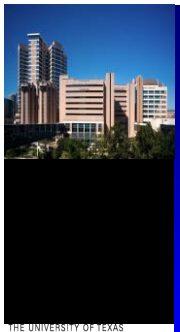

Introduction to Myeloproliferative Neoplasms (MPNs)

Post-ASH 2017 Wrap-Up

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Disclosures

- Research support, honorarium, consulting:
  - Incyte
  - Novartis
  - Stemline
  - Cellectis
  - LFB
  - Grant Funding: Affymetrix, Stemline
  - Abbvie
  - Samus

Overview/Objectives

- Introduction to MPN/MF
- ASH 2017 Wrap-Up: Clinical trials
- Translational Focus: Bench to Bedside and Back to the Bench
- MPN: Symptom Burden: Why it Matters

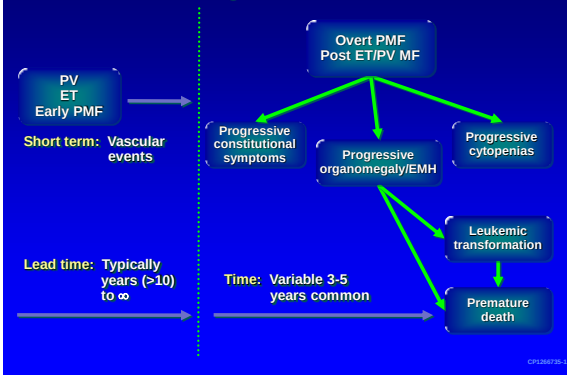
"Some Speculations on the myeloproliferative syndromes"

William Dameshek
(1900-1966) www.hematology.org (ASH website)

- *"It is possible that these various conditions—'myeloproliferative disorders'—are all…variable manifestations of proliferative activity of the bone marrow cells, perhaps due to a hitherto undiscovered stimulus."*—William Dameshek, 1951, Blood

Natural History of MPNs

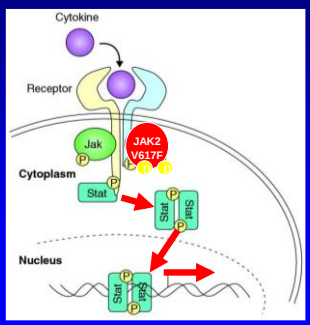
courtesy Dr. Ruben Mesa, MD, Mayo Clinic



JAK2 V617F

- Constitutively active kinase
- Over-signals via STAT, ERK, MAP kinase, RAS pathways
- Autonomous growth, cell survival & differentiation

Slide courtesy of Alison Moliterno, MD, Johns Hopkins Hospital

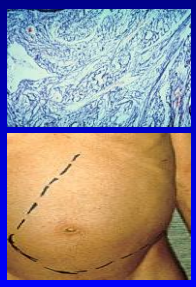


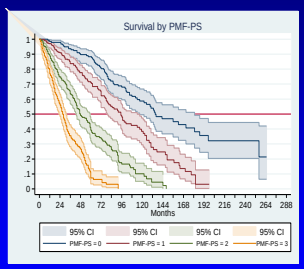
CALR

- Chromosome 19p13.3
  - Exon 9 of CALR (insertions or deletions)
- Calreticulin= protein →Ca++binding fucntion or the Endoplasmic reticulum
- Also found in nucleus; possible role transcription regulation
- Klampfel et al NEJM 2013: CALR in 25% pts with JAK2 negative ET, and in 35% in JAK2 negative MF

Klampfl T et al. N Engl J Med 2013;369:2379-2390.

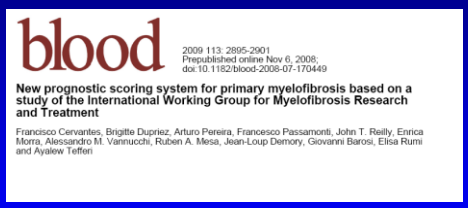
Heterogeneous clinical outcomes in MF





Cervantes et al., Blood 2009;113:2895-2901

Slide Courtesy: S. Verstovsek



blood

2009 113: 2895-2901
Prepublished online Nov 6, 2008;
doi:10.1182/blood-2008-07-170449

New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment

Francisco Cervantes, Brigitte Dupriez, Arturo Pereira, Francesco Passamonti, John T. Reilly, Enrica Morra, Alessandro M. Vannucchi, Ruben A. Mesa, Jean-Loup Demory, Giovanni Barosi, Elisa Rumi and Ayalew Tefferi

MF: Risk Stratification: Poor prognostic variables

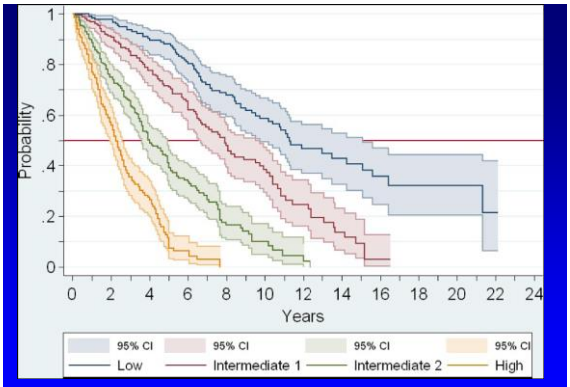
- Age >65 y
- Presence of Constitutional symptoms
- Hgb <10
- WBC >25
- Circulating blasts cells ≥1%
- P values were all <0.001
- 1054 pts at 7 centers

Cervantes et al, Blood 2009;113:2895-2901

MF-New Prognostic Scoring System

	#factors	Patients %	Med survival (months)	Deaths %
Low	0	22	135	32
Int-1	1	29	95	50
Int-2	2	28	48	71
High	>3	21	27	73

Cervantes et al, Blood 2009;113:2895-2901

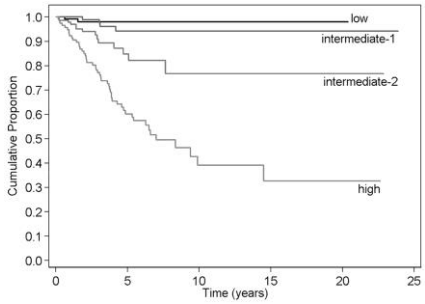


Cervantes et al, Blood 2009;113:2895-2901

MF: Further scoring systems

- **DIPSS (dynamic)—Mayo (Blood 2010;115)**
  - **Modified IPSS to be able to calculate over time: all 1 pt except Hb (2 points)**
  - **Age >65**
  - **WBC >25K**
  - **Hb <10: 2 points**
  - **Circulating blasts greater than or equal to 1%**
  - **Constitutional sxs**
- **DIPSS Plus—adds 3 new factors, each 1 point (Mayo, 2011 JCO)**
  - **Unfavorable karyotype**
  - **Plt count <100K**
  - **Transfusion need**

Kaplan-Meier estimate of blast phase–free survival in primary myelofibrosis according to the DIPSS. Risk categories were according to the score obtained anytime during follow-up.



Francesco Passamonti et al. Blood 2010;116:2857-2858

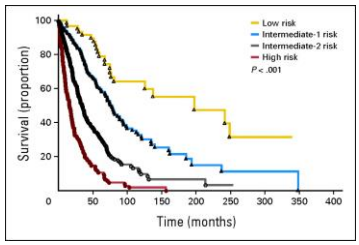
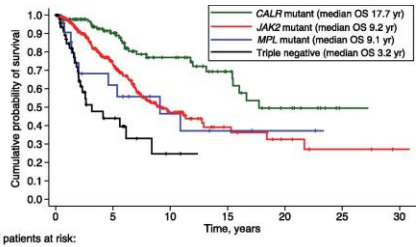


Fig 3 Survival data of 793 patients with primary myelofibrosis evaluated at time of their first Mayo Clinic referral and stratified by their Dynamic International Prognostic Scoring System (DIPSS) + karyotype + platelet count + transfusion status prognostic scores. Low risk, zero adverse points; n = 66; median survival, approximately 185 months. Intermediate-1 risk, one adverse point; n = 174; median survival, approximately 78 months. Intermediate-2 risk, two or three adverse points; n = 360; median survival, approximately 35 months. High risk, four to six adverse points; n = 193; median survival, approximately 16 months. Scale for DIPSS: high risk, three adverse points; intermediate-2, two adverse points; intermediate-1, unfavorable karyotype, platelets < 100 x 109/L, and transfusion need; one adverse point.

Published in: Naseema Gangat; Domenica Caramazza; Rakhee Vaidya; Geeta George; Kebede Begna; Susan Schwager; Daniel Van Dyke; Curtis Hanson; Wenting Wu; Animesh Pardanani; Francisco Cervantes; Francesco Passamonti; Ayalew Tefferi; *JCO* **2011,** 29, 392-397.
DOI: 10.1200/JCO.2010.32.2446

Kaplan-Meier analysis of survival of PMF patients stratified according to their driver mutation.



No. of patients at risk:

CALR mutant	140	72	37	19	9	1
JAK2 mutant	396	135	39	13	7	3
MPL mutant	25	10	5	3	2	0
Triple negative	53	11	2	0	0	0

Elisa Rumi et al. Blood 2014;124:1062-1069

blood

ASH 2017: MIPSS70

- **ASH 2017: Abstract 200 MIPSS70: Mutation-Enhanced Prognostic System for Transplant Age Patients with Primary Myelofibrosis**
  - ***Alessandro M. Vannucchi, MD[1]**, et al, ASH 2017*

- ***MVA for OS:***
- ***1)Anemia Hb <10***
- ***2)WBC >25K***
- ***3)plts <100***
- ***4)circulating blasts ≥ 2%***
- ***5)BM fibrosis ≥ 2***
- ***6)Constitutional sxs***
- ***7)absence of CALR Type 1mutation***
- ***8)Presence of HR molecular mutation [ASXL1; EZH2; SRSF2; IDH1/2]***
- ***9)Presence of two or more HR molecular mutations***

Guglielmelli P et al JCO 2017; 36: 310-318;

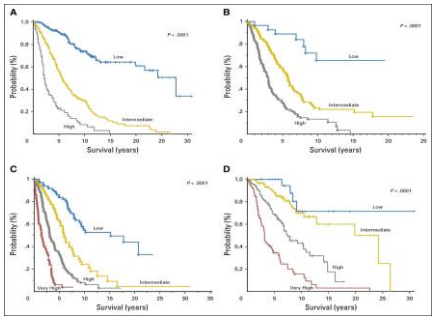


Fig A1. Overall survival (OS) in (A) learning and (B) validation cohorts by the MIPSS70 prognostic scoring system risk classification in all age–inclusive cohorts. OS in (C) learning and (D) validation cohorts by the MIPSS70-plus prognostic scoring system risk classification in all age–inclusive cohorts. Appendix Table A2 lists details.

Published in: Paola Guglielmelli, Terra L. Lasho, Giada Rotunno, Mythri Mudireddy, Carmela Mannarelli, Maura Nicolosi, Annalisa Pacilli, Animesh Pardanani, Elisa Rumi, Vittorio Rosti, Curtis A. Hanson, Francesco Mannelli, Rhett P. Ketterling, Naseema Gangat, Alessandro Rambaldi, Francesco Passamonti, Giovanni Barosi, Tiziano Barbui, Mario Cazzola, Alessandro M. Vannucchi, Ayalew Tefferi, JCO **2018**, 36, 310-318.
DOI: 10.1200/JCO.2017.76.4886

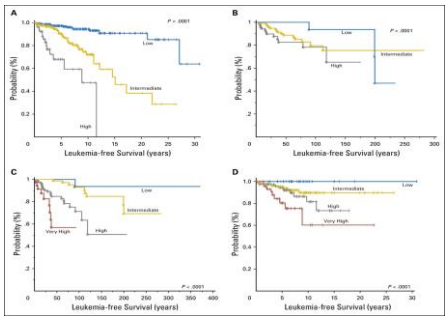


Fig A2. Leukemia-free survival (LFS) in (A) learning and (B) validation cohorts by the MIPSS70 prognostic scoring system risk classification. LFS in (C) learning and (D) validation cohorts by the MIPSS70-plus prognostic scoring system risk classification. Appendix Table A3 lists details.

Published in: Paola Guglielmelli, Terra L. Lasho, Giada Rotunno, Mythri Mudireddy, Carmela Mannarelli, Maura Nicolosi, Annalisa Pacilli, Animesh Pardanani, Elisa Rumi, Vittorio Rosti, Curtis A. Hanson, Francesco Mannelli, Rhett P. Ketterling, Naseema Gangat, Alessandro Rambaldi, Francesco Passamonti, Giovanni Barosi, Tiziano Barbui, Mario Cazzola, Alessandro M. Vannucchi, Ayalew Tefferi, JCO **2018,** 36, 310-318.
DOI: 10.1200/JCO.2017.76.4586

WHO 2016

- New categories/items to note:
- SM: now its own separate myeloid neoplasm outside of MPN
- Creation of new “pre-fibrotic MF” (ET/MF)
- Lowering of PV Hb threshold
- CALR
- CSF3R

Symptom Burden in MF: Total Symptom Score (MPN-TSS)

- **Fatigue**
- **Early Satiety**
- **Abdominal discomfort**
- **Inactivity**
- **Concentration problems**
- **Night Sweats**
- **Pruritis**
- **Bone pain**
- **Fever**
- **Weight loss**

Emmanuel/Mesa JCO 2012, Mesa et al Cancer 2007, Geyer/Mesa Blood 2014

#MPNSM: An ongoing Twitter conversation about MPNs

- Inspired by: CTO (based on #hcsm & #btsm) (Katz et al Disease-Specific hashtags for online communication about cancer care - JCO. 2015;33 suppl abstr 6520); and for hematology specific influence, #mmsm
- Founder of #MPNSM Twitter community : Naveen Pemmaraju, MD @doctorpemm
  - With key co-founders: @mtmdphd, @Vikas_Gupta_1, @mpdrc
- First tweet: @doctorpemm [Aug 2014]→but #mpnsm did not really take off as a regular hashtag until Dec'14-Jan'15: during/after #ASH15 meeting
- As of Sept,13,2015: For #MPNSM, According to @symplur @healthcarehashtags project: Jan'15-Sept'15
  - 2013 tweets from 285 participants
  - Resulting in: 4,049,415 impressions

Pemmaraju N, et al Current Hematologic Malignancy Reports10(4), 413-420. 9/28/15 online
Pemmaraju N, et al Curr Hematol Malig Rep. 2016 Aug 4. [Epub ahead of print]

- Brings together, in real-time: investigators/researchers, MPN healthcare providers, patients, advocates, organizations for discussion of basic science, translational, and clinical topics in MPNs

Slide: courtesy Mike Thompson, MD, PhD

Thank you

- Please email me npemmaraju@mdanderson.org or call me 713-792-4956 if you have any questions
- #MPNSM: Twitter/social media
- Thank you to Dr Serge Verstovsek, our chief of MPNs, research RNs, and MPN team at MDACC

Beyond single-agent JAK inhibitors: New therapies and combinations from ASH 2017

Aaron T. Gerds, MD, MS
Assistant Professor of Medicine
Hematology and Medical Oncology
@AaronGerds

Cleveland Clinic Taussig Cancer Institute
L&MD Leukemia & Myeloid Disorders Program

Beyond single-agent JAK inhibitors – ASH 2017

	Abstract No.	Comments
• New drugs		
• Givinostat	253/1648	HDACi, CR/PR 86% (ITT, n=30) in PV
• LCL-161	256	Oral Smac Mimetic, ORR 30% in MF
• Glasdegib	258	Modest symptom and spleen reduction in MF
• Sotatercept	255	New "ESA," activin receptor IIA ligand trap
• Idasanutlin	254	MDM2 inhibitor, in PV/ET, Ph1 study
• Alisertib	1631	Aurora kinase inhibitor
• SL-401	2908	Recombinant IL-3 fused to diphtheria toxin
• Combination therapy		
• Pracinostat + ruxolitinib	1632	Modest benefit over single-agent ruxolitinib
• Vismodegib + ruxolitinib	4179	No clear benefit over single-agent ruxolitinib
• Azacitidine + ruxolitinib	1649	AP/BP, ORR 33% (2 of 6 evaluable patients)
• Old is new again!		
• Interferons	321/323/320	Front-line and beyond, Ropeginterferon α-2b
• Fedratinib	4197	Wernicke's exposé from JAKARTA studies

@AaronGerds Cleveland Clinic

SOTATERCEPT (ACE-011) ALONE AND WITH RUXOLITINIB IN PATIENTS WITH MPN-ASSOCIATED MYELOFIBROSIS (MF) AND ANEMIA

Prithviraj Bose, Naval G. Daver, Naveen Pemmaraju, Elias J. Jabbour, Zeev Estrov, Allison M. Pike, Julie Huynh-Lu, Madeleine Nguyen-Cao, Xuemei Wang, Lingsha Zhou, Sherry Pierce, Hagop M. Kantarjian, and Srdan Verstovsek

Slide courtesy of Prithviraj Bose

Supported by Celgene Corporation

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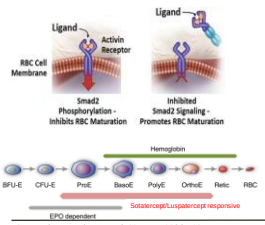
Sotatercept



Phase II Study Design

- MF with Hgb <10 g/dL x ≥ 84 days
- 2 cohorts:
  - Sotatercept alone q3 wk
  - Sotatercept q3 wk in patients on stable dose of ruxolitinib
- Response (on study x ≥ 84 days):
  - Anemic patients: ≥1.5 g/dL ↑ from baseline x ≥ 84 d
  - Tx-dependent patients: transfusion independence per 2013 IWG-MRT criteria

Suragani RN, et al. Nat Med. 2014 Apr;20(4):408-14
Bose P, et al. Blood. 2017 Dec;130(supp1):225

Cleveland Clinic

Variable	Value/Category	Sotatercept (n=24)	Sotatercpt + Rux (n=11)
Median age (range)	years	66.5 (47-84)	68 (57 – 84)
Diagnosis	PMF	20	9
	Post-ET/PV MF	4	2
Sex	Male	14	7
Median baseline hemoglobin (range)	g/dl	7.5 (4.7 – 8.7)	7.2 (4.6 – 9.1)
Driver mutation	*JAK2*	16	8
	CALR	3	2
	MPL	3	1
	Triple negative	1, *CALR* mutation status unknown in 1	0
Karyotype	Abnormal	8, insufficient metaphases in 1	6
DIPSS category	Intermediate-2	19	7
	High	5	4
Bone marrow fibrosis grade	MF-2	8	5
	MF-3	16	5
Splenomegaly	Present	13	11
Previously treated	Yes	19	
Median rux dose (range)	mg PO BID		10 (5-20)

Bose P, et al. Blood. 2017 Dec;130(supp1):225

@AaronGerds Cleveland Clinic

Summary of results

Sotatercept (n=18 evaluable)

- 40% response (7/18); 3/11 transfusion-dependent
- Median time to response 7d (1-22d)
- Median response duration 12 (5-24+) months
- Multiple drug holds in 3 patients due to Hgb levels ≥11.5 g/dl

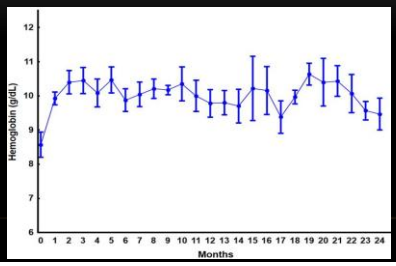
Sotatercept + Rux(n=10 evaluable)

- 30% response (3/10); 0/4 transfusion-dependent
  - 1.5 g/dl ↑ in Hgb from baseline in 1 additional patient (s/p 3 cycles)
- Responses began at 7, 14 and 140 d
- Response durations of 3+, 4+ and 15+ months
- Multiple drug holds in 1 patient due to Hgb levels ≥11.5 g/dl

Bose P, et al. Blood. 2017 Dec;130(supp1):225

Cleveland Clinic

MEAN HEMOGLOBIN OVER TIME IN RESPONDERS (N=10)



Slide courtesy of Prithviraj Bose

Sotatercept in MF

ADVERSE EVENTS POSSIBLY RELATED TO SOTATERCEPT (N = 35)

Adverse event	Grade	No. of patients
Hypertension	3	3
	2	2
Pain (joints/muscle)	3	1
	2	1
	1	1
Elevated UMACR	1	2
Limb edema	1	1
Headache (in the context of HTN)	2	1
	1	1
Nausea	1	1

Slide courtesy of Prithviraj Bose

Comclusions

- Sotatercept effective for MPN-associated anemia
  - Planned enrollment 60 subjects
- Multi-center phase 2 trial of luspatercept in MF open
  - ClinicalTrials.gov Identifier: NCT03194542

Bose P, et al. Blood. 2017 Dec;130(supp1):225

Open Label Phase I Study of Single Agent Oral RG7388 (idasanutlin) in Patients with Polycythemia Vera and Essential Thrombocythemia

Mascarenhas J[1], Lu M[1], Virtgaym E[1], Kosiorek H[2], Stal M[1], Sandy L[1], Orellana A[1], Xia L[1], Rampal R[3], Kremyanskaya M[1], Petersen B[4], Dueck A[2], Hoffman R[1]

[1] Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, New York
[2] Mayo Clinic Scottsdale, Scottsdale, Arizona
[3] Leukemia Service, Memorial Sloan Kettering Cancer Center, New York, New York
[4] Department of Pathology, Icahn School of Medicine at Mount Sinai, New York, New York 10029

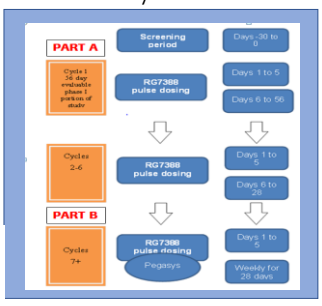
Slide courtesy of John Mascarenhas

Background: P53/MDM2

- P53 regulates cell cycle, apoptosis, DNA repair, and senescence
- Wild type P53 seen in chronic phase MPN and mutated P53 in advanced phase
- Down regulation of P53 by MDM2 overexpression
  - Promotes proteosomal degradation
  - Inhibits P53 transcription
  - Inhibits transactivation
  - Facilitates export from nucleus
- Nutlins Block the MDM2:P53 interaction and activate the p53 pathway

Nakatake M et al. Oncogene. (2012); Cassinat and Kiladjian Blood (2012); Shangary and Wang. Clin Cancer Res. (2008); Lu and Hoffman Oncotarget (2012). *Slide courtesy of John Mascarenhas*

Study Schema and Design



- 2 dose cohorts evaluated
  - 100 mg daily, days 1-5
  - 150 mg daily, days 1-5
- DLT is defined as:
  - non-hematologic AE of G3+
  - hematologic AE of G2+ thrombocytopenia, G3+ neutropenia, or G3+ anemia
- Dosing after cycle 3 dependent on attaining HCT >42% and/or PLT >400K at Day 1

Slide courtesy of John Mascarenhas

Baseline Demographics

	100 mg (N=6)	150 mg (N=6)	Total (N=12)
Diagnosis			
Essential Thrombocythemia	1 (16.7%)	0 (0.0%)	1 (8.3%)
Polycythemia Vera	5 (83.3%)	6 (100.0%)	11 (91.6%)
Age, median (years)	62 (52-83)	63 (48-68)	63.5 (52-83)
Gender, female	5 (83.3%)	2 (33.3%)	7 (58.3%)
Disease duration, mos (prior to study)	41.6 (14.9-80.1)	65.4 (21.0-154.3)	43.9 (14.9-154.3)
Previous thrombosis	3 (50.0%)	0 (0.0%)	3 (25.0%)
Prior hydroxyurea therapy	5 (83.3%)	5 (83.3%)	10 (83.3%)
Spleen length by palpation, median (cm)	1.0 (1.0-7.0)	2.5(0.0-18.0)	1.0 (0.0-18.0)
Leukocytes , median ($x10^9$/L)	10.3 (4.9-15.9)	12.2 (7.4-28.3)	11.3 (4.9-28.3)
Hemoglobin, median (g/dL)	13.4 (12.8-15.6)	13.7 (12.3-14.7)	13.6 (12.3-15.6)
Hematocrit , median (%)	41.5 (38.3-46.7)	43.0 (40.7-47.8)	42.3 (38.3-47.8)
Platelets median, ($x 10^9$/L)	443.5 (118.0-1339.0)	412.0 (153.0-700.0)	443.5 (118.0-1339.0)
LDH median, (U/L)	252.0 (184.0-370.0)	252.0 (177.0-616.0)	252.0 (177.0-616.0)
JAK2V617F Variant Allele Frequency, median (%)	23.7 (5.3-69.3)	63.7 (6.3-88.6)	40.6 (5.3-88.6)

Slide courtesy of John Mascarenhas

TEAE occurring in at least 2 patients regardless of attribution

	100 mg (n=6)		150 mg (n=6)		Total (n=12)
	Grade 1/2	Grade 3	Grade 1/2	Grade 3	Any grade
Fatigue	5 (83.3%)	1 (16.7%)	4 (66.7%)		10 (91.7%)
Headache	4 (66.7%)	1 (16.7%)	1 (16.7%)		6 (50%)
Dry skin	2 (33.3%)		2 (33.3%)		4 (33.3%)
Pain	1 (16.7%)	1 (16.7%)	1 (16.7%)		3 (25%)
Arthralgia	3 (50%)				3 (25%)
Dizziness	3 (50%)				3 (25%)
Atrial fibrillation			2 (33.3%)		2 (16.7%)
Cough	2 (33.3%)				2 (16.7%)
Decreased appetite	1 (16.7%)		1 (16.7%)		2 (16.7%)
Epistaxis	1 (16.7%)		1 (16.7%)		2 (16.7%)
Flushing	2 (33.3%)				2 (16.7%)
Jaw pain	2 (33.3%)				2 (16.7%)
Oropharyngeal pain	1 (16.7%)		1 (16.7%)		2 (16.7%)
URI	1 (16.7%)		1 (16.7%)		2 (16.7%)
Weight gain	1 (16.7%)		1 (16.7%)		2 (16.7%)

- 3 patients had grade 3 non-hematologic AE (all at 100 mg)
  - Pt #1 – grade 3 fatigue
  - Pt #2 – grade 3 headache
  - Pt #3 – grade 3 pain
- No grade 4 non-hematologic adverse events at either dose level noted
- No hematologic AE of any grade noted

Slide courtesy of John Mascarenhas

Focus on Gastrointestinal TEAE (regardless of attribution)

	100 mg (n=6)		150 mg (n=6)		Total (n=12)
	Grade 1/2	Grade 3	Grade 1/2	Grade 3	Any grade
Constipation	6 (100%)		4 (66.7%)		10 (91.7%)
Nausea	5 (83.3%)		4 (66.7%)		9 (75%)
Diarrhea	5 (83.3%)		3 (50%)		8 (66.7%)
Dyspepsia	4 (33.3%)		3 (16.7%)		7 (58.3%)
Abdominal pain	4 (66.7%)		1 (16.7%)		5 (41.7%)
Anorexia	2 (33.3%)		2 (33.3%)		4 (33%)
Vomiting	3 (50%)				3 (25%)
Abdominal distension	2 (33.3%)		1 (16.7%)		3 (25%)
Dysgeusia	1 (16.7%)		2 (33.3%)		3 (25%)
Flatulence	1 (16.7%)		1 (16.7%)		2 (16.7%)

- No G3/4 GI TEAE were observed
- GI prophylaxis:
  - Ondansetron
  - Lorazepam
  - Decadron
- Constipation likely due to 5-ht3 antagonist

Slide courtesy of John Mascarenhas

Responses by 2013 ELN-IWG[1] criteria

By 6 cycles of therapy with idasanutlin monotherapy in PART A and combination pegylated interferon-α in PART B

	Not evaluable (NE)	No response (NR)	Partial Response (PR)	Complete Response (CR)	Overall Response (PR+CR)
PART A (n=12)	1#	4	3*	4	7 (58%)
PART B (n=4)^	1+	1	1	1	2 (50%)
				PART A + PART B ORR	9 (75%)

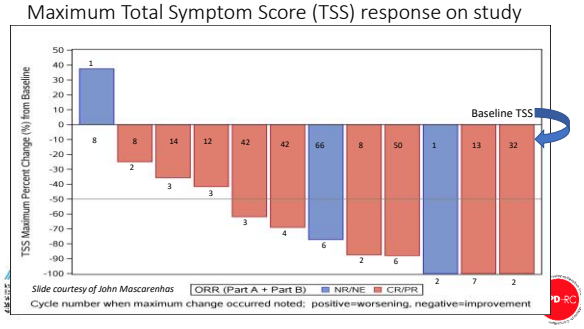
- # not evaluable due to patient decision to withdraw from study after 4 cycles due to GI toxicity
- *Residual splenomegaly likely due to known portal vein thrombosis, likely a CR (n=1)
- ^4 subjects from PART A that had NR continued on to PART B combination idasanutlin + interferon-α
- + not yet completed cycle 7

Icahn School of Medicine at Mount Sinai

Slide courtesy of John Mascarenhas [1]Barosi et al Blood 2013

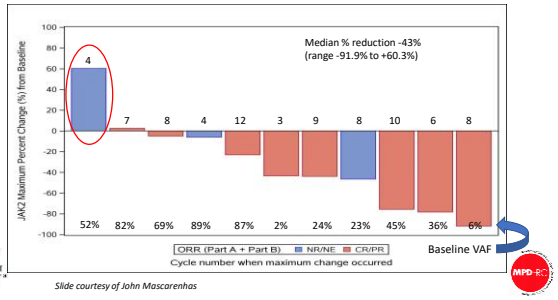
MPD-RC

Maximum Total Symptom Score (TSS) response on study



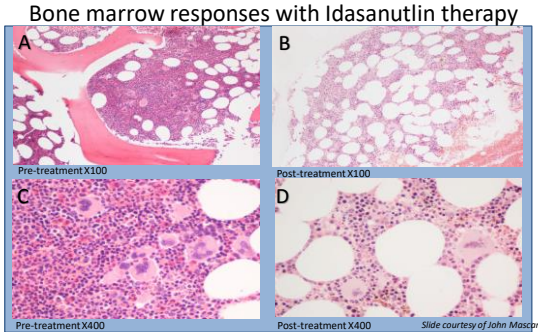
Slide courtesy of John Mascarenhas

Driver mutation responses with idasanutlin therapy



Slide courtesy of John Mascarenhas

Bone marrow responses with Idasanutlin therapy



Slide courtesy of John Mascarenhas

Conclusions

- Idasanutlin is well tolerated in patients with PV after multiple cycles of exposure and expected GI toxicity is manageable
- No DLT was observed and 150 mg x 5 days/cycle was chosen to be RPTD
- Idasanutlin may also be safely combined with pegylated IFN to improve upon the response (PART B)
- On target P53 pathway activation was demonstrated with idasanutlin treatment
- Normalization of the hematologic profile and improvement in symptom burden were observed with idasanutlin monotherapy and in combination with Pegasys
- Extended treatment-free-periods are possible with idasanutlin therapy
- Bone marrow morphologic and molecular responses were attained with idasanutlin therapy
- A global, multicenter, single arm phase II trial of idasanutlin in patients with hydroxyurea resistant/intolerant PV is underway (ClinicalTrials.gov Identifier: NCT03287245)

Slide courtesy of John Mascarenhas

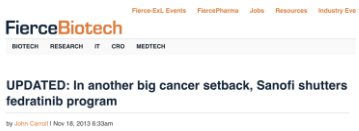
Fedratinib clinical activity

- JAKARTA-1 (randomized placebo-controlled)
  - 47% (400mg) and 50% (500mg) of patients with intermediate 2 or high risk myelofibrosis (MF) had SRV of ≥35% at 24 weeks
- JAKARTA-2 (open-label)
  - 53% of MF intermediate/high-risk patients who were resistant and 63% of patients who were intolerant to ruxolitinib had ≥35% reduction in spleen volume at Week 24

Pardanani A, et al. JAMA Oncol. 2015 Aug;1(5):643-51.
Harrison CN, et al. Lancet Haematol. 2017;4(7):e317-e324.

US FDA: Hold it!

- Clinical hold placed on November 15, 2013 as a result of neurological symptoms, suggestive of Wernicke's encephalopathy in 8/877 patients, exposed to fedratinib


Fierce-ExL Events FiercePharma Jobs Resources Industry Eve

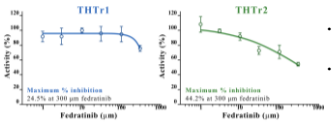
FierceBiotech

BIOTECH RESEARCH IT CRO MEDTECH

UPDATED: In another big cancer setback, Sanofi shutters fedratinib program

by John Carroll | Nov 18, 2013 8:33am

Thiamine uptake and fedratinib



- Fedratinib IC_{50} >300 µm against THTr1 and THTr2
- Clinical C_{max} = 3-5 µM at 400 & 500 mg doses, respectively

	Thiamine (nmol/L)		
	Patients (N)	Mean	Median
End of fedratinib treatment	161	171	198

Normal range of thiamine levels: 74-224 nmol/L

Harrison CN, et al. Blood. 2017 Dec;130(supp1):4197

Patient	WE Diagnosis	Summary of case
1	Confirmed	• Clinical evidence and MRI consistent with diagnosis of WE with unambiguous malnutrition as likely cause • Entered trial with >10% weight loss and severe ataxia (bedridden) in month prior to study • ECOG status dropped ~1-2 weeks before study (confined to bed) to ECOG 3-4, should have been ineligible for study • Started fedratinib 500 mg, Grade 2/3 nausea and vomiting for ~2 months • Hospitalized for nausea and vomiting, fedratinib discontinued, refused feeding tube • Treated with IV thiamine, WE considered resolved ~2 months later
2	Unconfirmed	• MRI findings suggest WE, but presence of additional confounding abnormalities • On fedratinib 500 mg • Unambiguous cerebral infarction at time of neurological symptoms • Recovered after treatment for infarction without interruption of fedratinib or thiamine supplementation
3	Unconfirmed	• Clinical evidence and MRI findings suggest WE but presence of additional confounding abnormalities • Started on fedratinib 200 mg, increased to 500 mg in 100-mg steps • Hospitalized for neurological symptoms due to suspected vertebro-basilar stroke and protracted GI disorders • Recovered from neurological symptoms in 1 week after treatment with oral thiamine and without interruption to fedratinib
4	Unlikely	• Clinical evidence and MRI findings inconsistent with regard to WE • On fedratinib 500 mg, but discontinued when hospitalized 11 months later for GI disorder • Neurological symptoms (stupor, confusion) emerged while off fedratinib
5	Unlikely	• Clinical evidence inconsistent with WE and significant confounding abnormality • On fedratinib 500 mg • H&N squamous cell cancer with disseminated metastases arising during trial including edematous CNS metastases, difficulty eating, and Grade 3 anorexia
6	Not WE	• On fedratinib 500 mg • Normal plasma thiamine levels; MRI findings inconsistent with WE
7	Not WE	• On fedratinib 500 mg • MRI findings inconsistent with WE, showed evidence of stroke; history of vestibular neuritis
8	Not WE	• Started on fedratinib 400 mg, increased to 500 mg ~4 months later • Clinical evidence and MRI findings inconsistent with WE; diagnosed as hepatic encephalopathy

Harrison CN, et al. Blood. 2017 Dec;130(suppl):4197

Summary

- Treatment with fedratinib did not decrease thiamine levels in patients from the clinical trials
  -
- A single confirmed case of WE from 877 treated patients
  - 2 patients with unconfirmed diagnosis (symptoms and MRI findings consistent with WE but presence of confounding abnormalities)
- Prevalence of WE in the trials was less than what has been published for people with MPNs
  - Prevalence 0.1%-0.4%

Harrison CN, et al. Blood. 2017 Dec;130(suppl):4197

Summary and Conclusions

- New, non-JAK inhibitor agents being developed
- Combination therapy remains burdened with toxicity and limited additive benefit
- Many challenges remain
  - Separate normal biology from pathogenesis
  - Spectrum of fitness
  - Long time observation until outcome of interest (PV/ET)
  - “Ruxolitinib failure” not defined (MF)
  - Dealing with cytopenias (MF)

Thanks!

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Justine DeAngelis, BA
Oliovia Kodramaz
Caitlin Swann, PharmD

And Our Patients!!!

@AaronGerds

Cleveland Clinic Taussig Cancer Institute

L&MD Leukemia & Myeloid Disorders Program

Cleveland Clinic

Inflammation in MPN

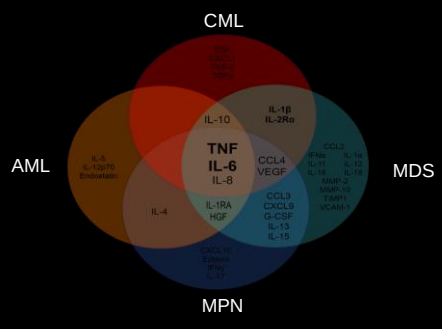
Angela Fleischman M.D. Ph.D.
University of California, Irvine
Feb 26, 2018

Chao Family Comprehensive Cancer Center
University of California, Irvine

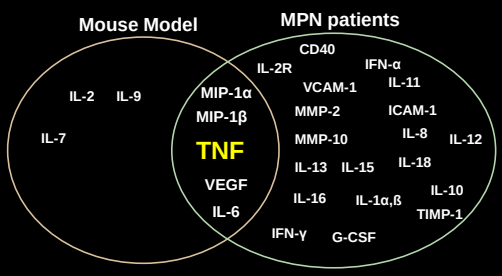
Angela Fleischman Disclosures

- Incyte (speakers bureau)

Elevated Inflammatory Cytokines in Many Hematologic Malignancies



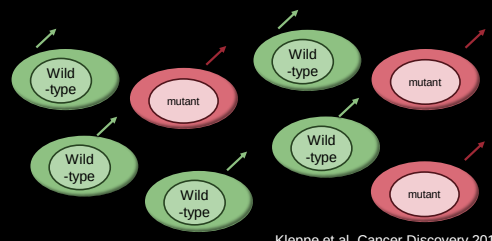
Elevated Inflammatory Cytokines in MPN



(Tyner et al, 2010)

(Verstovsek et al, 2010 Slezak et al, 2009, Boissinot et al, 2010, Tefferi et al 2011)

Both mutant and wild-type cells produce excessive inflammatory cytokines in MPN

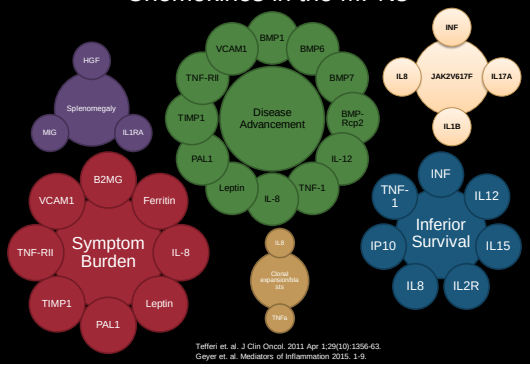


Kleppe et al, Cancer Discovery 2015

Specific Cytokines Drive Specific Symptoms in MPN

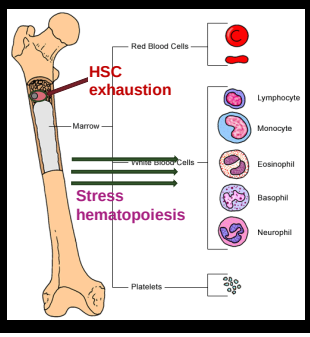
Geyer et. al. Mediators of Inflammation 2015

Impact of Inflammatory Cytokines and Chemokines in the MPNs



Tefferi et. al. J Clin Oncol. 2011 Apr 1;29(10):1356-63.
Geyer et. al. Mediators of Inflammation 2015. 1-9.

Chronic inflammation Exhausts Blood stem cells



What are methods to control inflammation?

- Prescription Medications
- Over the counter medications and supplements
- Stress reduction/mindfulness
- Exercise
- Diet

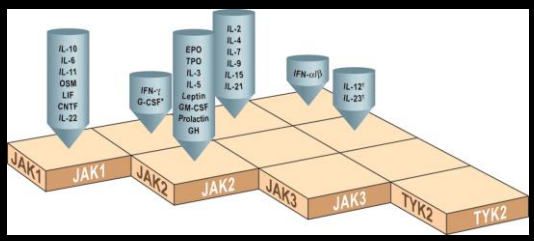
Inflammation as a Treatment Target in MPNs
Understanding Our Current Therapies

Aspirin:
- Contributes both to:
  - Platelet aggregation inhibition
  - Inhibit the activity of cyclooxygenase which leads to the formation of prostaglandins.

Interferon:
- Alters the inflammatory pathway and has been one of the only therapeutic options which has been able to alter the stem cell clone

Ruxolitinib:
- Initially developed as an anti-inflammatory in RA
- Associated with reduced inflammatory markers (previously described)
- Proposed to be one of the most powerful non-steroidal anti-inflammatories available.

JAK usage by cytokine receptors



JAK inhibitors are anti-inflammatory drugs

From Murray P, Journal of Immunology 2007

JAK inhibitors in development for MPN

Agent	Company	Activity	Status
Ruxolitinib (INCB18424)	Novartis/Incyte	JAK1/JAK2	FDA-approved
Fedratinib (TG101348/SAR302503) (ON HOLD; Wernicke's encephalopathy)	Celgene	JAK2, FLT3	Phase 3
Momelotinib (CYT387) (ON HOLD, failed to meet endpoint goals in phase 3)	Gilead	JAK1/JAK2/ TYK2	Phase 3
Pacritinib (SB1518) (ON HOLD, then back to dose-finding)	CTI BioPharma	JAK2, FLT3, IRAK1	Phase 3
Lestaurtinib (CEP701)	Cephalon	JAK2/FLT3	Phase 1/2
BMS-911453	Bristol-Myers Squibb	JAK2	Phase 1
NS-018	Nippon-Shinyaku	JAK2/Src	Phase 1/2
AZD1480 (discontinued due to neurotoxicity and other side effects)	Astra Zeneca	JAK1/JAK2	Phase 1
Gandotinib (LY2784544)	Eli Lily	JAK2 V617F	Phase 1
INCB039110	Incyte	JAK1 (alone)	Phase 2
INCB054329	Incyte	JAK1	Phase 1/2

Rationale for JAK1 inhibitor

- Blockade of inflammatory signaling pathways that use JAK1 while sparing myelosuppression attributable to the inhibition of JAK2-mediated hematopoiesis
- INCB039110 (itacitinib) is a potent and selective inhibitor of JAK1 with low *in vitro* affinity for JAK2 (>20-fold selectivity for JAK1 over JAK2) and other members of the JAK family (>100-fold selectivity for JAK1 over JAK3 and TYK2)

Phase II Open-Label Trial Of INCB039110, A Selective JAK1 Inhibitor, In Patients With Myelofibrosis

Simon two-stage design to assess the efficacy and safety of different doses of INCB039110
83 patients evaluable for primary endpoint
10 patients in 100 mg twice-daily
42 patients in 200 mg twice-daily
31 patients in 600 mg once-daily cohorts, respectively

Inclusion criteria:
intermediate- or high-risk myelofibrosis
Plt≥50×10^9/L, Hgb ≥8.0 g/dL, ANC ≥1×10^9/L
palpable spleen or prior splenectomy
active myelofibrosis-related symptoms

Mascarenhas et al, Haematologica 2017

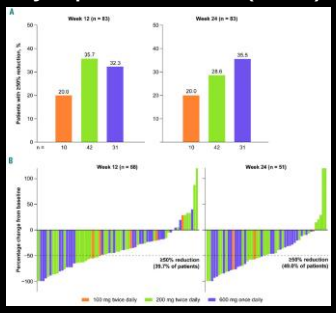
Phase II Open-Label Trial Of INCB039110, A Selective JAK1 Inhibitor, In Patients With Myelofibrosis

Primary endpoint:
- proportion of patients in each dose group with a ≥50% reduction from baseline to week 12 in total symptom score (TSS

Secondary endpoints:
- proportion of patients with a ≥50% reduction in TSS from baseline to week 24
- proportions of patients with a ≥35% reduction in spleen volume from baseline to weeks 12 and 24
- percentage changes from baseline to weeks 12 and 24 in TSS and spleen volume
- proportion of patients who exhibited a ≥50% decrease in transfusion frequency over any 12-week period during the study

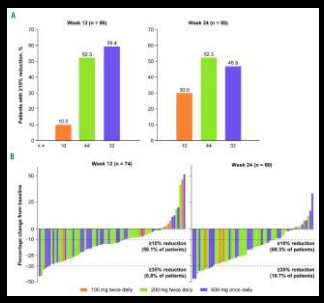
Mascarenhas et al, Haematologica 2017

Treatment Effects on Total Symptom Score (TSS)



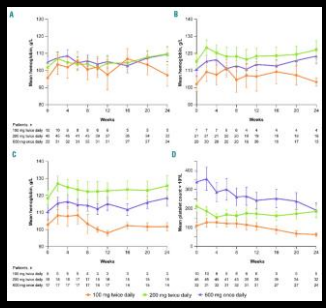
Mascarenhas et al. Haematologica 2017;102:327-335

Treatment Effects on Spleen Volume



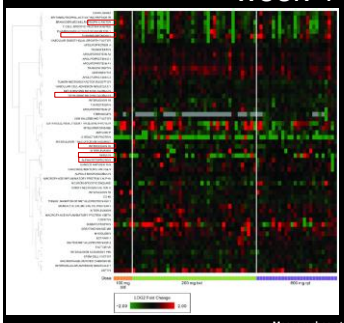
Mascarenhas et al. Haematologica 2017;102:327-335

Effects on Blood Counts



Mascarenhas et al. Haematologica 2017;102:327-335

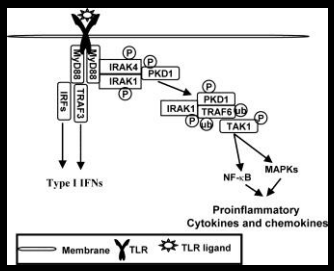
Impact on plasma cytokines at week 4



Plasma levels of a number of key inflammatory markers, such as C-reactive protein, interleukin-6, interleukin-10, CD40 ligand, RANTES, and vascular endothelial growth factor, decreased in most patients following 4 weeks of treatment

Mascarenhas et al. Haematologica 2017;102:327-335

IRAK1 is involved in production of inflammatory cytokines ligands to IL-1R and TLRs



Jeoung-Eun Park et al. J Immunol 2009;182:6316-6327

Pacritinib is an IRAK1 inhibitor

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Take Home Points

- Inflammation is high in MPN and drives symptom burden and potentially disease progression
- JAK inhibitors reduce inflammation
- Each JAK inhibitor has a unique spectrum of signaling molecules which it inhibits

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