024

Treatment: Risk and Symptom based approach



NCCN Guidelines v1.2024

Treatment: Risk and Symptom based approach



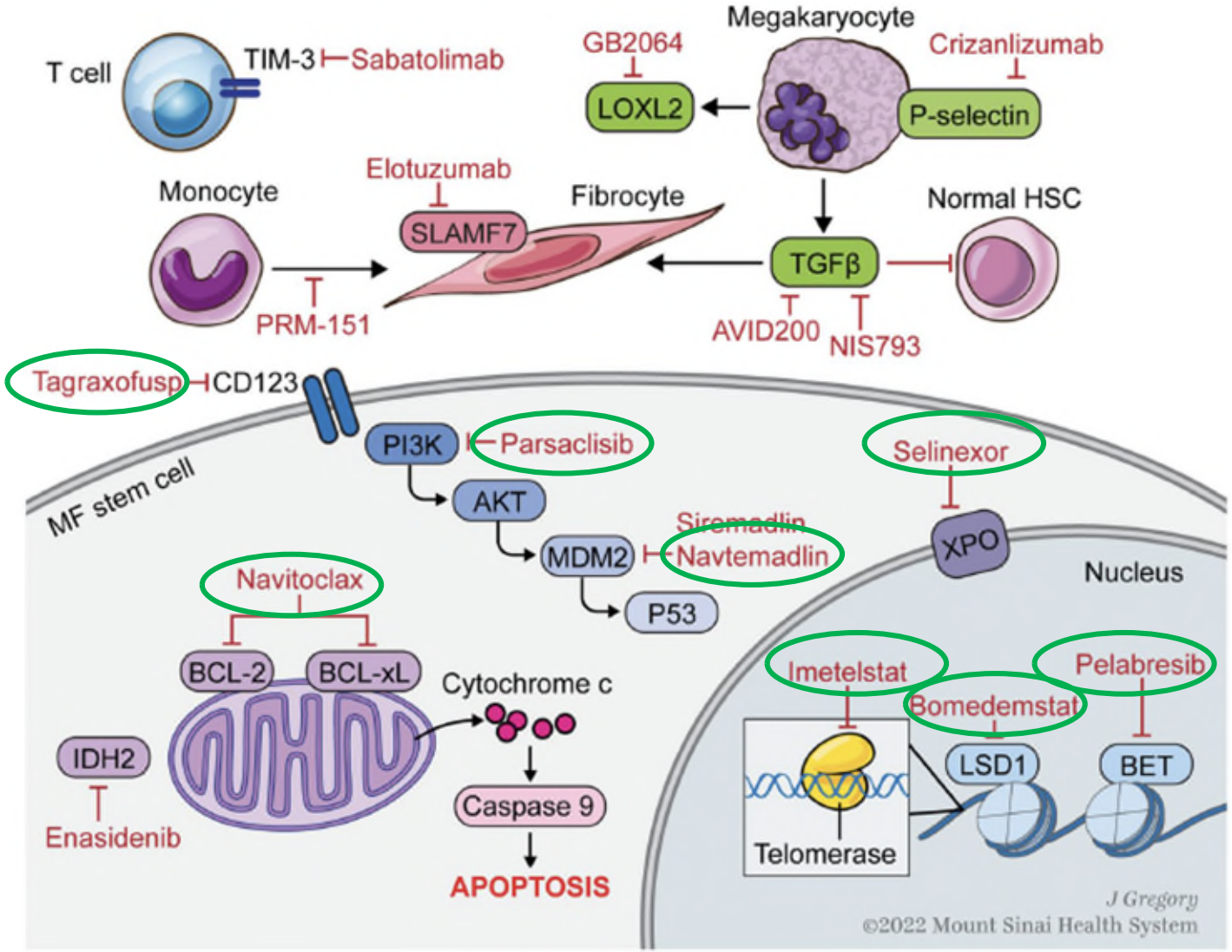
NCCN Guidelines v1.2024

Current JAKi

	Ruxolitinib	Fedratinib	Pacritinib	Momelotinib
Myelofibrosis symptom-relevant targets	JAK1/2	JAK2	JAK2 ACRV1	JAK1/2 ACRV1
FDA-approved indication	IPSS* High/intermediate risk	IPSS* High/Intermediate-2 risk First-line and Second-line	DIPSS** High/Intermediate risk First-line and Second-line for platelet count <50 × 10^9/L	DIPSS High/Intermediate risk With Anemia
FDA-approved dose and schedule	20 mg twice-daily (Platelet count >200 × 10^9/L) 15 mg twice-daily (Platelet count 150–200 × 10^9/L)	400 mg twice-daily (Platelet count ≥50 × 10^9/L)	200 mg twice-daily (Platelet count <50 × 10^9/L)	200mg daily
Spleen volume reduction ≥35% (radiographic)	42%% (COMFORT-1) 29% (COMFORT-2) 29% (SIMPLIFY-1)	36% (JAKARTA-1)	19% (PERSIST-1)	27% (SIMPLIFY-1)
Spleen response by palpation	32% (Mayo study)	83% (Mayo study)	Not reported	47% (Mayo study)
Anemia response in transfusion-dependent patients	30% (Mayo study)	10% (Mayo study)	25% (PERSIST-1)	51% (Mayo study)
Symptom response	57% (Mayo study) 46% (COMFORT-1) 42% (SIMPLIFY-1)	65% (Mayo study) 36% (JAKARTA-1)	19% (PERSIST-1)	48% (Mayo study) 28% (SIMPLIFY-1)
Adverse effects	Anemia Thrombocytopenia Withdrawal syndrome Opportunistic infections Poor response to COVID vaccines	Anemia Thrombocytopenia GI symptoms ↑Liver function tests ↑Amylase/lipase Wernicke's encephalopathy (Rare event)	GI symptoms (substantial) Peripheral edema Pneumonia Cardiac failure	Thrombocytopenia ↑Liver function tests ↑Amylase/lipase Peripheral neuropathy First-dose effect (Dizziness, Hypotension, Flushing, Nausea)

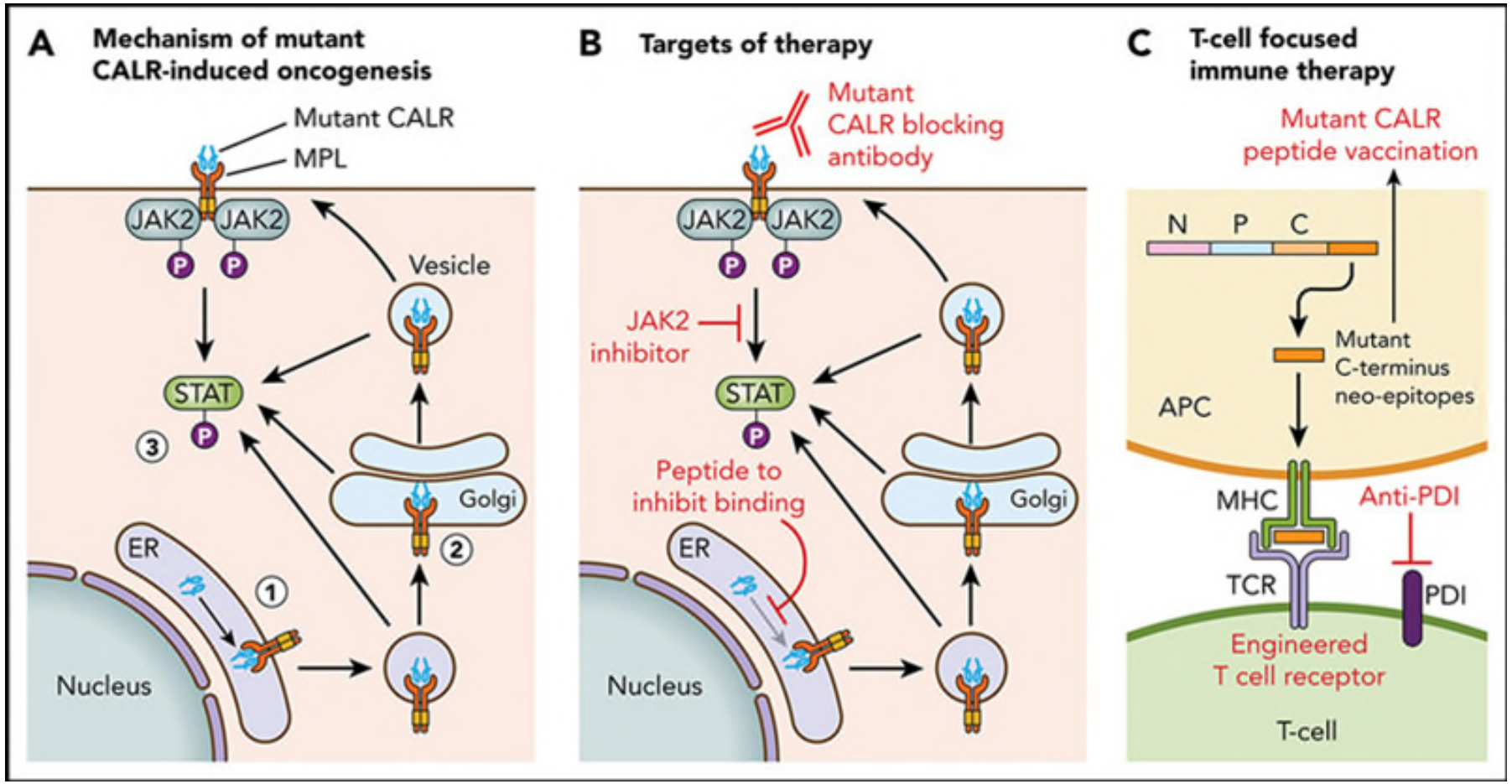
Tefferi: PMF. 2023 update. Am J Hematol; 2023;1-23

Novel Treatments in Myelofibrosis



Tremblay et al. Novel treatments in MF: beyon JAKi. Int Jour hem. 115, pages 645–658 (2022)

Novel Treatments in Myelofibrosis

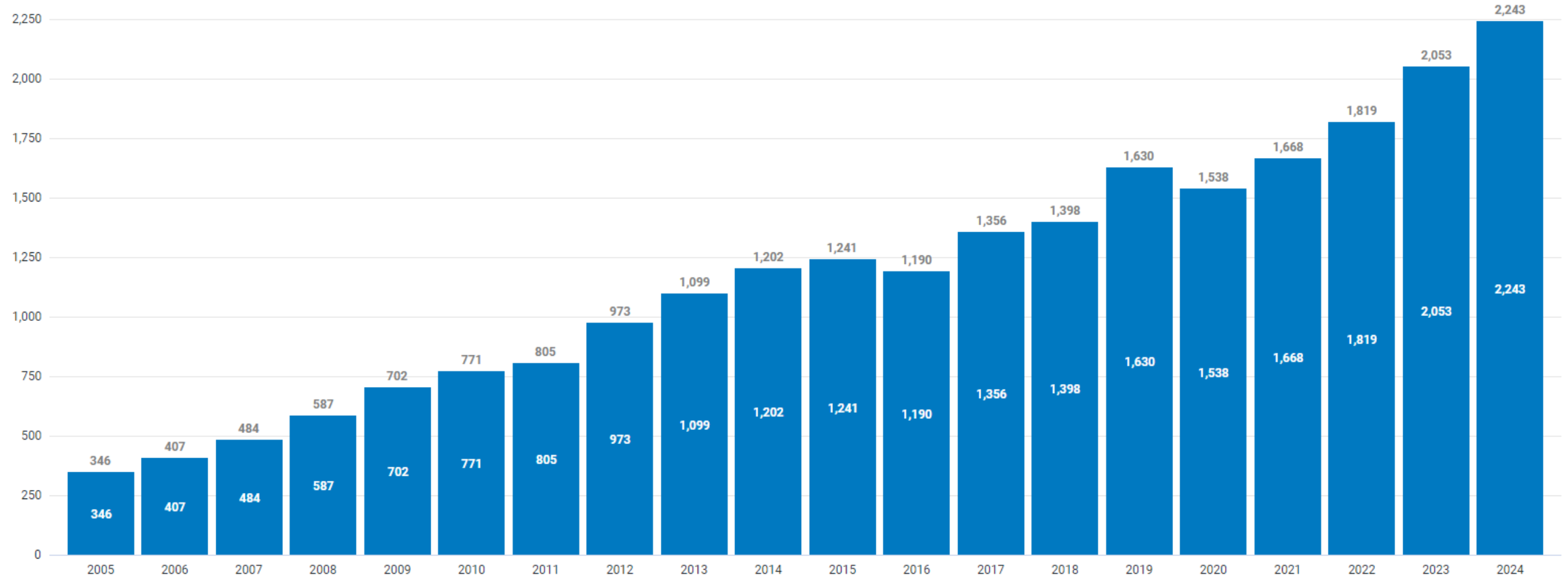


How et al. Mut CALR in MPNs. Blood. 2019 134(25). 2242-2248

Allogeneic Transplant in Myelofibrosis

- The only curative treatment modality
- Associated with some risk of transplant-related morbidity/mortality: GVHD, infection, graft rejection, and regimen-related toxicities
- What is optimal
  - Timing
  - Conditioning regimen
  - GVHD prophylaxis are not well-established
  - Impact of JAKi on transplant outcomes

Trends of MPN Transplants

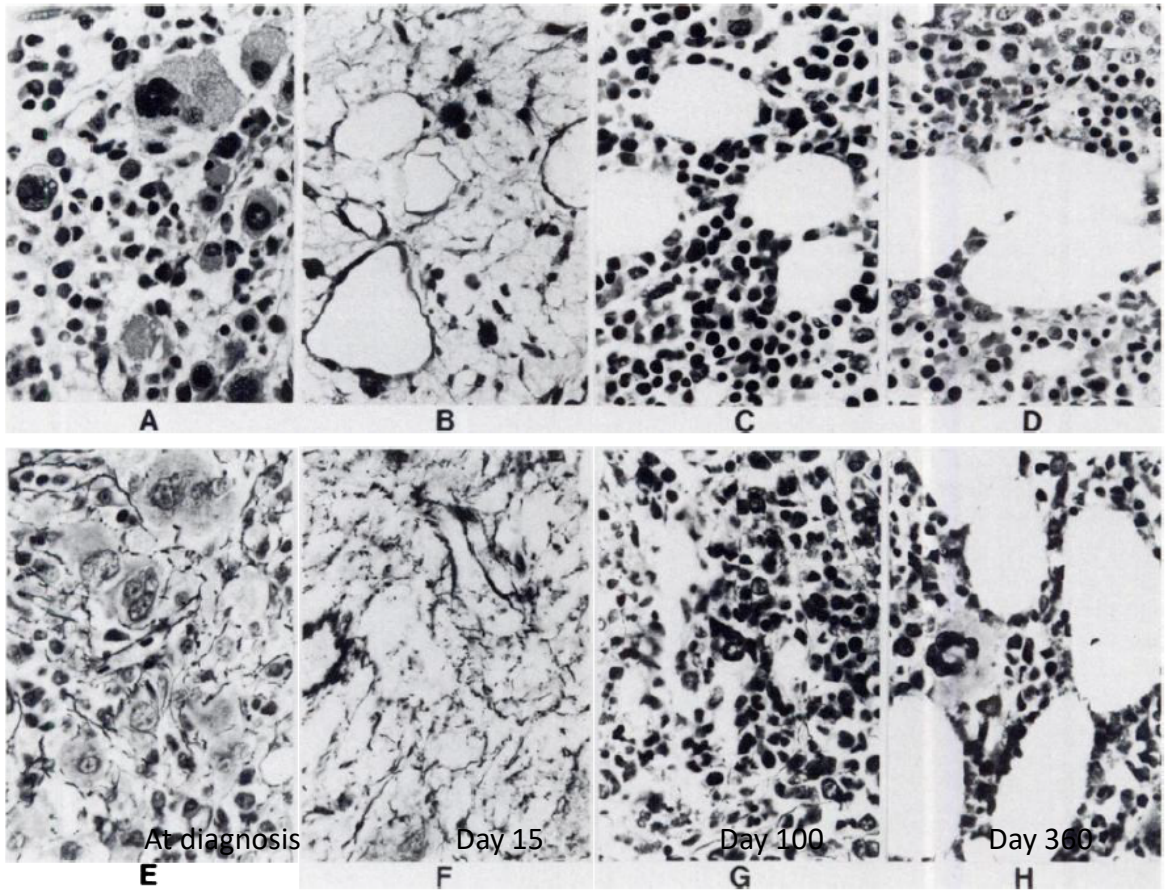


Time trend of HCT for Myelofibrosis: Data from NMDP

CONCISE REPORT

Reversal of Acute ("Malignant") Myelosclerosis by Allogeneic Bone Marrow Transplantation

By Jeffrey L. Wolf, Wayne E. Spruce, Robert M. Bearman, Stephen J. Forman, Edward P. Scott, John L. Fahey, Mark J. Farbstein, Henry Rappaport, and Karl G. Blume



Blood, Vol. 59, No. 1 (January), 1982

Conditioning Regimen

- Cytoreduce malignant clone
- Immunosuppression to prevent graft rejection while preserving graft versus leukemia effect
- Regimen can be myeloablative or reduced intensity conditioning
- Choice of conditioning
  - Performance status
  - Comorbid conditions

Retrospective Studies of MF Transplants

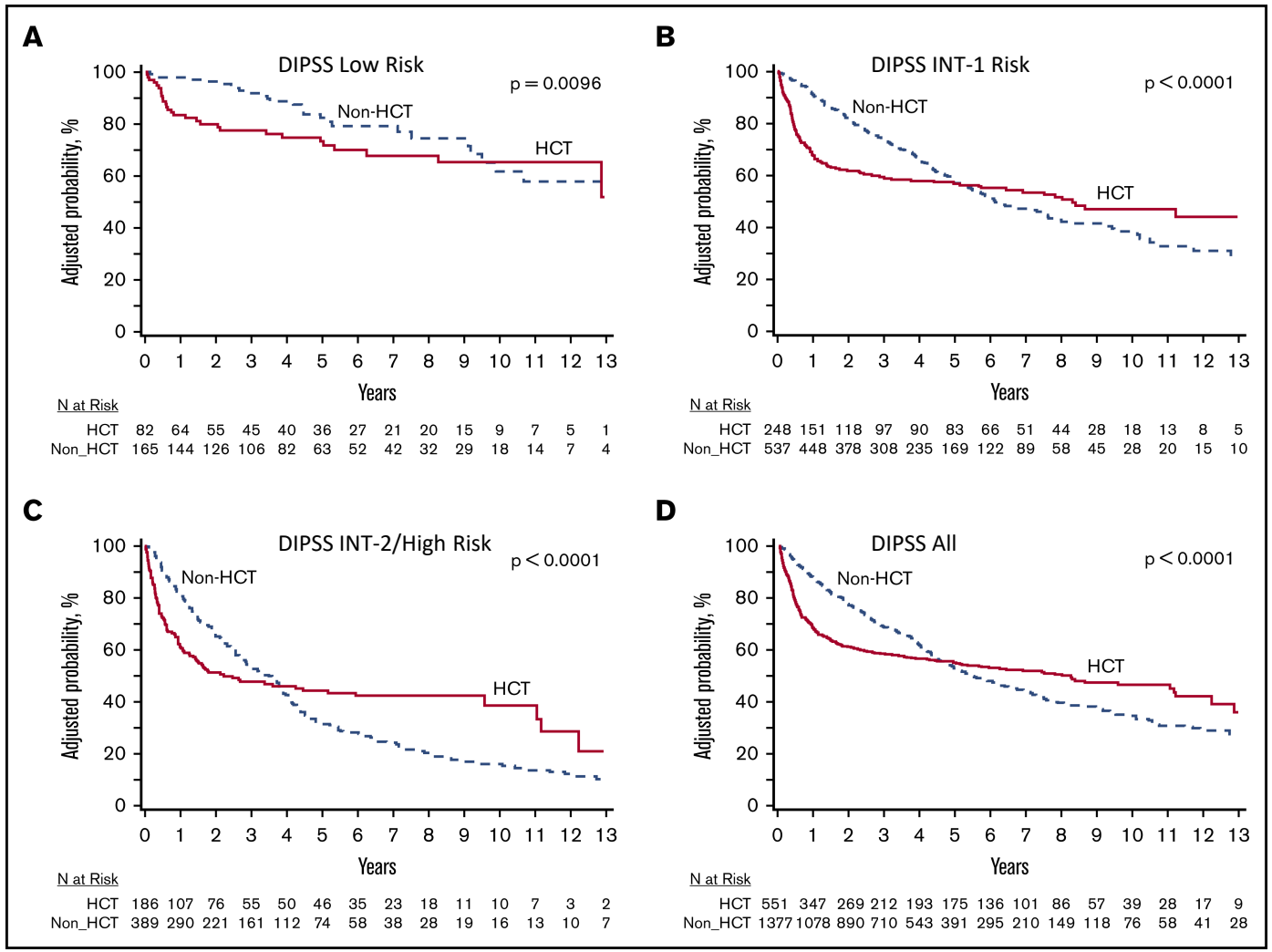
Study	Years	N	Conditioning Regimen	Median Age	Median Follow-up	OS% (years)	NRM
Patriarca et al.	1986-2006	100	RIC and MAC	49	34 mon	42 (3)	43%
Ballen et al.	1989-2002	289	RIC and MAC	47	41-46 mon	37-30% (5)	35-50%
Scott et al.	1990-2009	170	RIC and MAC	51	71 mon	57% (5)	34%
Lussana et al.	1994-2010	250	RIC and MAC	56	13 mon	55% (3)	28%
Robin et al.	1997-2008	147	RIC and MAC	53	35 mon	39% (4)	39%
Gupta et al.	1997-2010	233	RIC	55	50 mon	47% (5)	24%
Chiusolo et al	2000-2019	120	RIC and MAC	56	22 mm	62% (5)	22%
Kroger et al.	2000-2014	169	RIC Flu/Bu	58	74 mon	56% (5)	21%
Ali et al.	2004-2017	110	RIC Flu/Mel	59	64 mon	65%(5)	17%

Prognostic Scoring System

Study	Prognostic System	N	Age	Era	Conditioning	OS % (yrs)
Scott et al.	DIPSS	170	12-78	1990-2009	Majority MAC Bu/Cy Bu/Flu	Low = NR Intermediate -1 = NR Intermediate -2 = 7 yr High = 2.5 yr
Bannow et al.	DIPSS-Plus	233	13-79	1990-2014	RIC (18%) MAC (82%)	Low/int-1 78 % (5) High 35% (5)
Ali et al.	MIPSS 70	93	29-72	2004-2017	RIC Flu/Mel	Intermediate 89% (5) High 54% (5)
Ali et al.	MIPSS 70 Plus	93	29-72	2004-2017	RIC Flu/Mel	Int 91% (5) High 77%(5) Very High 30% (5)
Gagelmann et al.	MTSS*	361	18-75	NA	RIC 64% MAC 36%	Low 83 (5) Intermediate 64 % (5) High 37% (5) Very High 22% (5)

*Age >57, KPS <90%, Platelets <150, WBC >25, HLA mismatched, ASXL1 mutation, Non CALR/MPL driver mutation

HCT vs Non HCT Survival



Gowin et al. Survival following allogeneic transplant in patients with myelofibrosis. *Blood Adv* (2020) 4 (9): 1965–1973.

Thank you