

INCB18424, an Oral, Selective JAK2 Inhibitor, Shows Significant Clinical Activity in a Phase I/II Study in Patients With Primary Myelofibrosis (PMF) and Post Polycythemia Vera/Essential Thrombocythemia Myelofibrosis (Post-PV/ET MF)

Srdan Verstovsek, MD, PhD¹; Hagop Kantarjian, MD¹;
Animesh Pardhanani, MD, PhD²; Deborah Thomas, MD¹;
Jorge Cortes, MD¹; Ruben Mesa, MD²; John Redman, MD³;
Carl-Michael Staschen, MD, PhD³; Jordan Fridman, PhD³;
Kris Vaddi, PhD³; and Ayalew Tefferi, MD²

¹ Leukemia Department, M.D. Anderson Cancer Center, Houston, Texas

² Mayo Clinic, Rochester, Minnesota

³ Incyte Corporation, Wilmington, Delaware

Disclosures

- Srdan Verstovsek, Hagop Kantarjian, Animesh Pardanani, and Ayalew Tefferi are participants of the scientific advisory board for Incyte's Jak2 inhibitor program
- John Redman, Carl-Michael Staschen, Jordan Fridman and Kris Vaddi are employees of Incyte Corporation

Preclinical Summary (abstract #3538)

- Potent and selective ATP competitive JAK inhibitor

INCB18424	JAK1	JAK2	JAK3	Tyk2
IC ₅₀ (nM)	2.7	4.5	322	19

- 100-fold selectivity against a broad panel of kinases
- Excellent preclinical pharmacokinetic properties
- High oral availability
- Efficacious and well-tolerated in a JAK2^{V617F}-driven animal model
- Preclinical toxicology:
 - Findings restricted to myelosuppression and reduced lymphoid organ cellularity at high doses
 - No hERG liability (IC₅₀ >100 μM)

Phase I/II Study Design and Aims

- **Design:** 3+3 dose escalation and expansion of the MTD cohort
- **Eligibility:** Advanced PMF or post-PV/ET MF patients with platelets $>100 \times 10^9/L$ and ANC $>1 \times 10^9/L$
- **Primary objectives:** safety and determination of MTD
- **Secondary objectives:** PK, PD, safety of extended dosing, and preliminary efficacy
- **Administration:** oral, twice daily, continuously
- **Current status:** 32 pts accrued from June–November 2007
 - Dose escalation completed (11 pts; MTD established)
 - Phase II expansion cohort fully enrolled (21 pts)

Dose Escalation Patient Characteristics

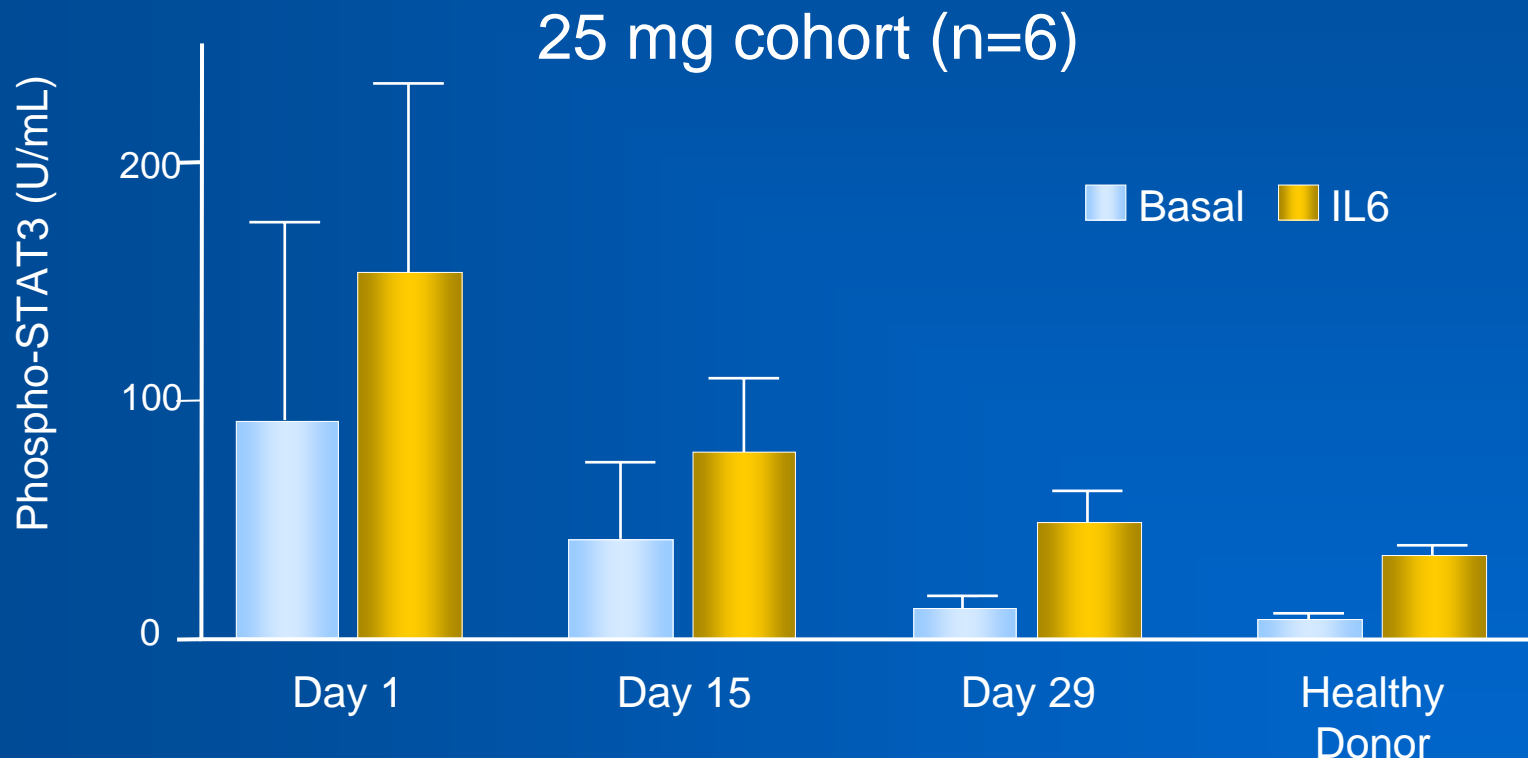
	25 mg BID	50 mg BID
Number of patients	6	5
Mean age (years)	63	64
Gender (Male:Female)	4:2	3:2
MPD Diagnosis	4 Post-PV, 2 Post-ET	2 Post-PV, 3 PMF
JAK2 status	5 V617F, 1 Wild Type	3 V617F, 1 Mpl ^{W515K} , 1 Wild Type
Splenomegaly (mean cm below costal margin)	21	13
Transfusion dependent	3	3
Leukocytosis	2	2
Thrombocytosis	2	1

Clinical Pharmacokinetics

- Half-life consistent with once or twice daily dosing
- Linear pharmacokinetics over the dose range studied
- No accumulation upon repeated dosing
- Clearance is predominantly via hepatic metabolism
- INCB18424 is a substrate for CYP3A4
- No evidence of induction or inhibition of CYP enzymes
 - Probability of drug interactions is low

Clinical Pharmacodynamics

pSTAT3: A downstream marker for JAK2 activation



INCB18424 normalizes pSTAT3 levels within 1 month

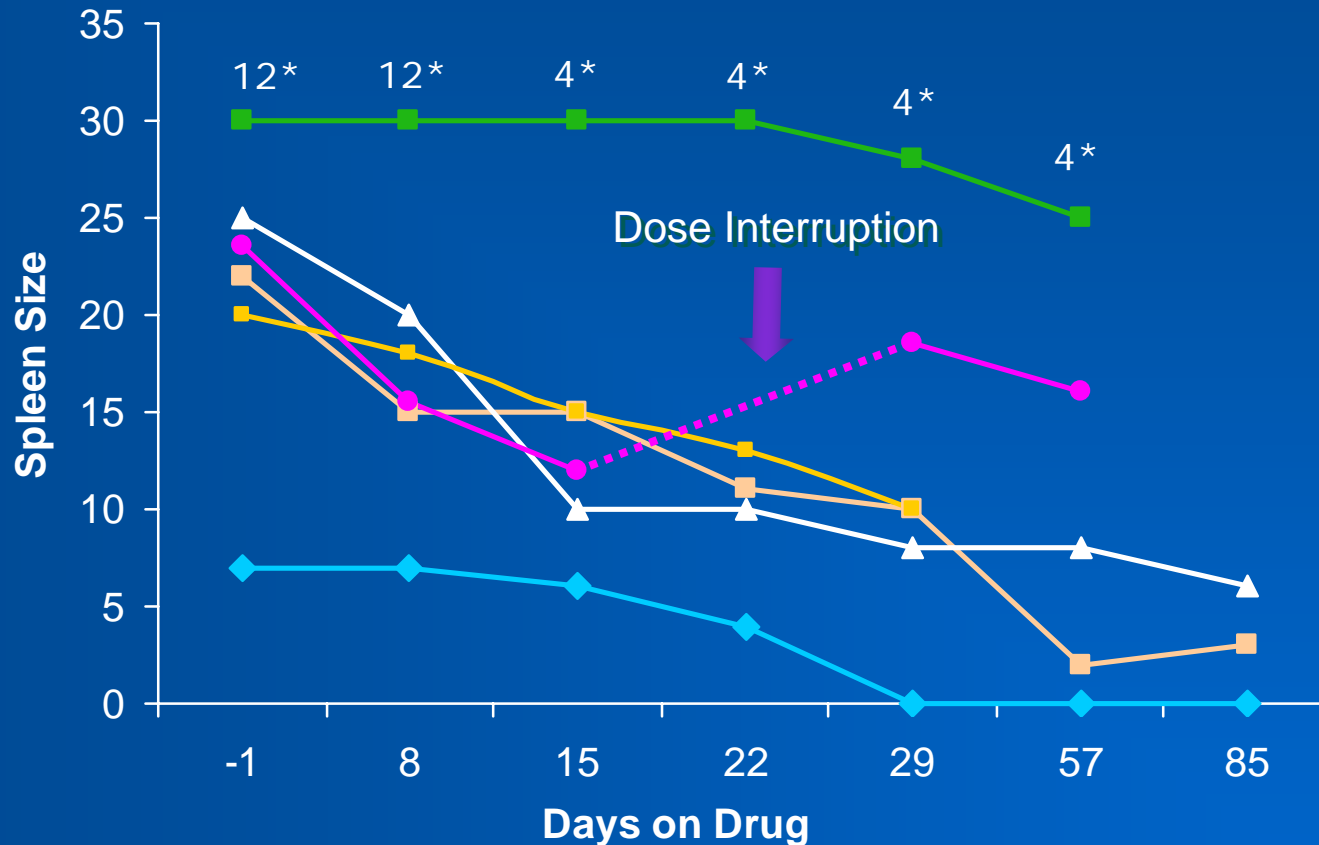
Dose Escalation Patients: Safety

- **25 mg BID: 6 patients**
 - Duration of treatment: 2–6 months
 - Grade 3 thrombocytopenia in one patient
- **50 mg BID: 5 patients**
 - Duration of treatment: 2–4 months
 - 2 patients developed grade 4 thrombocytopenia at day 14 (dose limiting toxicity)
- **Overall Safety**
 - No other toxicity
 - No patients have been discontinued from the study

Dose Escalation Patients: Efficacy

- All patients have experienced a marked and rapid reduction in splenomegaly (regardless of the mutation status)
- IWG-MRT Consensus Criteria for clinical improvement, based on durable reduction in spleen size, achieved in all 6 patients dosed for minimum of 3 months
- Quality of life improved in all patients
- Leukocytosis normalized in 2 of 4 patients; Thrombocytosis normalized in 2 of 3 patients
- Transfusion independence, now lasting for 3 months, achieved in one patient treated for 6 months

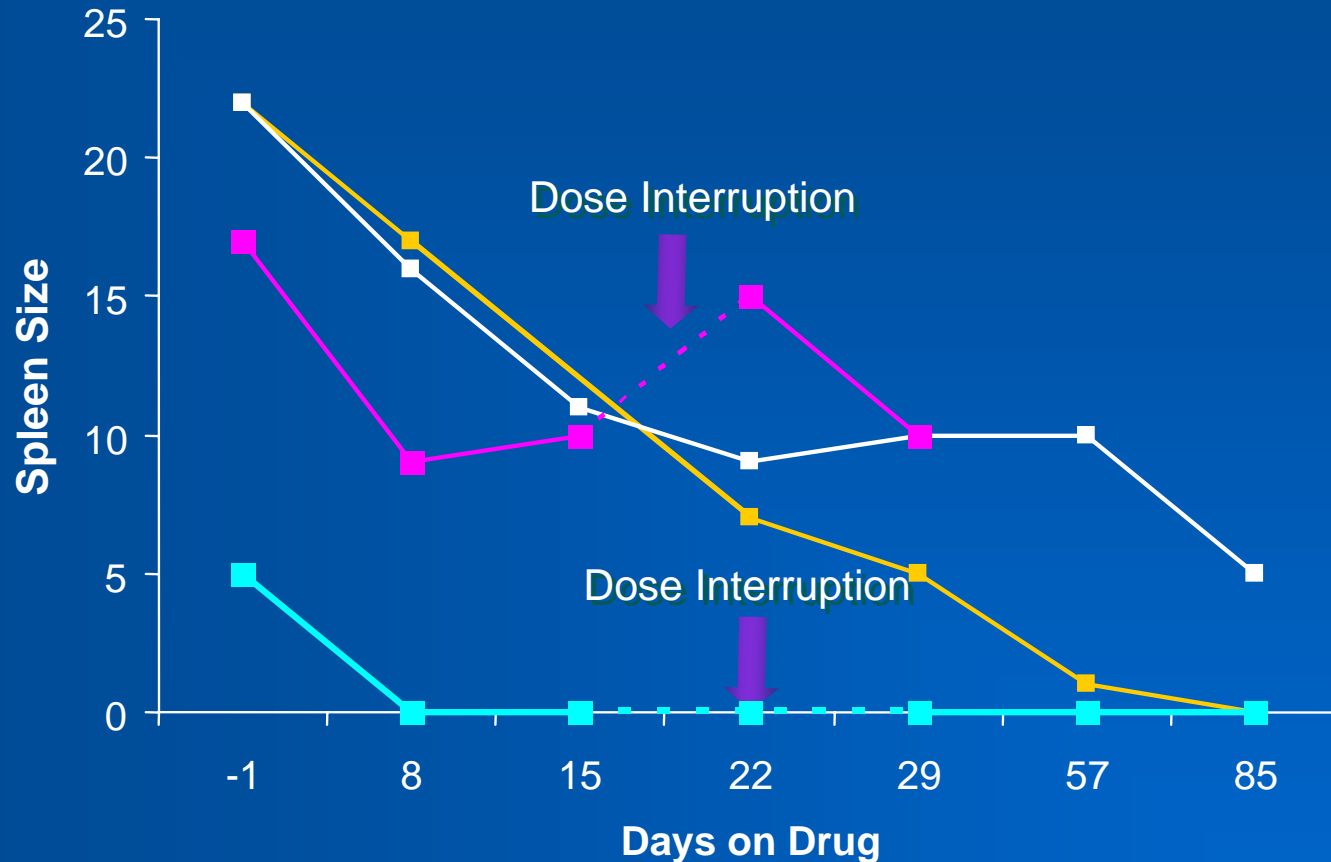
Effect of INCB18424 on Splenomegaly (25 mg BID)



- In patients that received 25 mg BID of INCB18424 without interruption, mean reduction in spleen size was 46%, 58% and 83% at 1, 2 and 3 months, respectively

* Spleen extended initially into the pelvis (approx. measure) and to the right from umbilicus (cm indicated)

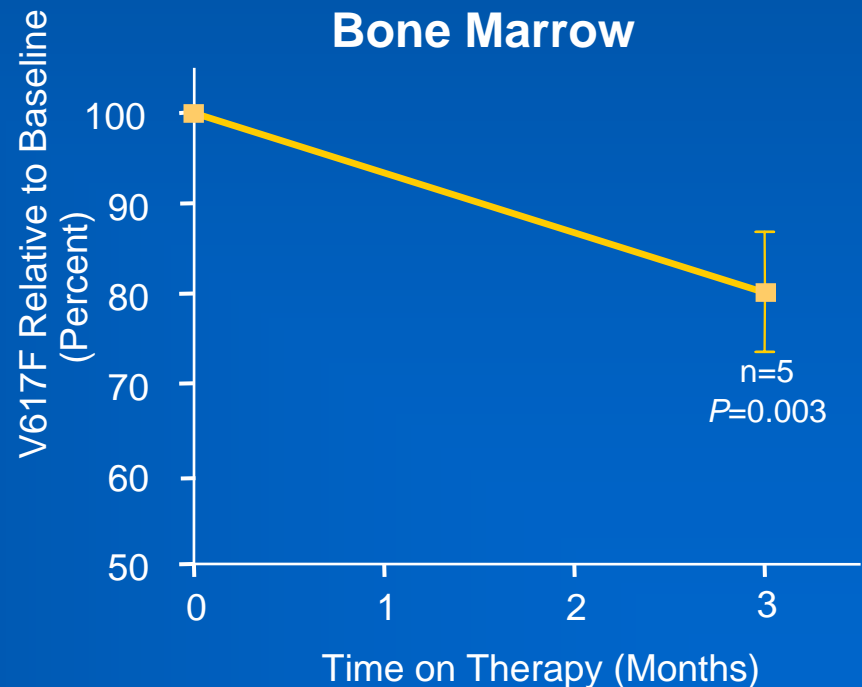
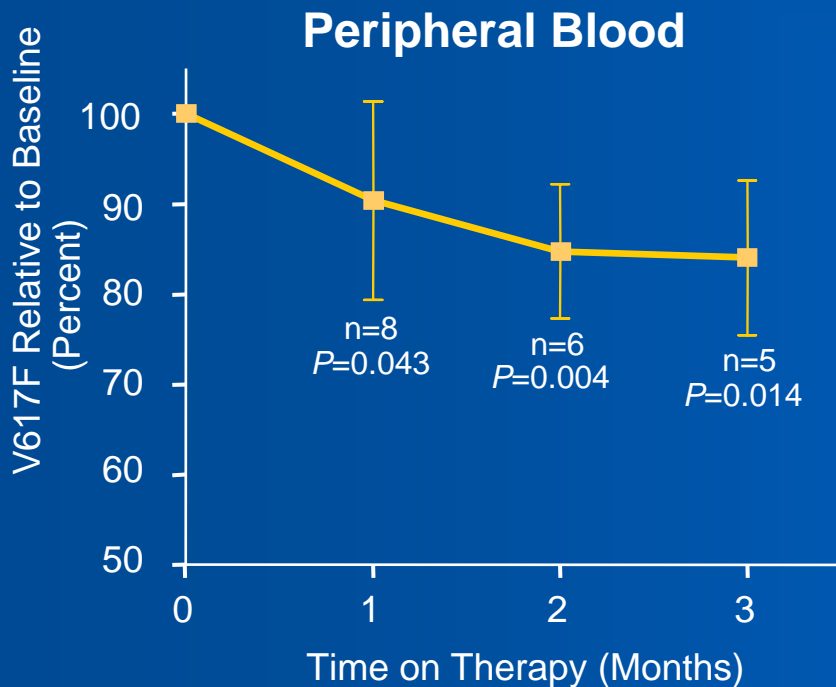
Effect of INCB18424 on Splenomegaly (50 mg BID)



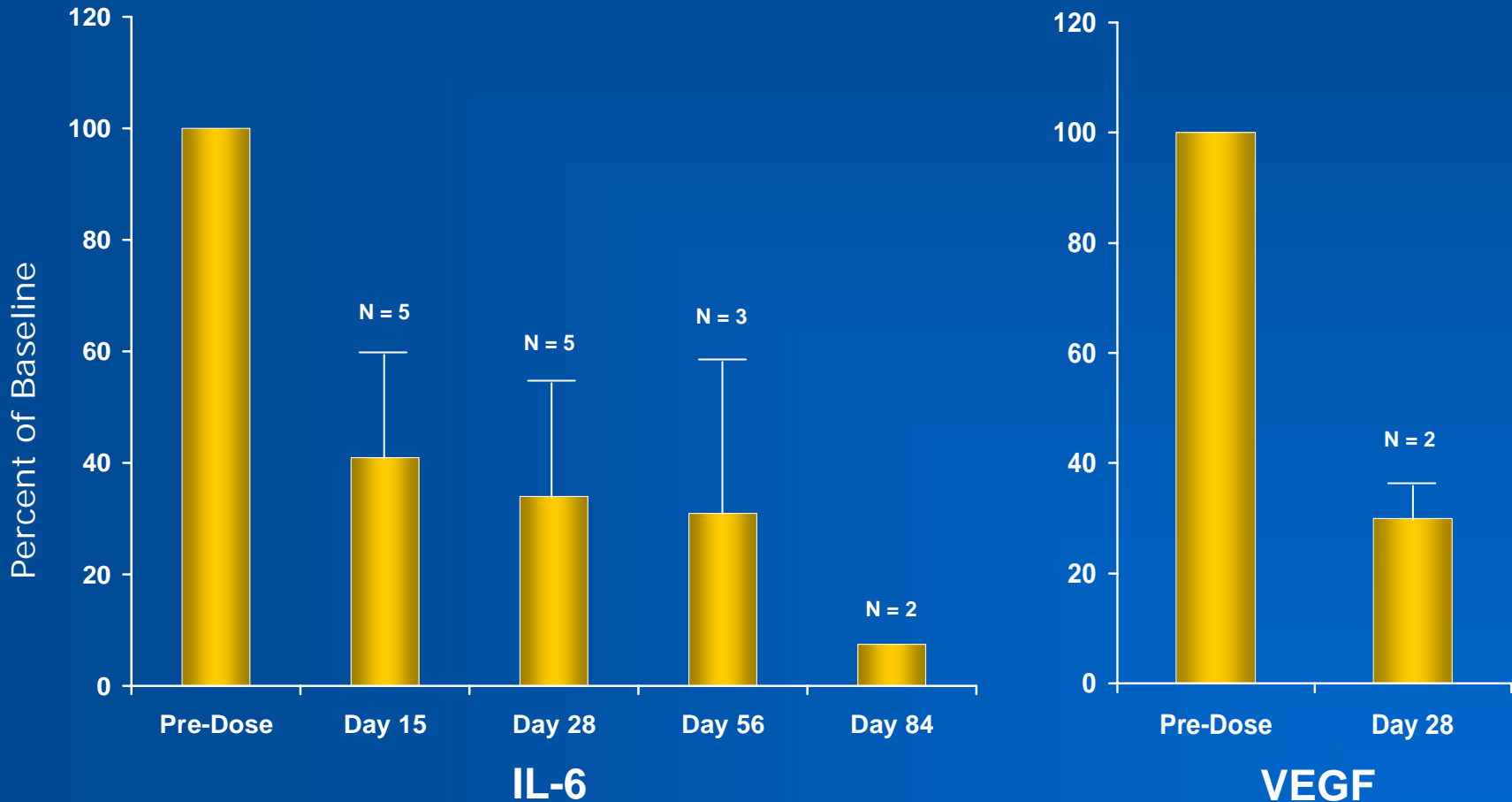
- In patients that received 50 mg BID of INCB18424 without interruption, mean reduction in spleen size was 66%, 75% and 89% at 1, 2 and 3 months respectively.

Effect of INCB18424 on Mutated JAK2 Allele Burden

- Ratio of V617F to WT JAK2 assessed by quantitative genotypic analysis

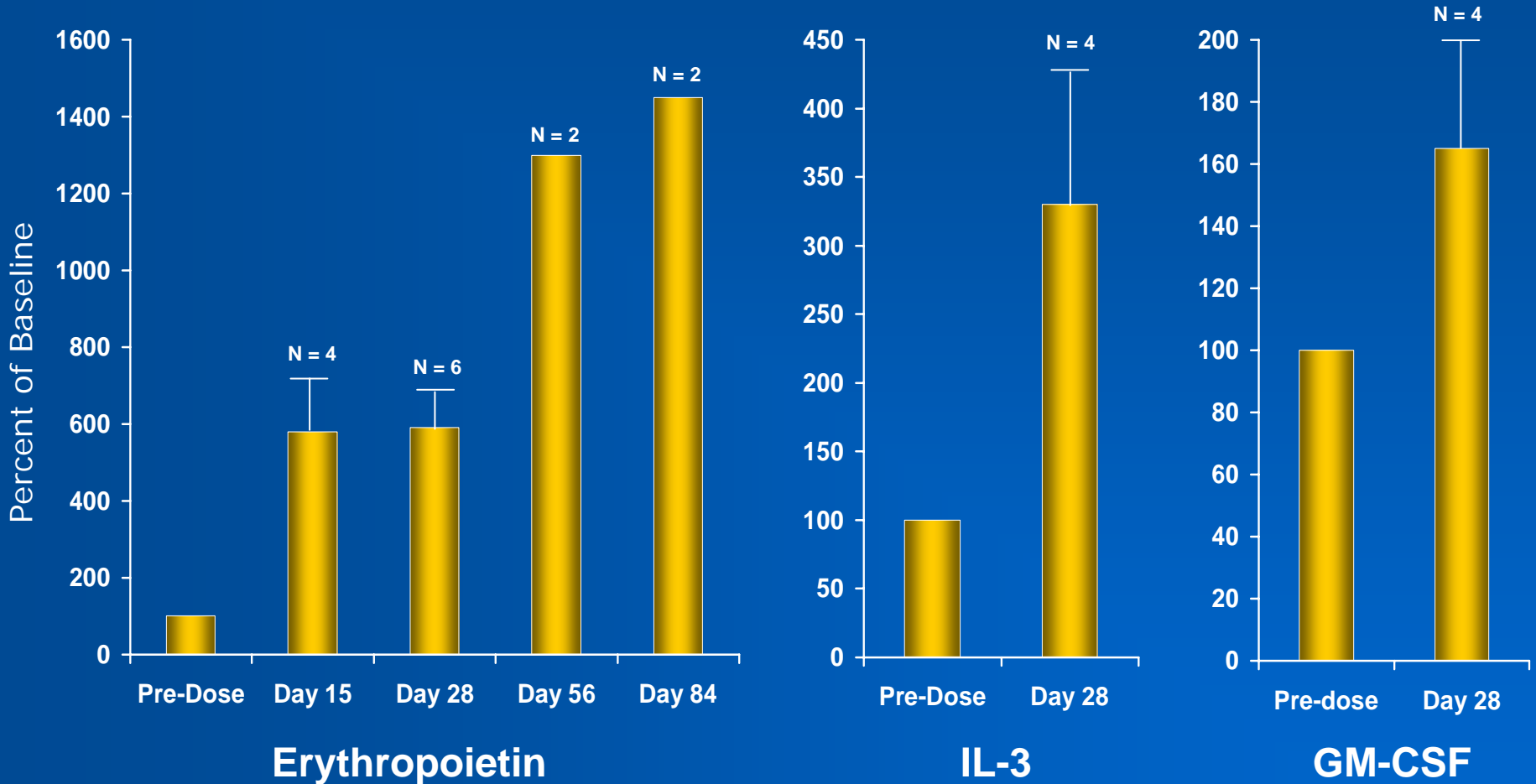


Effect of INCB18424 on Angiogenic Factors & Pro-inflammatory Cytokines



Reduced inflammatory and angiogenic cytokines may improve QOL, delay disease progression, and improve hematopoiesis

Effect of INCB18424 on Hematopoietic Growth Factors



Increased levels of hematopoietic cytokines suggest the potential for restoration of normal hematopoiesis

Phase II: Expanded MTD Cohort

- Twenty one patients dosed at 25 mg BID with up to 4 weeks of follow up (all accrued in November 2007)
- Rapid clinical responses seen, in reduced spleen size and improved constitutional symptoms
- First patient treated for 4 weeks:
 - spleen 20 cm bcm and liver 9 cm bcm at baseline, reduced to 8 and 6 cm, respectively
 - patient gained 8 lbs
- No toxicity so far

Summary

INCB18424 has significant efficacy as a therapy for patients with PMF or post-PV/ET MF

- Marked reduction in spleen size and improvement in quality of life in all patients
- Durable transfusion independence achieved in the first patient entered on the study
- Very well tolerated
- Thrombocytopenia the only toxicity
- Reductions in the mutant JAK2 allele burden recorded
- Reductions in the levels of inflammatory cytokines and elevations in hematopoietic growth factors noted