## Disclosures for Ayalew Tefferi

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

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

• Noteworthy abstracts from ASH 2017
2016 WHO Classification of Myeloid Malignancies

**Acute Myeloid Leukemia (AML)**
- *BCR-ABL1* 100% mutated

**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)**
- 97% *JAK2* V617F
- 3% other *JAK2* mutations

**Essential Thrombocythemia (ET)**
- 60% *JAK2* mutated
- 22% *CALR* mutated
- 3% *MPL* mutated
- 15% triple-negative

**Primary Myelofibrosis (PMF)**
- 60% *JAK2* mutated
- 23% *CALR* mutated
- 7% *MPL* mutated
- 10% triple-negative

**MPN Unclassifiable (MPN-U)**

**MDS/MPN overlap**

**Myelodysplastic Syndromes (MDS)**

**Myeloproliferative Neoplasms (MPN)**

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

Bone marrow biopsy with mutation screening and cytogenetics

Primary myelofibrosis suspected

BM biopsy required to confirm diagnosis and distinguish ET from prefibrotic PMF

BM biopsy advised to confirm diagnosis and perform karyotype

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
Survival in myeloproliferative neoplasms

Comparison of survival in 826 Mayo Clinic patients with essential thrombocythemia vs polycythemia vera vs primary myelofibrosis.
Survival and prognosis in young patients with myeloproliferative neoplasms

- **ET vs PV vs PMF:** $p < 0.001$
- **PMF:** $N=107$  
  Median survival = 14.6 yrs
- **ET:** $N=168$  
  Median survival = 32.7 yrs
- **PV:** $N=114$  
  Median survival = 23.8 yrs

*Blood 2014*
Survival of 1,002 patients with primary myelofibrosis stratified by the revised three-tiered cytogenetic risk model

Very high risk category; N=75; median survival 1.2 years

Unfavorable risk category; N=190; median survival 2.9 years

Favorable risk category; N=737; median survival 4.4 years

Leukemia 2018
Survival of 709 primary myelofibrosis patients from the Mayo Clinic, stratified by driver mutational status

- **Triple-negative mutational status**
  - N=68, median survival=3.3 years

- **JAK2 mutated**
  - N=467, median survival=3.8 years

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

- **MPL mutated**
  - N=38, median survival=5.9 years

- **Type 1/like CALR mutated**
  - N=112, median survival=8.1 years
Survival in 436 patients with primary myelofibrosis stratified by presence or absence of *ASXL1* or *SRSF2* mutations

Survival

**No adverse mutations**
N=226
Median survival 6.5 years

**ASXL1/SRSF2 present**
N=210
Median survival 3 years

2018 Mayo Clinic updated data
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 10⁹/l 1
- PB blasts ≥2% 1
- Constitutional symptoms 1

Low risk
0-2 points
N=86
Median 20 years

Intermediate risk
3 points
N=63
Median 6.3 years

High risk
4-6 points
N=127
Median 3.9 years

Very high risk
≥7 points
N=39
Median 1.7 years

http://www.mipss70score.it/
Treatment Algorithm in Myelofibrosis

- **MIPSS70+ very high risk**
  - Allogenic stem cell transplant
  - Transplant ineligible

- **MIPSS70+ high risk**
  - Novel agent clinical trial

- **MIPSS70+ intermediate risk**
  - Otherwise
  - Symptomatic
    - Anemia
      - Androgens
      - Danazol
      - Thalidomide
      - Prednisone
      - Lenalidomide
      - Pomalidomide
    - Spleen
      - Hydroxyurea
      - Ruxolitinib
      - Splenectomy
    - Constitutional symptoms
      - Ruxolitinib
      - Splenectomy
  - Asymptomatic
    - Bone pain EMH
      - Involved-field radiation

- **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.

- DIPSS-stratified
- Karyotype-stratified
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**
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

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

**Low-risk Disease**
- No history of thrombosis
- Age \( \leq 60 \text{ years} \)

**High-risk disease**
- History of thrombosis
- Age \( > 60 \text{ years} \)

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

- Hydroxyurea (500 mg BID starting dose)

- **Arterial thrombosis history**
  - Consider twice-daily aspirin
  - Pegylated IFN-\( \alpha \) (Age \(< 65 \text{ years} \))
  - Busulfan (Age \( \geq 65 \text{ years} \))
  - Ruxolitinib (If all the above fails)

- **Venous thrombosis history**
  - Add systemic anticoagulation
  - Hydroxyurea intolerant or resistant
Current Treatment Algorithm in Essential Thrombocytemia

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

Yes
- Observation alone
- Once-daily aspirin
- Twice-daily aspirin

Arterial
- Hydroxyurea
- Twice-daily aspirin

Venous
- Hydroxyurea
- Systemic anticoagulation
- 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

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>PR</th>
<th>1-2-3 years discontinuation rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Momelotinib (n=100)</td>
<td>0%</td>
<td>1%</td>
<td>31%-52%-71%</td>
</tr>
<tr>
<td>Ruxolitinib (n=51)</td>
<td>0%</td>
<td>0%</td>
<td>49%-71%-86%</td>
</tr>
<tr>
<td>Fedratinib (n=15)</td>
<td>0%</td>
<td>0%</td>
<td>20%-67%-80%</td>
</tr>
</tbody>
</table>

#### JAK inhibitors and their targets

<table>
<thead>
<tr>
<th>JAK inhibitor</th>
<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>TRK-B, ACK1, FAK, LCK, RET</td>
<td>Yes</td>
<td>32-42% (MRI)</td>
<td>14%</td>
<td>↓Hgb/Plts Ruxolitinib withdrawal synd. Opportunistic infections</td>
</tr>
<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>
<td>↓Hgb/Plts Nausea/Diarrhea ↑LFTs/Lipase/amylose Encephalopathy</td>
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<tr>
<td>Pacritinib (SB1518) Phase-3 completed</td>
<td>JAK2</td>
<td>FLT3</td>
<td>Yes</td>
<td>37% (MRI)</td>
<td>NR</td>
<td>Diarrhea/Nausea</td>
</tr>
<tr>
<td>Momelotinib (CYT387) Phase-3 completed</td>
<td>JAK1, JAK2</td>
<td>PKD3, PKCιιι, CDK2, ROCK2, JNK1, TBK1, ALK-2</td>
<td>Yes</td>
<td>39% (PE)</td>
<td>53%</td>
<td>↓Plts ↑LFTs/Lipase/amylose 1st dose effect ↓BP/dizzy Neuropathy/Headache</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

Median survival, 4.3 years

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

- Ruxolitinib-treated, n=51
- No ruxolitinib, n=410

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