Long-Term Follow up and Optimized Dosing Regimen of INCB 18424 in Patients with Myelofibrosis: Durable Clinical, Functional and Symptomatic Responses with Improved Hematological Safety

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INCB18424-251: Phase I/II Study Of JAK1 And JAK2 Inhibitor INCB 18424 In Myelofibrosis - Previously Reported Findings

- **Phase 1:**
  - Established 25 mg BID and 100 mg QD as maximum tolerated doses (MTDs)
    - Thrombocytopenia was dose limiting toxicity (DLT)
- **Phase 2:**
  - Expansion of 25 mg BID cohort
  - Individualized dose optimization based on safety and efficacy
- **Key Findings:**
  - Clinical Improvement (CI by IWG response criteria) in the majority of patients
    - Rapid reduction of splenomegaly
    - Rapid alleviation of symptoms
  - Well tolerated

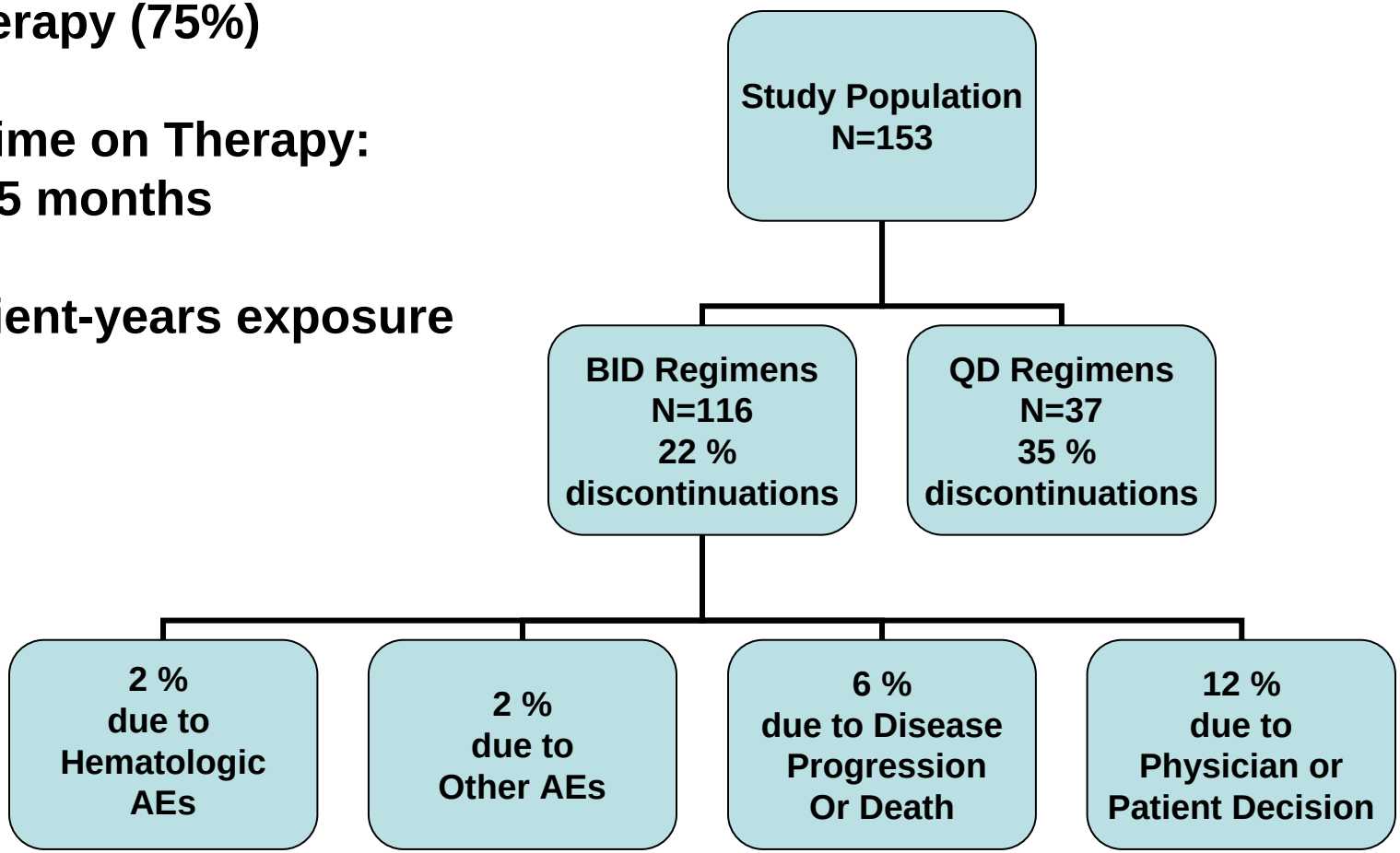
Baseline Patient Characteristics

Parameter	All Subjects
N	153
Age (median)	65.0
Male/Female (%)	63/37
Risk Category[a] (%) Intermediate-2 High Not Determined	 27.5 65.4 7.1
PMF / PPV-MF / PET-MF (%)	53/32/15
Time from Diagnosis (median, years)	6.0
Previously treated (%)	86
Number of Prior Therapies (median)	2.0
Peripheral Blasts ≥ 1% (%)	97.5
Cytogenetic Abnormality (%)	45
JAK2 Mutation Positive (%)	82
History of Prior Transfusions (%)	34

[a] risk category determined using IWG criteria (Cervantes et al., Blood 2009)

Current Patient Status

- **115/153 patients currently on therapy (75%)**
- **Median time on Therapy: ~15 months**
- **>150 patient-years exposure**



Non-Hematological Toxicities

Related Adverse Events*	Frequency All Grades	Frequency Grade 3**
Diarrhea	5.9%	0
Fatigue	4.6%	1.3%
Headache	3.3%	0
Peripheral Edema	2.6%	0
Urinary Tract Infection	2.6%	0
Pain in Extremities	2.6%	0
Dizziness	2.6%	0
Dyspnea	2.6%	0.6%

* Assessed as at least possibly related in at least 2% of study population

** NO Grade 4 toxicity recorded

Pneumonia (Grades 3 /4) occurred in 6.5% of subjects (within the expected range based on other clinical trials in MF)

Serious Adverse Events

Patient	Related SAE(s)
1	Myelosuppression
2	Anemia
3	Febrile neutropenia
4	Fever, anemia, syncope
5	Fever, asthenia, URI, myalgia, pharyngitis, sinusitis
6	Anxiety, insomnia, weakness, constitutional symptoms
7	Anxiety, insomnia, weakness, constitutional symptoms
8	Pneumonitis
9	B-cell lymphoma, SIRS (post-drug withdrawal)
10	CMMoL
11	Intracerebral hemorrhage (subject was non thrombocytopenic)
12	SIRS (post-drug withdrawal)

Optimized Dose Regimen

- Not all subjects can tolerate 25 mg BID (thrombocytopenia)
- Optimized dose regimen:
  - start at 15 mg BID (or at 10 mg BID if platelet count < 200,000/µL)
  - increase to 20 mg BID after 1 month if response inadequate and no toxicity
  - Second increase, to 25 mg BID allowed if still inadequate response and no toxicity after 2 months of therapy
  - Decrease the dose if platelets fall below 100,000/µL

Current Distribution of Dose Regimens
(All Subjects Currently on Study)

<10 BID	10 BID	15 BID to 20 BID	25 BID	QD
9.5 %	27.0 %	27.8 %	20.0 %	15.7 %

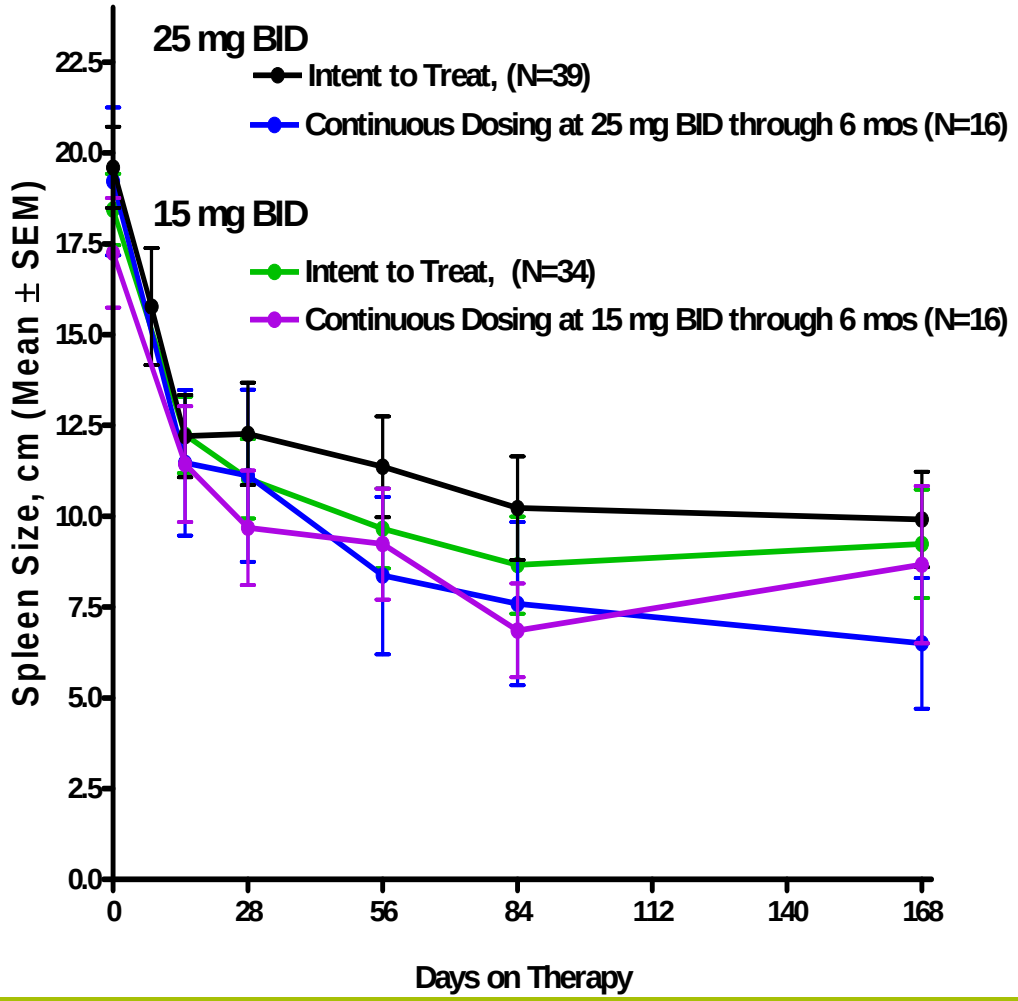
Optimized Dosing Improves Hematological Safety

CTCAE v3.0 Grade	15 mg BID With Dose Optimization N=35		25 mg BID N=47	
	New Onset Anemia N=24*	Platelets	New Onset Anemia N=30*	Platelets
Grade 3	2 (8.3%)	1 (2.9%)	7 (23%)	11 (23%)
Grade 4	0	0	1 (3.3%)	3 (6.4%)

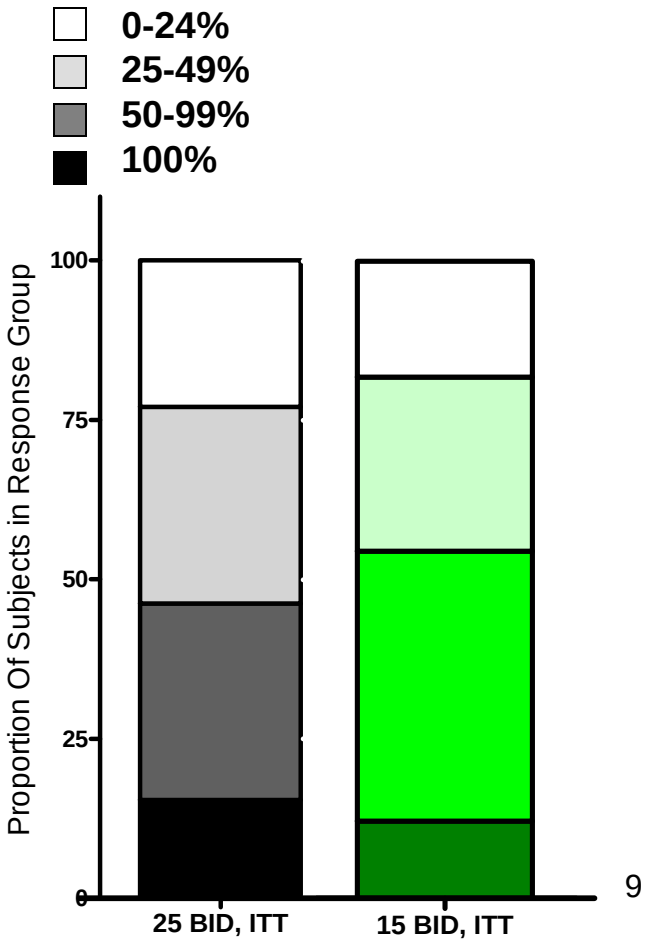
* Transfusion independent. New onset anemia was defined as hemoglobin decline of > 20 g/L, to the Grade 3 or Grade 4 level in previously transfusion independent subjects

Optimized Dosing Regimen Maintains Efficacy

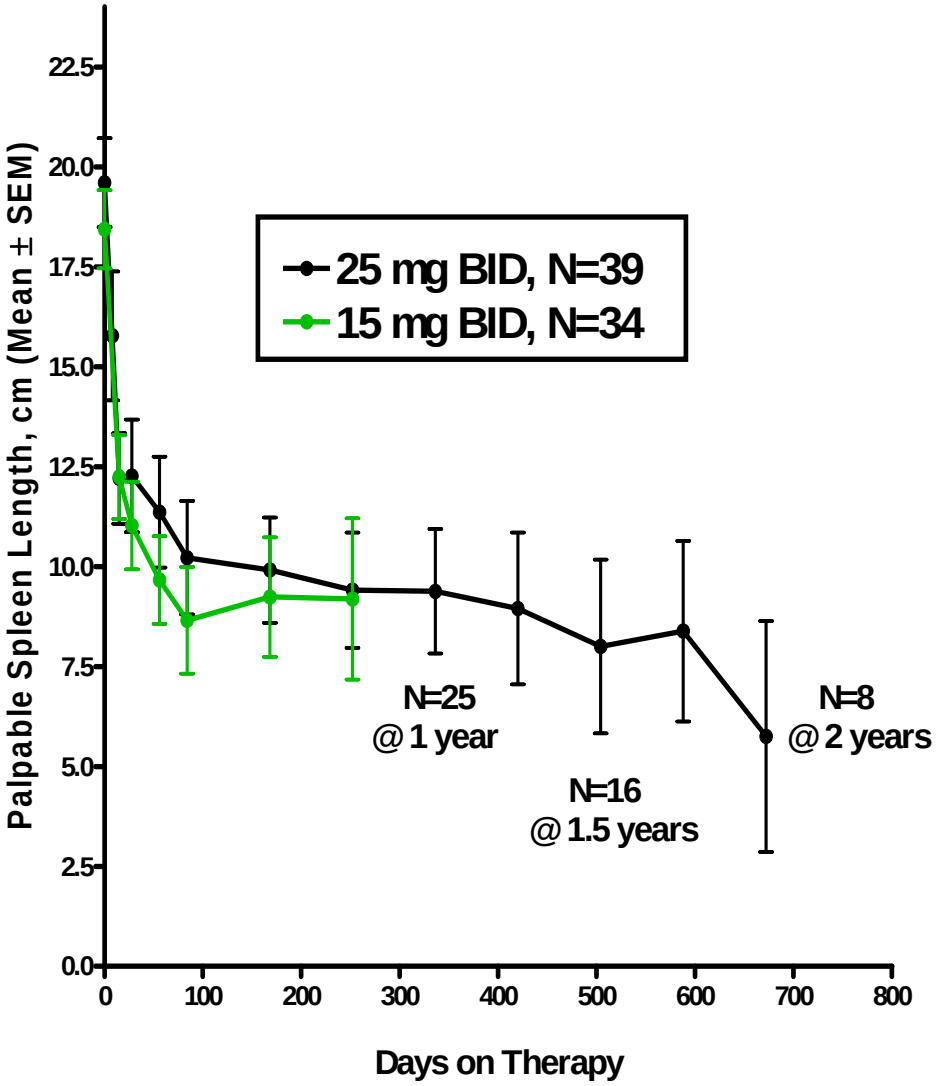
Reduction in Palpable Spleen Length



Response analysis based on % spleen reduction (last on-therapy value)

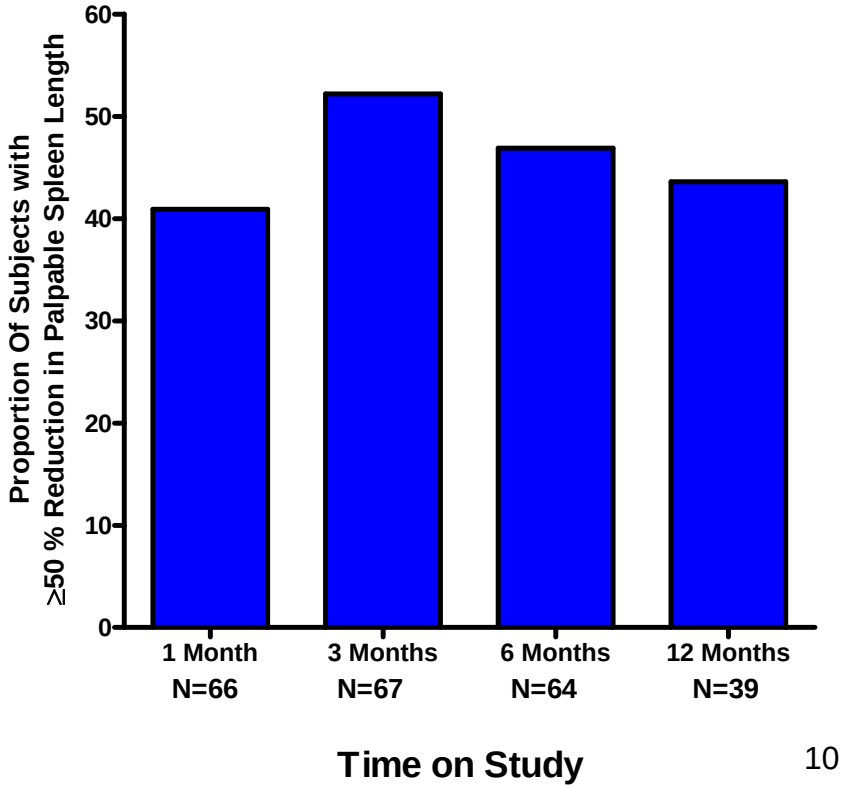


Response To Therapy Is Durable



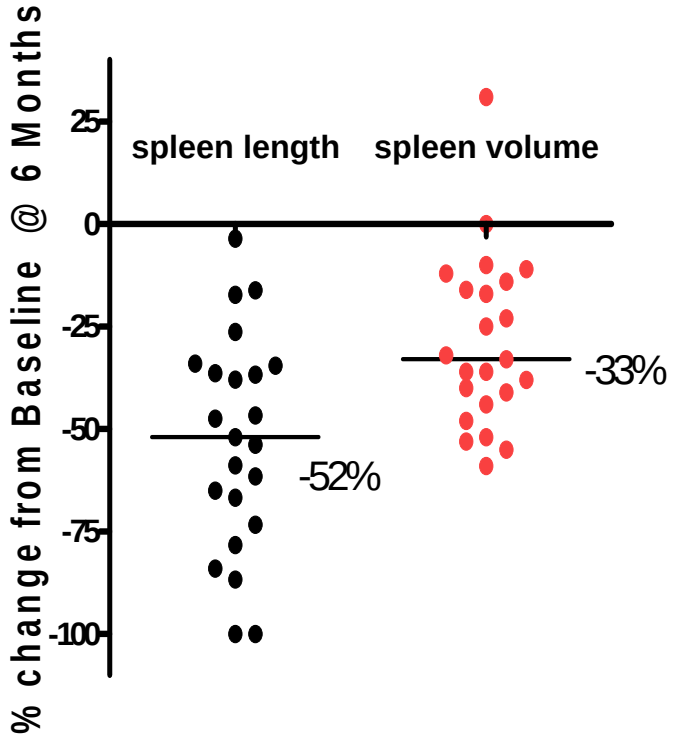
Percent of subjects with ≥ 50% decrease in palpable spleen length

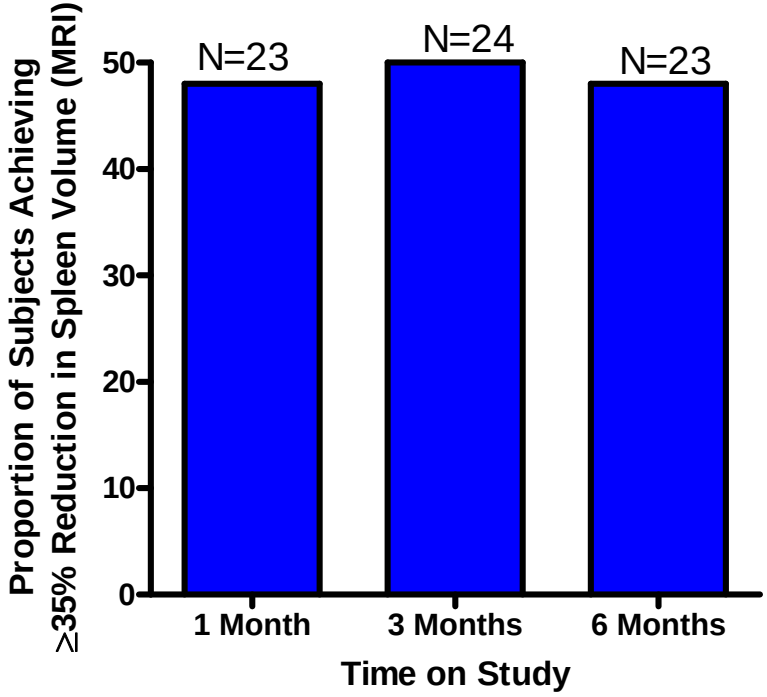
- **Dropouts = non responders**
- **Combined 15 and 25 mg BID dose groups**



Objective Measurement Of Spleen Size: MRI Analysis

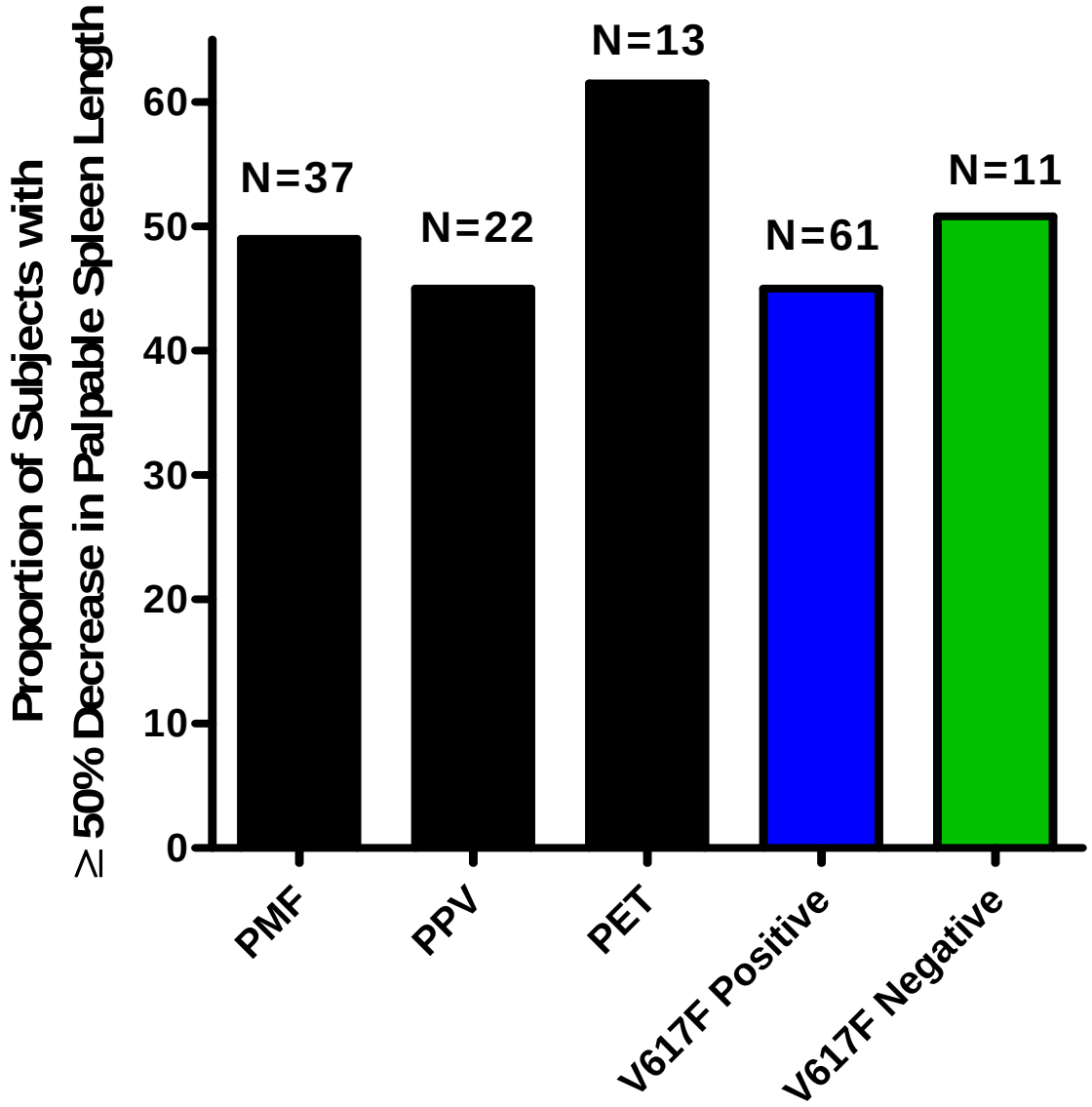
A 50% reduction in palpable spleen length corresponds to ~ 35% reduction in spleen volume by MRI





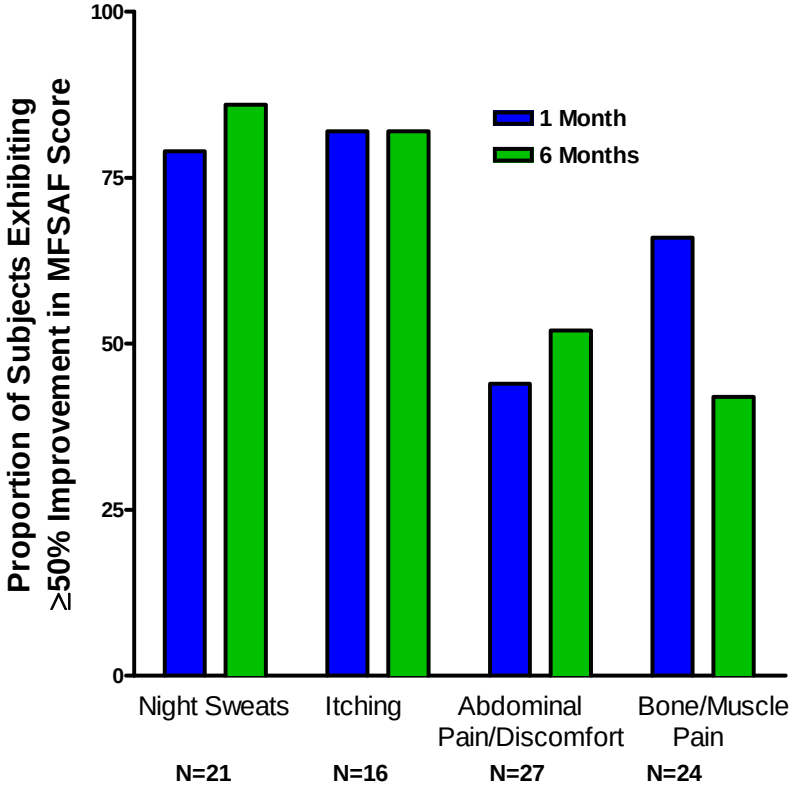
48% of subjects at 15 mg BID had a ≥ 35% decrease in spleen volume by MRI at 6 months

Spleen Size Reduction Is Independent Of JAK Mutation Status Or Disease Subtype

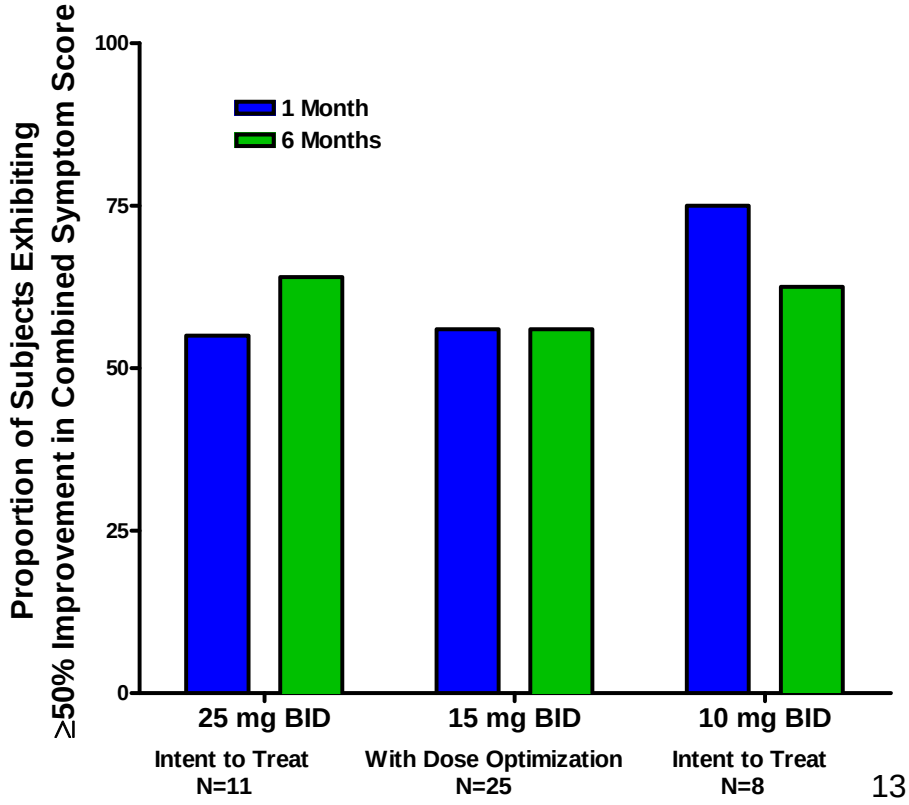


Rapid And Durable Improvement Of Disease-Related Symptoms

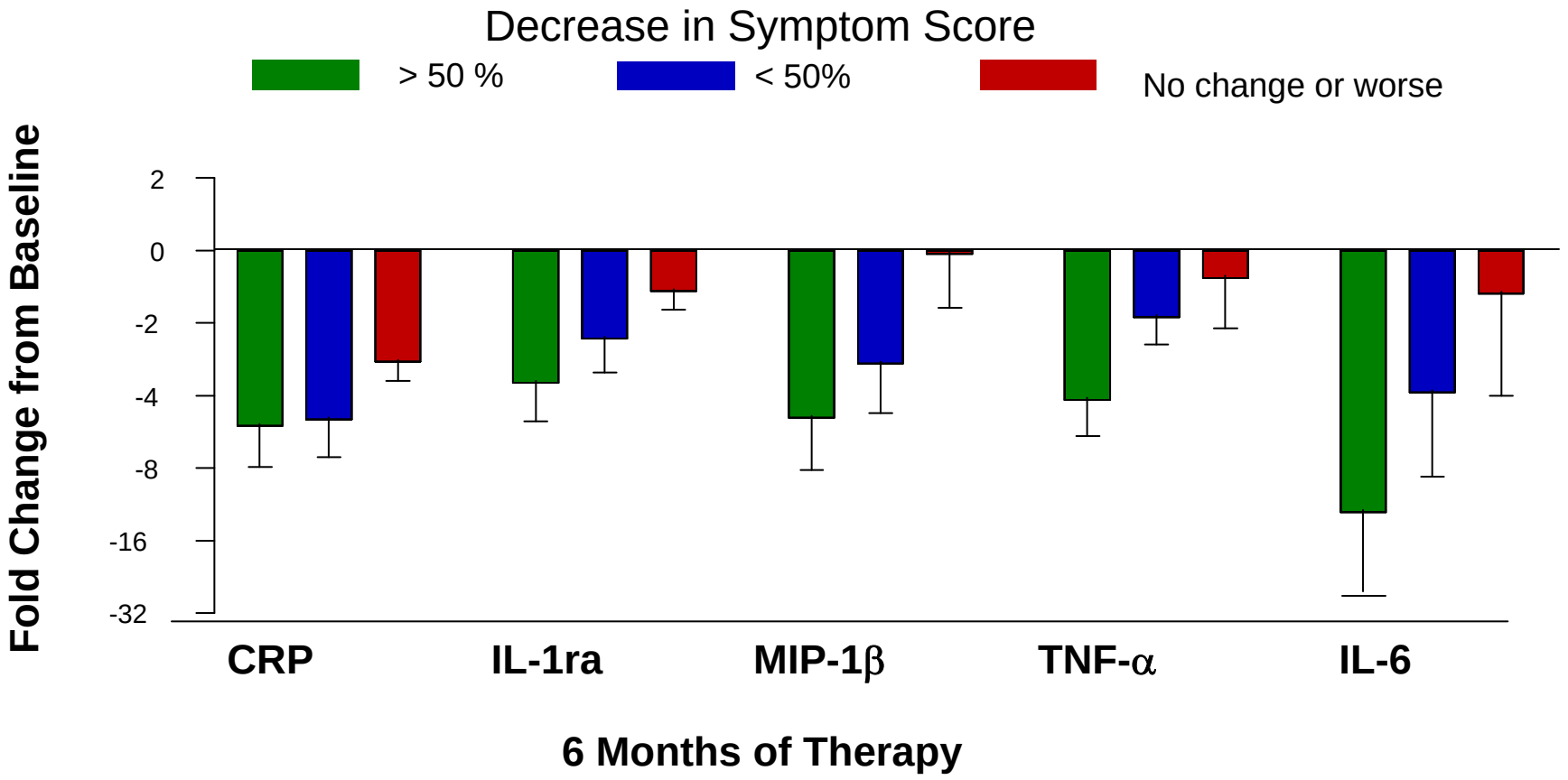
Majority of subjects receiving 15 to 25 mg BID show ≥ 50% improvement of individual MF symptoms on therapy



The combined symptom score is improved by ≥ 50 % in the majority of patients

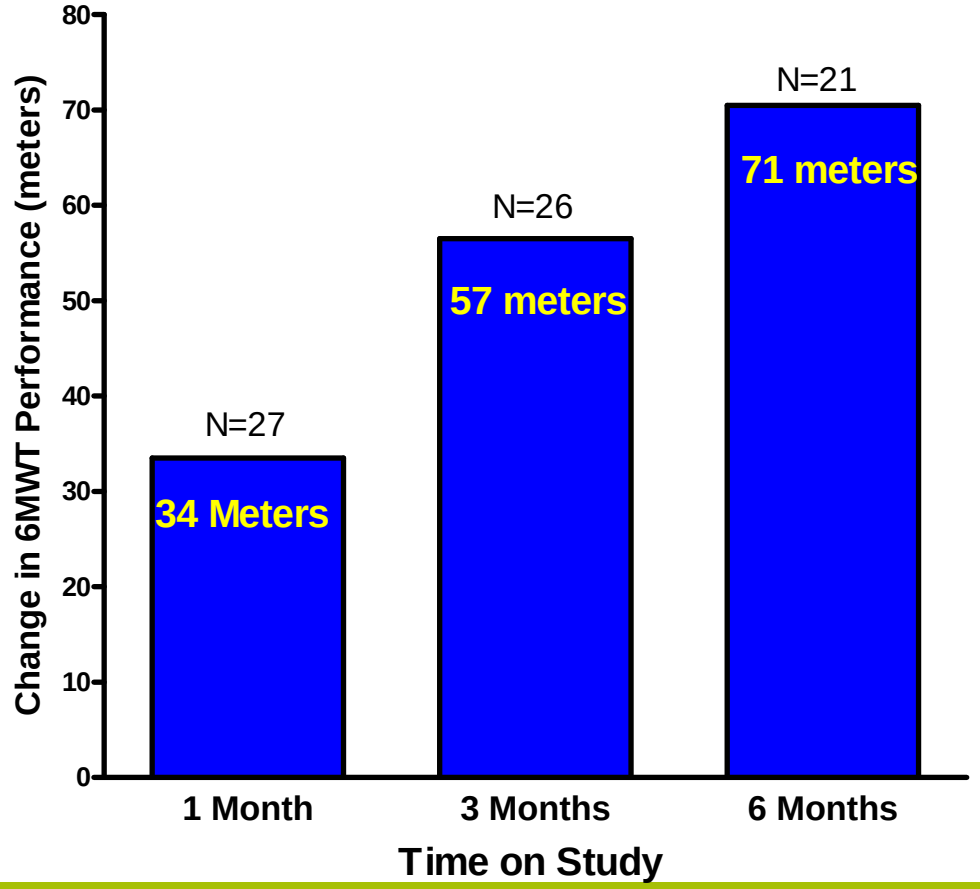


Improvement In Symptoms Is Associated With Durable Suppression Of Inflammatory Cytokines In Plasma



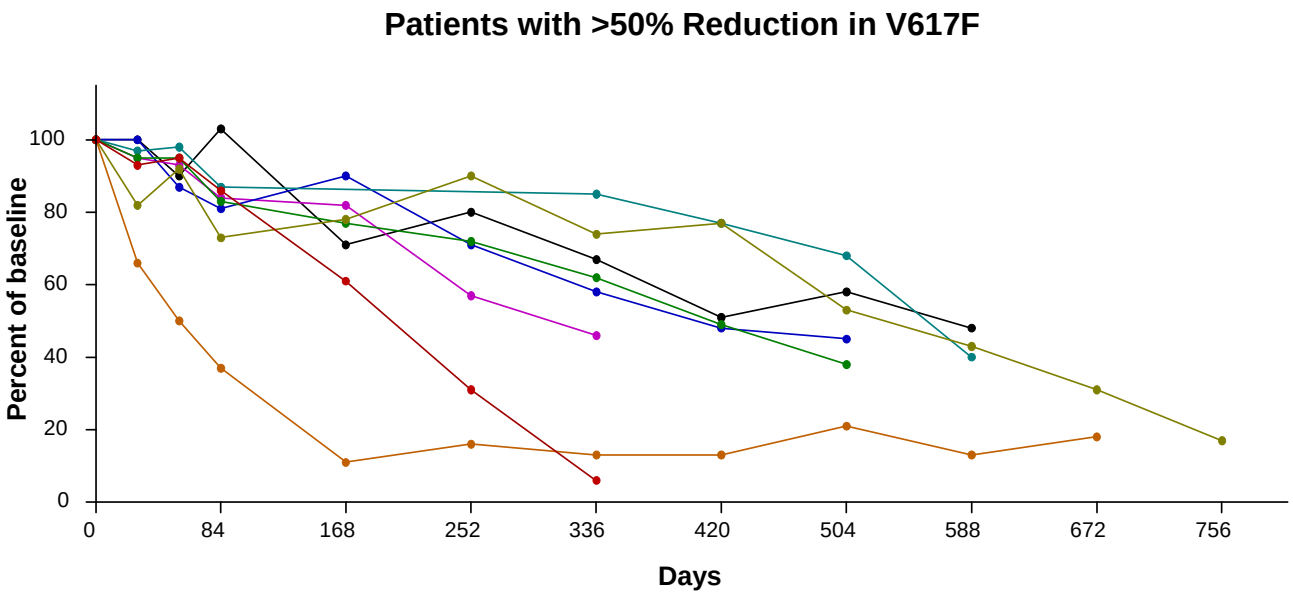
Improved Exercise Capacity

- 6-minute walk test (6MWT) is a well established measure of exercise capacity
- MF subjects walk 60-90 meters less than age-matched healthy volunteers (Mesa et al., ASCO 2008)

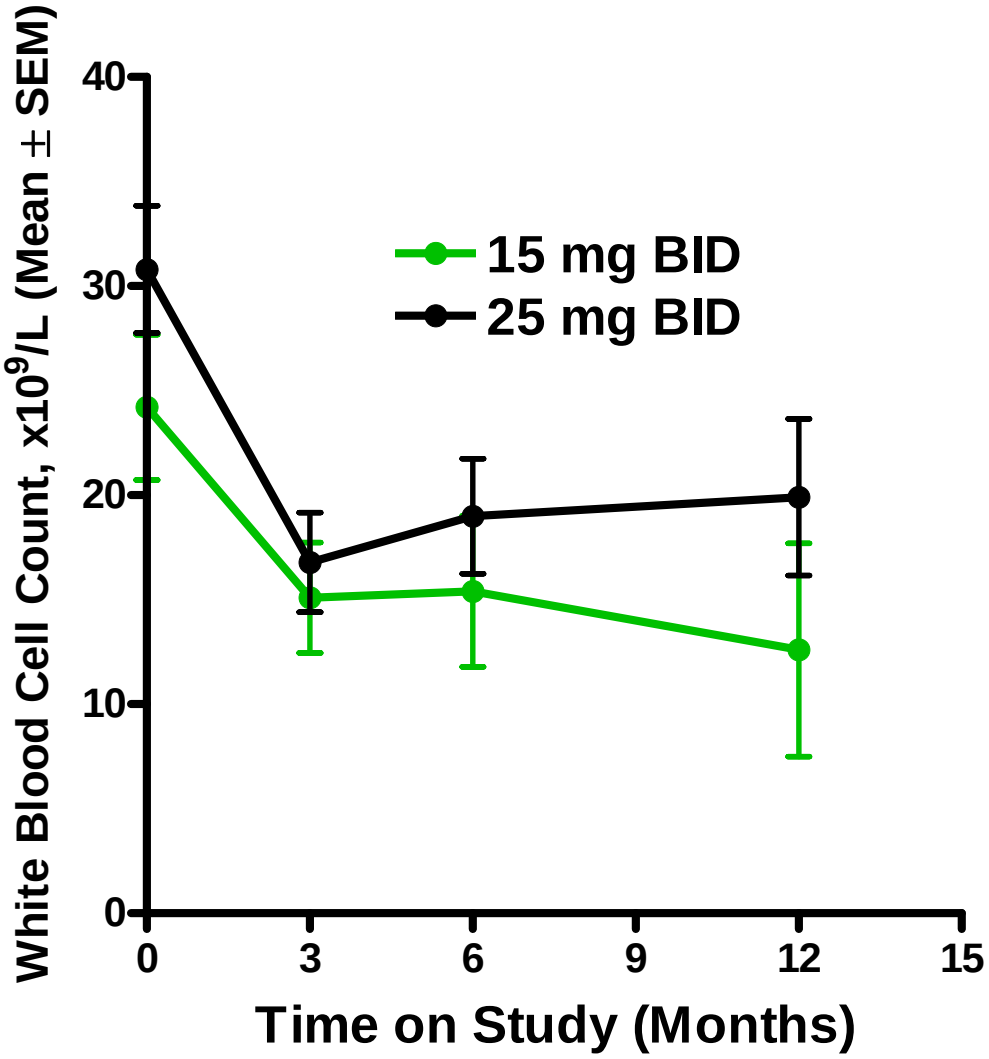


JAK2 Allele Burden

- **110 patients with JAK2V617F data following 3 months of treatment**
- **Median Allele burden 70%**
- **Impact of INCB18424 Therapy**
  - Average decrease of 11% at 1 year (n=81, p<0.001)
  - Average decrease of 18% at 2 year (n=12, p=0.05)
  - Greater than 25% reduction in JAK2V617F in 19 patients
  - Greater than 50% reduction in JAK2V617F in 8 patients



Sustained Reduction Of Leukocytosis



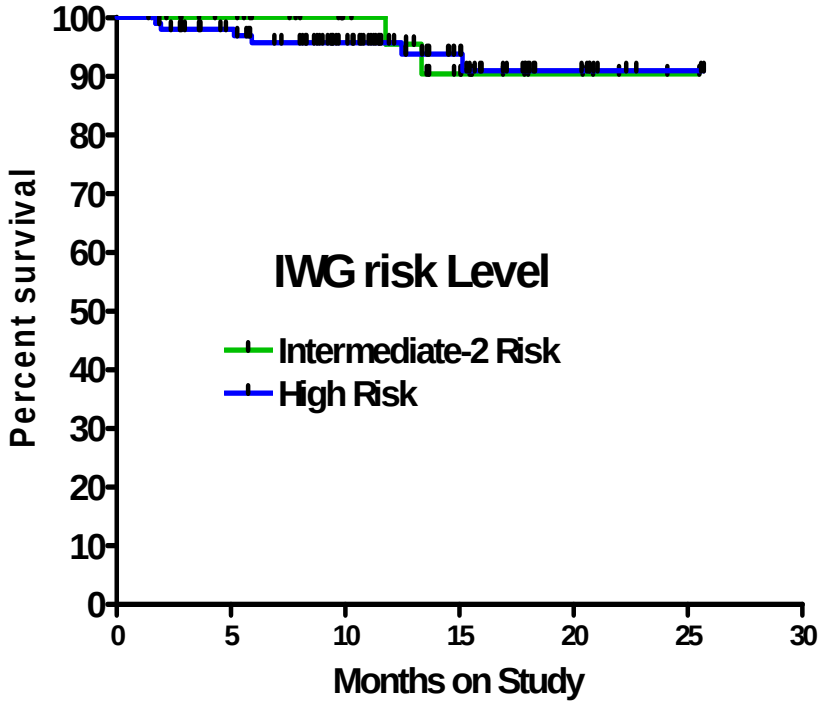
Leukemic Transformation

- 3 transformations to AML (corresponds to a rate of transformation of 0.016/patient year)
- Limited historical data on the rate of transformation
  - Barosi et al (2007) – 21 transformations in 174 patients with a median follow up of 26 months (rate of transformation = 0.056/patient year)
  - Guglielmelli et al (2009) – 15 transformations in 186 patients with a median follow up of 17.2 months (rate of transformation = 0.056/patient year)
- Expected number of transformations based on 153 patients and a 15 month follow-up is approximately 11 patients

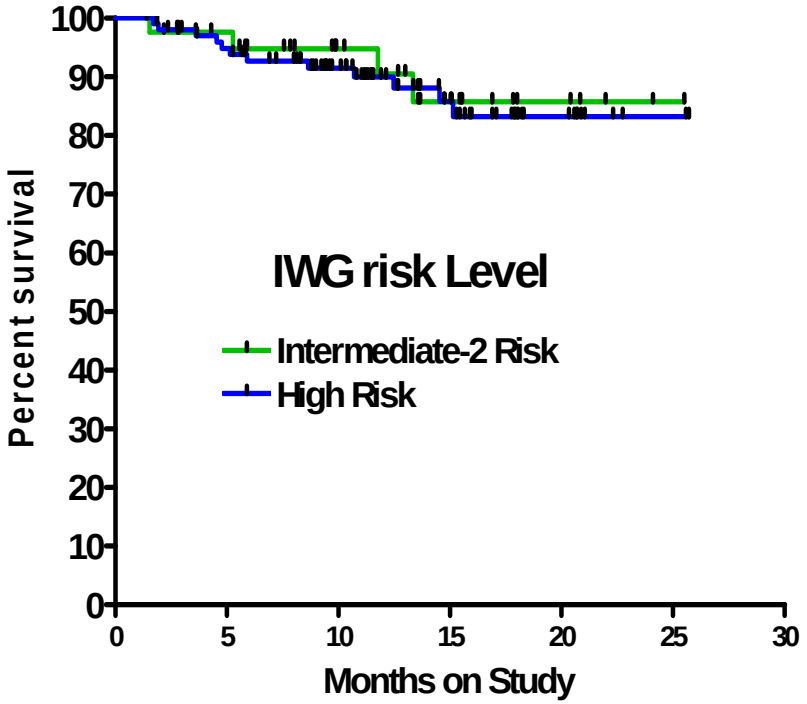
Barosi et al, Blood, 2007; 110:4030-4036
Guglielmelli et al, Blood, 2009; 114:1477-1483

Overall Survival (N=153)

Survival - Deaths on study or within 30 days of drug discontinuation



Survival - Deaths on study or post-study follow-up



Published median survival of 48 months (intermediate risk level-2) and 27 months (high risk level), IWG, Cervantes et al, Blood 2009.

INCB 18424-251: SUMMARY

- Well tolerated
  - 15 mg BID with dose optimization improves hematologic safety while maintaining efficacy compared to the MTD of 25 mg BID
- Durable benefits
  - Reduction in spleen size demonstrated by palpation length (median decrease ~50%) and MRI (median decrease ~35%)
  - Durable reduction in symptomatic burden with >50% median reduction in total symptom score
  - Symptomatic improvement associated with reduction in inflammatory cytokines
- Comparisons to historical controls suggests:
  - Decreased rate of leukemic transformation
  - Improved survival
- Randomized controlled phase III studies are in progress
  - For further information and patient referral contact:

    http://www.comfortstudy.com