### Disclosures for Ayalew Tefferi

<table>
<thead>
<tr>
<th>Principal investigator role</th>
<th>Janssen, Geron, Celgene, Sanofi-Aventis, Gilead Sciences, Incyte</th>
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<tr>
<td>Employee</td>
<td>None</td>
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<tr>
<td>Consultant</td>
<td>None</td>
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<tr>
<td>Major Stockholder</td>
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</tr>
<tr>
<td>Speakers’ Bureau</td>
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<td>Scientific Advisory Board</td>
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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
Myeloproliferative Neoplasms—2018 Update

Ayalew Tefferi, MD
Professor of Medicine and Hematology
Mayo Clinic College of Medicine
Objectives

- 2016 WHO highlights
- Practical diagnostic algorithms
- Genetic prognostication
- Treatment algorithms
Myelodysplastic Syndromes (MDS)
Myeloproliferative Neoplasms (MPN)
MDS/MPN overlap
Myeloid/Lymphoid neoplasms with eosinophilia and PDGFR/FGFR1/PCM1-JAK2 mutation

2016 WHO Classification of Myeloid Malignancies

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 Thrombocytopenia (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>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>
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<tr>
<td><strong>Hemoglobin</strong></td>
<td><strong>Platelets</strong></td>
<td><strong>Bone marrow</strong></td>
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<tr>
<td>&gt;16.5 g/dl in men</td>
<td>≥450 x 10⁹/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>
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<tr>
<td><strong>Bone marrow</strong></td>
<td></td>
<td>&lt;grade 2 fibrosis (prePMF)</td>
</tr>
<tr>
<td>Tri-lineage myeloproliferation</td>
<td></td>
<td>≥grade 2 fibrosis (overt PMF)</td>
</tr>
<tr>
<td>Pleomorphic megakaryocytes</td>
<td></td>
<td></td>
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<tr>
<td><strong>JAK2 mutated</strong></td>
<td><strong>Bone marrow</strong></td>
<td><strong>Not meeting WHO criteria</strong></td>
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<tr>
<td></td>
<td>Megakaryocyte proliferation</td>
<td>for other myeloid neoplasms</td>
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<tr>
<td></td>
<td>large and mature forms</td>
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<td></td>
<td>loose clusters</td>
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<tr>
<td><strong>JAK2/CALR/MPL mutated</strong></td>
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<td><strong>JAK2/CALR/MPL mutated</strong></td>
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<td></td>
<td></td>
<td>or other clonal marker present</td>
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<td></td>
<td></td>
<td>or no evidence for reactive marrow fibrosis</td>
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<tr>
<td><strong>Minor criteria</strong></td>
<td><strong>Not meeting WHO criteria</strong></td>
<td><strong>Minor criteria</strong></td>
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<tr>
<td>Subnormal serum erythropoietin</td>
<td></td>
<td>Anemia</td>
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<tr>
<td></td>
<td></td>
<td>Leukocytosis</td>
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<tr>
<td></td>
<td></td>
<td>Palpable splenomegaly</td>
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<tr>
<td></td>
<td></td>
<td>Increased LDH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leukoerythroblastosis (overt)</td>
</tr>
</tbody>
</table>

*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
  - Normal or elevated **Not PV**

- **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
  - BM biopsy advised to confirm diagnosis and perform karyotype
  - BM biopsy required to confirm diagnosis and distinguish ET from prefibrotic PMF

**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**

- Start with serum erythropoietin level
- **Epo** subnormal
  - **EPOR** mutation
- **Epo** normal or increased
  - **p50**
    - Left-shifted ≤21 mmHg
      - High-oxygen affinity hemoglobin variants
      - 2,3-bisphosphoglycerate deficiency
    - Normal ≥26 mmHg
      - **Epo** normal
        - VHL (von Hippel-Lindau)
      - **Epo** increased
        - **HIF2A** (hypoxia-inducible factor-2 alpha subunit)
        - **PHD2** (prolyl hydroxylase domain-2)

**Acquired or unknown duration**

- **Epo** “compensated normal” or mildly increased
  - Cardiopulmonary disease
  - Sleep apnea/Pickwickian
  - High altitude habitat
  - Chronic CO poisoning/smoking
  - Testosterone or other drug use
  - Contracted volume
- **Epo** markedly increased
  - Epo-producing tumors
  - Renal artery stenosis
  - Post-transplant erythrocytosis
  - TEMPI (VEGF normal)
    - telangiectasias
    - erythrocytosis with ↑Epo
    - monoclonal gammopathy (IgGκ)
    - perinephric-fluid collections
    - intrapulmonary shunting
Survival in myeloproliferative neoplasms

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

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

- **ET:** N=168
  - Median survival: 32.7 years
  - ET vs Expected p = 0.254

- **PMF:** N=107
  - Median survival: 14.6 years

- **PV:** N=114
  - Median survival: 23.8 years

*Blood. 2014;6;124(16):2507-13*
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

*P < .001*
MIPSS70/MIPSS70+

*mutation-enhanced international prognostic system for transplant-age patients*

GIPSS

*genetically-inspired prognostic scoring system*
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**
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:

- 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

Survival data on 488 Mayo Clinic patients stratified by number of GIPSS-relevant adverse mutations:

- No adverse mutations
  - N=247 (51%)
  - Median 7 years

- One adverse mutation
  - N=178 (36%)
  - Median 3.9 years

- ≥2 adverse mutations
  - N=63 (13%)
  - Median 2.7 years

P<0.001
MIPSS70: mutation-enhanced international prognostic scoring system

Survival of 315 patients with primary myelofibrosis and age ≤70 years, stratified according to MIPSS70-plus

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
- Leukocyte count >25 x 10^9/l 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

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

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

http://www.mipss70score.it/

**J Clin Oncol.** 2018 Feb 1;36(4):310-318
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
ASXL1 mutation = 1 point
SRSF2 mutation = 1 point
U2AF1 Q157 mutation = 1 point

Leukemia 2018 in press
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.
GIPSS- and MIPSS70-plus-based Treatment Algorithm in Myelofibrosis

- **GIPSS high risk**
  - Allogenic stem cell transplant
  - Transplant ineligible
  - Novel agent clinical trial

- **GIPSS intermediate-2 risk**
  - MIPSS70+ very high risk
  - Decision to be made on case-by-case basis

- **GIPSS intermediate-1 risk**
  - MIPSS70+ high risk
  - Treatment requiring
    - Yes
    - Anemia: Androgens, Danazol, Thalidomide, Prednisone
    - Splenomegaly: Hydroxyurea, Ruxolitinib, Splenectomy
    - Constitutional symptoms: Ruxolitinib, Hydroxyurea, Splenectomy
    - Localized bone pain or symptomatic extramedullary hematopoiesis: Involved-field radiotherapy

  - No

- **GIPSS low risk**
  - MIPSS70+ intermediate risk
  - MIPSS70+ low risk

First do no harm “observation only”
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)
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*

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**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
- 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)

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

**Very low-risk**
- No thrombosis history
- Age ≤60 years
- JAK2/MPL un-mutated

**Low-risk**
- No thrombosis history
- Age ≤60 years
- JAK2/MPL mutated

**Intermediate-risk**
- No thrombosis history
- Age >60 years
- JAK2/MPL un-mutated

**High-risk**
- Thrombosis history
- Age ≥60 years and JAK2/MPL mutated

**Cardiovascular risk factors**
- No
  - Observation alone
- Yes
  - Once-daily aspirin

**Arterial**
- Hydroxyurea + Twice-daily aspirin
- Hydroxyurea + Systemic anticoagulation

**Venous**
- Hydroxyurea + Once-daily aspirin

**Additional points:**
- 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

| 2013 revised IWG-MRT response rates for 166 JAKi treated Mayo Clinic patients |
|---------------------------------|-----------------|-----------------|----------------|
|                                 | CR  | PR  | 1-2-3 years discontinuation rates |
| Momelotinib (n=100)             | 0%  | 1%  | 31%-52%-71%                     |
| Ruxolitinib (n=51)              | 0%  | 0%  | 49%-71%-86%                     |
| Fedratinib (n=15)               | 0%  | 0%  | 20%-67%-80%                     |

<table>
<thead>
<tr>
<th>JAK targets</th>
<th>Other targets</th>
<th>Symp. resp.</th>
<th>Spleen resp.</th>
<th>Anemia resp.</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruxolitinib (FDA-approved)</td>
<td>JAK1, JAK2</td>
<td>Yes</td>
<td>32-42% (MRI)</td>
<td>14%</td>
<td>↓Hgb/Plts Ruxolitinib withdrawal synd. Opportunistic infections</td>
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<tr>
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<td>TRK-B, ACK1 FAK, LCK RET</td>
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<tr>
<td>Fedratinib (SAR302501) Phase-3 completed</td>
<td>JAK2</td>
<td>FLT3, RET, ACK1 JNK1</td>
<td>Yes</td>
<td>47% (MRI)</td>
<td>NR</td>
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<td>FDA approval pending</td>
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<td>Pacritinib (SB1518) Phase-3 completed</td>
<td>JAK2</td>
<td>FLT3</td>
<td>Yes</td>
<td>37% (MRI)</td>
<td>NR</td>
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</tr>
<tr>
<td>Momelotinib (CYT387) Phase-3 completed</td>
<td>JAK1, JAK2</td>
<td>PKD3, PKCμ, CDK2, ROCK2 JNK1, TBK1 ALK-2</td>
<td>Yes</td>
<td>39% (PE)</td>
<td>53%</td>
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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

Probability of survival over time:
- Ruxolitinib (n = 146)
- BAT (ITT), n = 73
- BAT (RPSFT), n = 73

Risk of:
- AML: 5.5% with ruxo and 6.8% with BAT
- Skin cancer: 17% with ruxo and 3% with BAT

P = 0.06
Survival impact of ruxolitinib in myelofibrosis: MC study

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

BCJ 2018 in press
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.

Survival Years

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

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 101 Italian patients with blast-phase myeloproliferative neoplasm, stratified by year of diagnosis

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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