WELCOME & INTRODUCTIONS
Advances in Treating Myeloproliferative Neoplasms

Welcome to LLS Community
We are a community of blood cancer patients, survivors and caregivers. We’re here to support you, give you trusted information and resources, and help you feel connected. No one should have to face a blood cancer diagnosis alone.

To join LLS Community, visit www.LLS.org/community.

Program will begin shortly

ADVANCES IN TREATING MYELOPROLIFERATIVE NEOPLASMS

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Instructor in Medicine
Division of Hematology and Oncology
Weill Cornell Medicine
New York, NY
As of 1/19/21, there are 1763 clinical trials worldwide registered in clinicaltrials.gov to advance MPN treatment

We need treatments to improve quality of life, prevent complications, and improve survival of MPN patients. Ideally, we need a cure!

https://clinicaltrials.gov/ct2/results/map?cond=myeloproliferative+neoplasm&map=
Outline

- MPN diagnosis, symptoms and complications
- Treatment of PV
- Treatment of ET
- Treatment of MF

Classical Myeloproliferative Neoplasms (MPN) are classified into 3 major subtypes

- Essential Thrombocythemia (ET)
- Polycythemia Vera (PV)
- Primary Myelofibrosis (PMF)
>90% of MPNs share driver mutations in JAK2, CALR, or MPL

![Diagram showing the distribution of mutations in Essential Thrombocythemia (ET), Polycythemia Vera (PV), and Primary Myelofibrosis (PMF).]

Driver mutations occur in blood stem cells and lead to overproduction of cells, inflammation and fibrosis.

![Diagram illustrating the effects of JAK2 mutations on red cells, white cells, and platelets, leading to fibrosis.]

Klampfl T. et al. NEJM 2013
First step towards optimal treatment is making an accurate diagnosis
Bone marrow histology is crucial!

Essential Thrombocythemia (ET)

Polycythemia Vera (PV)

Overt Myelofibrosis

Primary Myelofibrosis (PMF)

Rumi E, Cazzola M, Blood 2017

Courtesy of Geoffrey Mikita

MPNs can impair quality of life

Data adapted from MPN-SAF, Robyn S et al. Blood 2011

MPN Landmark Study

Courtesy of Maureen Thyne, PA-C
MPNs can cause serious complications

Jean-Jacques Kiladjian Hematology 2012

MPNs **MAY** shorten survival

Tefferi A et al. Blood 2014
Disease-modifying treatments are needed in MPN treatment

- A disease-modifying treatment is one that not only improves symptoms, spleen size, blood counts, and prevents complications, but also prevents natural progression and enforces disease regression.

- By doing so, a disease-modifying treatment is potentially capable of inducing long-term remission and improving survival.

Outline

- MPN diagnosis, symptoms and complications
  - Treatment of PV
  - Treatment of ET
  - Treatment of MF
  - COVID-19 and MPN
PV initial treatment approach:

What do guidelines recommend? What do we recommend?

**RISK of THROMBOSIS**

- **Age < 60**
  - No thrombosis

- **Age 60+**
  - + thrombosis

**National guidelines**

Initial treatment by risk group

- **Age < 60**
  - Low risk
    - Assess for new blood clots and major bleeding
    - Manage cardiovascular risk factors
    - Aspirin
  - No thrombosis

- **Age 60+**
  - High risk
    - Assess for new blood clots and major bleeding
    - Manage cardiovascular risk factors
    - Aspirin
    - Hydroxyurea or interferons

**Weill Cornell practice**

- ? + INTERFERON (IFN)
- IFN or Hydroxyurea (HU)

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**IFN in PV is disease-modifying**

**Histologic response**

- Pretreatment
- Posttreatment

- **Fibrosis reversion**

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Masarova L et al. Hematol Oncol. 2017
IFN is associated with improved survival outcomes in PV

Abu-Zeinah G et al. Oral abstract at the 2020 annual meeting of the American Society of Hematology
Manuscript accepted to Leukemia

Side effects leading to discontinuation of treatment (IFN vs HU)

- 13% had IFN discontinued for side effects.
- 16% had HU discontinued for side effects.
Ropeg-IFN is possibly better than HU in a randomized trial of high-risk PV (CONTI-PV)

Ropeginterferon α-2b (Ropeg-FN) is a longer-acting, biweekly dosed form of Interferon-alpha

Gisslinger H et al. Lancet Hematology 2020

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PV initial treatment approach:
What do guidelines recommend? What do we recommend?

<table>
<thead>
<tr>
<th>Initial treatment by risk group</th>
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<tbody>
<tr>
<td><strong>Low risk</strong></td>
</tr>
<tr>
<td>NCCN</td>
</tr>
<tr>
<td>ELN</td>
</tr>
<tr>
<td>WCM</td>
</tr>
</tbody>
</table>

PHL-O causes chronic iron deficiency, Chronic iron deficiency is associated with:
1. Fatigue
2. Decline in physical performance
3. Cognitive impairment

Ginzburg et al, Leukemia 2018

PHL-O increased fibrosis risk

Abu-Zeinah et al. ASH 2020


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IFN> PHL-O in recent randomized trial of low-risk PV
Better hematocrit control, less progression at 1 year

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Barbul T et al. EHA oral abstract 2020
Second-line treatments and clinical trials in PV: Ruxolitinib

**RESPONSE trial: Ruxolitinib versus “Standard therapy”**

*Patients [%]*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Ruxolitinib</th>
<th>Standard Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite Primary End Point</td>
<td>49</td>
<td>24</td>
</tr>
<tr>
<td>≥33% Reduction in Spleen Volume</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Hematocrit Control</td>
<td>60</td>
<td>19.6</td>
</tr>
</tbody>
</table>

P<0.001; Odds ratio, 28.6 (95% CI, 4.8–1206)

*Vannucchi et al. N Engl J Med. 2015*

**Second-line treatments and clinical trials in PV: Rux+IFN for patients refractory to IFN alone**

*PV – blood count remission*

*MF – blood count remission*

*Serensen et al. Haematologica. 2020*
Second-line treatments and clinical trials in PV: PTG-300 hepcidin mimetic

Outline

- MPN diagnosis, symptoms and complications
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- COVID-19 and MPN
Risk adapted treatment of ET by IPSET-thrombosis score:
Interferon or HU is recommended first line for high-risk ET

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>HR</th>
<th>Score</th>
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<tbody>
<tr>
<td>Age &gt; 60 years</td>
<td>1.50</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>1.56</td>
<td>1</td>
</tr>
<tr>
<td>risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous</td>
<td>1.93</td>
<td>2</td>
</tr>
<tr>
<td>thrombosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JAK2V617F</td>
<td>2.04</td>
<td>2</td>
</tr>
</tbody>
</table>

Low risk implies a score = 0–1; intermediate risk, score = 2; and high risk, score ≥ 3

• Low-Intermediate risk (0-2): Low dose ASA for select cases

• High risk patients (≥3):
  - Low dose ASA
  - First line Hydroxyurea (HU) or Interferon (rIFNα)

• Special considerations to prompt cytoreductive treatment:
  • Plt count > 1500 x10^9/L (or less with acquired von willebrand disease)
  • myeloproliferative symptoms exist
  • Young women desiring pregnancy

Barbui T et al.
the European LeukemiaNet recommendations. Leukemia 2018

Second-line treatments and clinical trials in ET:
MAJIC-ET trial: For HU resistant or intolerant patients,
Ruxolitinib is NOT superior to best available therapy (BAT)

• BAT = HU(71.1%), anagrelide (48.1%), and interferon (40.4%).

• No evidence of improvement in complete response within 1 year reported in 27 (46.6%) ruxolitinib patients vs 23 (44.2%) with BAT (P 5 .40). At 2 years, rates of thrombosis, hemorrhage, and transformation were not significantly different.

Second-line treatments and clinical trials in ET: Ropeg-IFN

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Management of PMF depends on prognosis/risk: DIPSS-plus is a widely used risk score in clinic and clinical trials

DIPSS-plus stratified OS of PMF patients

<table>
<thead>
<tr>
<th>Clinical factor</th>
<th>Points</th>
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<tr>
<td>Age &gt;65</td>
<td>1</td>
</tr>
<tr>
<td>WBC &gt;25 x10^3 /µL</td>
<td>1</td>
</tr>
<tr>
<td>Hgb &lt;10 g/dL</td>
<td>2</td>
</tr>
<tr>
<td>Circulating blasts ≥1%</td>
<td>1</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>1</td>
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</table>

PLUS:
- Platelet count <100 x10^3 /µL
- Anemia requiring transfusion
- Unfavorable karyotype

Stem cell transplant is currently the only potentially curative therapy but is not suitable for all patients

HSCT for PMF: OS after transplant by DIPSS plus score

Gangat N, et al. JCO 2011
Molecular risk should be considered in the management of MF

- **High molecular risk (HMR):** mutations in ASXL1, SRSF2, IDH1/2, EZH2. ASXL1 portends worse outcome independent of DIPSS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Overall Frequency (%)</th>
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<tr>
<td>JAK2</td>
<td>59.2</td>
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<tr>
<td>ASXL1</td>
<td>21.7</td>
</tr>
<tr>
<td>TET2</td>
<td>9.7</td>
</tr>
<tr>
<td>SRSF2</td>
<td>8.5</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>5.7</td>
</tr>
<tr>
<td>MPL</td>
<td>5.2</td>
</tr>
<tr>
<td>EZH2</td>
<td>5.1</td>
</tr>
<tr>
<td>CBL</td>
<td>4.4</td>
</tr>
<tr>
<td>IDH1/2</td>
<td>2.6</td>
</tr>
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</table>

Vannucchi et al. Leukemia 2013

Risk-adapted treatment guidelines for myelofibrosis

- **Low to intermediate-1 risk** (by IPSS/DIPSS/DIPSS-plus score)
  - Observation alone for asymptomatic patients
  - First line HU for symptomatic splenomegaly
  - Ruxolitinib for highly symptomatic splenomegaly or constitutional symptoms
  - consider Interferon (rIFNα)

- **Intermediate-2 to High risk** (by IPSS/DIPSS/DIPSS-plus score)
  - Allogeneic **stem cell transplant (SCT)** for eligible patients
  - First line **Ruxolitinib** for splenomegaly

Additional considerations:
- Anemia treatment with transfusion and ESAs, +/- prednisone, androgens, iMids,

Barbui T et al; the European LeukemiaNet recommendations. Leukemia 2018
JAK inhibitor, Ruxolitinib was first FDA approved (2011) treatment for MF based on symptom and spleen size improvements. Fedratinib later approved (2019).

What about Interferon in Myelofibrosis?

WCM experience:

- IFN should be used at low doses for sufficient duration (>12mo).

- Patients who are most likely to benefit are those with:
  - low-grade (grade 1-2) BM fibrosis,
  - No massive splenomegaly (<10cm on exam),
  - lower DIPPS score (low-int 1),
  - absence of high molecular risk mutations.
rIFN-α may delay progression of early MF

**Patients:**
- 17 Primary MF patients with Low (11) and Intermediate-1 (6) DIPSS.
- “early” by virtue of grade 1-2 bone marrow reticulin fibrosis

**Results**
- >80% had clinical benefit or stable disease (2 CR, 7 PR, 1 CI, 4 SD, 3 PD)
- Improvement in marrow morphology occurred in 4 patients

HMR correlates with poor response to rIFN-α in early MF

<table>
<thead>
<tr>
<th>DIPSS Prognostic</th>
<th>Total</th>
<th>CR</th>
<th>PR</th>
<th>CI</th>
<th>SD</th>
<th>PD</th>
<th>Died</th>
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<tr>
<td>Low</td>
<td>22 (73)</td>
<td>1 (0)</td>
<td>8 (27)</td>
<td>2 (6)</td>
<td>4 (13)</td>
<td>4 (13)</td>
<td>3 (10)</td>
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<tr>
<td>Intermediate-1</td>
<td>8 (27)</td>
<td>1 (0)</td>
<td>1 (3)</td>
<td>2 (6)</td>
<td>3 (10)</td>
<td>0 (0)</td>
<td>1 (3)</td>
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<tr>
<td>Total</td>
<td>30</td>
<td>2 (6)</td>
<td>9 (30)</td>
<td>4 (13)</td>
<td>7 (23)</td>
<td>4 (13)</td>
<td>4 (13)</td>
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<table>
<thead>
<tr>
<th>Mutation</th>
<th>Total</th>
<th>CR</th>
<th>PR</th>
<th>CI</th>
<th>SD</th>
<th>PD</th>
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<tr>
<td>ASXL1 + MTC</td>
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<tr>
<td>TET2</td>
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<td>2</td>
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<td>TET2 + MTC</td>
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<td>WT1</td>
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<tr>
<td>SETBP1 + KDM6A + FLT3</td>
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<tr>
<td>MPL</td>
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<td>1</td>
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<tr>
<td>Single mutation</td>
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<td>1</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SRSF2 + TET2</td>
<td>1</td>
<td>2</td>
<td>7</td>
<td>3</td>
<td>6</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>2b</td>
<td>2</td>
<td>7</td>
<td>3</td>
<td>6</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Silver RT et al. Blood 2011
Silver RT, the 10th international Congress on Myeloproliferative Neoplasms and Chronic Myeloid Leukemia
Pizzi M et al. Mod Path 2015
Silver RT et al. Cancer 2017
Therapies in the clinical trial pipeline for Myelofibrosis:

- JAK inhibitor: pacritinib
- BET inhibitor: CPI-0610
- Bcl-xl/ Bcl2 inhibitor: navitoclax
- Telomerase inhibitor: imetelstat
- TGF-beta pathway inhibitors: vactosertib, luspatercept, AVID 200
- Many others….
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• COVID-19 and MPN

Treatment of MPN during COVID-19: Lessons learned

Barbui et al. Leukemia 2020
COVID-19 vaccination recommendations from the CDC

Vaccination of persons with underlying medical conditions

mRNA COVID-19 vaccines may be administered to persons with underlying medical conditions who have no contraindications to vaccination (see 'contraindications' section below). Clinical trials

Contraindications

CDC considers a history of the following to be a contraindication to vaccination with both the Pfizer-BioNTech and Moderna COVID-19 vaccines:

- Severe allergic reaction (e.g., anaphylaxis) after a previous dose of an mRNA COVID-19 vaccine or any of its components
- Immediate allergic reaction of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components (including polyethylene glycol (PEG))
- Immediate allergic reaction of any severity to polysorbate (due to potential cross-reactive hypersensitivity with the vaccine ingredient PEG)

CDC recommendations: https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html

Thank you for your attention!

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Our patients!
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Funding
Q&A SESSION
Advances in Treating Myeloproliferative Neoplasms

- **Ask a question by phone:**
  - Press star (*) then the number 1 on your keypad.

- **Ask a question by web:**
  - Click “Ask a question”
  - Type your question
  - Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

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HOW TO CONTACT US:

To contact an Information Specialist about disease, treatment and support information, resources and clinical trials:

- **Call:** (800) 955-4572
  Monday to Friday, 9 a.m. to 9 p.m. ET
- **Chat live online:** www.LLS.org/InformationSpecialists
  Monday to Friday, 10 a.m. to 7 p.m. ET
- **Email:** infocenter@LLS.org
  All email messages are answered within one business day.

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Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical-trial process.

www.LLS.org/Navigation

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NUTRITION CONSULTATIONS

Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email.

www.LLS.org/Consult.
The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancer: [www.LLS.org/Finances](http://www.LLS.org/Finances)

To order free materials: [www.LLS.org/Booklets](http://www.LLS.org/Booklets)
We have one goal: A world without blood cancers

THANK YOU