Updates on Diagnosis, Prognosis, and Management of Myeloproliferative Neoplasms

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Mayo Clinic
Presentation includes discussion of the following off-label use of a drug or medical device: Hydroxyurea, Interferon-alpha, Busulfan, Thalidomide, Lenalidomide, Pomalidomide, Ruxolitinib, Androgen preparations, Erythropoiesis stimulating agents

Off Label/Investigational Discussion

In accordance with Annenberg Center policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.
Which mutation adversely affects survival in patients with blast phase myeloproliferative neoplasm

1. Triple-negative driver mutational status

2. ASXL1 mutation

3. RUNX1 mutation

4. SRSF2 mutation

5. TP53 mutation
Which of the following statements is true regarding cytogenetic risk and allogenic stem cell transplant in primary myelofibrosis

1. Favorable karyotype in primary myelofibrosis includes +21

2. Allogenic stem cell transplant overcomes the adverse impact of unfavorable and very high risk karyotype in primary myelofibrosis

3. Unfavorable karyotype in primary myelofibrosis includes single abnormalities of chromosome 1 translocations or duplications

4. Transplanted patients with favorable karyotype live longer than transplanted patients with unfavorable karyotype

5. Allogeneic stem cell transplant should not be offered to patients with primary myelofibrosis and very high risk karyotype
Objectives

- 2016 WHO highlights
- Practical diagnostic algorithms
- Genetic prognostication
- Treatment algorithms
Acute Myeloid Leukemia (AML)

Myelodysplastic Syndromes (MDS)

Myeloproliferative Neoplasms (MPN)

MDS/MPN overlap

Myeloid/Lymphoid neoplasms with eosinophilia and PDGFR/FGFR1/PCM1-JAK2 mutation

Chronic Myeloid Leukemia (CML)  
BCR-ABL1 100% mutated

Chronic Neutrophilic Leukemia (CNL)  
CSF3R 80-100% mutated

Chronic Eosinophilic Leukemia Not Otherwise Specified (CEL-NOS)

Polycythemia vera (PV)

Essential Thrombocythemia (ET)

Primary Myelofibrosis (PMF)

MPN Unclassifiable (MPN-U)

The JAK2/CALR/MPL mutated MPNs

97% JAK2 V617F  
3% other JAK2 mutations

60% JAK2 mutated  
22% CALR mutated  
3% MPL mutated  
15% triple-negative

60% JAK2 mutated  
23% CALR mutated  
7% MPL mutated  
10% triple-negative

Blood. 2016 May 19;127(20):2391-405
**2016 WHO Diagnostic Criteria for PV, ET and PMF**

<table>
<thead>
<tr>
<th>Polycythemia vera (PV)</th>
<th>Essential thrombocythemia (ET)</th>
<th>Primary myelofibrosis (PMF)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major criteria</strong></td>
<td><strong>Major criteria</strong></td>
<td><strong>Major criteria</strong></td>
</tr>
<tr>
<td>Diagnosis requires all major criteria or first 2 major plus minor</td>
<td>Diagnosis requires all major criteria</td>
<td>Diagnosis requires all major criteria plus one minor</td>
</tr>
<tr>
<td><strong>Hemoglobin</strong></td>
<td><strong>Platelets</strong></td>
<td><strong>Bone marrow</strong></td>
</tr>
<tr>
<td>&gt;16.5 g/dl in men</td>
<td>≥450 x 10^9/l</td>
<td>Megakaryocytes in tight clusters</td>
</tr>
<tr>
<td>&gt;16 g/dl in women</td>
<td></td>
<td>Hyperchromatic/irregularly folded nuclei</td>
</tr>
<tr>
<td><strong>Bone marrow</strong></td>
<td><strong>Bone marrow</strong></td>
<td>&lt;grade 2 fibrosis (prePMF)</td>
</tr>
<tr>
<td>Tri-lineage myeloproliferation</td>
<td>Megakaryocyte proliferation</td>
<td>≥grade 2 fibrosis (overt PMF)</td>
</tr>
<tr>
<td>Pleomorphic megakaryocytes</td>
<td>large and mature forms</td>
<td></td>
</tr>
<tr>
<td><strong>JAK2 mutated</strong></td>
<td><strong>JAK2/CALR/MPL mutated</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Not meeting WHO criteria for other myeloid neoplasms</strong></td>
<td><strong>Not meeting WHO criteria for other myeloid neoplasms</strong></td>
<td><strong>JAK2/CALR/MPL mutated</strong> or other clonal marker present or no evidence for reactive marrow fibrosis</td>
</tr>
</tbody>
</table>

**Minor criteria**

- Subnormal serum erythropoietin
- Other clonal marker present or no evidence for reactive thrombocytosis
- Anemia
- Leukocytosis
- Palpable splenomegaly
- Increased LDH
- Leukoerythroblastosis (overt)

*Blood. 2016 May 19;127(20):2391-405*
Practical diagnostic algorithm

**Polycythemia vera suspected**

- Blood JAK2 mutation screening
  - JAK2 mutated
    - JAK2 negative
      - Check serum erythropoietin level
        - Subnormal
          - BM biopsy advised to confirm diagnosis and perform karyotype
  - JAK2 negative

**Essential thrombocythemia suspected**

- Blood mutation screening
  - JAK2V617F
    - If negative
      - CALR
        - If negative
          - MPL
            - If negative
              - "Triple-negative"

**Primary myelofibrosis suspected**

- Bone marrow biopsy with mutation screening and cytogenetics

Diagnosis considered If bone marrow morphology is consistent with PMF and
1. JAK2, CALR or MPL mutated or
2. trisomy 9 or del(13q) present or
3. Other myeloid malignancies are excluded
Practical work up for non-PV erythrocytosis

Life-long

- Epo subnormal
- Epo normal or increased
- p50
  - Normal ≥26 mmHg
  - Left-shifted ≤21 mmHg
    - High-oxygen affinity hemoglobin variants
    - 2,3-bisphosphoglycerate deficiency

Acquired or unknown duration

- Epo “compensated normal” or mildly increased
- Epo markedly increased

Cardiopulmonary disease
- Sleep apnea/Pickwickian
- High altitude habitat
- Chronic CO poisoning/smoking
- Testosterone or other drug use
- Contracted volume

- Epo producing tumors
- Renal artery stenosis
- Post-transplant erythrocytosis
- TEMPI (VEGF normal)
  - Telangiectasias
  - Erythrocytosis with ↑Epo
  - Monoclonal gammopathy (IgGκ)
  - Perinephric-fluid collections
  - Intrapulmonary shunting

Start with serum erythropoietin level

- EPOR mutation
- Epo normal or increased
  - Epo normal
  - Epo increased
  - VHL (von Hippel-Lindau)
    - HIF2A (hypoxia-inducible factor-2 alpha subunit)
    - PHD2 (prolyl hydroxylase domain-2)
Take home message for diagnosis of MPN and erythrocytosis

• Work up for erythrocytosis or suspected polycythemia vera should start with peripheral blood screening for JAK2 mutation (both exons 14 and 12) and serum erythropoietin (Epo) level.

• Non-PV erythrocytosis requires “internal medicine” approach and if congenital causes are suspected, serum P50 and screening for germline mutations of EPOR, VHL, PHD2, and HIF2A might be required.

Please remember that more than 80% of mutation screening for suspected congenital erythrocytosis will be unrevealing.

• Primary thrombocytosis requires attention to the possibilities of all three MPNs and also CML, prefibrotic PMF and RARS-T.
Survival in myeloproliferative neoplasms

Comparison of survival in 826 Mayo Clinic patients with essential thrombocythemia vs polycythemia vera vs primary myelofibrosis.

![Survival curve graph showing comparison of survival between essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF) with expected survival.](image-url)

- **ET**: N=292, Median survival = 19.8 yrs
- **PMF**: N=267, Median survival = 5.9 yrs
- **PV**: N=267, Median survival = 13.7 yrs

*Blood. 2014;6;124(16):2507-13*
Survival and prognosis in young patients with myeloproliferative neoplasms

Blood. 2014;6;124(16):2507-13
DIPSS-plus prognostication in myelofibrosis

Survival data of 793 patients with primary myelofibrosis evaluated at time of their first Mayo Clinic referral and stratified by their Dynamic International Prognostic Scoring System (DIPSS-plus) that employs eight variables:

- Age >65 yr
- Hb <10 g/dl; transfusion-dependent
- platelets <100 x 10^9/l
- WBC > 25 x 10^9/l
- ≥1% circulating blasts
- constitutional symptoms
- unfavorable karyotype

Median survival:
- 0 risk factors: 15.4 years
- 1 risk factor: 6.5 years
- 2 or 3 risk factors: 2.9 years
- 4 or more risk factors: 1.3 years

Survival data of 793 patients with primary myelofibrosis evaluated at time of their first Mayo Clinic referral and stratified by their Dynamic International Prognostic Scoring System (DIPSS-plus) that employs eight variables:

Survival (proportion) over time (months) for different risk groups:
- Low risk
- Intermediate-1 risk
- Intermediate-2 risk
- High risk

P < .001
MIPSS70
*(mutation-enhanced international prognostic system for transplant-age patients)*
*J Clin Oncol.* 2018 Feb 1;36(4):310-318

MIPSS70+
*(karyotype-enhanced MIPSS70)*
*J Clin Oncol.* 2018 Feb 1;36(4):310-318

MIPSS70+ *version 2.0.*
*J Clin Oncol.* In press

GIPSS
*(genetically-inspired prognostic scoring system)*
*Leukemia* (2018) doi:10.1038/s41375-018-0107
Survival of 709 primary myelofibrosis patients from the Mayo Clinic, stratified by driver mutational status

- **Triple-negative mutational status**
  - N=68 (10%), median survival=3.3 years

- **JAK2 mutated**
  - N=467 (66%), median survival=3.8 years

- **Type 2/like CALR mutated**
  - N=24 (3.4%), median survival=3.1 years

- **MPL mutated**
  - N=38 (5.4%), median survival=5.9 years

- **Type 1/like CALR mutated**
  - N=112 (16%), median survival=8.1 years

Survival data on 367 Mayo Clinic patients stratified by number of MIPSS70-relevant adverse mutations: ASXL1, SRSF2, EZH2 and IDH1, IDH2

- No adverse mutations: N=180 (49%), Median 6.7 years
- One adverse mutation: N=148 (40%), Median 3.8 years
- ≥2 adverse mutations: N=39 (11%), Median 2.7 years

P<0.001
Survival of 211 Mayo Clinic patients with primary myelofibrosis and age ≤70 years, stratified according to MIPSS70

Low risk = 0-1; Intermediate risk = 2-4; High risk ≥5 adverse points

**Adverse points**
- Presence of ≥2 high risk mutations
- Leukocytes >25 x 10⁹/L
- Platelets <100 x 10⁹/L
- Presence of ≥2 high risk mutations
- Leukocytes >25 x 10⁹/L
- Platelets <100 x 10⁹/L
- Presence of 1 high risk mutation
- Absence of type 1/like CALR
- BM fibrosis grade ≥2
- Hemoglobin <10 g/dL
- PB blasts ≥2%
- Constitutional symptoms

**Survival**
- Low risk
  - N=27
  - Median not reached
  - 5-year survival 96%
- Intermediate risk
  - N=105
  - Median 6.3 years
  - 5-year survival 67%
- High risk
  - N=79
  - Median 3.1 years
  - 5-year survival 35%

Source: [J Clin Oncol. 2018 Feb 1;36(4):310-318](http://www.mipss70score.it/)
MIPSS70+: karyotype and mutation-enhanced international prognostic scoring system
Survival of 315 patients with primary myelofibrosis and age ≤70 years

Adverse points

Genetic risk factors:
- Karyotype (unfavorable) 3
- Driver mutation (type 1/like CALR absent) 2
- Two or more high risk mutations 2
- One high risk mutation 1

Clinical risk factors:
- Hemoglobin <10 g/dl 1
- PB blasts ≥2% 1
- Constitutional symptoms 1

Low risk
0-2 points
N=86 (27.3%)
Median 20 years

Intermediate risk
3 points
N=63 (20%)
Median 6.3 years

Very high risk
≥7 points
N=39 (12.4%)
Median 1.7 years

High risk
4-6 points
N=127 (40.3%)
Median 3.9 years

Surviving

Surviving Years

J Clin Oncol. 2018 Feb 1;36(4):310-318
http://www.mipss70score.it/
Survival of 1,002 patients with primary myelofibrosis stratified by the revised three-tiered cytogenetic risk model

- Very high risk category; N=75 (7%); median survival 1.2 years
- Unfavorable risk category; N=190 (19%); median survival 2.9 years
- Favorable risk category; N=737 (74%); median survival 4.4 years

Leukemia (2018) doi:10.1038/s41375-018-0018-z
Survival data on 490 patients with primary myelofibrosis stratified by *U2AF1* mutation types: Q157 vs S34 vs unmutated

- N=414, Median 5.5 years
- N=50, Median 2.9 years
- N=26, Median 5.8 years

P<0.01 for Q157 vs unmutated
P<0.01 for Q157 vs S34
P=0.7 for S34 vs unmutated

Survival data on 370 transplant-age patients (age ≤70 years) with primary myelofibrosis stratified by *U2AF1* Q157 vs S34 vs unmutated

- N=322, Median 6.7 years
- N=29, Median 3.8 years
- N=19, Median 6 years

P<0.01 for Q157 vs unmutated
P=0.04 for Q157 vs S34
P=0.8 for S34 vs unmutated

**U2AF1** Q157 is an independent predictor of poor survival in primary myelofibrosis

*Leukemia* (2018)
doi:10.1038/s41375-018-0078-0
Figure 1a: Survival of 1109 patients with primary myelofibrosis stratified by the degree of anemia

Severe anemia:
- vs Moderate anemia P<0.0001
- vs Mild anemia P<0.0001
- vs No anemia P=0.0001

Moderate anemia:
- vs Mild anemia P<0.0001
- vs No anemia P=0.0001

Mild anemia:
- vs No anemia P=0.007

Leukemia (2018)
doi:10.1038/s41375-018-0028

Figure 1b: Survival of 694 men with primary myelofibrosis stratified by the degree of anemia

Severe anemia:
- vs Moderate anemia P=0.002
- vs Mild anemia P=0.0001
- vs No anemia P=0.0001

Moderate anemia:
- vs Mild anemia P=0.0001
- vs No anemia P=0.0001

Mild anemia:
- vs No anemia P=0.002

Figure 1c: Survival of 415 women with primary myelofibrosis stratified by the degree of anemia

Severe anemia:
- vs Moderate anemia P=0.001
- vs Mild anemia P=0.002
- vs No anemia P=0.001

Moderate anemia:
- vs Mild anemia P=0.001
- vs No anemia P=0.003

Mild anemia:
- vs No anemia P=0.001
Survival data on Mayo Clinic patients with primary myelofibrosis stratified by MIPSS70+ version 2.0

Risk categories: very high risk ≥9 points; high risk 5-8 points; intermediate risk 3-4 points; low risk 1-2 points; and very low risk zero points

Age 70 years or younger
311 patients

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>n</th>
<th>Median Survival</th>
<th>10-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high risk</td>
<td>44</td>
<td>1.8 years</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>High risk</td>
<td>124</td>
<td>4.1 years</td>
<td>13%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>64</td>
<td>7.7 years</td>
<td>37%</td>
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<tr>
<td>Low risk</td>
<td>61</td>
<td>16.4 years</td>
<td>56%</td>
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<tr>
<td>Very low risk</td>
<td>18</td>
<td>Median not reached</td>
<td>92%</td>
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</tbody>
</table>

All ages
406 patients

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>n</th>
<th>Median Survival</th>
<th>10-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high risk</td>
<td>69</td>
<td>1.8 years</td>
<td>&lt;3%</td>
</tr>
<tr>
<td>High risk</td>
<td>172</td>
<td>3.5 years</td>
<td>10%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>76</td>
<td>7 years</td>
<td>30%</td>
</tr>
<tr>
<td>Low risk</td>
<td>70</td>
<td>10.3 years</td>
<td>50%</td>
</tr>
<tr>
<td>Very low risk</td>
<td>19</td>
<td>Median not reached</td>
<td>86%</td>
</tr>
</tbody>
</table>

Surviving Years

Very high risk karyotype 4 points
Unfavorable karyotype 3 points
≥2 HMR mutations 3 points
One HMR mutation 2 points
Type 1/like CALR mutation absent 2 points
Constitutional symptoms 2 points
Severe anemia 2 points
Moderate anemia 1 point
≥2% circulating blasts 1 point

J Clin Oncol. In press

http://www.mipss70score.it/
GIPSS

genetically-inspired prognostic scoring system-stratified survival data
in 641 patients with primary myelofibrosis

**Low risk**
N=58; 9%
Zero points
5-yr survival 94%

**Intermediate-1**
N=260; 41%
One point
5-yr survival 73%

**Intermediate-2**
N=192; 30%
2 points
5-yr survival 40%

**High risk**
N=131; 20%
≥3 points
5-yr survival 14%

**Karyotype:**
Very high risk = 2 points
Unfavorable = 1 point

**Driver mutations:**
Type 1/like CALR absent = 1 point

**High risk mutations:**
ASXL1 mutation = 1 point
SRSF2 mutation = 1 point
U2AF1 Q157 mutation = 1 point

Leukemia (2018)
doi:10.1038/s41375-018-0107
Risk distribution among 641 patients with primary myelofibrosis according to GIPSS (genetically-inspired prognostic scoring system) and MIPSS70-plus (mutation-enhanced international prognostic system including karyotype) numbers in cells indicate percentages.
Take home message on GIPSS and MIPSS70 and MIPSS70+ version 2.0

- During prognostication of patients with primary myelofibrosis (PMF), one can simply start with the genetics only GIPSS prognostic model
  - Very high risk (VHR) karyotype automatically puts a patient into high risk category and no additional prognostic information might be needed
  - In the absence of VHR karyotype, high risk category assignment requires three adverse genetic features: absence of type 1/like CALR, unfavorable karyotype, high molecular risk mutation such as ASXL1, SRSF2 and U2AF1 Q157

- About 10% of patients with PMF are lucky enough not to display any adverse genetic features and their 5-year survival is over 90%

- MIPSS70+ version 2.0 includes clinical risk factors (anemia, circulating blasts, constitutional symptoms), in addition to genetic risk factors used in GIPSS, and offers additional information on prognosis
Treatment Algorithm in Myelofibrosis
based on risk stratification according to MIPSS70+ version 2.0

Very high risk
10-yr survival <3%
- Allogenic stem cell transplant
  - Transplant ineligible
  - Novel agent clinical trial

High Risk
10-yr survival 10%
- Treatment requiring
  - Preferred option is clinical trials
  - Otherwise

Intermediate risk
10-yr survival 30%
- Treatment requiring

Low risk
10-yr survival 50%
- Preferred option

Very low risk
10-yr survival 86%
- First do no harm “observation only”

Anemia
- Androgens
- Danazol
- Thalidomide
- Prednisone

Splenomegaly
- Hydroxyurea
- Ruxolitinib
- Splenectomy

Constitutional symptoms
- Ruxolitinib
- Hydroxyurea
- Splenectomy

Localized bone pain or symptomatic extramedullary hematopoiesis
- Involved-field radiotherapy

J Clin Oncol. In press
Transplant myelofibrosis ($n=56$) vs no transplant primary myelofibrosis ($n=56$), stringently matched for age, DIPSS and karyotype

Genetic prognostication in polycythemia vera

- Prevalence of mutations other than JAK2/CALR/MPL = 53%
- Most frequent were ASXL1 and TET2
- 30%, 20% and 3% harbored 1, 2 or ≥3 such mutations
- “3” genes were identified as being affected by adverse mutations/variants
  
  **ASXL1, SRSF2, IDH2 (15% carried at least one of these adverse mutations)**

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**Figure 2a**

- Patients with neither adverse nor other variants
  - N=50
  - Median 15.8 years
- Patients with “other” variants
  - N=50
  - Median 15.4 years
- Patients with “adverse” variants
  - N=20
  - Median 15.1 years

**Figure 2b**

- Without adverse variants
  - N=192
  - Median 25 years
- With adverse variants
  - N=93
  - Median 15.7 years

*P=0.03*
Genetic prognostication in essential thrombocythemia

- Prevalence of mutations other than JAK2/CALR/MPL = 53%
- Driver mutational status did not affect prevalence
- Most frequent were ASXL1 and TET2
- 41%, 8% and 4% harbored 1, 2 or ≥3 mutations
- “6” genes were identified as being affected by adverse mutations/variants: SF3B1, SH2B3, EZH2, TP53, U2AF1, IDH2 (15% affected)
Current Treatment Algorithm in Polycythemia Vera

Blood Cancer J. 2018 Jan 10;8(1):3

Current Treatment Algorithm Series

Phlebotomy to hematocrit <45% in both male and female patients
+
Once-daily baby aspirin (81 mg)

Low-risk Disease
• No history of thrombosis
• Age ≤60 years

Consider twice-daily aspirin in the presence of:
• Cardiovascular risk factors
• Hypertension
• Leukocytosis
• Persistent microvascular symptoms

High-risk disease
• History of thrombosis or
• Age >60 years

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 (Age <65 years)
Busulfan (Age ≥65 years)
Ruxolitinib (If all the above fails)
Current Treatment Algorithm in Essential Thrombocythemia

- Must consider the possibility of AvWS before instituting aspirin therapy, especially in the presence of extreme thrombocytosis.
- Second-line treatment in hydroxyurea intolerant or refractory patients is pegylated IFN-α or busulfan.
### Phase-3 tested JAK2 inhibitors in myelofibrosis

<table>
<thead>
<tr>
<th>JAK inhibitor</th>
<th>CR</th>
<th>PR</th>
<th>1-2-3 years discontinuation rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Momelotinib</td>
<td>0%</td>
<td>1%</td>
<td>31%-52%-71%</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>0%</td>
<td>0%</td>
<td>49%-71%-86%</td>
</tr>
<tr>
<td>Fedratinib</td>
<td>0%</td>
<td>0%</td>
<td>20%-67%-80%</td>
</tr>
</tbody>
</table>

### 2013 revised IWG-MRT response rates for 166 JAKi treated Mayo Clinic patients

<table>
<thead>
<tr>
<th>JAK inhibitor</th>
<th>JAK targets</th>
<th>Other targets</th>
<th>Symp. resp.</th>
<th>Spleen resp. (MRI)</th>
<th>Anemia resp.</th>
<th>Side effects</th>
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</thead>
<tbody>
<tr>
<td>Ruxolitinib</td>
<td>JAK1, JAK2</td>
<td>TRK-B, ACK1, FAK, LCK, RET</td>
<td>Yes</td>
<td>32-42%</td>
<td>14%</td>
<td>↓Hgb/Plts Ruxolitinib withdrawal syndrome, Opportunistic infections</td>
</tr>
<tr>
<td>Fedratinib</td>
<td>JAK2</td>
<td>FLT3, RET, ACK1, JNK1</td>
<td>Yes</td>
<td>47%</td>
<td>NR</td>
<td>↓Hgb/Plts Nausea/Diarrhea ↑LFTs/Lipase/amylase Encephalopathy</td>
</tr>
<tr>
<td>Pacritinib</td>
<td>JAK2</td>
<td>FLT3</td>
<td>Yes</td>
<td>37%</td>
<td>NR</td>
<td>Diarrhea/Nausea</td>
</tr>
<tr>
<td>Momelotinib</td>
<td>JAK1, JAK2</td>
<td>PKD3, PKCζ, CDK2, ROCK2, JNK1, TBK1, ALK-2</td>
<td>Yes</td>
<td>39% (PE)</td>
<td>53%</td>
<td>↓Plts 1st dose effect ↓BP/dizzy Neuropathy/Headache ↑LFTs/Lipase/Amylase</td>
</tr>
</tbody>
</table>

Leukemia 2014
COMFORT-2 Ruxolitinib vs best available therapy (BAT) long-term follow-up
Median f/u 4.3 years
27% ruxo-randomized patients completed 5-year treatment

AML
5.5% with ruxo and 6.8% with BAT

Skin cancer
17% with ruxo and 3% with BAT

Leukemia (2016) 30, 1701
Survival impact of ruxolitinib in myelofibrosis: MC study

![Graph showing survival impact of ruxolitinib in myelofibrosis. The graph compares survival rates between ruxolitinib-treated patients (n=51) and those without ruxolitinib (n=410). The P-value is 0.43.](image-url)

P=0.43
Ruxolitinib practice points

Indications
1. Marked splenomegaly that is symptomatic and resistant to hydroxyurea
2. Severe constitutional symptoms including pruritus, night sweats, fatigue and cachexia
3. Sometimes there is no other option, even in the presence of severe cytopenias

Short-term side effects
1. Anemia, including becoming transfusion-dependent
2. Thrombocytopenia

Long-term side effects
1. Immunosuppression
2. Opportunistic infections
3. Protracted myelosuppression

Special concerns
1. Might compromise future eligibility for clinical trials because of protracted myelosuppression
2. Effect lasts for an average of approximately one year; might be prudent to save it until HU fails
3. **BEWARE** of withdrawal symptoms that might include SIRS and overt and immediate relapse of splenomegaly/symptoms
Momelotinib therapy in 100 Mayo Clinic patients
7-year follow-up

• Accrued 2009-2010
• 91% discontinued to date
• Median treatment duration 1.4 years
• 44% anemia response
• 43% Spleen response
• Response worse in ASXL1 mutated and with increased circulating blasts
• Response more durable in type 1/like CALR mutated
• 47% grade 1 sensory neuropathy
Momelotinib therapy in myelofibrosis 7-year follow-up
Comparison of survival between 100 momelotinib treated patients and 442 not receiving momelotinib

*DIPSS-plus high or intermediate-2 risk disease only*

- **Momelotinib-treated; N=100**
  - *ASXL1+CALR* mutation profile in 34 (36%) of 94 informative cases
  - Median survival 3.2 years

- **Not treated with momelotinib; N=442**
  - *ASXL1+CALR* mutation profile in 100 (35%) of 282 informative cases
  - Median survival 3 years

\[ P = 0.44 \]
Momelotinib therapy in myelofibrosis 7-year follow-up

Survival of 83 molecularly-annotated patients from time of momelotinib study entry to last follow-up or death, and stratified by age and mutation profile

- **Low risk**
  - N=7
  - Median survival not reached

- **Intermediate-1 risk**
  - N=21
  - Median survival 4.5 years

- **Intermediate-2 risk**
  - N=28
  - Median survival 3.1 years

- **High risk**
  - N=27
  - Median survival 1.5 years

**Risk Scoring System**

- Absence of CALR type 1/like = 2 points
- Presence of ASXL1 mutations = 1 point
- Presence of SRSF2 mutations = 1 point
- Age >65 years = 1 point

- **Low risk** = 0-1 points
- **Intermediate-1 risk** = 2 points
- **Intermediate-2 risk** = 3 points
- **High risk** = 4 or more points

BCJ 2018 in press
Survival data on 248 Mayo Clinic patients with blast-phase myeloproliferative neoplasm stratified by year of diagnosis:

- **Leukemic transformation date before 2000**
  - N=44
  - Median survival = 2.3 months
  - 1-year survival rate = 5%
  - 3-year survival rate = 0%

- **Leukemic transformation date before between 2000 and 2009**
  - N=94
  - Median survival = 3.5 months
  - 1-year survival rate = 17%
  - 3-year survival rate = 4%

- **Leukemic transformation date in 2010 or beyond**
  - N=110
  - Median survival = 4.9 months
  - 1-year survival rate = 20%
  - 3-year survival rate = 10%

Survival data on 162 Italian patients with blast-phase myeloproliferative neoplasm, stratified by year of diagnosis:

- **Leukemic transformation date before between 2000 and 2009**
  - N=44
  - Median survival = 2.3 months
  - 1-year survival rate = 5%
  - 3-year survival rate = 0%

- **Leukemic transformation date before between 2010 and 2017**
  - N=101
  - Median survival = 3.5 months
  - 1-year survival rate = 17%
  - 3-year survival rate = 4%

- **Leukemic transformation date in 2010 or beyond**
  - N=110
  - Median survival = 4.9 months
  - 1-year survival rate = 20%
  - 3-year survival rate = 10%

P=0.9

61 patients diagnosed between 2001 and 2009

101 patients diagnosed between 2010 and 2017

Survival data on 248 Mayo Clinic patients with blast-phase myeloproliferative neoplasm, stratified by specific treatment strategies

- **Transplanted patients; N=24**
  - 1-year survival rate = 66%
  - 3-year survival rate = 32%
  - 5-year survival rate = 10%

- **No transplant but achieved CR/CRi; N=24**
  - 1-year survival rate = 37%
  - 3-year survival rate = 19%
  - 5-year survival rate = 13%

- **No transplant and no CR/CRi; N=200**
  - 1-year survival rate = 8%
  - 3-year survival rate = 1%
  - 5-year survival rate = 1%

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*Leukemia. 2018 Feb 2. doi: 10.1038/s41375-018-0019-y.*