

Disclosures for A Pardanani

Research Support/P.I.	TargeGen, Cytopia/YM BioSciences, PharmaMar
Employee	None
Consultant	None
Major Stockholder	None
Speakers' Bureau	None
Scientific Advisory Board	None

Presentation includes discussion of the following off-label use of a drug or medical device.

Hydroxyurea, interferon-alpha, imatinib mesylate, 2-CdA, busulfan, anagrelide, thalidomide, lenalidomide, prednisone, androgens, erythropoiesis stimulating agents, campath, INCB18424, TG101348, CYT387, RAD001, PKC412

**Ph- Myeloproliferative neoplasms -
What is the (long term) prognosis for
JAK inhibitors?**

**A. Pardanani, MBBS, PhD
Mayo Clinic**

CML
PV
ET
PMF

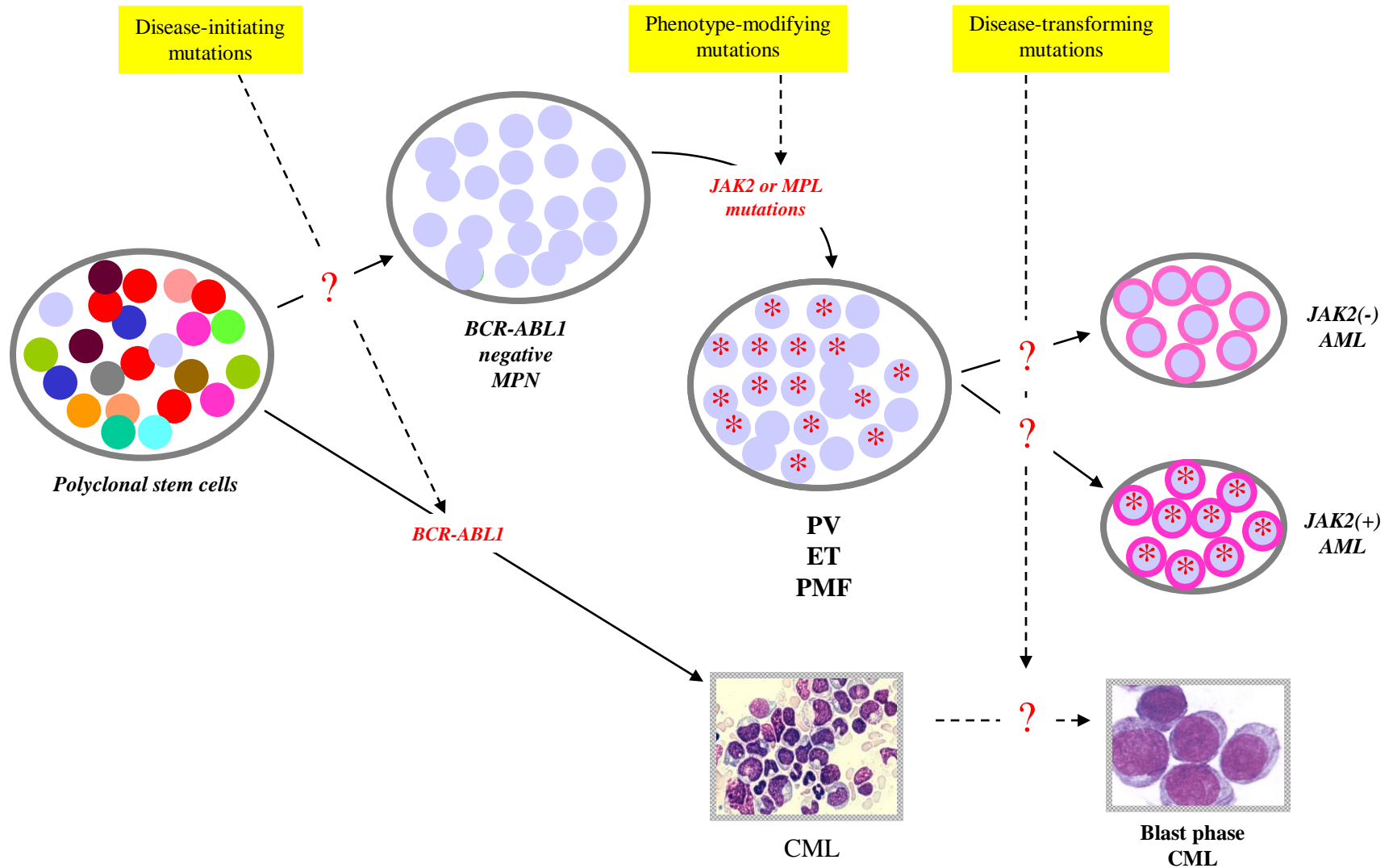
← **'Classic' MPNs**

Chronic phase → **Accelerated phase** → **Blast phase**

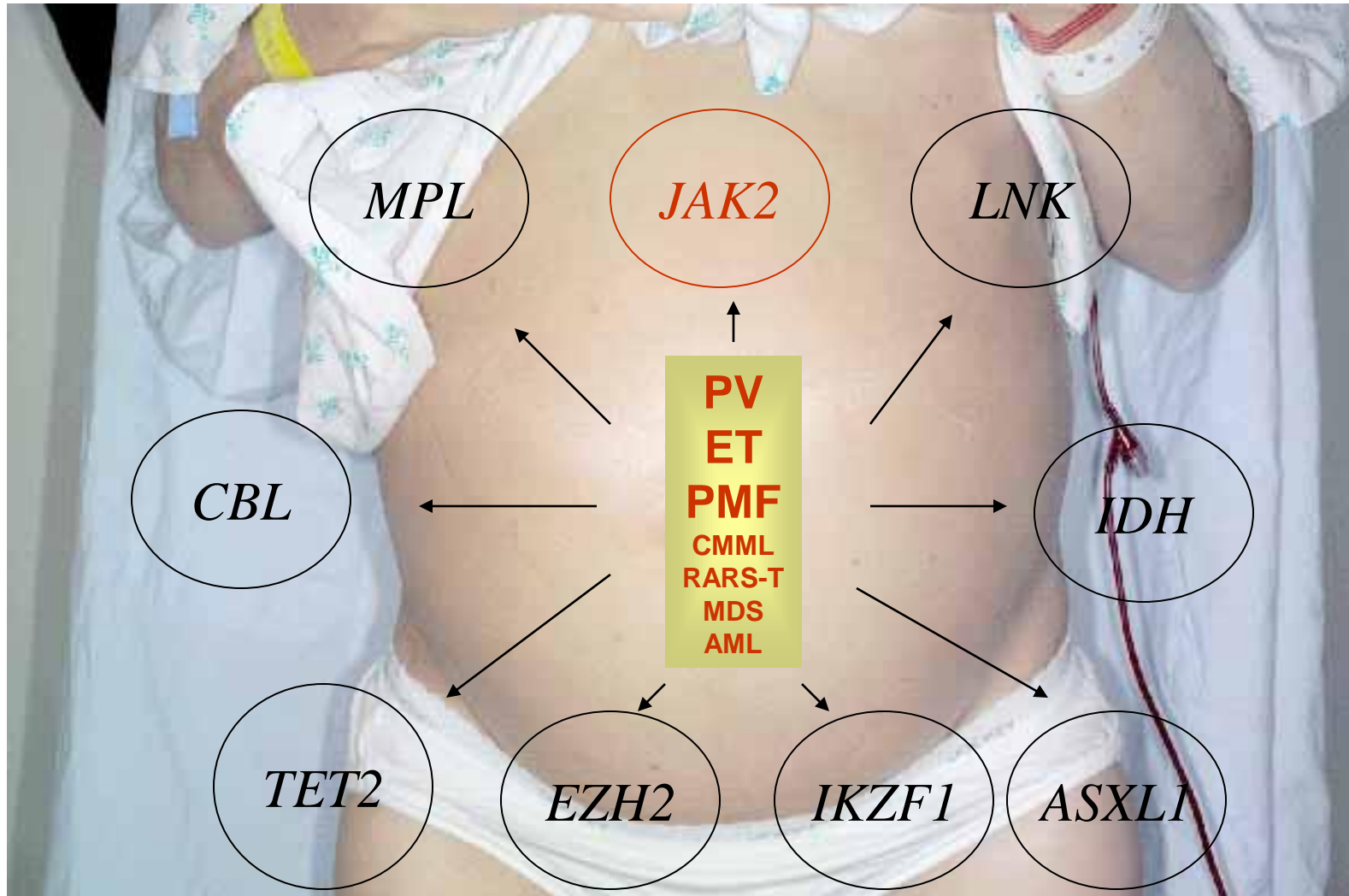


Chronic phase

Accel./blast phase

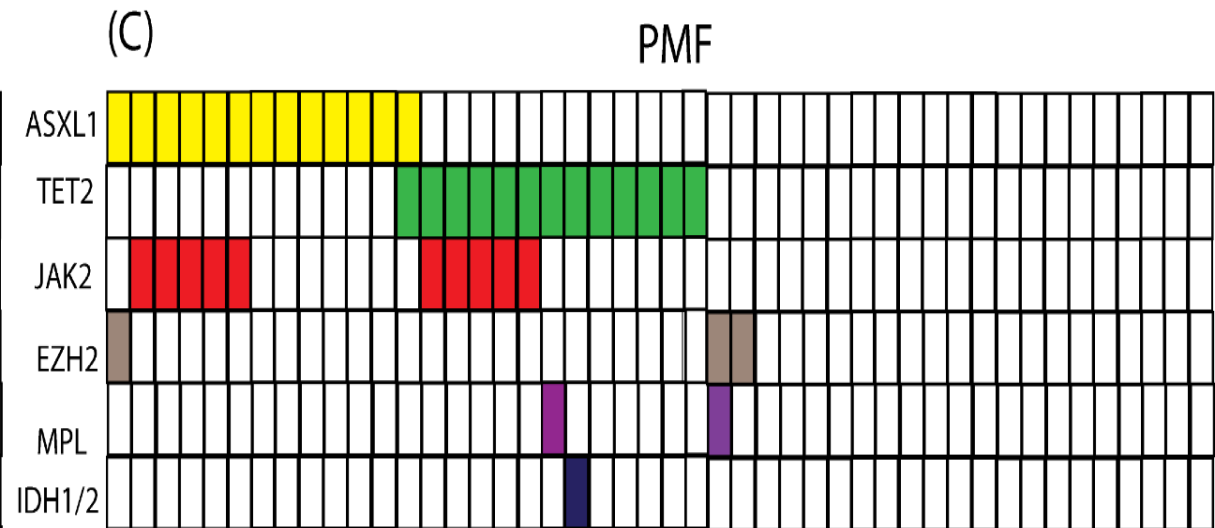
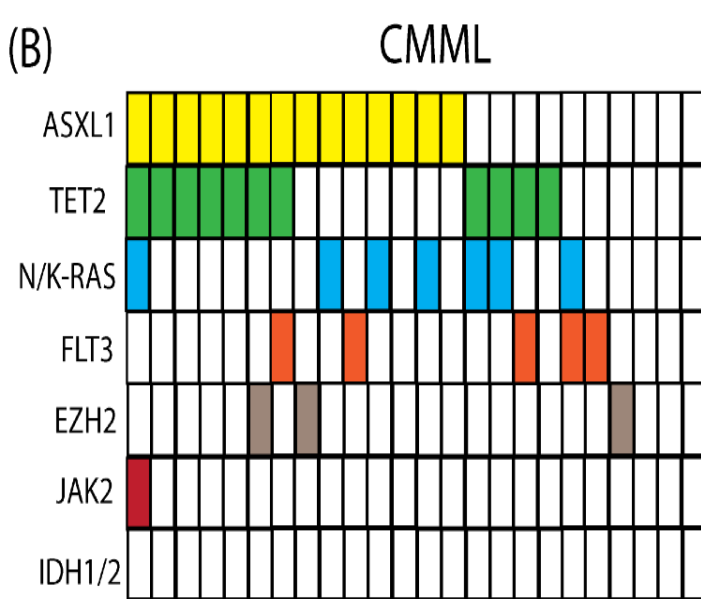


Mutations galore in *BCR-ABL1*-negative myeloid neoplasms



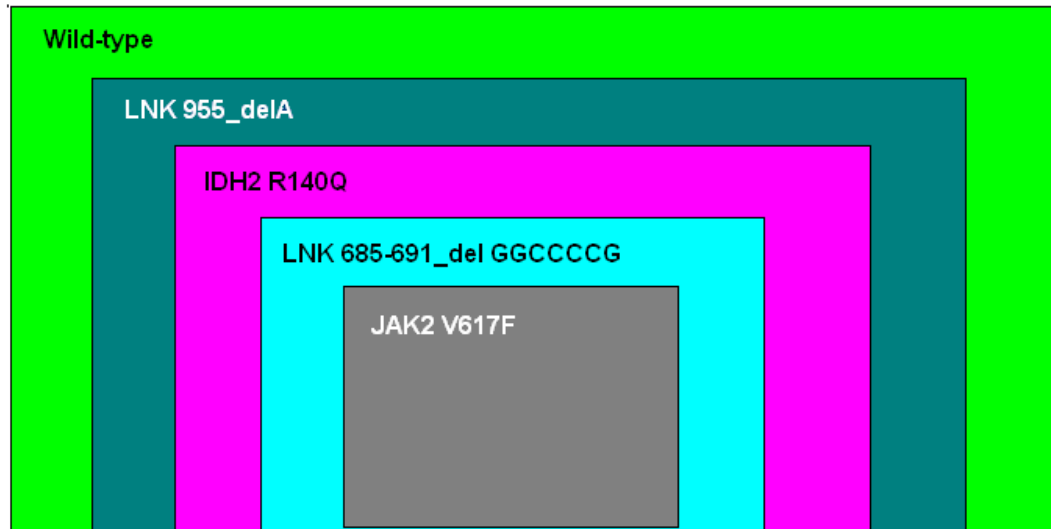
Concomitant Analysis of EZH2 and ASXL1 Mutations In Myelofibrosis, Chronic Myelomonocytic Leukemia and Blast-Phase Myeloproliferative Neoplasms

ASH 2010, abstract #3070



Clonal hierarchy in a patient with PMF and two distinct *LNK* mutations, *JAK2*V617F and *IDH2* R140Q

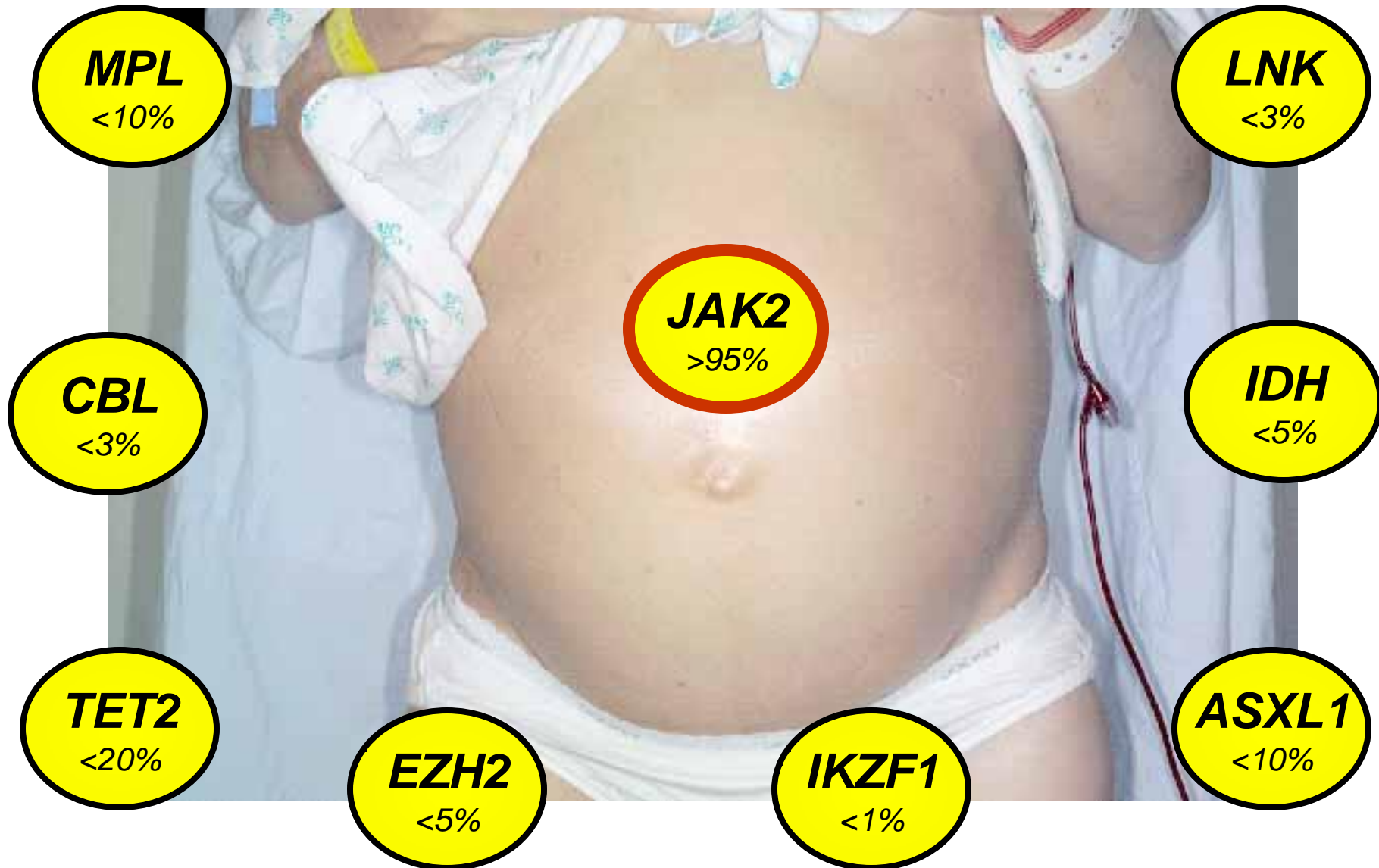
LNK Mutation Studies In Chronic- and Blast-Phase Myeloproliferative Neoplasms
and *JAK2* Mutation-Negative Erythrocytosis
ASH 2010, abstract #4105



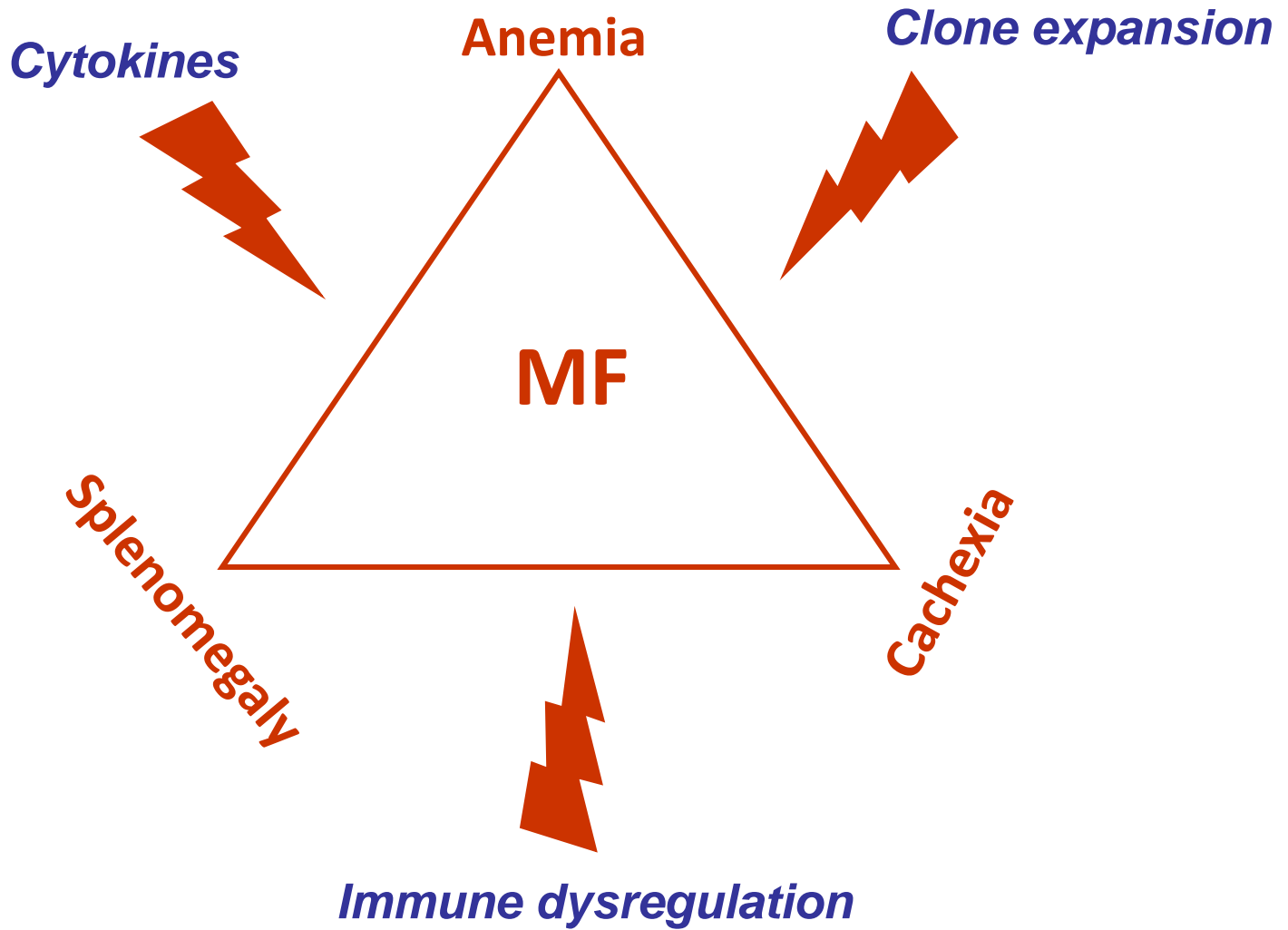
<p>Wild-Type LNK685-691_del GGCCCCG</p> <p>Heterozygous LNK 955_delA</p> <p>Wild-Type JAK2 V617F</p> <p>Wild-Type IDH2 R140Q</p> <p>n= 1 5%</p>	<p>Wild-Type LNK685-691_del GGCCCCG</p> <p>Heterozygous LNK 955_delA</p> <p>Wild-Type JAK2 V617F</p> <p>Heterozygous IDH2 R140Q</p> <p>n= 3 15%</p>	<p>Heterozygous LNK685-691_del GGCCCCG</p> <p>Heterozygous LNK 955_delA</p> <p>Heterozygous JAK2 V617F</p> <p>Heterozygous IDH2 R140Q</p> <p>n= 4 20%</p>	<p>Homozygous LNK685-691_del GGCCCCG</p> <p>Heterozygous LNK 955_delA</p> <p>Wild-Type JAK2 V617F</p> <p>Heterozygous IDH2 R140Q</p> <p>n= 7 35%</p>	<p>Homozygous LNK685-691_del GGCCCCG</p> <p>Heterozygous LNK 955_delA</p> <p>Heterozygous JAK2 V617F</p> <p>Heterozygous IDH2 R140Q</p> <p>n= 7 35%</p>
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'Targeted' therapy in MPN

What mutant molecule should we target?



JAK inhibitors for myelofibrosis treatment



Management of Myelofibrosis

- **Transplant options**

- Myeloablative
- Reduced-intensity

- **Non-transplant options**

- Treatment for anemia

- Erythropoietin
- Corticosteroids
- Androgen + Prednisone
- Danazol
- Thalidomide + Prednisone
- Lenalidomide

- Treatment for splenomegaly

- Hydroxyurea
- Splenectomy

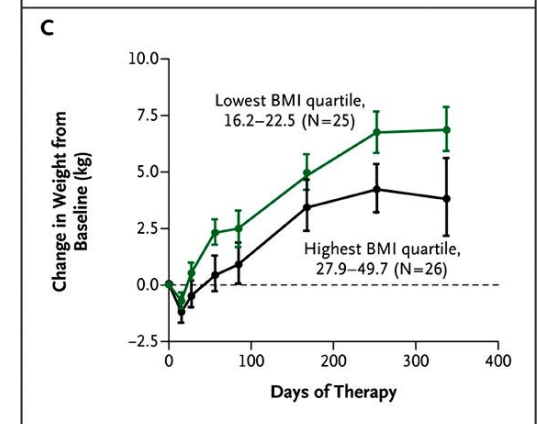
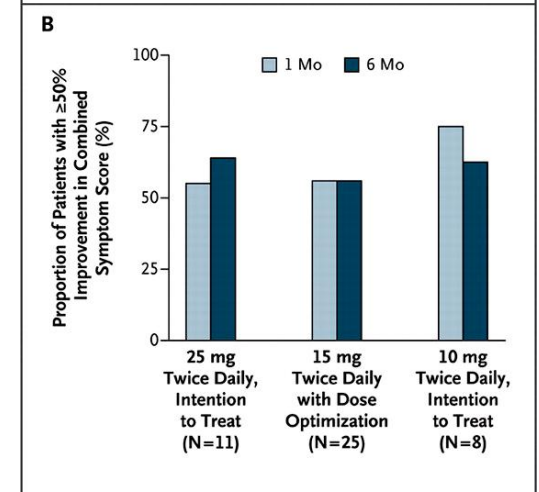
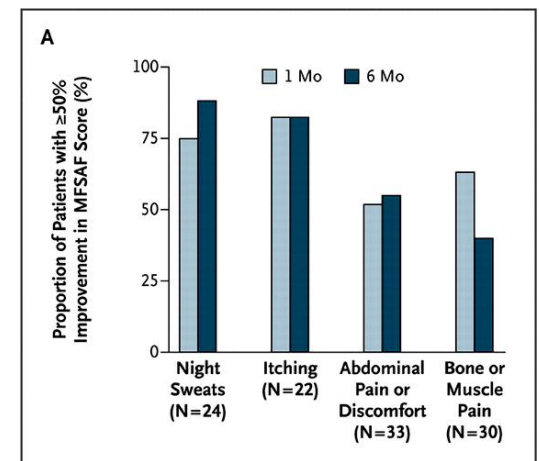
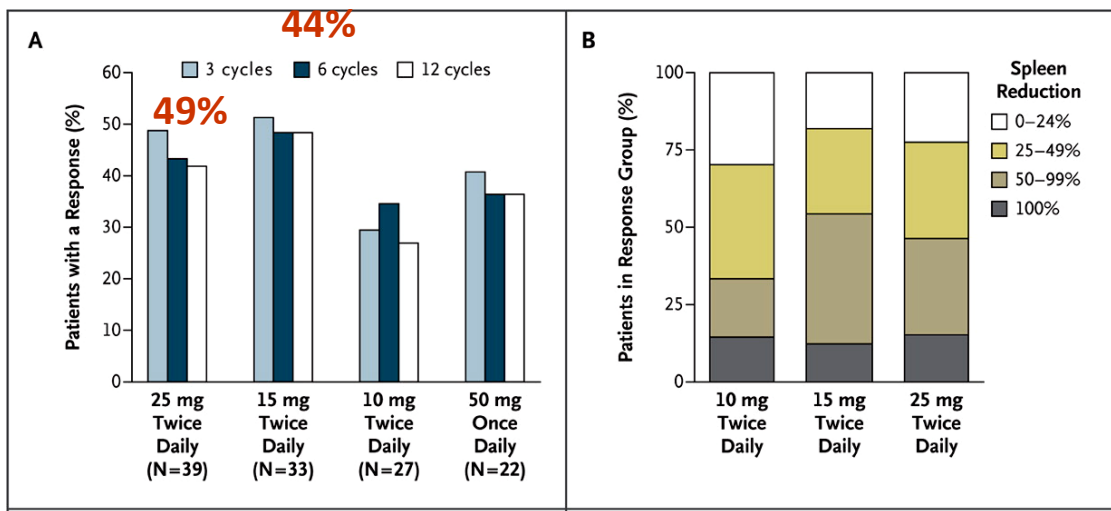
- Treatment for extramedullary hematopoiesis

- Low-dose irradiation

- Supportive care

Experimental drug therapy

1. Pomalidomide
2. JAK inhibitors
3. Others
 - a. Hypomethylating agents
 - b. HDAC inhibitors
 - c. mTOR inhibitors
 - d. Aplidin
 - e. Other others



INCB018424

- Phase 1/2 study
- N=153
- Median f/u=14.7 months
- DLT=Gr 3/4 thrombocytopenia
- MTD=25 mg BID or 100 mg QD

Table 2. Nonhematologic Adverse Events in 153 Patients.*

Event	All Grades	Grade 3 or 4
	<i>percent of patients</i>	
Diarrhea	5.9	0
Fatigue	4.3	1.3
Headache	3.3	0
Peripheral edema	2.6	0
Pain in extremities	2.6	0
Urinary tract infection	2.6	0
Dizziness	2.6	0
Dyspnea	2.6	0
Asthenia	2.0	2.0
Fever	2.0	0.7
Cardiac murmur	2.0	0
Musculoskeletal pain	2.0	0
Peripheral neuropathy	2.0	0
Edema	2.0	0
Anxiety	2.0	1.3
Insomnia	2.0	1.3
Epistaxis	2.0	0
Flatulence	2.0	0
Nausea	2.0	0

Study discontinuation rate=25%

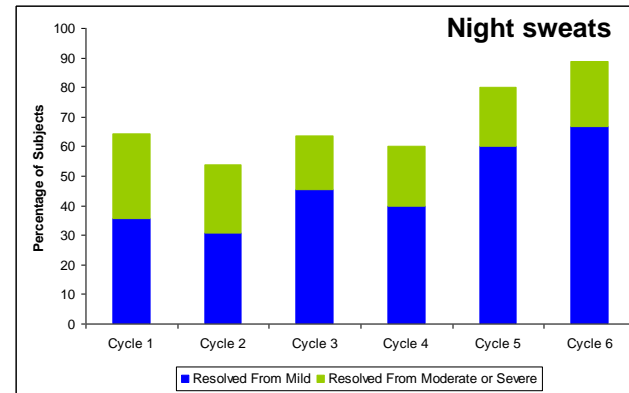
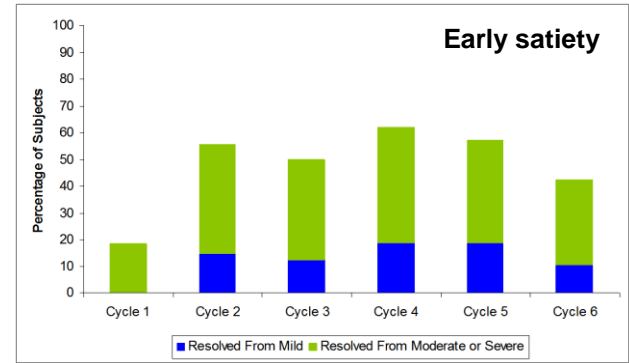
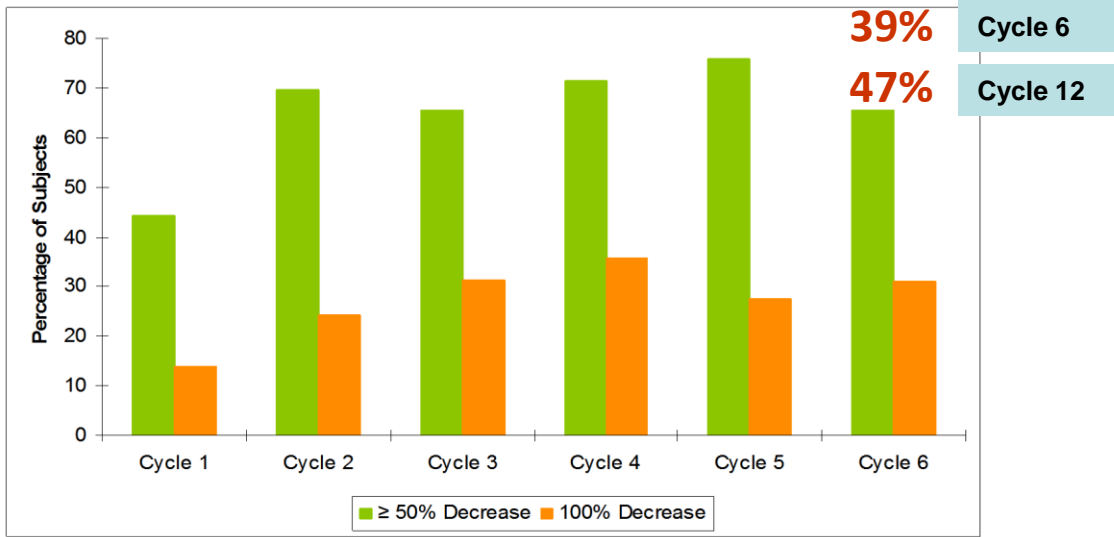
* Adverse events that were thought to be at least possibly related to the study medication and that occurred in 2% or more of the study population are included.

Table 3. Hematologic Adverse Events

Variable	10 mg Twice Daily	15 mg Twice Daily	25 mg Twice Daily	50 mg Twice Daily	25 mg Once Daily	50 mg Once Daily	100 mg Once Daily	200 mg Once Daily	Total
Thrombocytopenia — no./total no. (%) [*]									
Grade 3	3/29 (10)	1/35 (3)	11/47 (23)	3/5 (60)	0/6 (0)	6/22 (27)	2/6 (33)	0	26/153 (17)
Grade 4	0	0	3/47 (6)	1/5 (20)	0	2/22 (9)	0	1/3 (33)	4/153 (3)
New-onset anemia among patients who were transfusion-independent at baseline — no./total no. (%) [†]	3/19 (16)	2/24 (8)	8/30 (27)	0/2 (0)	1/4 (25)	5/15 (33)	1/4 (25)	3/3 (100)	23/101 (23)

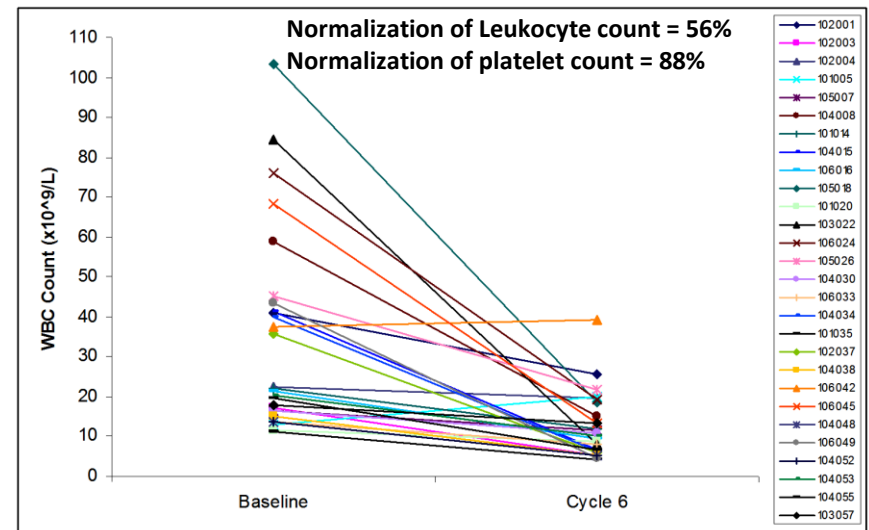
^{*} Values for platelet-count abnormalities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (grade 3 = 25×10^9 /liter to $<50 \times 10^9$ /liter, grade 4 = $<25 \times 10^9$ /liter).

[†] Anemia was defined as a decrease in the hemoglobin level of more than 20 g per liter to a grade 3 or 4 level (as defined according to the CTCAE, version 3.0) in patients who were not transfusion-dependent.



TG101348

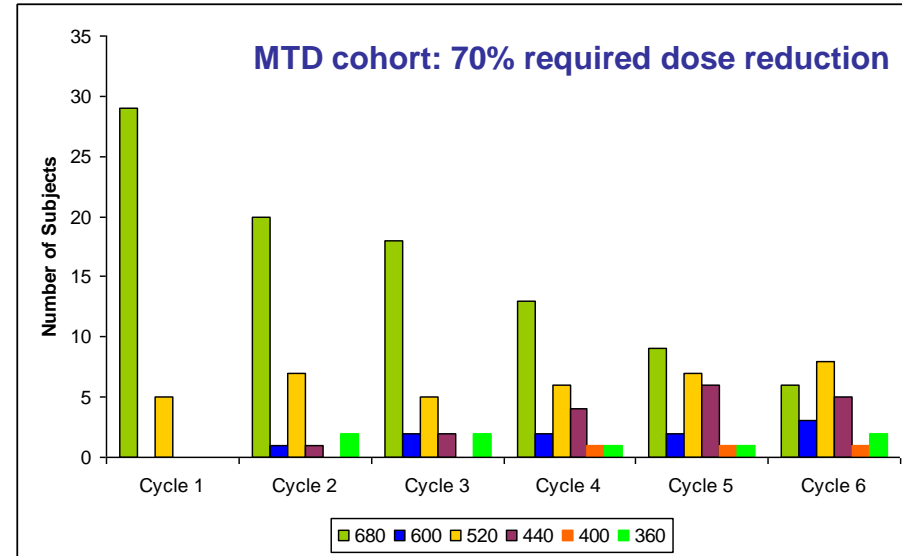
- Phase 1 study
- N=59
- Median f/u=380 days
- DLT=Gr 3/4 elevated amylase/lipase
- MTD=680 mg QD



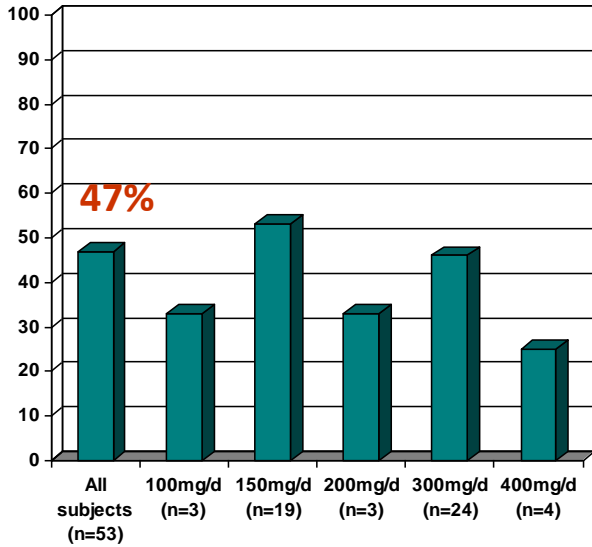
TG101348: safety and tolerability

study discontinuation rate = 44%

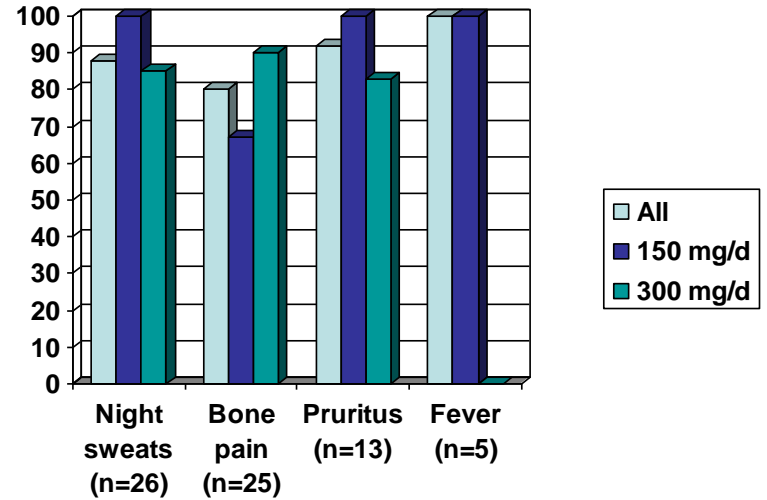
Adverse Event	All subjects N=59		MTD cohort N=40	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Nausea	66%	3%	78%	5%
Vomiting	54%	3%	68%	3%
Diarrhea	6%	0%	10%	0%
Lipase increased	17%	10%	23%	15%
ALT increased	19%	7%	23%	8%
AST increased	25%	2%	33%	3%
Creatinine increased	24%	0%	28%	0%
Alkaline phosphatase increased	17%	0%	23%	0%
Anorexia	14%	0%	15%	0%
Peripheral edema	10%	0%	10%	0%
Skin exfoliation	14%	0%	20%	0%



Adverse Event	All Subjects N= 59	MTD Cohort N= 40
	Grade 1/2	Grade 3/4
Anemia (N=37)	8%	54%
Thrombocytopenia	17%	28%
Neutropenia	63%	10%



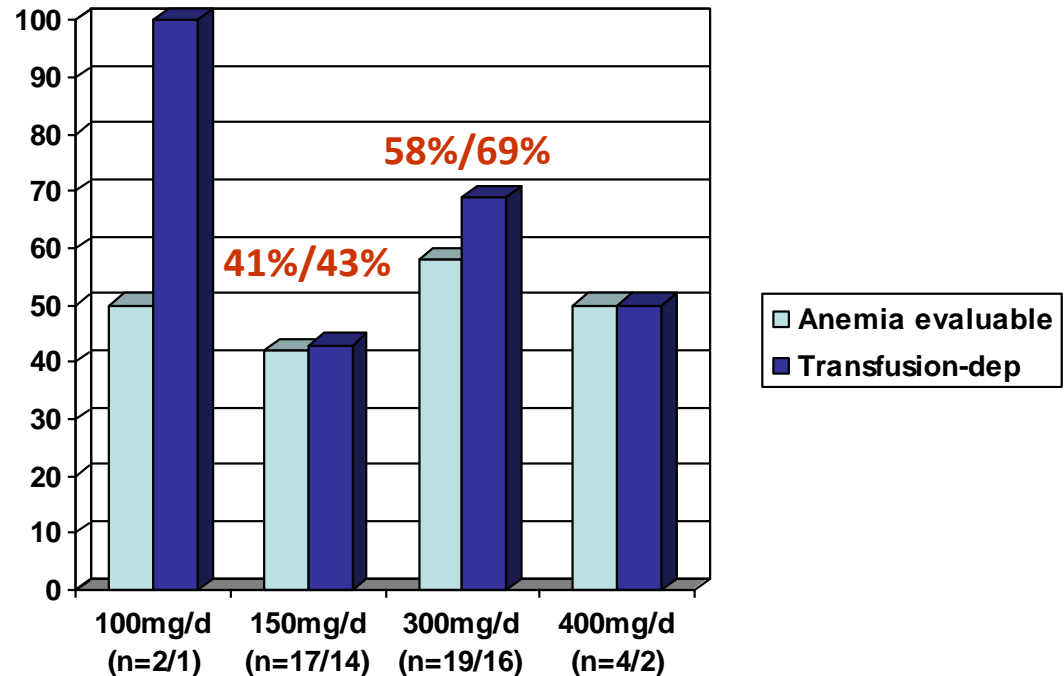
■ Spleen response (IWG)



■ All
■ 150 mg/d
■ 300 mg/d

CYT387

- Phase 1/2 study
- N=60
- Median f/u 4.9 months
- DLT Gr 3 elevated lipase/headache
- MTD 300 mg QD



■ Anemia evaluable
■ Transfusion-dep

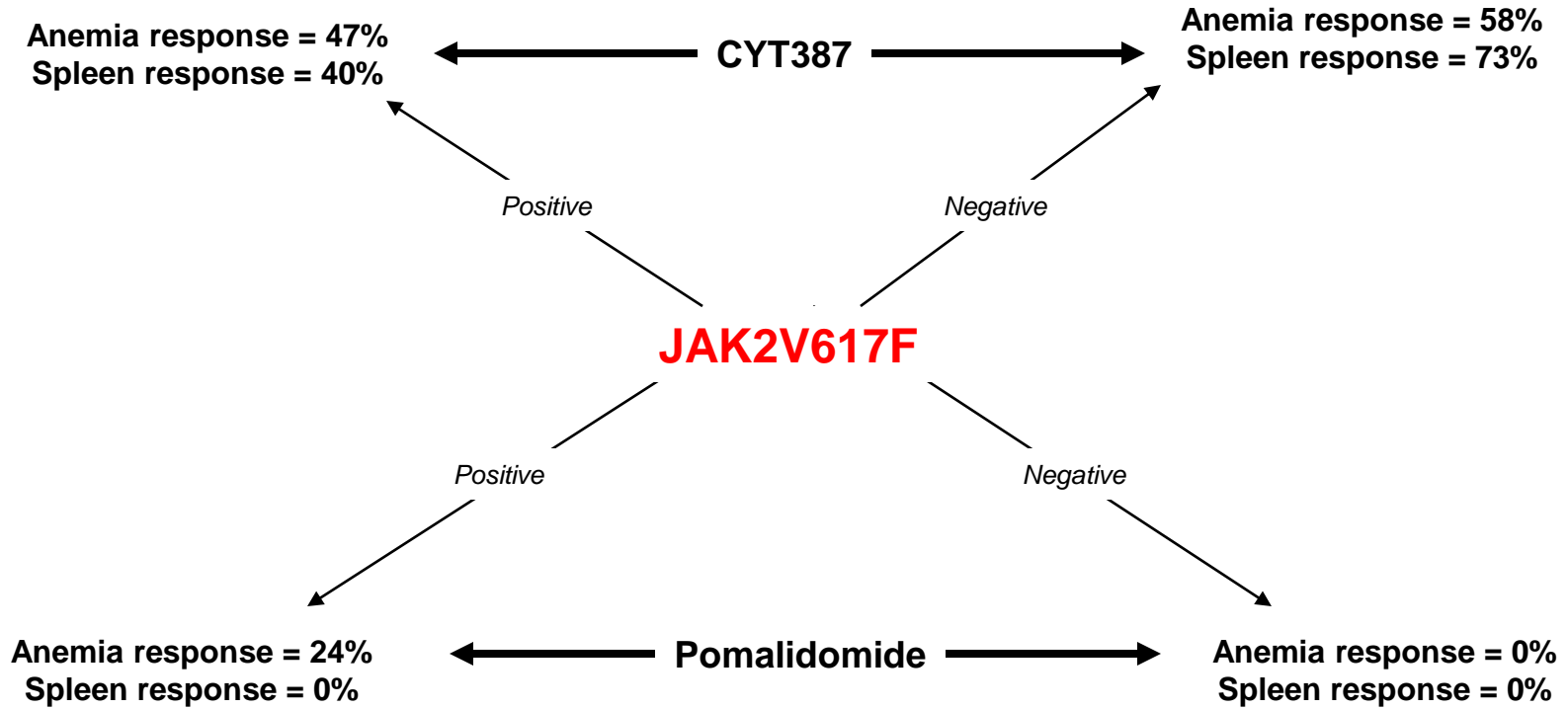
CYT387: safety and tolerability

study discontinuation rate = 5%

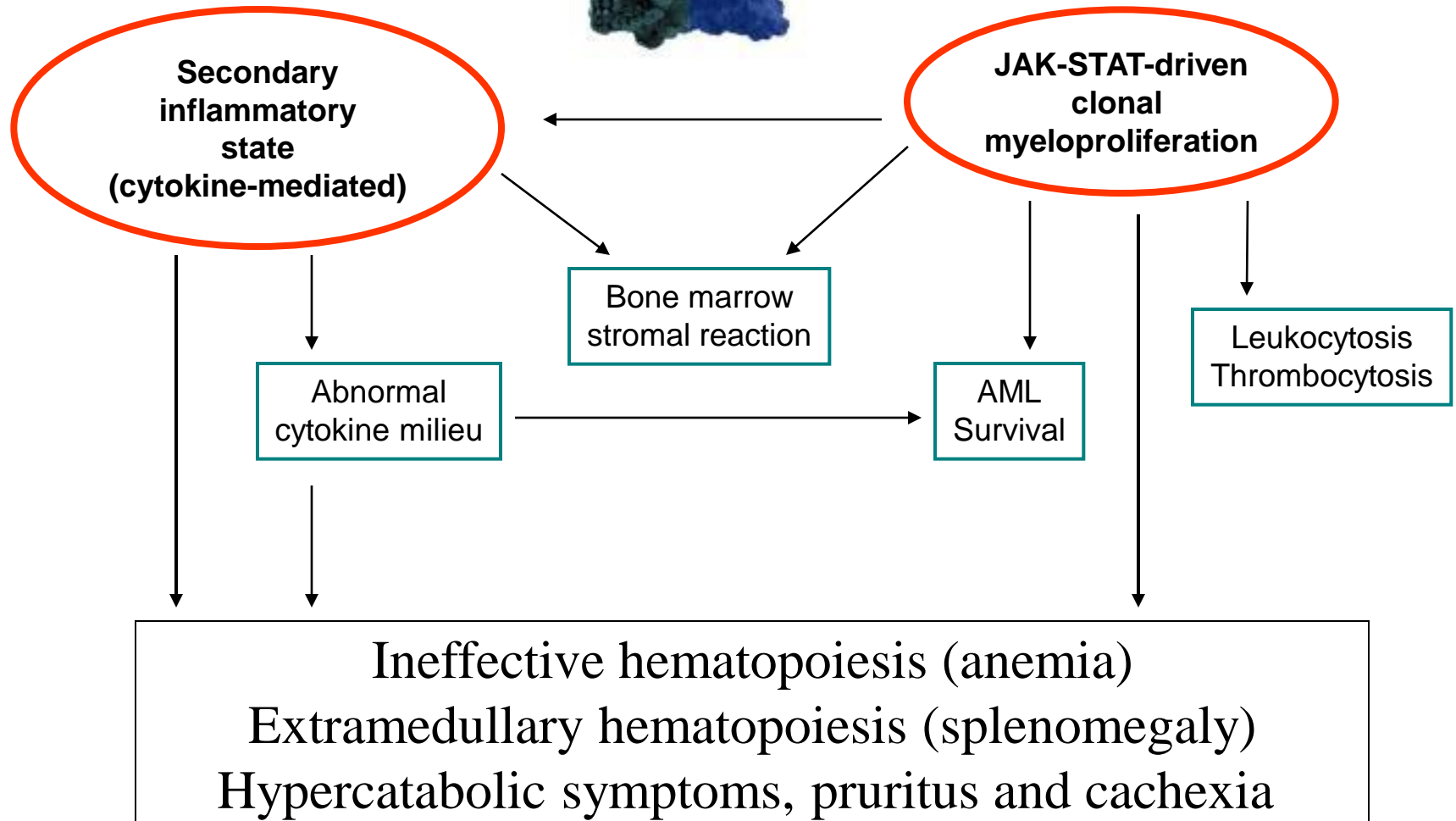
Adverse events	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	15%			
Diarrhea	12%			
Abdominal pain	7%			
Vomiting	3%			
Increased transaminases	20%		3%	
Increased bilirubin	16%			
Increased lipase	7%		5%	
Increased amylase	5%	5%		
Increased Alk Pase	7%	3%		
Increased creatinine	5%			
Numbness	5%			
Headache	10%		3%	
Prolonged QTc	3%			
Dry mouth	3%			

	Transient Lightheadedness	Systolic BP decrease >20 mm Hg
All patients (n=60)	43%	52%
Starting dose 150 mg/day	19%	33%
Starting dose 300 mg/day	59%	63%

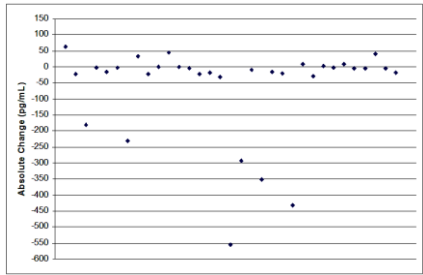
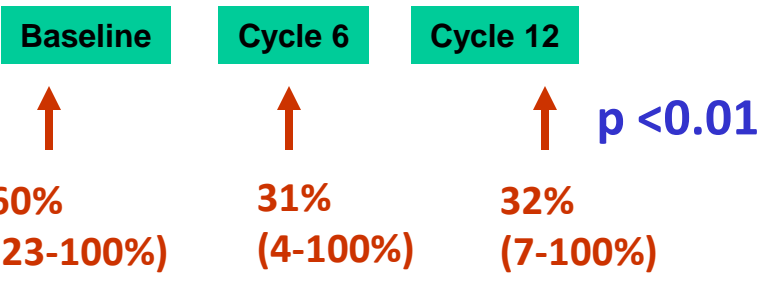
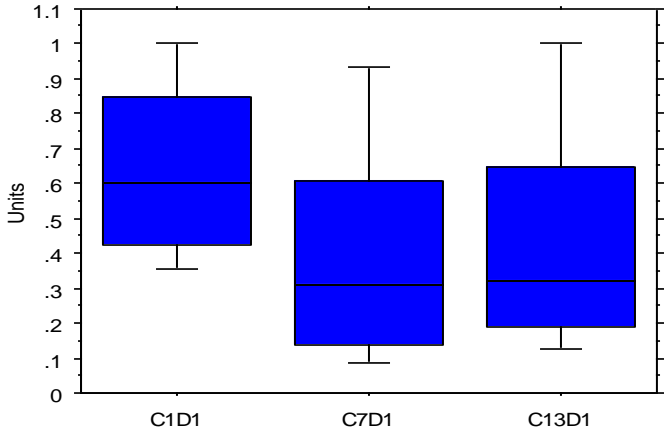
Adverse events	Grades 1/2	Grade 3	Grade 4
Anemia	7%	7%	
Thrombocytopenia	42%	18%	8%
Neutropenia	2%		5%



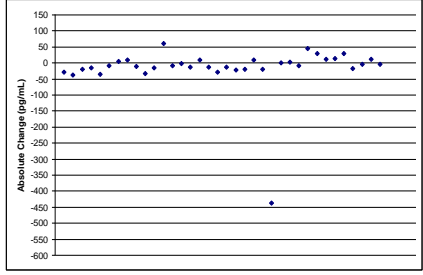
The two pathogenetic faces of myelofibrosis



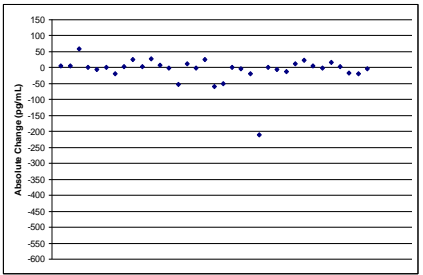
JAK2V617F allele burden



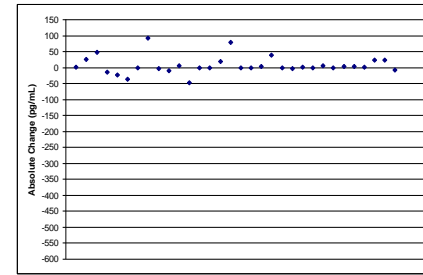
Interleukin-6



TNF-α



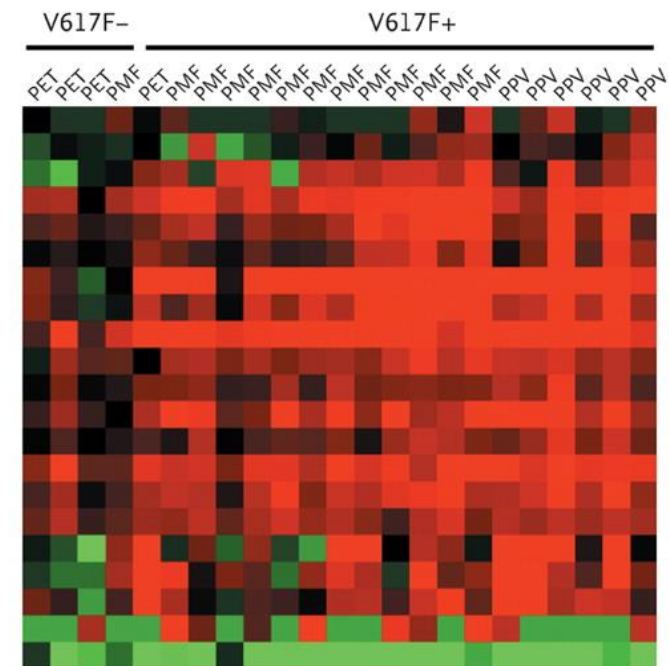
Interleukin-8



Interleukin-2

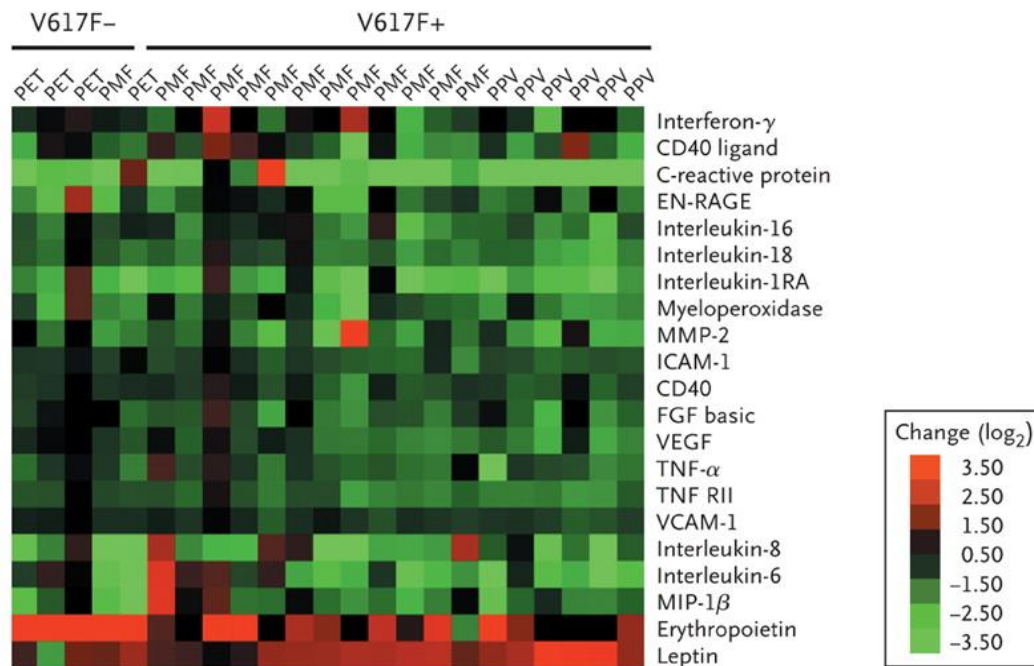


A Baseline, Patients with Myelofibrosis vs. Healthy Controls



Verstovsek S et al. N Engl J Med 2010;363:1117

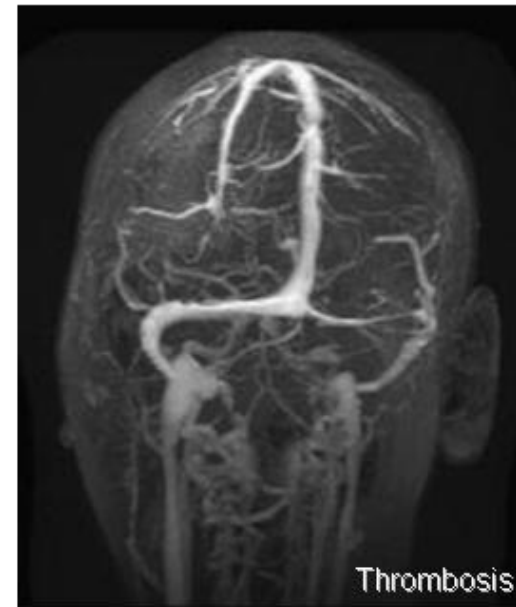
B Patients with Myelofibrosis, Day 28 vs. Baseline



Is there a role for JAK inhibitors for the treatment of PV or ET ?

Life-threatening complications in PV and ET

		ET	PV
AML risk	10-yr	<2%	<5%
	20-yr	<8%	<15%
MF risk	10-yr	<5%	<10%
	20-yr	<20%	<30%



PV
thrombosis risk
At diagnosis 22%
At follow-up 36%

ET
thrombosis risk
At diagnosis 23%
At follow-up 29%

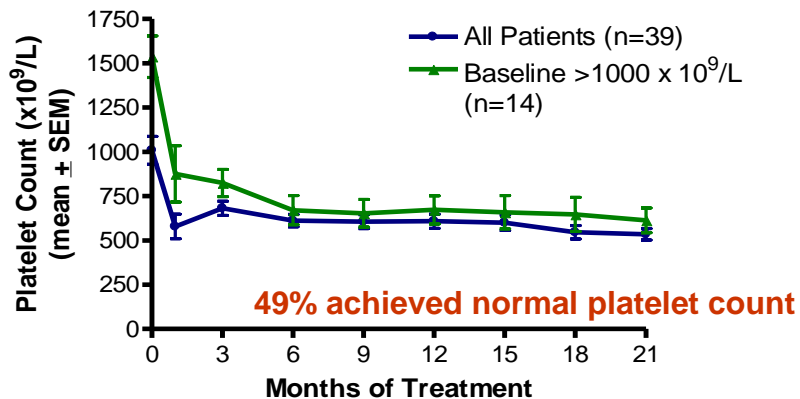


Clinically-relevant end points:

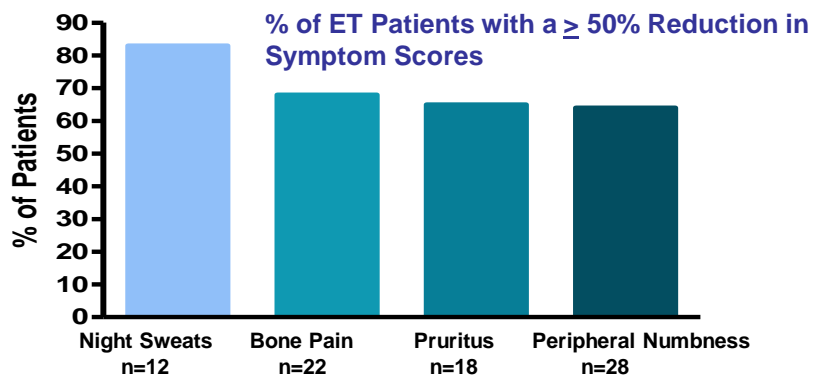
- Overall survival
- Thrombosis-free survival
- MF-free survival
- Leukemia-free survival

INCB018424

ET



- **N=39**
- **Dose=25 mg BID**
- **Median f/u=21 months**
- **Study discontinuation=28%**
- **Responses (ELN criteria):**
 - **Overall 90%**
 - **CR 26%**
 - **PR 64%**

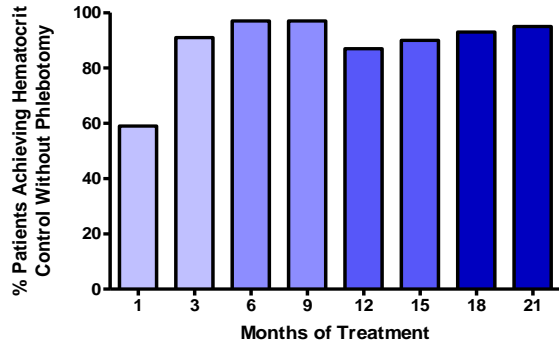


- All 11 subjects with WBC >11k had normalization of counts
- 4 subjects had palpable splenomegaly (median 5 cm)
 - 3 became non-palpable
 - 1 had ≥50% reduction
- 13 of 14 subjects with platelet count >1,000,000 had ≥50% reduction

Treatment-related AEs*	All Grades; n (%)	Grade 3; n (%)
Anemia	29 (74)	0
Weight increase	9 (23)	0
Herpes zoster	2 (5)	0
Hyperuricemia	2 (5)	0
Leukopenia	2 (5)	2 (5)
Pain in extremity	2 (5)	0
Palpitations	2 (5)	0

INCB018424 PV

97% Phlebotomy-free with Hct \leq 45%

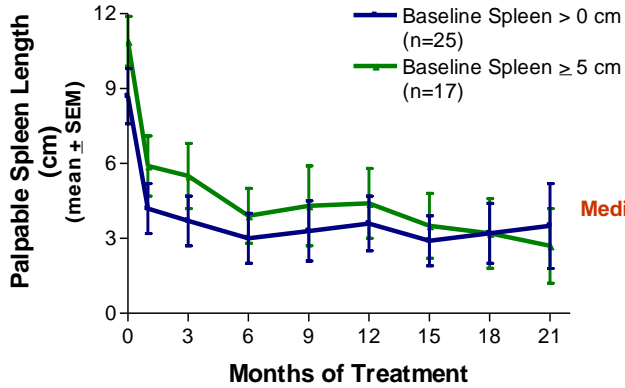


- N=34
- Dose=10 mg BID
- Median f/u=21 months

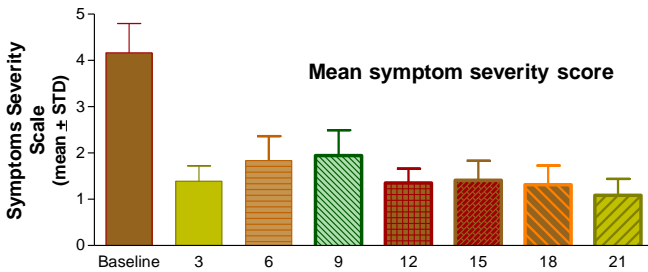
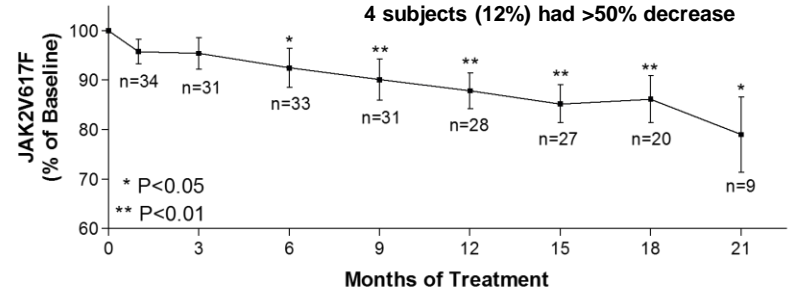
•Study discontinuation=18%

•Responses (ELN criteria):

- Overall 97%
- CR 50%
- PR 47%



Median palpable spleen size=9 cm
 ➢80% \geq 50% reduction
 ➢68% non-palpable



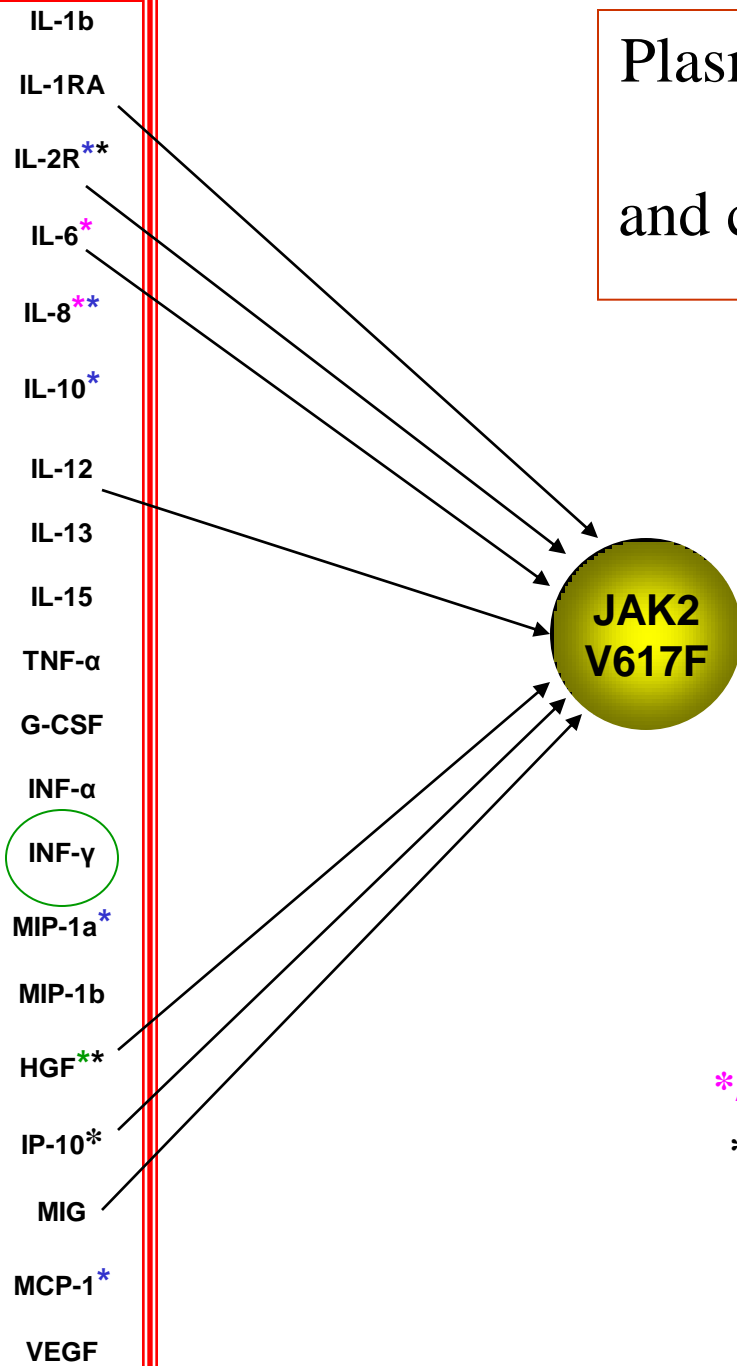
Alleviation of pruritus in most patients

Treatment-related AEs*	All Grades; n (%)	Grade 3; n (%)
Anemia	25 (74)	0
Thrombocytopenia	10 (29)	2 (6)
Leukopenia	5 (15)	0
Weight increase	5 (15)	0
Diarrhea	3 (9)	0
Hyperuricemia	3 (9)	0
Insomnia	3 (9)	0
Palpitations	3 (9)	0

**Could anti-JAK therapy affect survival
in myelofibrosis?**

Plasma cytokines in primary myelofibrosis are abnormally increased and correlate with phenotype and prognosis

Tefferi et al. ASH 2010 abstract #3068, JCO in press



***Association with constitutional symptoms**

***Association with leukocytosis**

***Association with marked splenomegaly**

***Association with transfusion need**

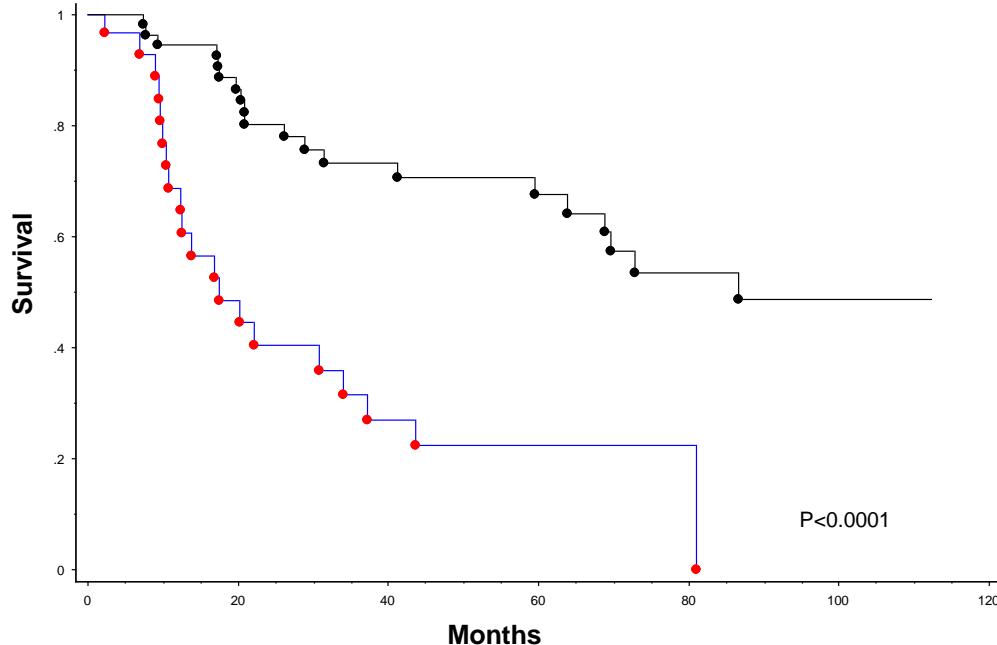
Plasma cytokines in primary myelofibrosis are abnormally increased and correlate with phenotype and prognosis

IL-8, IL-2R, IL-12, IL-15 and CXCL10 were independently associated with poor survival

Tefferi et al. ASH 2010 abstract #3068; JCO in press

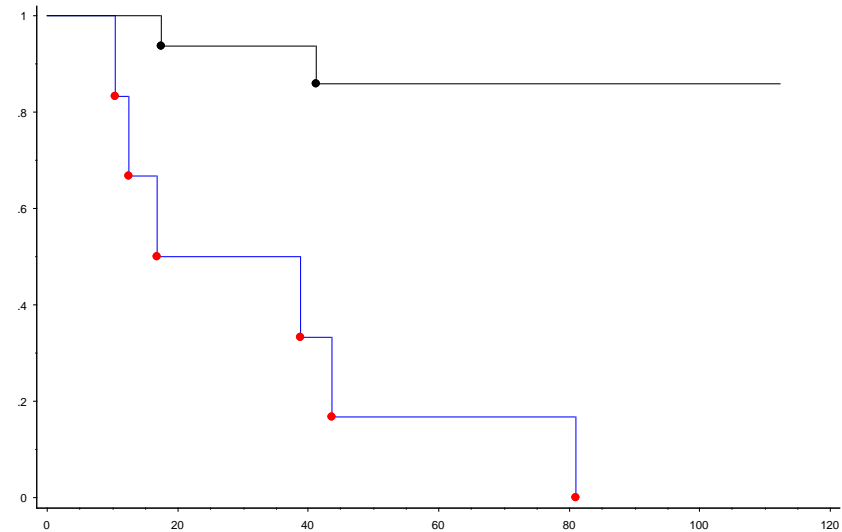
90 treatment-naive patients with PMF

- Plasma IL-8 and IL-2R in the normal range ($n=60$)
Median survival ~80 months
- One or both cytokines elevated ($n=30$)
Median survival ~17 months





Only intermediate-1 risk patients considered; $N = 27$

- Plasma IL-8 and IL-2R in the normal range ($n=21$)
Median survival "not reached"
- One or both cytokines elevated ($n=6$)
Median survival ~17 months



What is the prognosis for JAK inhibitors in Ph- myeloproliferative neoplasms?

- **Myelofibrosis** 
 - Well tolerated, significant palliation
 - Disease modifying?
 - Combination with other agents
- **Polycythemia vera / Essential thrombocythemia** 
 - limited niche (eg. refractory pruritus)
 - Improvement in clinically relevant end points?