Myeloproliferative Neoplasms: Management of Polycythemia Vera and Essential Thrombocythemia

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Managing PV and ET

• Setting the stage for a treatment plan in ET and PV
• ET
• PV
• Future Directions
NCCN Guidelines: Myeloproliferative Neoplasms (MPNs) Inaugural

- Diagnosis & Treatment Response
  - Myelofibrosis
  - Polycythemia Vera
  - Essential Thrombocythemia

- Disease Burden & Treatment Planning
  - Myelofibrosis
  - Polycythemia Vera
  - Essential Thrombocythemia

Treatment Guidelines
- Myelofibrosis

Treatment Guidelines (New 2017)
- Polycythemia Vera
- Essential Thrombocythemia

Diagnosis & Treatment (Forthcoming)
- Atypical MPNs
- HES, SMCD, etc.
NCCN Guidelines Version 2.2018
Myeloproliferative Neoplasms

WORKUP

- H&P, including spleen size by palpation, evaluation of thrombotic/hemorrhagic events and cardiovascular risk factors
- CBC with differential
- Comprehensive metabolic panel with uric acid, lactate dehydrogenase (LDH), and liver function tests (LFTs)
- FISH or RT-PCR for BCR-ABL1 to exclude the diagnosis of CML; if BCR-ABL1-positive, See NCCN Guidelines for Chronic Myelogenous Leukemia
- Examination of blood smear
- Bone marrow aspirate and biopsy with trichrome and reticulin stain
- Bone marrow cytogenetics (blood, if bone marrow is inaspirable) (karyotype ± FISH)
- Molecular testing (blood) for JAK2 V617F mutation; if negative, test for CALR and MPL mutations (for patients with ET and MF) and JAK2 Exon 12 mutations (for patients with PV)

Diagnosis and Risk Stratification

Suspicion of myeloproliferative neoplasms (MPN) → See MPN-2
NCCN Guidelines Version 2.2018
Myeloproliferative Neoplasms

WORKUP

- Assessment of symptom burden using MPN Symptom Assessment form (MPN-SAF)
- Documentation of transfusion/medication history
- Human leukocyte antigen (HLA) testing, if considering allogeneic hematopoietic cell transplant (HCT)
- Serum erythropoietin (EPO) level
- Serum iron studies
- Coagulation tests to evaluate for acquired von Willebrand disease (VWD) and/or other coagulopathies in selected patients
  - Prothrombin time (PT), partial thromboplastin time (PTT), Fibrinogen
  - Plasma von Willebrand Factor Antigen (VWFFA) measurement
  - Von Willebrand Ristocetin Cofactor (VWF:RCo) activity

Diagnosis and Risk Stratification

See MPN-2
DIAGNOSIS

- Primary myelofibrosis (PMF)
- Post-PV or Post-ET MF

RISK STRATIFICATION

- Low-risk (MF-1)
- Intermediate-risk 1 (INT-1) (MF-2)
- Intermediate-risk 2 (INT-2) and High-risk (MF-3)

Polycythemia vera (PV)

- Low-risk (PV-1)
- High-risk (PV-2)

Essential thrombocythemia (ET)

- Very low-risk/Low-Risk (ET-1)
- Intermediate-risk (ET-2)
- High-risk (ET-3)

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# PROGNOSTIC SIGNIFICANCE OF MUTATIONS IN MPN

<table>
<thead>
<tr>
<th>Mutated Gene</th>
<th>Primary Myelofibrosis (PMF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK2V617F</td>
<td>Intermediate prognosis and higher risk of thrombosis compared to patients with CALR mutation</td>
</tr>
<tr>
<td>MPLW515L/K</td>
<td>Intermediate prognosis and higher risk of thrombosis compared to patients with CALR mutation</td>
</tr>
<tr>
<td>CALR</td>
<td>Improved survival compared to JAK2 mutation and &quot;triple-negative&quot; PMF Lower risk of thrombosis compared to JAK2 mutation</td>
</tr>
<tr>
<td>CALR Type 1/Type 1-like</td>
<td>Improved overall survival compared to CALR type 2/type 2-like and JAK2 V617F mutation</td>
</tr>
<tr>
<td>&quot;Triple Negative&quot; (non-mutated JAK2, MPL, and CALR)</td>
<td>Inferior leukemia-free survival compared to patients with JAK2- and/or CALR-mutated PMF Inferior overall survival compared to patients with CALR-mutated PMF</td>
</tr>
<tr>
<td>ASXL1</td>
<td>Independently associated with inferior overall survival and leukemia-free survival</td>
</tr>
<tr>
<td>EZH2</td>
<td>Independently associated with inferior overall survival</td>
</tr>
<tr>
<td>IDH1/2</td>
<td>Independently associated with inferior leukemia-free survival</td>
</tr>
<tr>
<td>SRSF2</td>
<td>Independently associated with inferior overall survival and leukemia-free survival</td>
</tr>
<tr>
<td>Combined CALR and ASXL1 status</td>
<td>Survival longest for CALR(+).ASXL1(-) patients (median 10.4 years) and shortest in CALR(-).ASXL1(+) patients (median 2.3 years) Intermediate survival (median 5.8 years) for CALR(+).ASXL1(+) or CALR(-).ASXL1(-) patients</td>
</tr>
<tr>
<td>TP53</td>
<td>Associated with leukemic transformation</td>
</tr>
</tbody>
</table>
### PROGNOSTIC SIGNIFICANCE OF MUTATIONS IN MPN

<table>
<thead>
<tr>
<th>Mutated Gene</th>
<th>Polycythemia Vera (PV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASXL1/SRSF2/IDH1/2</td>
<td>The presence of at least 1 of these “adverse variants/mutations” is associated with inferior overall survival (compared to other sequence variants/mutations, or none) independent of age, IWG prognostic model for PV, and karyotype. Adverse variants/mutations also affected myelofibrosis-free survival.</td>
</tr>
<tr>
<td>JAK2 exon 12 mutation</td>
<td>Patients with JAK2 exon 12-mutated PV exhibit younger age, increased mean hemoglobin/hematocrit, and lower mean white blood cell and platelet counts at diagnosis compared to those with JAK2 V617F-mutated PV. However, both JAK2 mutations are associated with similar rates of thrombosis, evolution to myelofibrosis or leukemia, and death.</td>
</tr>
<tr>
<td>Mutated Gene</td>
<td>Essential Thrombocythemia (ET)</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td><strong>CALR</strong></td>
<td>Lower-risk of thrombosis compared to JAK2-mutated ET</td>
</tr>
<tr>
<td></td>
<td>No difference in overall survival or myelofibrotic or leukemic transformation compared to JAK2-mutated ET</td>
</tr>
<tr>
<td></td>
<td>CALR mutation does not modify the IPSET score for predicting thrombosis in patients with ET</td>
</tr>
<tr>
<td><strong>TP53</strong></td>
<td>Associated with inferior leukemia-free survival in multivariate analysis</td>
</tr>
<tr>
<td><strong>SH2B3/IDH2/U2AF1/SF3B1/EZH2/TP53</strong></td>
<td>The presence of at least 1 of these ‘adverse variants/mutations’ is associated with inferior overall survival (compared to other sequence variants/mutations, or none) independent of age and karyotype</td>
</tr>
<tr>
<td></td>
<td>Adverse variants/mutations also affect myelofibrosis-free survival</td>
</tr>
</tbody>
</table>
2016 WHO DIAGNOSTIC CRITERIA FOR POLYCYTHEMIA VERA AND ESSENTIAL THROMBOCYTHEMIA

Polycythemia Vera (PV)
[Diagnosis requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion]

• Major criteria
  ‣ Hemoglobin >16.5 g/dL in men, >16.0 g/dL in women
    OR
    Hematocrit >49% in men, >48% in women
    OR
    Increased red cell mass (RCM)
  ‣ Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
  ‣ Presence of JAK2 V617F or JAK2 exon 12 mutation

• Minor criteria
  ‣ Subnormal serum EPO level
Assessing MPN Burden

WHO Diagnosis Does Not Tell Whole Story

**Vascular Events**
- PV/ET > MF
- Counts matter
- Can be unrecognized

**Progression**
- PV/ET to MF
- PV/ET to AML
- MF to AML
- ? 2nd MDS

**MPN Symptoms**
- MF>PV>ET
- Multifactorial
- Some ET/PV > MF
- Cytoreductive rx frequently not effective

**Baseline Health AGE/ Medicines Comorbidities**

**Cytopenias**
- MF> ET/PV
- Anemia
  - MF 75%
  - TX Dep 25%
  - TPN 30%

**Splenomegaly**
- MF> ET/PV
- Pain not always a function of size

**Baseline Health**

**Cytopenias**

**Splenomegaly**
## MYELOPROLIFERATIVE NEOPLASM SYMPTOM ASSESSMENT FORM (MPN-SAF)¹

(Recommended for assessment of symptom burden at baseline)

Circle the one number that describes, during the past week, how much difficulty you have had with each of the following symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filling up quickly when you eat (early satiety)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td></td>
</tr>
<tr>
<td>Inactivity</td>
<td></td>
</tr>
<tr>
<td>Problems with headaches</td>
<td></td>
</tr>
<tr>
<td>Problems with concentration-compared to prior to my MPD</td>
<td></td>
</tr>
<tr>
<td>Dizziness/Vertigo/Lightheadedness</td>
<td></td>
</tr>
<tr>
<td>Numbness/Tingling (in my hands and feet)</td>
<td></td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td></td>
</tr>
<tr>
<td>Depression or sad mood</td>
<td></td>
</tr>
<tr>
<td>Problems with sexual desire or function</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td></td>
</tr>
<tr>
<td>Night sweats</td>
<td></td>
</tr>
<tr>
<td>Itching (pruritus)</td>
<td></td>
</tr>
<tr>
<td>Bone pain (diffuse not joint pain or arthritis)</td>
<td></td>
</tr>
<tr>
<td>Fever (&gt;100 F)</td>
<td></td>
</tr>
<tr>
<td>Unintentional weight loss last 6 months</td>
<td></td>
</tr>
<tr>
<td>What is your overall quality of life?</td>
<td>(As good as it can be) 0 1 2 3 4 5 6 7 8 9 10 (As bad as it can be)</td>
</tr>
</tbody>
</table>

Classic Signs and Symptoms of MPNs
Managing PV and ET

• Setting the stage for a treatment plan in ET and PV
• ET
• PV
• Future Directions
### 2013 IWG-MRT and ELN RESPONSE CRITERIA FOR ESSENTIAL THROMBOCYTHEMIA (ET)

<table>
<thead>
<tr>
<th>Complete remission</th>
<th>Durable* resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement, † AND</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Durable* peripheral blood count remission, defined as: platelet count ≤400 x 10^9/L, WBC count &lt;10 x 10^9/L, absence of leukoerythroblastosis, AND</td>
</tr>
<tr>
<td>B</td>
<td>Without signs of progressive disease, and absence of any hemorrhagic or thrombotic events, AND</td>
</tr>
<tr>
<td>C</td>
<td>Bone marrow histologic remission defined as disappearance of megakaryocyte hyperplasia and absence of &gt;grade 1 reticulin fibrosis</td>
</tr>
<tr>
<td>D</td>
<td>Partial remission</td>
</tr>
<tr>
<td>A</td>
<td>Durable* resolution of disease-related signs including palpable hepatosplenomegaly, and large symptoms improvement, AND</td>
</tr>
<tr>
<td>B</td>
<td>Durable* peripheral blood count remission, defined as: platelet count ≤400 x 10^9/L, WBC count &lt;10 x 10^9/L, absence of leukoerythroblastosis, AND</td>
</tr>
<tr>
<td>C</td>
<td>Without signs of progressive disease, and absence of any hemorrhagic or thrombotic events, AND</td>
</tr>
<tr>
<td>D</td>
<td>Without bone marrow histologic remission, defined as the persistence megakaryocyte hyperplasia</td>
</tr>
<tr>
<td>No response</td>
<td>Any response that does not satisfy partial remission</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>Transformation into PV, post-ET myelofibrosis, myelodysplastic syndrome or acute leukemia</td>
</tr>
</tbody>
</table>

WBC White Blood Count
*Lasting at least 12 weeks
†Large symptom improvement (≥10-point decrease) in MPN-SAF TSS.

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TREATMENT FOR INTERMEDIATE-RISK ESSENTIAL THROMBOCYTHEMIA

**Asymptomatic with no indications for cytoreductive therapy**
- New thrombosis, acquired VWD, and/or disease-related major bleeding
- Symptomatic or progressive splenomegaly
- Symptomatic thrombocytosis
- Progressive leukocytosis
- Progressive disease-related symptoms (e.g., pruritus, night sweats, fatigue)
- Vasomotor/ microvascular disturbances not responsive to aspirin (e.g., headaches/ chest pain, erythromelalgia)

**Symptomatic with potential indications for cytoreductive therapy**

**Intermediate-risk (Age >60 years, no JAK2 mutation, no prior history of thrombosis)**
- Monitor for new thrombosis, acquired VWD, and/or disease-related major bleeding
- Manage cardiovascular risk factors (see MPN-G)
- Aspirin (81–100 mg/d) for vascular symptoms

**Evaluate for indications of cytoreductive therapy and monitor signs/symptoms of disease progression every 3–6 months or more frequently if clinically indicated**

**Disease progression to MF/AML**

**Continue aspirin**

**Post-ET MF, see MPN-2; Advanced phase MF/AML, see MF-5**

**Initiate cytoreductive therapy**
- See High-risk ET (ET-3)
NCCN Guidelines Version 2.2018
Essential Thrombocythemia

TREATMENT FOR HIGH-RISK ESSENTIAL THROMBOCYTHEMIA

- Monitor for new thrombosis, acquired VWD, and/or disease-related major bleeding
- Manage cardiovascular risk factors (see MPN-G)
- Aspirin (81–100 mg/d) for vascular symptoms
- Hydroxyurea or Interferons (based on other patient-specific variables)
- Anagrelide

Adequate response

High-risk (History of thrombosis at any age or age >60 years with JAK2 mutation)

Potential indications for change of cytoreductive therapy:
- Intolerance or resistance to hydroxyurea or interferon
- New thrombosis, acquired VWD, and/or disease-related major bleeding
- Symptomatic or progressive splenomegaly
- Symptomatic thrombocytosis
- Progressive leukocytosis
- Progressive disease-related symptoms (eg, pruritus, night sweats, fatigue)
- Vasomotor/microvascular disturbances not responsive to aspirin (eg, headaches/chest pain, erythromelalgia)

Inadequate response or Loss of response

Disease progression to MF/AML

Continue treatment

Hydroxyurea if not previously used or Interferons if not previously used (Interferon alfa-2b, peginterferon alfa-2a, or peginterferon alfa-2b) or Anagrelide if not previously used or Clinical trial

Post-ET MF, see MPN-2; Advanced phase MF/AML, see MF-5

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Final results from the Phase 3 trial ARETA comparing a novel, extended-release \textit{anagrelide} formulation to placebo in essential thrombocythemia patients with defined risk status

\textbf{Heinz Gisslinger, Christoph Klade, Kudrat Abdulkadyrov, Sławomira Kyrcz-Krzemien, Elena Karyagina, Anait Melikyan, Kryztof Warzocha, Barbara Grohmann-Izay, Juri Hodisch, Rudolf Widmann, Robert Kralovics, Petro E. Petrides, Jiri Schwarz, and Jean-Jacques Kiladjian}

ARETA
Phase III, multicenter, randomized, subject- and sponsor-blinded, placebo-controlled study – early intervention in ET

Eligible patients
ET diagnosed according to WHO 2008 with “at risk” status

Stratification by JAK2 status
1:1

Randomization
6 weeks titration weekly visits
1 year main study visits every 3 months
Up to 3 years extension period visits every 3 months

Anagrelide ER
2-8 mg/day

Placebo

Primary endpoint:
Time to first ET-related cardiovascular events (as confirmed by independent blinded Endpoint Adjudication Committee), or disease progression or disease worsening (platelet increase >1000 G/l)

Definition of “at risk“ patients

• Platelet count < 1000 G/L and at least one of the following criteria:
  • Age 40 to 60 years
  • ET disease duration > 3 years
  • Any risk factor for thrombotic complications:
    a) JAK2 positivity
    b) Protein C and/or Protein S deficiency
    c) Antithrombin III deficiency
    d) Factor V Leiden or Prothrombin mutation
    e) Cardiovascular risk factors: essential hypertension, smoking (>5 cigarettes/d), obesity (BMI>30), cholesterol (HDL/LDL ratio < 4), hormone replacement therapy, hormonal contraception

Primary Efficacy Endpoint: ET-related event-free survival

Primary Efficacy Endpoint met: p=0.0008 (ITT Analysis Set) HR 0.356 [0.16-0.79]

## ET-related events

<table>
<thead>
<tr>
<th>ET-related events* (EAC** assessed)</th>
<th>Ana-ER (N=77)</th>
<th>Placebo (N=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pts. (%)</td>
<td>No. of events</td>
<td>No. of pts. (%)</td>
</tr>
<tr>
<td>ET-related events* (Investigator assessed)</td>
<td>11 (14.3)</td>
<td>12</td>
</tr>
<tr>
<td>ET-related events (platelet criteria)</td>
<td>9 (11.7)</td>
<td>11</td>
</tr>
<tr>
<td>ET-related events (EAC assessed) and/or platelet criteria</td>
<td>2 (2.6)</td>
<td>2</td>
</tr>
<tr>
<td>ET-related events (EAC assessed) and/or platelet criteria</td>
<td>13 (16.9)</td>
<td>13</td>
</tr>
</tbody>
</table>

* Major and minor arterial, venous and bleeding events  
** Endpoint Adjudication Committee
SUMMARY & CONCLUSION

• Primary Endpoint time to first ET-related event met (p=0.0008).
• Platelet count normalization and delayed progression to high risk status.
• Safety profile consistent with conventional anagrelide formulations.
• More convenient dosing schedule compared to licensed immediate release formulations confirmed.

In conclusion, data from ARETA trial support a “treat early concept” for all ET patients where normalization of platelet count or symptom reduction is a goal.
MPD-RC 112 Study Schema

- WHO 2008 ET/PV
- High Risk
  - >60 years
  - Thrombosis
  - thrombocytosis
  - Symptomatic spleen
  - Uncontrolled CV risk factor
- Dx <5 years
- Treatment naïve

Randomized 1:1

HU n=39
PEG n=36

INTERIM ANALYSIS

HU n=86
PEG n=82

Planned analysis
75 subjects
treated for 1 year

Modified protocol
to include final analysis to be completed once all subjects enrolled for 1 year (n=168)

[anticipated date of 6/30/2017]

Mascarenhas JO et al. Blood 2016;128:Abstract 479
# Overall Response Rates at 12 Months by Treatment Arm

<table>
<thead>
<tr>
<th></th>
<th>HU (n=39)</th>
<th></th>
<th>PEG (n=36)</th>
<th></th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PR n (%)</td>
<td>CR n (%)</td>
<td>ORR n (%)</td>
<td>PR n (%)</td>
<td>CR n (%)</td>
</tr>
<tr>
<td>Entire cohort (n=75)</td>
<td>14 (36)</td>
<td>13 (33)</td>
<td>27 (69)</td>
<td>19 (53)</td>
<td>10 (28)</td>
</tr>
<tr>
<td>ET (n=31)</td>
<td>4/16 (25)</td>
<td>7/16 (44)</td>
<td>11/16 (69)</td>
<td>6/15 (40)</td>
<td>6/15 (40)</td>
</tr>
<tr>
<td>PV (n=44)</td>
<td>10/23 (44)</td>
<td>6/23 (26)</td>
<td>16/23 (70)</td>
<td>13/21 (62)</td>
<td>4/21 (19)</td>
</tr>
</tbody>
</table>

* CR comparison based on z-test; did not cross stopping boundary
Complete Histopathologic Bone Marrow Response at 12 Months by Blinded Central Review

Histopathology Criteria

- Normalized BM cellularity
- < grade 2 reticulin fibrosis
- ET: Disappearance of megakaryocyte hyperplasia, and abnormal megakaryocyte histotopography
- PV: Disappearance of trilineage hyperplasia

<table>
<thead>
<tr>
<th></th>
<th>HU</th>
<th>PEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET+PV</td>
<td>8/22</td>
<td>2/24</td>
</tr>
<tr>
<td>ET</td>
<td>5/10</td>
<td>2/10</td>
</tr>
<tr>
<td>PV</td>
<td>3/12</td>
<td>0/14</td>
</tr>
</tbody>
</table>

Mascarenhas JO et al. Blood 2016;128:Abstract 479
Managing PV and ET

• Setting the stage for a treatment plan in ET and PV
• ET
• PV
• Future Directions
### DEFINITION OF RESISTANCE/INTOLERANCE TO HYDROXYUREA

<table>
<thead>
<tr>
<th>Myeloproliferative Neoplasm</th>
<th>Definition of Resistance/Intolerance to Hydroxyurea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polycythemia vera</td>
<td>1. Need for phlebotomy to keep hematocrit &lt;45% after 3 months of at least 2 g/d of hydroxyurea, OR&lt;br&gt;2. Uncontrolled myeloproliferation (ie, platelet count &gt;400 x 10^9/L AND WBC count &gt;10 x 10^9/L) after 3 months of at least 2 g/d of hydroxyurea, OR&lt;br&gt;3. Failure to reduce massive splenomegaly by &gt;50% as measured by palpation OR failure to completely relieve symptoms related to splenomegaly after 3 months of at least 2 g/d of hydroxyurea, OR&lt;br&gt;4. Absolute neutrophil count &lt;1.0 x 10^9/L OR platelet count &lt;100 x 10^9/L OR hemoglobin &lt;10 g/dL at the lowest dose of hydroxyurea required to achieve a complete or partial clinicohematologic response, OR&lt;br&gt;5. Presence of leg ulcers or other unacceptable hydroxyurea-related nonhematologic toxicities, such as mucocutaneous manifestations, GI symptoms, pneumonitis, or fever at any dose of hydroxyurea</td>
</tr>
<tr>
<td>Essential thrombocythemia</td>
<td>1. Platelet count &gt;600 x 10^9/L after 3 months of at least 2 g/d of hydroxyurea (2.5 g/d in patients with a body weight &gt;80 kg), OR&lt;br&gt;2. Platelet count &gt;400 x 10^9/L and WBC count &lt;2.5 x 10^9/L at any dose of hydroxyurea, OR&lt;br&gt;3. Platelet count &gt;400 x 10^9/L and hemoglobin &lt;10 g/dL at any dose of hydroxyurea, OR&lt;br&gt;4. Presence of leg ulcers or other unacceptable mucocutaneous manifestations at any dose of hydroxyurea, OR&lt;br&gt;5. Hydroxyurea-related fever</td>
</tr>
</tbody>
</table>

*Organ extending by >10 cm from the costal margin.<br>†Complete response is defined as hematocrit less than 45% without phlebotomy, platelet count ≤400 x 10^9/L, WBC count ≤10 x 10^9/L, and no disease-related symptoms. Partial response is defined as hematocrit less than 45% without phlebotomy or response in three or more of other criteria.
TREATMENT FOR LOW-RISK POLYCYTHEMIA VERA

Low-risk (Age <60 years and no prior history of thrombosis)

- Monitor for new thrombosis or bleeding
- Manage cardiovascular risk factors (see MPN-G)
- Aspirin for vascular symptoms (81–100 mg/d)
- Phlebotomy (to maintain hematocrit <45%)

Evaluate for indications of cytoreductive therapy and monitor signs/symptoms of disease progression every 3-6 months or more frequently if clinically indicated

Asymptomatic with no indications for cytoreductive therapy

- New thrombosis or disease-related major bleeding
- Frequent and/or persistent need for phlebotomy, but with poor tolerance of phlebotomy
- Symptomatic or progressive splenomegaly
- Symptomatic thrombocytosis
- Progressive leukocytosis
- Progressive disease-related symptoms (eg, pruritus, night sweats, fatigue)

Disease progression to MF/AML

Symptomatic with potential indications for cytoreductive therapy

Continue aspirin with phlebotomy

Post-PV MF, see MPN-2; Advanced phase MF/AML, see MF-5

Initiate cytoreductive therapy See PV-2

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TREATMENT FOR HIGH-RISK POLYCYTHEMIA VERA

- Monitor for new thrombosis or bleeding
- Manage cardiovascular risk factors (see MPN-G)
- Aspirin for vascular symptoms (81–100 mg/d)
- Phlebotomy (to maintain hematocrit <45%)
- Hydroxyurea or Interferons (based on age and other patient specific variables)

High-risk (Age ≥60 years and/or no prior history of thrombosis)

Monitor response and signs/symptoms of disease progression every 3–6 months or more frequently as clinically indicated

Adequate response

Potential indications for change of cytoReductive therapy
- Intolerance or resistance to hydroxyurea or interferon
- New thrombosis or disease-related major bleeding
- Frequent and/or persistent need for phlebotomy, but with poor tolerance of phlebotomy
- Symptomatic or progressive splenomegaly
- Symptomatic thrombocytosis
- Progressive leukocytosis
- Progressive disease-related symptoms (eg, pruritus, night sweats, fatigue)

Inadequate response or Loss of response

Disease progression to MF/AML

Ruxolitinib or Hydroxyurea if not previously used or Interferons if not previously used (Interferon alfa-2b, peginterferon alfa-2a, or peginterferon alfa-2b), or Clinical trial

Post-PV MF, see MPN-2; Advanced phase MF/AML, see MF-5

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Final results from PROUD-PV, a randomized controlled phase 3 trial comparing peginterferon alfa-2b to hydroxyurea in polycythemia vera patients

Naïve patients in need of cytoreduction

Stratified Randomization by Age, prev. HU, prev. TE

Eligible PV patient population per WHO2008 criteria

12 months treatment

Up to 3-5 years treatment

Expected outcome: * non-inferiority: Hematologic Response

** benefit: durable Hematologic Response, PFS, PV symptom relief

Ropeginterferon alfa-2b phase III development: PROUD/CONTI-PV

Ropeginterferon

Hydroxyurea

BAT

Complete Hematologic Response at 12 months

<table>
<thead>
<tr>
<th></th>
<th>AOP2014</th>
<th>HU</th>
<th>Difference % (95% CI)</th>
<th>P-value *)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete hematologic response rate (ITT)</td>
<td>43.1%</td>
<td>45.6%</td>
<td>-2.5 (-14.9 to 9.9)</td>
<td>0.0028</td>
</tr>
<tr>
<td>Responding patients/n</td>
<td>53/123</td>
<td>57/125</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete hematologic response rate (PP)</td>
<td>44.3%</td>
<td>46.5%</td>
<td>-2.2 (-15.2 to 10.7)</td>
<td>0.0036</td>
</tr>
<tr>
<td>Responding patients/n</td>
<td>50/113</td>
<td>53/114</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

→ non-inferiority is demonstrated, p=0.0028

*) Non-inferiority margin 20.0%
Complete hematologic response over time: preliminary outlook
(only CONTI patients & local lab data as available)

What does intolerance/resistance to Hydroxyurea in PV Mean?

1. Need for phlebotomy (HCT<45%)
2. PLT >400 x 10^9/L & WBC >10 x 10^9/L
3. No reduction of spleen by 50%
4. No reduction of spleen symptoms

N.B.
1. After > 3 Months
2. At MTD or 2g/day

N.B.
At lowest dose to achieve either a PR or CR by ELN Criteria

Adapted from ELN Criteria – Barosi et. al. BJH 2010;148:961-3.
<table>
<thead>
<tr>
<th></th>
<th>2013 IWG-MRT and ELN RESPONSE CRITERIA FOR POLYCYTHEMIA VERA (PV)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete remission</strong></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Durable* resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement, † AND</td>
</tr>
<tr>
<td>B</td>
<td>Durable* peripheral blood count remission, defined as: hematocrit lower than 45% without phlebotomies; platelet count ≤400 x 10^9/L, WBC count &lt;10 x 10^9/L, AND</td>
</tr>
<tr>
<td>C</td>
<td>Without progressive disease, and absence of any hemorrhagic or thrombotic event, AND</td>
</tr>
<tr>
<td>D</td>
<td>Bone marrow histologic remission defined as the presence of age-adjusted normocellularity and disappearance of trilineage hyperplasia, and absence of &gt;grade 1 reticulin fibrosis</td>
</tr>
<tr>
<td><strong>Partial remission</strong></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Durable* resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement, † AND</td>
</tr>
<tr>
<td>B</td>
<td>Durable* peripheral blood count remission, defined as: hematocrit lower than 45% without phlebotomies; platelet count ≤400 x 10^9/L, WBC count &lt;10 x 10^9/L, AND platelet count ≤400 x 10^9/L, WBC count &lt;10 x 10^9/L, AND</td>
</tr>
<tr>
<td>C</td>
<td>Without progressive disease, and absence of any hemorrhagic or thrombotic event, AND</td>
</tr>
<tr>
<td>D</td>
<td>Without bone marrow histologic remission defined as persistence of trilineage hyperplasia</td>
</tr>
<tr>
<td><strong>No response</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any response that does not satisfy partial remission</td>
</tr>
<tr>
<td><strong>Progressive disease</strong></td>
<td>Transformation into post-PV myelofibrosis, myelodysplastic syndrome or acute leukemia</td>
</tr>
</tbody>
</table>

**Notes:**

- WBC: White blood cell count
- *Durable* resolution of disease-related signs means the patient is free of disease-related symptoms, with no new or progressive evidence of disease for at least 12 weeks
- †Large symptom improvement (≥10-point decrease) in MPN-SAF TSS.

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Ruxolitinib (Single Agent) in Polycythemia Vera

- Resistance to or intolerance of HU (modified ELN criteria)
- Phlebotomy requirement
- Splenomegaly

Pre-randomization (Day −28 to Day −1)
Hct 40%-45%

Randomized (1:1)

Ruxolitinib 10 mg BID
n = 110

Extended Treatment Phase
Week 208

Crossover to ruxolitinib

Week 208

Hct 40%

BAT
n = 112

Week 32
(Primary analysis)

Week 80

Ruxolitinib (post HU) compared to Best Alternative Therapy in PV
1. Superior control of hematocrit
2. Superior reduction in splenomegaly
3. Superior reduction in PV related symptoms
4. Trend for less thrombotic events

Primary Response at Week 32

77% of patients randomized to ruxolitinib met at least 1 component of the primary endpoint.

Improvement in Symptoms (Week 32)

Percentage of Patients with a ≥ 50% Improvement in MPN-SAF Total Symptom Score at Week 32

- **49%** for **Ruxolitinib**
- **5%** for **BAT**

**Cytokine Symptom Cluster**
- Tiredness
- Itching
- Muscle ache
- Night sweats
- Sweating while awake

**Hyperviscosity Symptom Cluster**
- Headache
- Dizziness
- Skin redness
- Vision problems
- Numbness/tingling in hands/feet

**Splenomegaly Symptom Cluster**
- Fullness/early satiety
- Abdominal discomfort

Impact of Ruxolitinib on Pruritus by the PSIS* Scale at Week 32

Mean Change From Baseline at Week 32

-2.2  -2.0  -1.5  -1.9  -1.4  0.0  0.30  0.30

-5  -4  -3  -2  -1  0  1  2  3  4  5

How severe was PV-related itching during the past 7 days?
How bothered by PV-related itching during the past 7 days?
How much PV-related itching interfered with daily life during the past 7 days?
How bothered by PV-related itching during the past 24 hours?
How much PV-related itching interfered with daily life during the past 24 hours?

- Pruritus severity and its interference on daily life improved with ruxolitinib and was unchanged/worsened with BAT

*Patients responded to each question on a scale of 0 (not at all) to 10 (worst imaginable)
Managing PV and ET

• Setting the stage for a treatment plan in ET and PV
• ET
• PV
• Future Directions
Treatment Gaps - ET

1. What is the optimal front line therapy for ET?

2. How do we prevent disease progression?

3. What is the role of JAK inhibition?
Treatment Gaps - PV

1. What is the optimal front line therapy for PV?
2. How do we prevent disease progression?
3. How early should we consider JAK inhibition?
P53/MDM2 in MPNs

- P53 regulates cell cycle, apoptosis, DNA repair, and senescence
- Wild type p53 seen in chronic phase MPN
- Inactivating p53 mutations frequent in MPN-BP
- Down regulation of p53 by MDM2 overexpression
  - Promotes proteosomal degradation
  - Inhibits p53 transcripition
  - Inhibits transactivation
  - Facilitates export from nucleus

A PHASE II, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF IDASANUTLIN MONOTHERAPY IN PATIENTS WITH HYDROXYUREA-RESISTANT/INTOLERANT POLYCYTHEMIA VERA

Idasanutlin
150 mg Daily x 5
N~20
PK/MIC-1

PV WHO 2016
HU resistance/intolerance
Phlebotomy dependent

Consider 200 mg for incomplete responders
(NR*: No HCT Control*)

Week 32 (end cycle 8)
then every 3 cycles up to 2yrs

12 weeks
Continue Dose to wk 32

Composiive Response
(Hct control, spleen)

ELN Response*
Hematocrit Response**
(+ Jak-2, PROs*)
CA PK/MIC-1
(for 200 mg esc only)

Molecular Response (Jak-2)
PROs*
& Histologic Response

*Per 2009 ELN Criteria  **Patients without measurable splenomegaly at baseline  ^spleen imaging at end C6 only if <35% reduction at end C3
*MPN-SAF-TSS, EORTC QLQ-C30, PGIC  ^Bone Marrow biopsy every 6 cycles post-week 32 per PI discretion in context of ELN CHR response
New MPN Therapies – Possible Positioning

- **Myelofibrosis**
  - Front Line: Ruxolitinib, Momelotinib?, Pacritinib?
  - Second Line: Momelotinib?, Pacritinib?, PRM151?, Imetelstat?
  - Third Line: Ruxolitinib

- **Polycythemia Vera**
  - HU, ? INF

- **Essential Thrombocythemia**
  - HU, ? INF

- **Hypersplenism, ? INF**
  - Ruxolitinib

- **Anagrelide**

- **Ruxolitinib**
Putting It All Together – MPNs and QOL

MPN Patient
• Disease Prognosis
• Vascular Risk
• Symptom Burden
• Impact of Disease on QOL
• Patient Choice and Input
• Treatment Options

Role of Hematopoietic Cell Transplant (HCT)

Improving Symptom Burden & QOL

Avoiding Progression

Preventing Vascular Events

Reduction of Splenomegaly

Prolonging Survival

Preventing Vascular Events

Avoiding Progression

Role of Hematopoietic Cell Transplant (HCT)