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

BEATING CANCER IS IN OUR BLOOD.

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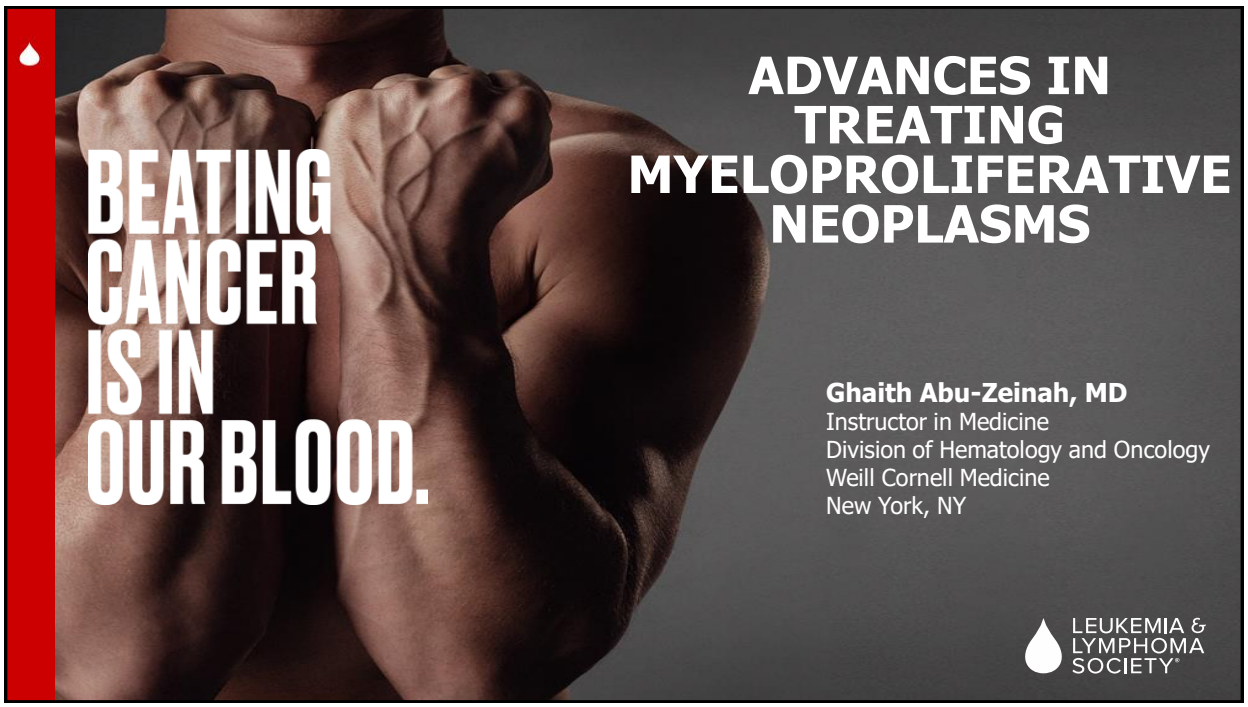

ADVANCES IN TREATING MYELOPROLIFERATIVE NEOPLASMS

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Instructor in Medicine
Division of Hematology and Oncology
Weill Cornell Medicine
New York, NY

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DISCLOSURES

Advances in Treating Myeloproliferative Neoplasms

Ghaith Abu-Zeinah, MD has affilations with PharmaEssentia.

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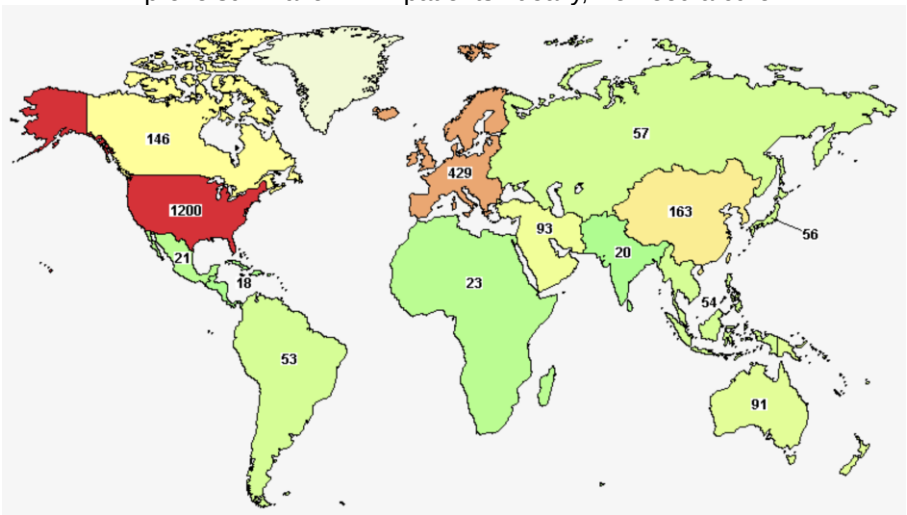
As of 1/19/21, there are 1763 clinical trials worldwide registered in clinicaltrials.gov to advance MPN treatment

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=

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Outline

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

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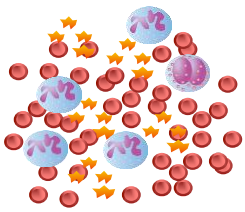
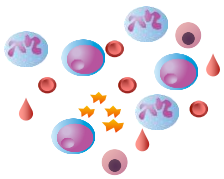
Classical Myeloproliferative Neoplasms (MPN) are classified into 3 major subtypes

Essential Thrombocythemia (ET)

Polycythemia Vera (PV)



Primary Myelofibrosis (PMF)



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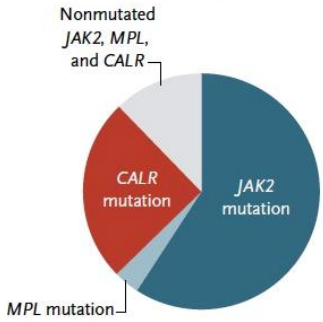
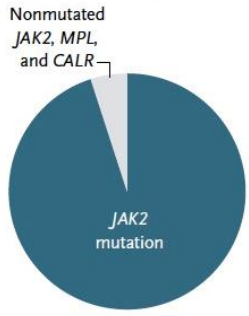
>90% of MPNs share driver mutations in JAK2, CALR, or MPL

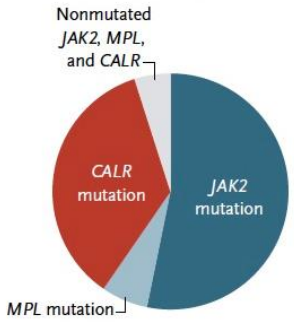
Essential Thrombocythemia (ET)



Polycythemia Vera (PV)



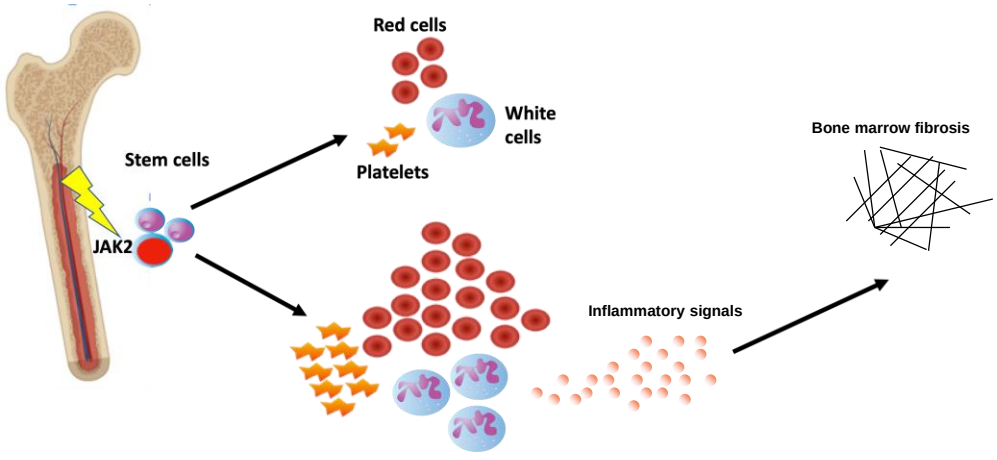
Primary Myelofibrosis (PMF)



Klampfl T. et al. NEJM 2013

7

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



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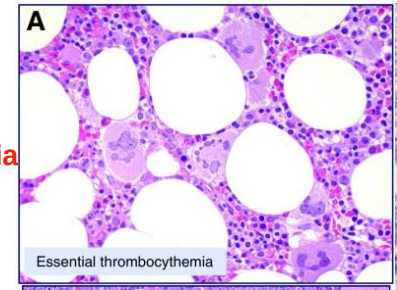
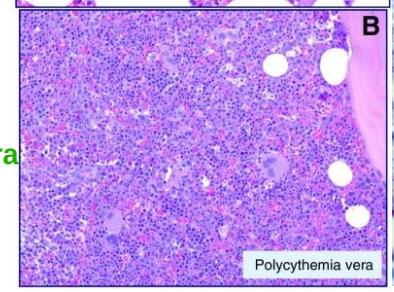
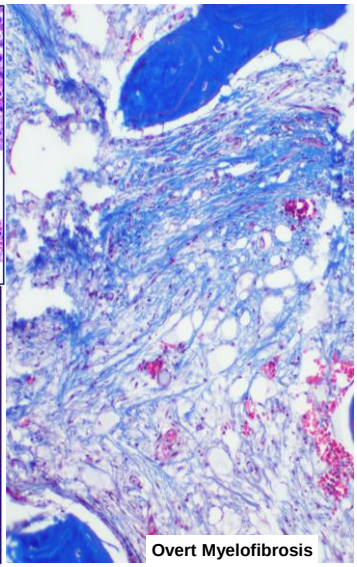
First step towards optimal treatment is making an accurate diagnosis
Bone marrow histology is crucial!

Essential Thrombocythemia (ET)



Polycythemia Vera (PV)





Primary Myelofibrosis (PMF)

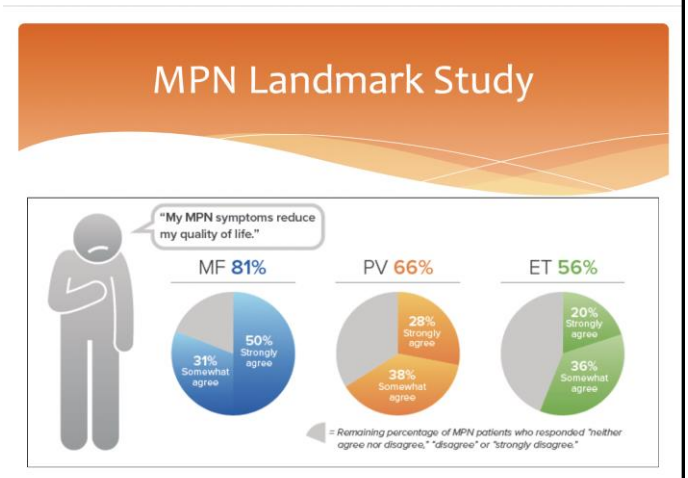
Rumi E, Cazzola M, Blood 2017

Courtesy of Geoffrey Mikita

9

MPNs can impair quality of life

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



Mesa R, Miller CB, Thyne M, et al. Myeloproliferative neoplasms (MPNs) have a significant impact on patients' overall health and productivity: the MPN Landmark survey. *BMC Cancer*. 2016;16:167.

Courtesy of Maureen Thyne, PA-C

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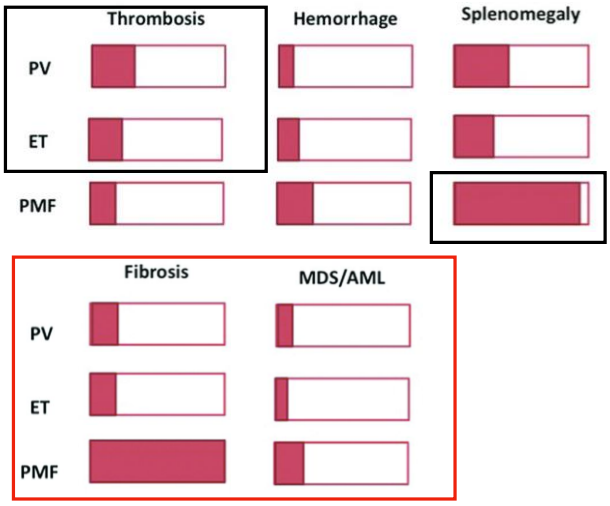
MPNs can cause serious complications



Jean-Jacques Kiladjian Hematology 2012

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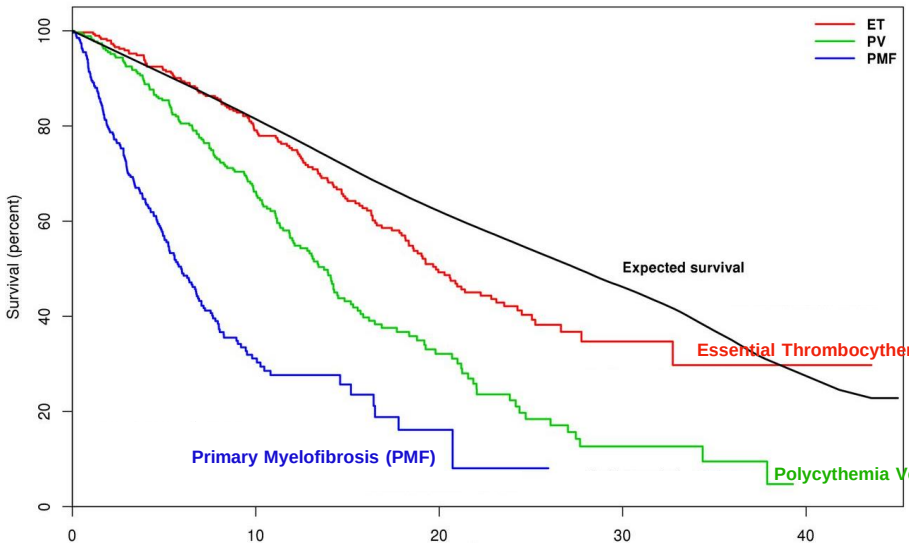
MPNs MAY shorten survival



Age at diagnosis (median)

55

64

63

Tefferi A et al. Blood 2014

12

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.

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Outline

- MPN diagnosis, symptoms and complications
- Treatment of PV
- Treatment of ET
- Treatment of MF
- COVID-19 and MPN

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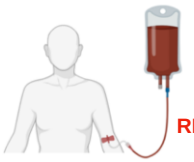
PV initial treatment approach:
What do guidelines recommend? What do we recommend?

PHLEBOTOMY (PHL)



National guidelines

Initial treatment by risk group		
Low risk	Age < 60 No thrombosis	• Assess for new blood clots and major bleeding • Manage cardiovascular risk factors • Aspirin
RISK of THROMBOSIS		
High risk	Age 60+ + thrombosis	• Assess for new blood clots and major bleeding • Manage cardiovascular risk factors • Aspirin • Hydroxyurea or interferons

NCCN Guidelines for Patients®: Myeloproliferative Neoplasms, 2019

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Weill Cornell practice

? + INTERFERON (IFN)

IFN or Hydroxyurea (HU)

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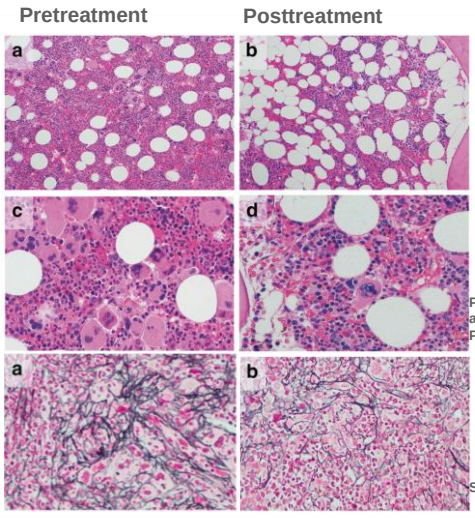
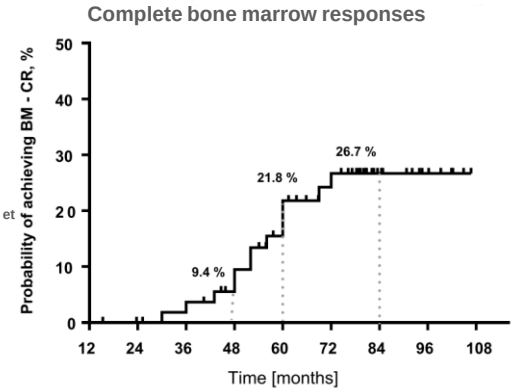
2 IFN in PV is disease-modifying



Pizzi M, Silver RT, et al. Modern Pathology. 2015

Silver RT et al. Blood 2011



Masarova L et al. Hematol Oncol. 2017

American Society of Hematology

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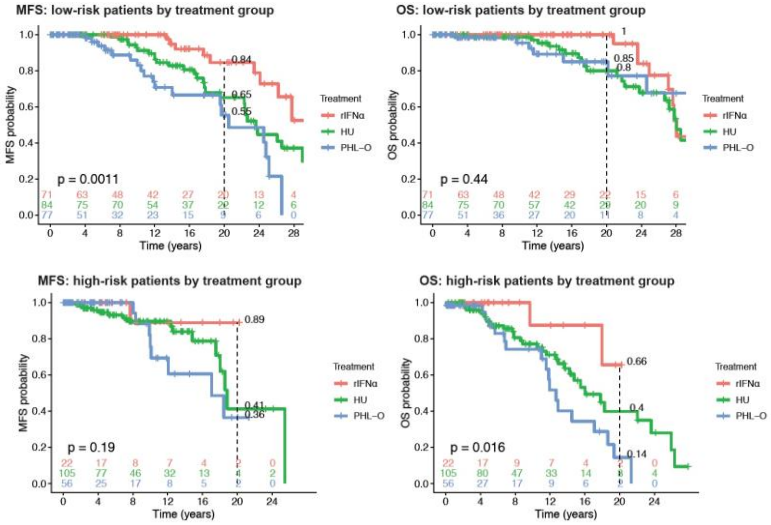
IFN is associated with improved survival outcomes in PV



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

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

	IFN (n = 199)	HU (n = 285)
Time on therapy (patient-years)	1137	1671
Organ system adverse events, n (%)		
Hematologic		
Anemia	2 (1.0)	3 (1.0)
Neutropenia	0 (0.0)	1 (0.4)
Thrombocytopenia	1 (0.5)	7 (2.5)
Other	2 (1.0)	7 (2.5)
Allergy & Immunology		
Allergic response	2 (1.0)	1 (0.4)
Autoimmune disorder	2 (1.0)	0 (0.0)
Musculoskeletal		
Arthralgia	4 (2.0)	0 (0.0)
Myalgia	3 (1.5)	0 (0.0)
Other	1 (0.5)	2 (1.0)
Gastrointestinal		
Mucositis oral	0 (0.0)	3 (0.7)
Nausea & Vomiting	0 (0.0)	5 (1.8)
Other	1 (0.5)	2 (0.7)
Neuropsychiatric		
Agitation	1 (0.5)	0 (0.0)
Depression	1 (0.5)	0 (0.0)
Peripheral neuropathy	3 (1.5)	4 (1.4)
Other	1 (0.5)	1 (0.4)
Constitutional		
Fatigue & Malaise	5 (2.5)	3 (0.7)
Fever	1 (0.5)	1 (0.4)
Other	2 (1.0)	1 (0.4)
Cardiopulmonary		
Cardiomyopathy	1 (0.5)	0 (0.0)
Heart failure	1 (0.5)	0 (0.0)
Pericarditis	1 (0.5)	0 (0.0)
Skin & soft tissue		
Rash	1 (0.5)	1 (0.4)
Skin ulceration	1 (0.5)	9 (3.2)
Other	0 (0.0)	6 (2.1)
Total of events	37 (18)	57 (20)
Total of patients	25 (13)	46 (16)

- 13% had IFN discontinued for side effects.
- 16% had HU discontinued for side effects.

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

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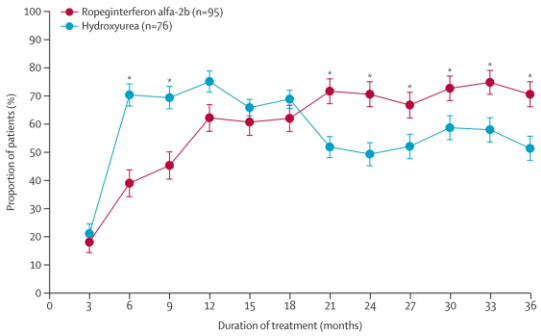
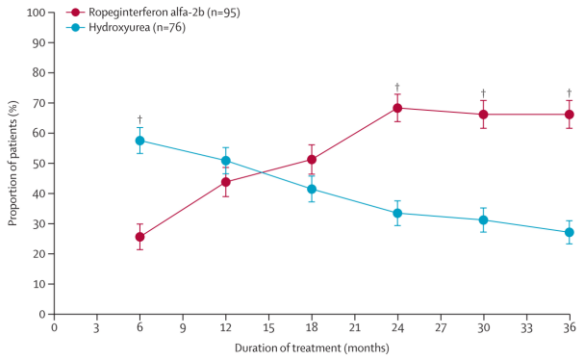
Ropeg-IFN is possibly better than HU in a randomized trial of high-risk PV (CONTI-PV)

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

Complete hematologic response



Partial molecular response



Gisslinger H et al. Lancet Hematology 2020

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

	Initial treatment by risk group	
	Low risk	**High risk**
NCCN	PHL-O	HU or IFN
ELN	PHL-O	HU or IFN
WCM	**IFN** > PHL-O	**IFN** > HU

Bose P et al. NCCN 2020 Myeloproliferative Neoplasms.
Barbui T. et al. Leukemia 2018

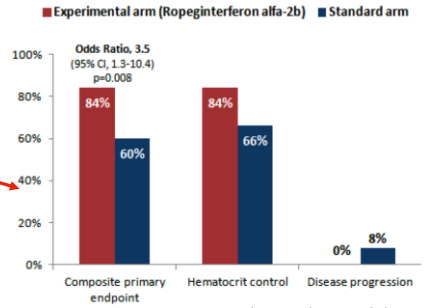
PHL-O causes chronic iron deficiency,
Chronic iron deficiency is associated with:
1. Fatigue
2. Decline in physical performance
3. Cognitive impairment

Ginzburg et al, Leukemia 2018

PHL-O
increased fibrosis risk

Abu-Zeinah et al. ASH 2020
Najean Y et al. Br. J. Haematol. 1994

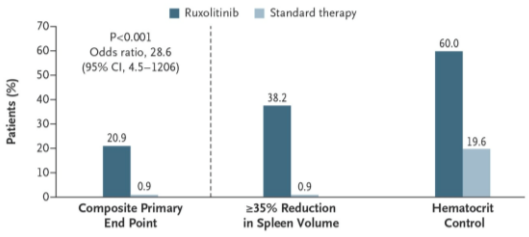
IFN> PHL-O in recent randomized trial of low-risk PV
Better hematocrit control, less progression at 1 year

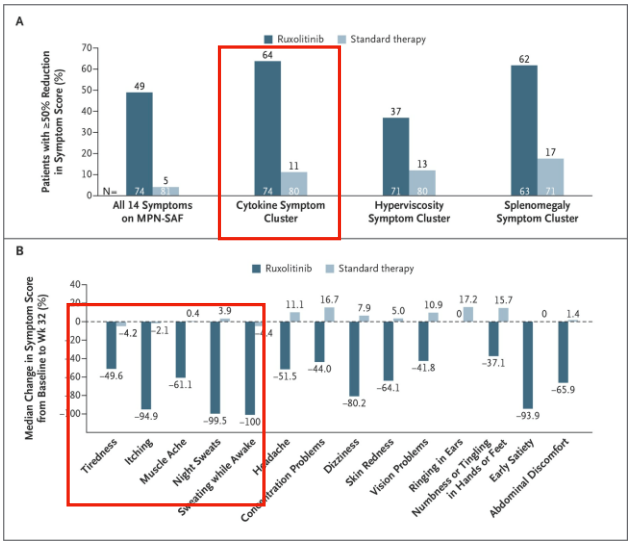


Barbui T et al. EHA oral abstract 2020

20

Second-line treatments and clinical trials in PV: Ruxolitinib





Vannucchi et al. N Engl J Med. 2015

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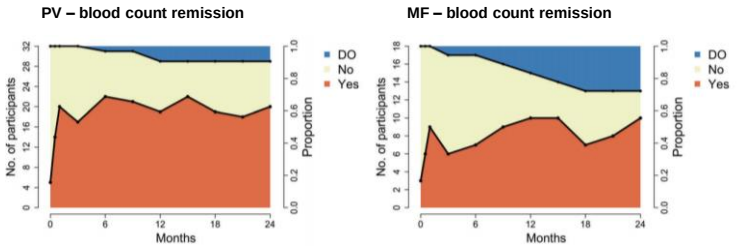
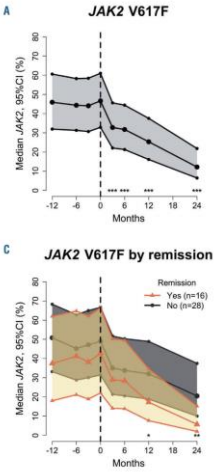
Second-line treatments and clinical trials in PV: Rux+IFN for patients refractory to IFN alone





Sørensen et al. Haematologica. 2020

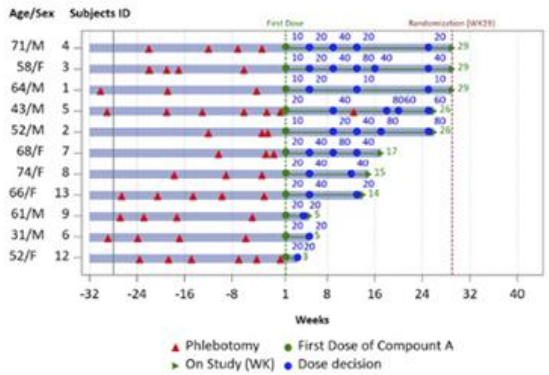
22

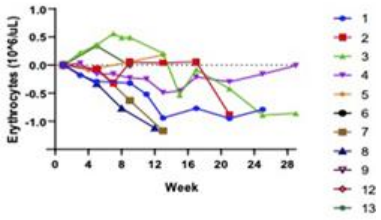
Second-line treatments and clinical trials in PV: PTG-300 hepcidin mimetic

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL | NOVEMBER 5, 2020

PTG-300 Eliminates the Need for Therapeutic Phlebotomy in Both Low and High-Risk Polycythemia Vera Patients

Marina Kremyanskaya, Yelena Ginzburg, MD, Andrew T. Kuykendall, MD, Abdulraheem Yacoub, MD, Jay Yang, MD, Suneel K Gupta, PhD, Frank Valone, MD, Sarita Khanna, PhD, Srdan Verstovsek, MD PhD, Ronald Hoffman, MD





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Outline

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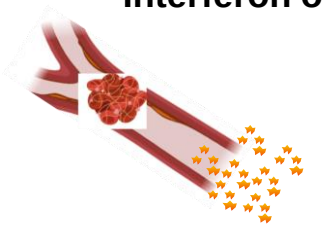
Risk adapted treatment of ET by IPSET-thrombosis score: Interferon or HU is recommended first line for high-risk ET



Risk factor	HR	Score
Age > 60 years	1.50	1
Cardiovascular risk factors	1.56	1
Previous thrombosis	1.93	2
JAK2V617F	2.04	2

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

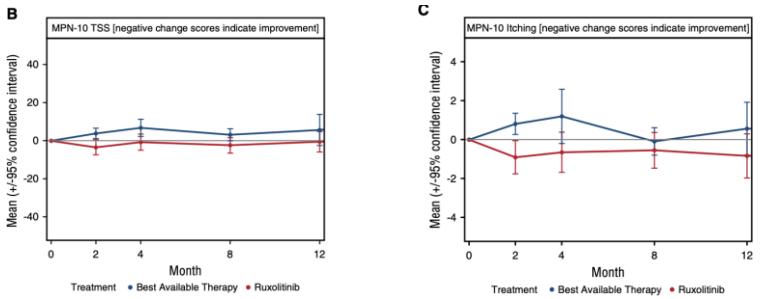
- **Low- Intermediate risk (0-2):** Low dose ASA for select cases
- **High risk patients (>=3):**
  - Low dose ASA
  - **First line** Hydroxyurea (HU) or **Interferon (rIFNα)**
- **Special considerations to prompt cytoreductive treatment:**
  - Plt count > 1500 x10^9/L (or less with acquired von willebrand disease)
  - myeloproliferative symptoms exist
  - Young women desiring pregnancy

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

25

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.



Harrison C, et al. Blood 2017

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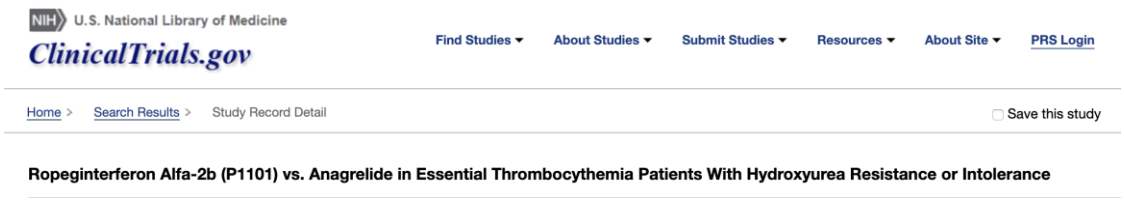
Second-line treatments and clinical trials in ET: Ropeg-IFN



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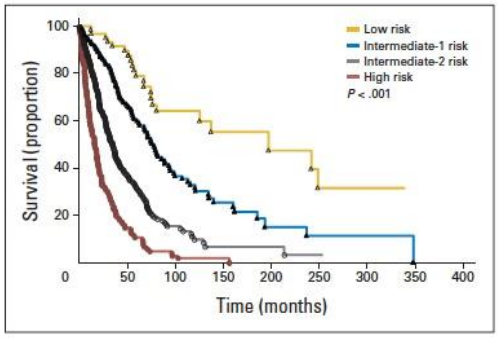
Management of PMF depends on prognosis/risk: DIPSS-plus is a widely used risk score in clinic and clinical trials

DIPSS-plus stratified OS of PMF patients



Clinical factor	Points
Age >65	1
WBC >25 x10^3 /µL	1
Hgb <10 g/dL	2
Circulating blasts ≥1%	1
Constitutional symptoms	1
PLUS:	
•Platelet count <100 x10^3 /µL	1
•Anemia requiring transfusion	1
•Unfavorable karyotype	1

Gangat N, et al. JCO 2011

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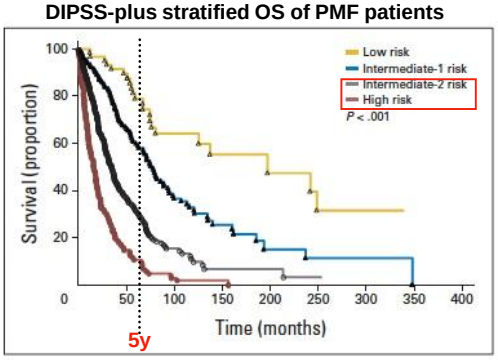
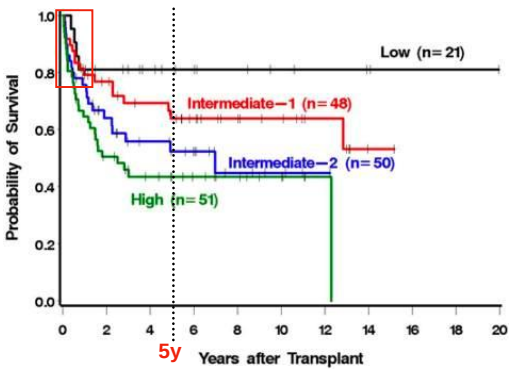
Stem cell transplant is currently the only potentially curative therapy but is not suitable for all patients

DIPSS-plus stratified OS of PMF patients



HSCT for PMF: OS after transplant by DIPSS plus score



Gangat N, et al. JCO 2011
Scott BL, et al. Blood 2012

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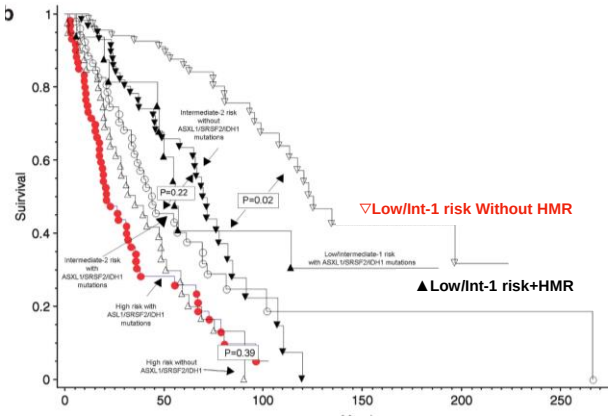
Molecular risk should be considered in the management of MF

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

Gene	Overall Frequency (%)
JAK2	59.2
ASXL1	21.7
TET2	9.7
SRSF2	8.5
DNMT3A	5.7
MPL	5.2
EZH2	5.1
CBL	4.4
IDH1/2	2.6



Vannucchi et al. Leukemia 2013

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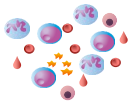

Risk-adapted treatment guidelines for myelofibrosis

- **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

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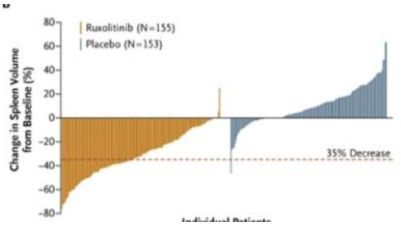
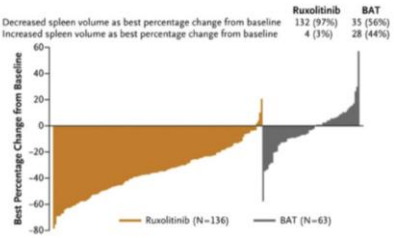
JAK inhibitor, Ruxolitinib was first FDA approved (2011) treatment for MF based on symptom and spleen size improvements. Fedratinib later approved (2019)

COMFORT I

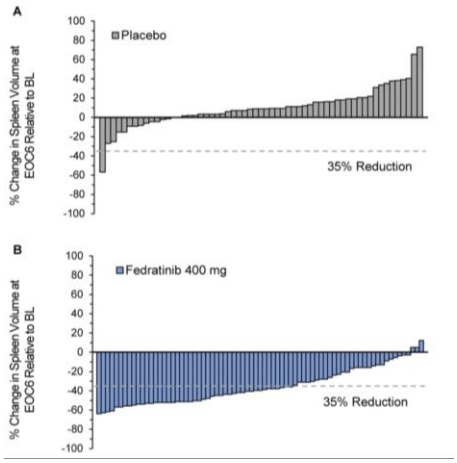


COMFORT II



Verstovsek et al. N Engl J Med. 2012
Harrison C, et al. N Engl J Med. 2012

JAKARTA Trial



Pardanani et al. JAMA Oncol. 2015

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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.

Silver RT et al. Blood 2011
Silver RT, *the 10th international Congress on Myeloproliferative Neoplasms and Chronic Myeloid Leukemia*
Silver RT et al. Cancer 2017

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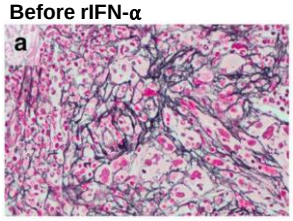
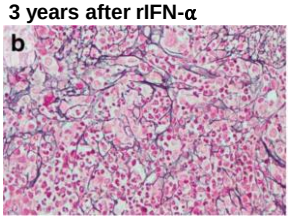
rIFN-α may delay progression of early MF

- **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

Before rIFN-α



3 years after rIFN-α



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

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

	IWG-MRT Response: No. of Patients (%)[b]						
DIPSS Prognostic	Total	CR	PR	CI	SD	PD	Died
Prognostic Risk							
Low	22 (73)	1 (3)	8 (27)	2 (6)	4 (13)	4 (13)[c]	3 (10)
Intermediate-1	8(27)	1 (3)	1 (3)	2 (6)	3 (10)	0 (0)	1 (3)
Total	30	2 (6)	9 (30)	4 (13)	7 (23)	4 (13)	4 (13)

	No. of Responses						
Mutation	Total	CR	PR	CI	SD	PD	Death
JAK2							
Single mutation	5	1	2			1	1
ASXL1	1				1		
ASXL1 + MISC	1					1	
DNMT3A	2			1	1		
MISC	1			1			
SH2B3	1				1		
TET2	4			1	2	1	
TET2 + MISC	1		1				
WT1	1				1		
CALR							
Single mutation	2		2				
ASXL1 + SETBP1	1						1
MISC	1		1				
SETBP1 + KDM6A + FLT3	1					1	
TET2	1	1					
MPL							
Single mutation	1		1				
SRSF2 + TET2	1						1
Total	25	2	7	3	6	4	3

Silver RT et al. Cancer 2017

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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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How do we select the most promising therapies for myelofibrosis to advance in clinical trials?

- It is difficult to study overall survival in a clinical trial in MPN. It would require several years and many patients because of the chronicity of these diseases.
- **Symptom and spleen size** responses are important but are not optimal endpoints to decide if a treatment is disease modifying and potentially life-prolonging
- **Molecular responses** (reduction in JAK2, CALR, MPL mutation burden) do not strongly correlate with clinical responses.
- **Marrow fibrosis reversion** is hypothesized but not proven to be translated to a survival benefit.

- **We need a reliable biomarker** to predict disease-modifying benefits of drugs and patients at risk of progression

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Outline

- MPN diagnosis, symptoms and complications
- Treatment of PV
- Treatment of ET
- Treatment of MF
- COVID-19 and MPN

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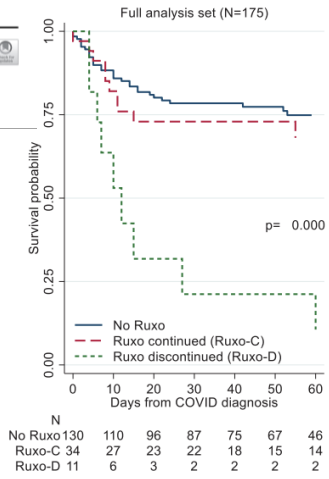
Treatment of MPN during COVID-19: Lessons learned

Leukemia
https://doi.org/10.1038/s41375-020-01107-y

ARTICLE

Chronic Myeloproliferative Neoplasms

High mortality rate in COVID-19 patients with myeloproliferative neoplasms after abrupt withdrawal of ruxolitinib



Barbui et al. Leukemia 2020

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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 Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

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

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Thank you for your attention!

Weill Cornell Medicine

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CR&T Cancer Research & Treatment Fund, Inc. Established 1968
MPN Research Foundation CHANGE YOUR PROGNOSIS

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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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LLS EDUCATION & SUPPORT RESOURCES

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.

CLINICAL TRIAL SUPPORT CENTER
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

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.

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LLS EDUCATION & SUPPORT RESOURCES

Online Chats
Online Chats are free, live sessions, **moderated by oncology social workers**. To register for one of the chats below, or for more information, please visit **www.LLS.org/Chat**.

Education Videos
View our free education videos on disease, treatment, and survivorship. To view all patient videos, please visit **www.LLS.org/EducationVideos**.

Patient Podcast
The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit **www.TheBloodline.org**.

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LLS EDUCATION & SUPPORT RESOURCES

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

To order free materials: **www.LLS.org/Booklets**

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THANK YOU
We have one goal: A world without blood cancers
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