Updates in Myeloproliferative Neoplasms

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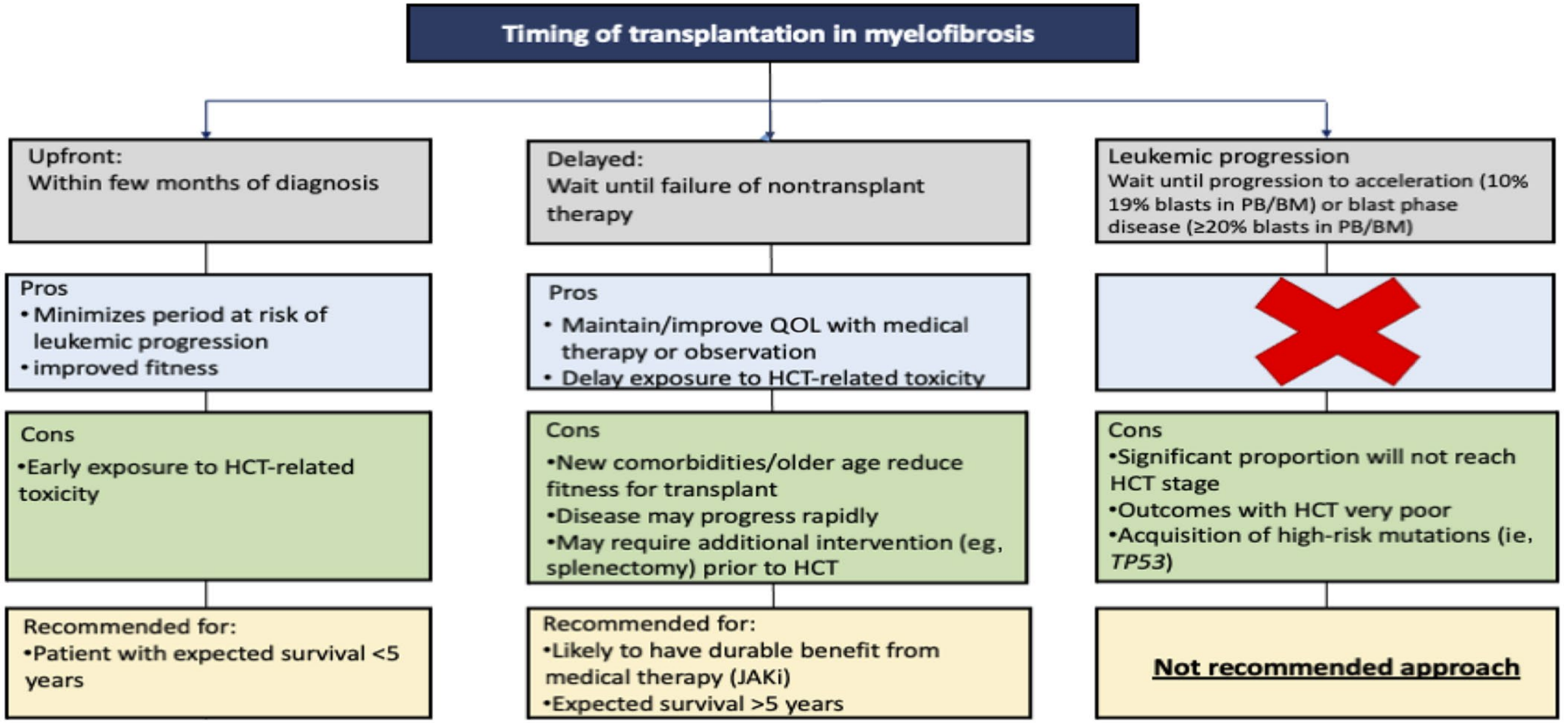
Disclosure of Conflicts of Interests

Hana Safah, MD has the following financial relationships to disclose:

Speaker – Astellas, BMS, GSK, Incyte,Jazz, Sanofi

Novel therapies vs HCT in MF

- Expert opinion is to recommend HCT to (DIPSS) intermediate-2/high-risk disease and intermediate-1 risk with additional risk factors
- Better outcome in low-risk disease with HCT, also very good results with JAKi , **no comparative trial**



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Optimal timing of HCT in MF

- No one-size fits all approach in patients with MF, optimal timing not well defined
- Strong recommendation against waiting to progress to AP/BP, poor outcome or patients will not reach the transplant stage
- Better understanding of the natural history of the disease, expected survival, likelihood of response to none transplant therapy
- Patients with an expected survival of less than 5 years and/or less likelihood of durable response from nontransplant therapy are defined as having high-risk MF
- Recommendation is upfront HCT in the appropriate patient-population
  - shared decision making
  - incorporating patient fitness, values, and preferences
  - noting that many patients will choose to delay or forgo transplant following counseling

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Optimal timing of HCT in MF

Identifying high-risk patients with survival less than 5 years in myelofibrosis

Risk stratification model	Risk group	Median OS, y	Pros	Cons
DIPSS[14]	Intermediate-2	4.0	Easy applicability based on clinical/laboratory variables	Does not include any information on genetic variables that may have significant impact on the natural history of the disease
	High	1.5		
DIPSS +[15]	Intermediate-2	2.9	Includes cytopenias and cytogenetic data	No mutational data
	High	1.3		
MIPSS70[*16]	High	3.1	Includes impact of MPN driver genes and HMR[†] genes	No cytogenetic data
MIPSS70 + 2.0[*17]	High	4.1	Cytogenetic data Driver/HMR[‡] genes	
	Very high	1.8		
MPN personalized risk[§18]	TP53/−17p /−5/−5q	2.4	Combination of clinical/genetic /cytogenetic data	Study heavily weighted toward PV/ET patients Copy number variation not included in most clinical NGS reports

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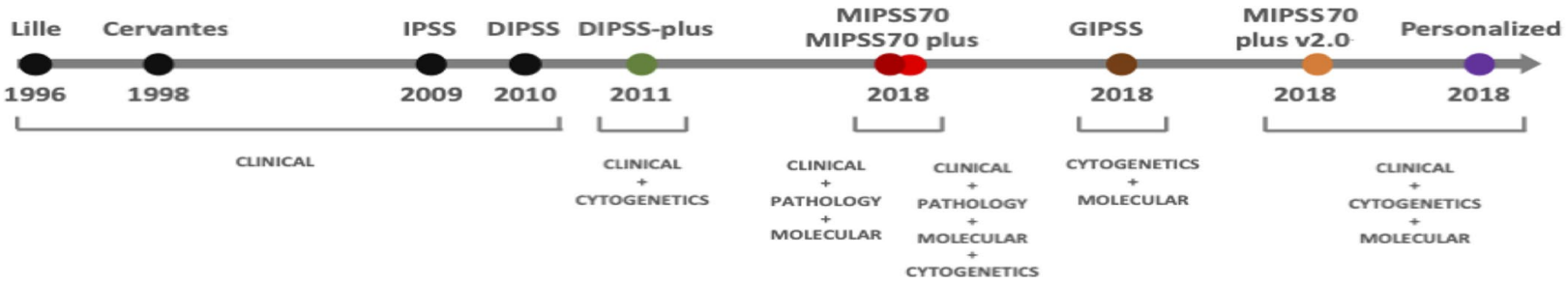
Evolution of risk assessment in MF

- IPSS valid at time of Diagnosis
- DIPSS any time during diagnosis
- DIPSS plus, Mayo clinic adding transfusion requiring cytopenias
- Impact of MPN driver mutation, type 1 *CALR* indolent course, poor risk with *ASXL1, EZH2,IDH1/2,SRSF2*
- MIPSS70 integrate all the above and mutational data
- MIPSS70 plus v2.0 including *U2AF1Q157*
- Personalized calculator incorporating all of the above plus TP53
- *RAS* pathway (*NRAS*, *KRAS*, and *CBL*) and *NFE2*, indicates poorer prognosis in MF



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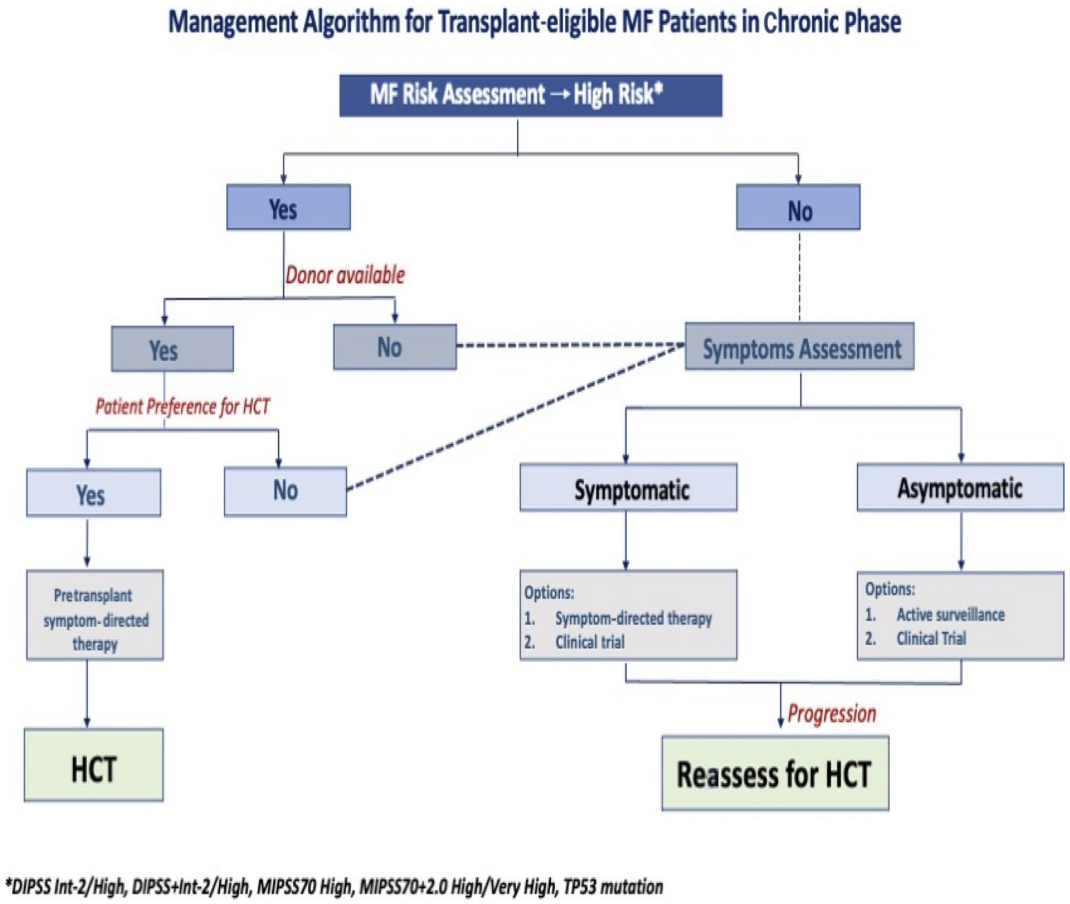
Evolution of risk assessment in MF

- Survival following HCT has been shown to correlate with DIPSS, but it does not include transplant-specific variables that may influence clinical outcomes [1]
- The clinical-molecular MF transplant scoring system, incorporating clinical data, donor type, and mutation status for *ASXL1/CALR/MPL*, predicts overall survival (OS) and non-relapse mortality (NRM) in primary and secondary MF [2]
- If mutational testing is available, recommendation is to use the MIPSS70 or MIPSS70 plus v2.0, otherwise use the DIPSS



1-Gowin K. *Blood Adv*. 2020;4(9):1965-1973
2-Gagelmann N. *Blood*. 2019;133(20):2233-2242

Nontransplant therapies in MF

- **Splenomegaly and constitutional symptoms**
- Jakafi, improvements in splenomegaly, MF-related symptoms burden, QOL [1]
  - Response dose dependent
  - Cytopenias rate limiting toxicity

- Fedratinib FDA approved [2]
- Momelotinib, Pacritinib may help in patients with anemia and severe thrombocytopenia, respectively [2]

- Factors that predict a shorter duration of response to front-line JAKi are higher DIPSS score, transfusion dependence, number of mutations, *ASXL1/EZH2* mutations specifically [3]

1- Harrison C. *N Engl JMed*. 2012;366 (9)
2- Mullally A. *Blood Adv*. 2020
3-Patel KP. *Blood*. 2015

Novel agents

- Deepening and prolonging the spleen and symptom response is a primary goal of many novel combination strategies adding additive/synergistic agents to ruxolitinib in symptomatic treatment-naive patients
- cytokine burden, disease progression, and JAKi resistance can be affected through aberrant activation of other pathways that mediate cell proliferation, survival, and cytokine signaling

Agent	Class of investigational agent	Trial	n	Phase 2 clinical benefit	Primary outcome	Key Secondary outcomes	Comparator	Population/key inclusion criteria
JAKi-naive patients								
Pelabresib + ruxolitinib	BET inhibitor	MANIFEST-2	310	Spleen reduction Less anemia BM fibrosis reduction	SVR ≥35% at 24 weeks	TSS at 24 weeks	Placebo + ruxolitinib	
Navitoclax + ruxolitinib	BCL2 inhibitor	TRANSFORM-1	230	Spleen reduction	SVR ≥35% at 24 weeks	TSS at 24 weeks OS Reduction in BM fibrosis	Placebo + ruxolitinib	
Parsaclisib + ruxolitinib	PI3Kδ inhibitor	LIMBER-313	440	Spleen reduction	SVR ≥35% at 24 weeks	TSS OS	Placebo + ruxolitinib	
Luspatercept + JAKi	ActRII ligand trap	INDEPENDENCE	309	Transfusion independence/anemia improvement	RBC transfusion independence at 24 weeks	Anemia improvement Duration of benefit	Placebo + JAKi	Transfusion dependent
Pacritinib	JAKi	PACIFICA	348	Spleen reduction Better tolerability in thrombocytopenic patients	SVR ≥35% at 24 weeks	TSS OS	Randomized 2:1 Physician selected BAT	Platelets <50 000/μL Includes patients with prior JAKi exposure
Jaktinib	JAKi	—	105		SVR ≥35% at 24 weeks	Transfusion dependence	Hydroxyurea	

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Novel agents

Following first-line JAKi exposure or failure								
Momelotinib	JAKi	MOMENTUM	180	Anemia improvement	TSS at 24 weeks	Transfusion independence Spleen response rate	Randomized 2:1 Danazol	Patients with anemia <100 g/L
Fedratinib	JAKi	FREEDOM-2	192	Spleen reduction	SVR ≥35% at 24 weeks	TSS OS	Randomized 2:1 BAT	
Navitoclax + ruxolitinib	BCL2 inhibitor	TRANSFORM-2	330	Spleen reduction	SVR ≥35% at 24 weeks	TSS at 24 weeks OS Reduction in BM fibrosis	BAT	
Parsaclisib + ruxolitinib	PI3Kδ inhibitor	LIMBER-304	212	Spleen reduction	SVR ≥35% 24 weeks	TSS OS	Placebo + ruxolitinib	
Imetelstat	Telomerase inhibitor	IMpactMF	320	Symptom score reduction OS	OS	TSS at 24 weeks PFS SVR ≥35% at 24 weeks Reduction in BM fibrosis	BAT	

BAT, best available therapy; BCL2, B-cell lymphoma 2; BET, bromodomain and extraterminal; PFS, progression-free survival; SVR, spleen volume response; TSS, total symptom score.

Source: https://www.clinicaltrials.gov accessed on April 30, 2021.

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Novel agents

Cytopenias

- Anemia and thrombocytopenia, current data is limited to erythropoiesis-stimulating and danazol
- Single-agent Pelabresib is being investigated for improving anemia as monotherapy for patients who do not have an indication for JAKi therapy [1]
- Enhancement of late-stage erythrocyte development through the inhibition of transforming growth factor β/SMAD signaling with activin receptor ligand traps (luspatercept), efficacy in improving anemia and reducing transfusion, Phase III INDEPENDENCE trial

Asymptomatic

- Consider treatment in the setting of a clinical trial for an agent with disease-modifying potential.
  - Immune therapies, including interferon agents [2], and antifibrotic agents such as PRM-151 have shown some promise (decrease in symptom burden, cellularity and degree of fibrosis) [3]

1-Bankar A , Gupta V. *Expert Opin Investig Drugs*. 2020 ;
2-Sørensen AL. *Haematologica*. 2020;105(9):2262-2272
3-Verstovsek S, *HemaSphere*. 2019

Jakafi failure

Table 3.

Survival and predictive factors following ruxolitinib failure/discontinuation

Referenoe	Median OS (95% CI) following ruxolitinib failure, mo	Faotors predioting lower survival
Newberry et al. (2017)[39]	14 (10-18)	Platelets <260 at ruxolitinib start Platelets <100 at discontinuation Emergent mutations at discontinuation
Kuykendall et al. (2018)[40]	13	Lack of salvage therapy
Mascarenhas et al. (2020)[41]	11.1 (8.4-14.5)	Age >65 years Charlson Comorbidity Index
Palandri et al. (2020)[42]	13.2 (8.0-22.7)	Blast phase at failure Hb <100 g/L Peripheral blasts >1%

- Due to poor prognosis of JAKi failure, recommendation is to refer HCT in any patient with first-line JAKi failure

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Pretransplant and Transplant considerations

Pre-transplant

- JAK-ALLO use of JAKi demonstrated improved safety [1]
- Continue JAKi therapy prior to HCT in patients with sig MF-related symptoms
- Tapering schedule leading up to or a few days after the start of conditioning
- ? Effect on GVHD post HCT

Alternative donors

- Inferior outcomes using mismatched unrelated donor [2]
- haploidentical donors in MF, including the use of posttransplant cyclophosphamide to prevent GVHD

1-Robin M, Porcher R, Orvain C et al. *Bone Marrow Transplant*
. 2021;56 (8):1-12.
2-Gupta V, Malone AK, Hari PN, et al. *Biol Blood Marrow Transplant*. 2014;20 (1):89-97

Treatment of venous thromboembolism in patients with MPN

- High risk of TE, affect morbidity and mortality, especially in younger patients
- risk factors for a first VTE episode
  - age >60
  - previous history of thrombosis
  - history of major bleeding,
  - leukocytosis
  - inherited thrombophilia (in younger patients)
  - *JAK2*V617F (in ET and PMF)
- 30% present with a thrombotic event before or at diagnosis, 4-fold increased risk of ATE, 10-fold increased risk of VTE shortly after diagnosis

Prevention

- low-dose aspirin (75-100mg) once daily in high- and low-risk PV, in low-/intermediate-risk ET (*JAK2* mutated or age >60 years and no thrombosis history)
- phlebotomy in all PV patients and myelosuppression with cytoreductive therapy in high-risk PV and ET

Treatment of acute VTE and secondary prevention of VTE recurrence

Treatment

- initial treatment for acute VTE is LMWH or fondaparinux followed by vitamin K antagonists (VKAs), targeting an (INR) of 2.5
- Treatment for life with splanchnic cerebral vein thrombosis [1], duration is controversial for usual venous thrombosis
  - VKA treatment was associated with a significant reduction in VTE recurrences in all 4 studies and ATEs in 1 study [2]
  - VKA suspension resulted in a 2- to 3-fold increased risk of recurrence up to 5 years [3]
  - cumulative incidence of VTE recurrence in MPN patients receiving adequate VKA treatment greater than that of the general population (7.8% vs 1.8%-3.5% at 1 year, respectively) [3]
- bleeding complications with VKAs look higher in MPN compared to non-MPN patients (up to 2.8% vs 1.2%-2.2% in patient-years, respectively),[4] especially when combined with aspirin
- DOAC????? limited data, DOACs and VKAs seem to have a comparable risk/benefit profile in the treatment and secondary prevention of VTE in MPN patients.

1-Finazzi G . *Blood Cancer J*. 2018;8 (7):64
2-Hernández-Boluda JC. *Ann Hematol* . 2015
3-De StefanoV. *Leukemia*. 2016;30
4-De Stefano V. *Blood Cancer J*. 2018;8 (7):65

Are DOACs an alternative to vitamin K antagonists for treatment of VTE in MPN?

DOACs *versus* VKA in MPN-associated VTE treatment

VKA

DOACs

	Similar rates of VTE recurrence	Similar rates of major bleeding	Pros	Cons
VKA	3-6% patients-year	0.9-2.8% patients-year	- Larger studies - Longer follow up - Protective from VTE recurrence also in the long term	- Laboratory monitoring - Increased treatment burden - Residual risk of recurrence
DOACs	3.4% patients-year	2.3-3.0% patients-year	- Easier administration - No laboratory monitoring - More appealing for indefinite treatment	- Only one large study on efficacy/safety - Shorter follow up - Residual risk of recurrence

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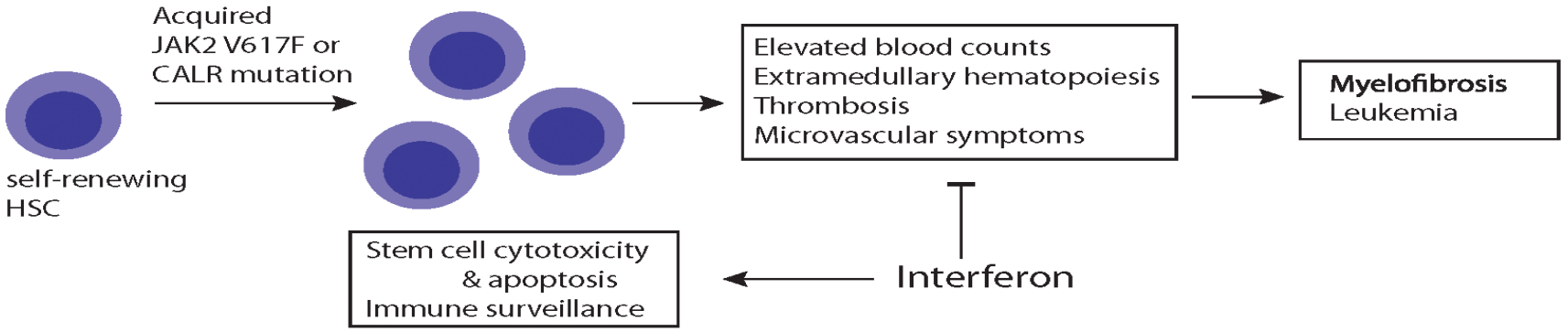
Ropeginterferon alfa-2b



1

- First IFN specifically approved for MPN in Nov 2021
- PROUD-PV : 1:1 SQ ropeginterferon alfa-2b, given biweekly at a starting dose of 100 µg, vs HU. At 1 year, patients had the opportunity of enrolling to the extension portion of the research, the CONTI-PV trial, the primary outcome was composed of hematologic response and normalization of spleen size at 12 months [2]

1-ASH education book 2021
2-Gisslinger H. *Lancet Haematol*. 2020;7(3):e196-e208

Phase 2 of PEGINVERA: Definition of Efficacy Endpoints of Interest

Complete hematologic response (CHR)[1,2,*]

Hct
<45%

Platelet count
≤400 x 10^9/L

Leukocyte count
≤10 x 10^9/L

+

- No phlebotomy in the preceding 2 months
- Normal spleen size†
- Absence of thromboembolic events (TEs)

Partial hematologic response[2]

- Hct < 45% without phlebotomy but with persistent splenomegaly or elevated (>400 x 10^9/L) platelet count OR
- Reduction of phlebotomy requirements by at least 50%

Molecular responses (exploratory)[2]

- *JAK2*-mutated allelic burden
- Complete molecular response (CMR): Reduction of any molecular abnormality to undetectable levels
- Partial molecular response: Reduction ≥50% in patients with <50% mutant allelic burden, OR a reduction ≥25% in patients with >50% mutant allelic burden

CHR, complete hematologic response; CMR, complete molecular response; Hct, hematocrit; PMR, partial molecular response; TE, thromboembolic event.
*In case of concomitant hydroxyurea use, at least 2 weeks after the last hydroxyurea administration had to pass in order to classify the patient as a complete responder.
†Normal spleen size was defined as longitudinal diameter of spleen ≤12 cm for females and ≤13 cm for males as measured via ultrasound.

1. Besremi. Package insert. PharmaEssentia Corporation; 2021. **2.** Data on file. PharmaEssentia Corporation.

Ropeginterferon alfa-2b

Efficacy

- CHR with improved disease burden; (21%)of patients in the ropeginterferon alfa-2b and (28%) in the HU at 12 mons, (53%) of patients achieved a in the ropeginterferon alfa-2b vs (38%) in HU at 36 mons
- CHR without the spleen criterion (43%) in the ropeginterferon alfa-2b versus (46%) in the HU arm at 12 mons, and (71%) versus (51%) of 74 at 36 mons
- Thromboembolic events were similarly rare
- Reductions in *JAK2V617F* allele improved over time, predominantly in the ropeginterferon alfa-2b, supporting the disease-modifying claim that appears to be unique to pegIFN as a class

- failing to achieve a complete molecular remission was associated with
  - the presence of mutations in *TET2*, *ASXL1*, *EZH2*, *DNMT3A*, and *IDH1/2*
  - leukemic progenitor cells with homozygous *JAK2V617F* mutations were more sensitive to IFN compared to cells with a single (heterozygous) *JAK2V617F* mutation and *CALR*-mutation
  - higher dose of IFN appeared to be important for effective clearance of the clone
  - response to IFN appears to be influenced by dosing, driver mutation type and zygosity, and by additional disease-associated mutations.

1-Gisslinger H. *Lancet Haematol*. 2020

PEGINVERA: Safety Data

53% of patients continued treatment for >5 years

Continued Treatment for >5 Years	Ropeginterferon alfa-2b TOTAL (N=51)
12 months or longer	71%
3 years or longer	63%
>5 years	53%

No deaths occurred related to treatment with ropeginterferon alfa-2b

Serious adverse reaction	Ropeginterferon alfa-2b TOTAL (N=51)
Urinary tract infection	8%
Transient ischemic attack	6%
Depression	4%

Clinically relevant adverse reactions (<10%): Atrial fibrillation

Adverse reaction	Ropeginterferon alfa-2b TOTAL (N=51)
Depression	8%
Arthralgia	4%
Fatigue	4%
General physical health deterioration	4%

Ropeginterferon alfa-2b

Safety

- Toxicities: Fatigue and flu-like symptoms, respond to acetaminophen or NSAID, decrease with time
  - Efforts to minimize AEs include low-dose run-in periods with dose-escalation algorithms.
  - Toxicity monitoring: CBC , TFTs, LFTS and and depression screening
  - Dose adjustments for cytopenias, liver dysfunction, and mood or neurocognitive effects are critical to safety and optimal response

1-Gisslinger H. *Lancet Haematol*. 2020

Pregnancy

- Limited available data in PV indicate that early fetal loss and intrauterine growth restriction, preterm delivery is common estimated fetal survival of 50% [1]
- continuation of aspirin is recommended for all pregnant women
- IFNs are considered safe and should generally be continued in patients for whom cytoreductive treatment was indicated pre-pregnancy, either for vascular risk reduction or symptomatic control
- PegIFN and aspirin to be continued through out the pregnancy, and prophylactic doses of low-molecular-weight heparin for 6 weeks postpartum

1-Gangat N. *Am J Hematol*. 2020

Thank You

- **Introduction:** (Thrombocytopenia, a hallmark of cytopenic myelofibrosis (MF), is associated with poor survival and quality of life impairment. Patients with MF and moderate or severe thrombocytopenia (platelet counts $<100x10^9/L$, $<50x10^9/L$) tend to have high symptom burden as measured by the Total Symptom Score (TSS), driven largely by physical functioning symptoms
- Pacritinib, an investigational JAK2/IRAK1 inhibitor, was studied in patients with platelet counts $\leq 100x10^9/L$ in the PERSIST-2 trial. Unlike the pivotal studies upon which available JAK1/2 inhibitors were approved that relied on a *modified* TSS version that excluded 'tiredness' from the response analysis, PERSIST-2 included 'tiredness' as part of TSS and found response rates of 25% for pacritinib vs. 14% for best available therapy (BAT), P=0.08.
- retrospectively analyzed TSS on PERSIST-2 using the *modified* scoring system. In addition, we evaluated the impact of pacritinib and BAT, including ruxolitinib, on MF symptoms including 'tiredness' and 'inactivity'.