



14TH CONGRESS
JUNE 4 - 7, 2009
BERLIN

Disclosure

Speaker: Ayalew Tefferi

Company	Affiliation:
TargeGen	Chair of ongoing clinical trial
Celgene	Chair of ongoing clinical trial
Cytosia	Chair of clinical trial in development
Incyte	Institutional PI of ongoing clinical trial
Novartis	Institutional PI of clinical trial in development
BMS	PI of laboratory research
Merck	PI of laboratory research
Bioreference	Scientific advisory board member
	No stocks, investments, capital, speakers bureau

TG101348, a JAK2-Selective Inhibitor, is Well Tolerated in Patients With Myelofibrosis and Shows Substantial Therapeutic Activity Accompanied by a Reduction in JAK2^{V617F} Allele Burden



Pardanani A



Gotlib J



Jamieson C



Stone R



Cortes J



Talpaz M



Shorr J
Silverman M



Gilliland DG

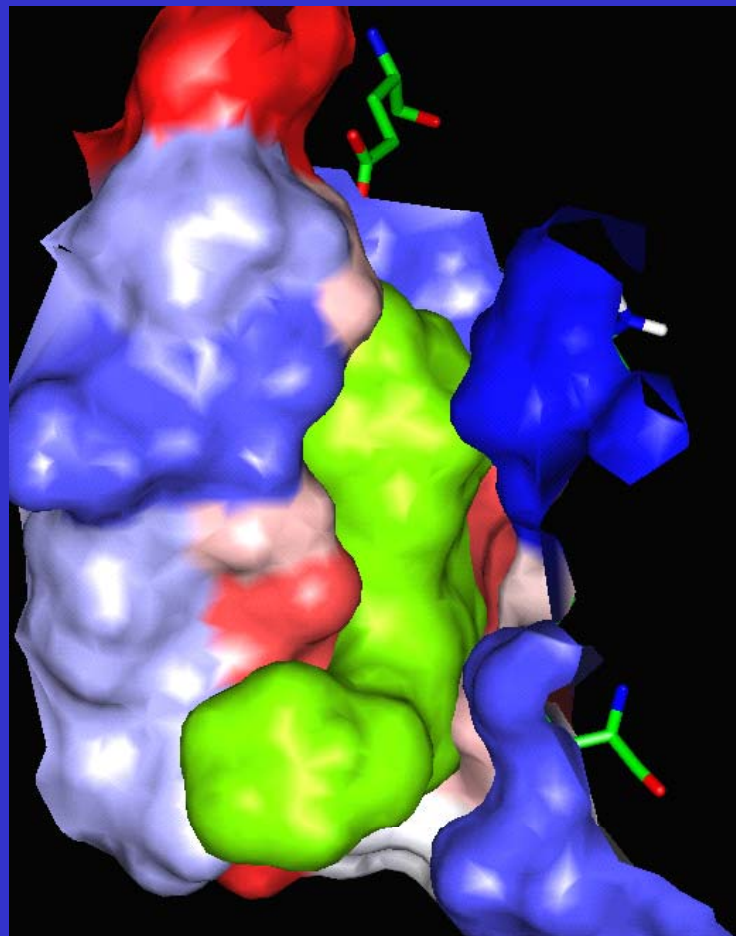
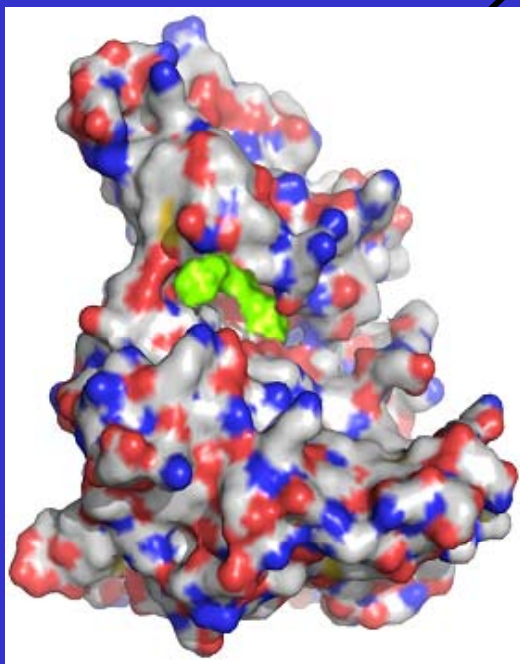


Tefferi A

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Stanford University, Stanford, CA, USA
UCSD, La Jolla, CA, USA
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MDACC, Houston TX, USA
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TargeGen Inc., San Diego, CA, USA

JAK2 Crystal Structure w/TG101348

- TG101348 co-crystallized with JAK2 JH1 domain produced in SF9 insect cells
- Bound in ATP pocket
- Key interactions confirmed



TG101348 is Potent & Selective

Compound	Primary Target	JAK Family Selectivity Profile (X-fold selectivity)		
		JAK2 vs. JAK3	JAK2 vs. JAK1	JAK2 vs. TYK2
TG101348	JAK2 IC ₅₀ (nM) 3nM	332x	35x	135x

INCB18424	4.5nM	72x	0.6x	4x
XL019	2nM	125x	65x	170x
CEP-701	1nM	3x	?	?

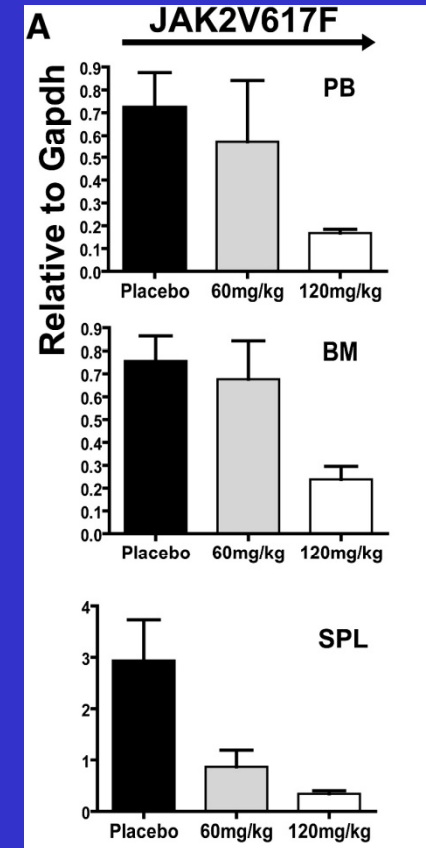
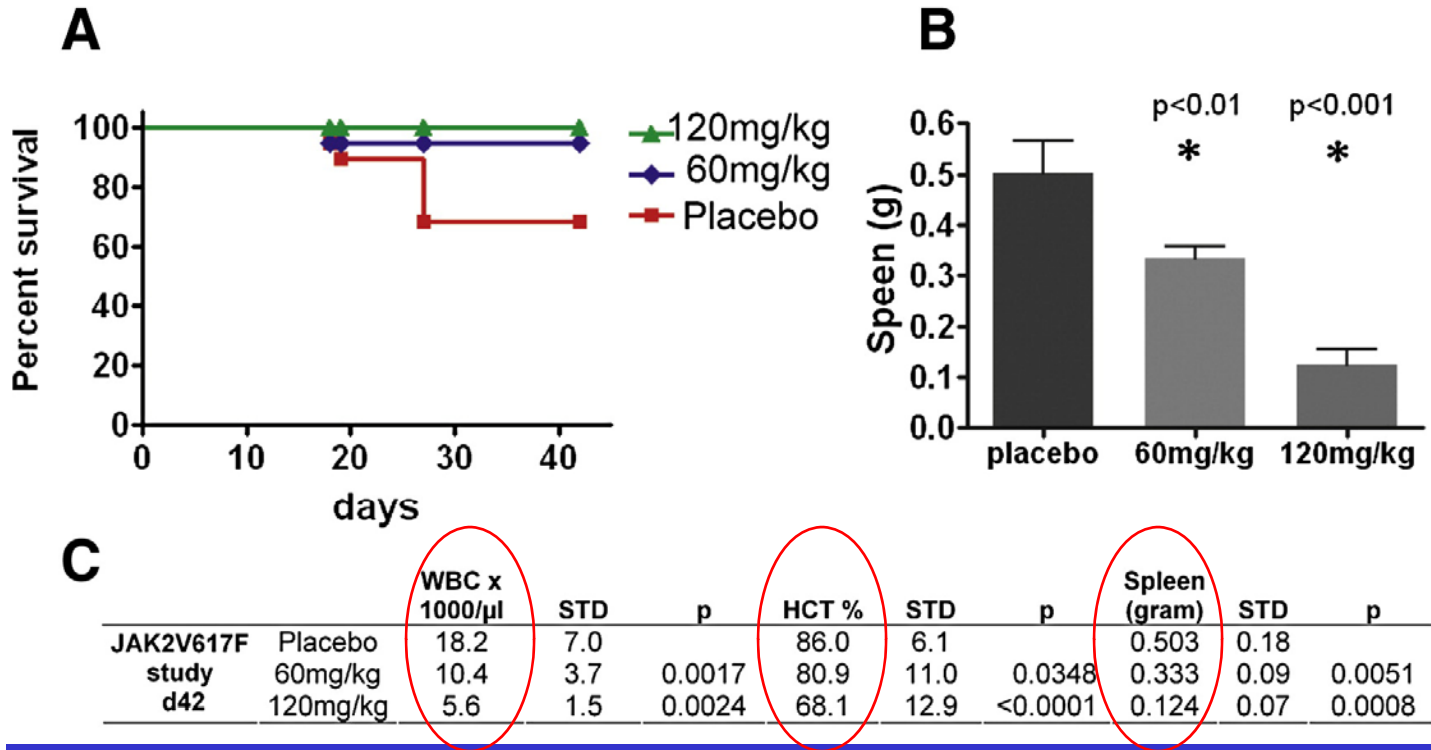
TG101348 profiled in 223 kinases: IC₅₀ < 50nM for 3 kinases: JAK2, Flt3, Ret

TG101348 inhibits erythroid colony growth in presence of JAK2V617F, MPLW515K or JAK2 exon 12 mutations

Lasho et al, *Leukemia* (2008) **22**, 1790–1792

- IC₅₀ nanomolar range
- Therapeutic window (normal progenitors)
- Inhibition of EEC (Epo-) >> BFU-e (Epo+)
- Selective suppression of mutated colonies (single colony genotyping)

Efficacy of TG101348, a selective JAK2 inhibitor, in treatment of a murine model of JAK2V617F-induced polycythemia vera



UCSD: C Jamieson
Cancer Cell. 2008;13:321-330



DG Gilliland, DFCI
Cancer Cell. 2008;13:311-320

Study Objectives and Design

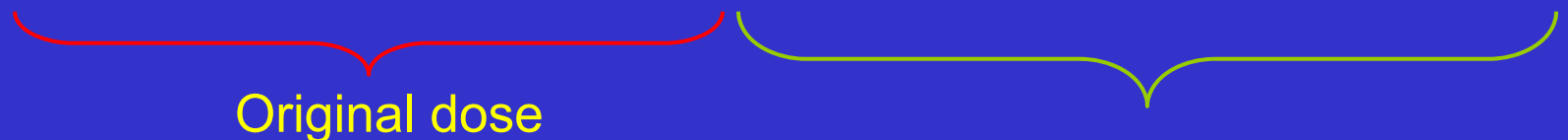
- Objectives
 - Primary - To determine safety/tolerability, DLT, MTD, and pharmacokinetics of TG101348 in patients with MF
 - Secondary - To evaluate preliminary clinical and pharmacodynamic activity
- Study design
 - Phase 1, open-label, multicenter, dose-escalation study
 - Expanded cohort dose confirmation at MTD

Key Eligibility Criteria

- Myelofibrosis (PMF or post-PV/ET MF)
 - High-risk or intermediate-risk with symptomatic splenomegaly/unresponsive to available therapy
 - ECOG performance status ≤ 2
 - ANC $\geq 1 \times 10^9/L$
 - Platelet count $\geq 50 \times 10^9/L$
 - Serum creatinine ≤ 2 mg/dL
 - Total bilirubin ≤ 2 mg/dL
 - AST/ALT $\leq 3X$ upper limit of normal

Dosing and Schedule

TG101348 taken orally, once a day, in consecutive 28-day cycles (30, 60, 120, 240, 360, 520, 680, and 800 mg)



Intra-subject dose escalation up to highest tolerated dose permitted after completion of 3 cycles of therapy at starting dose

Status and Treatment Duration

- Dose limiting toxicity identified at 800 mg/day
 - Asymptomatic grade 3 or 4 amylasemia, with grade 4 lipasemia in 1 subject, reversible upon holding drug
- MTD declared at 680 mg/day
- Dose-confirmation phase completed enrollment May 2009
- Total of 59 patients enrolled in study
 - 28 in dose-escalation phase – median treatment duration 29 weeks (range 0.3-64 weeks)
 - 31 in dose-confirmation phase – median treatment duration 5 weeks (range 0.2-7 weeks)
- Presentation to focus on preliminary data from 28 patients enrolled in dose-escalation phase

Demographics & Baseline Characteristics

	30-120 mg/day (n = 10)	240-360 mg/day (n = 6)	520-800 mg/day (n = 12)	Overall (N = 28)
Age (median; years)	64 (54-77)	68 (51-79)	67 (50-86)	67 (50-86)
Male	6 (60%)	4 (67%)	7 (58%)	17 (61%)
JAK-2 ^{V617F} Positive	9 (90%)	5 (83%)	11 (92%)	25 (89%)
PMF	6 (60%)	5 (83%)	8 (67%)	19 (68%)
Post-PV MF	4 (40%)	1 (17%)	2 (17%)	7 (25%)
Post-ET MF	0	0	2 (17%)	2 (7%)
High risk	1 (10%)	2 (33%)	10 (83%)	13 (46%)
Palpable splenomegaly	10 (100%)	6 (100%)	12 (100%)	28 (100%)
Transfusion dependent	2 (20%)	2 (33%)	5 (42%)	9 (32%)

Treatment-Emergent Non-Hematologic Adverse Events* (N = 28)

Event	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	19 (68%)	18 (64%)	1 (4%)	0	0
Vomiting	16 (57%)	13 (46%)	1 (4%)	2 (7%)	0
Diarrhoea	15 (54%)	10 (36%)	3 (11%)	2 (7%)	0
Abdominal pain	7 (25%)	5 (18%)	1 (4%)	1 (4%)	0
Cough	6 (21%)	6 (21%)	0	0	0
Oedema peripheral	6 (21%)	2 (7%)	2 (7%)	2 (7%)	0
Pruritus	6 (21%)	4 (14%)	2 (7%)	0	0
Anorexia	4 (14%)	2 (7%)	2 (7%)	0	0
Constipation	4 (14%)	3 (11%)	1 (4%)	0	0
Fatigue	4 (14%)	2 (7%)	2 (7%)	0	0
Flatulence	4 (14%)	4 (14%)	0	0	0
Muscle spasm	4 (14%)	3 (11%)	1 (4%)	0	0
Rash	4 (14%)	4 (14%)	0	0	0
Dyspnoea exertional	3 (11%)	2 (7%)	0	1 (4%)	0
Epistaxis	3 (11%)	2 (7%)	1 (4%)	0	0
Headache	3 (11%)	3 (11%)	0	0	0
ECG – QT prolonged	3 (11%)	2 (7%)	1 (4%)	0	0
Paresthesia	3 (11%)	3 (11%)	0	0	0

*Events reported for ≥ 3 patients; preferred terms for which event was considered at least possibly related for ≥ 1 patient.

Treatment-Emergent Non-Hematologic Laboratory Findings (N = 28)

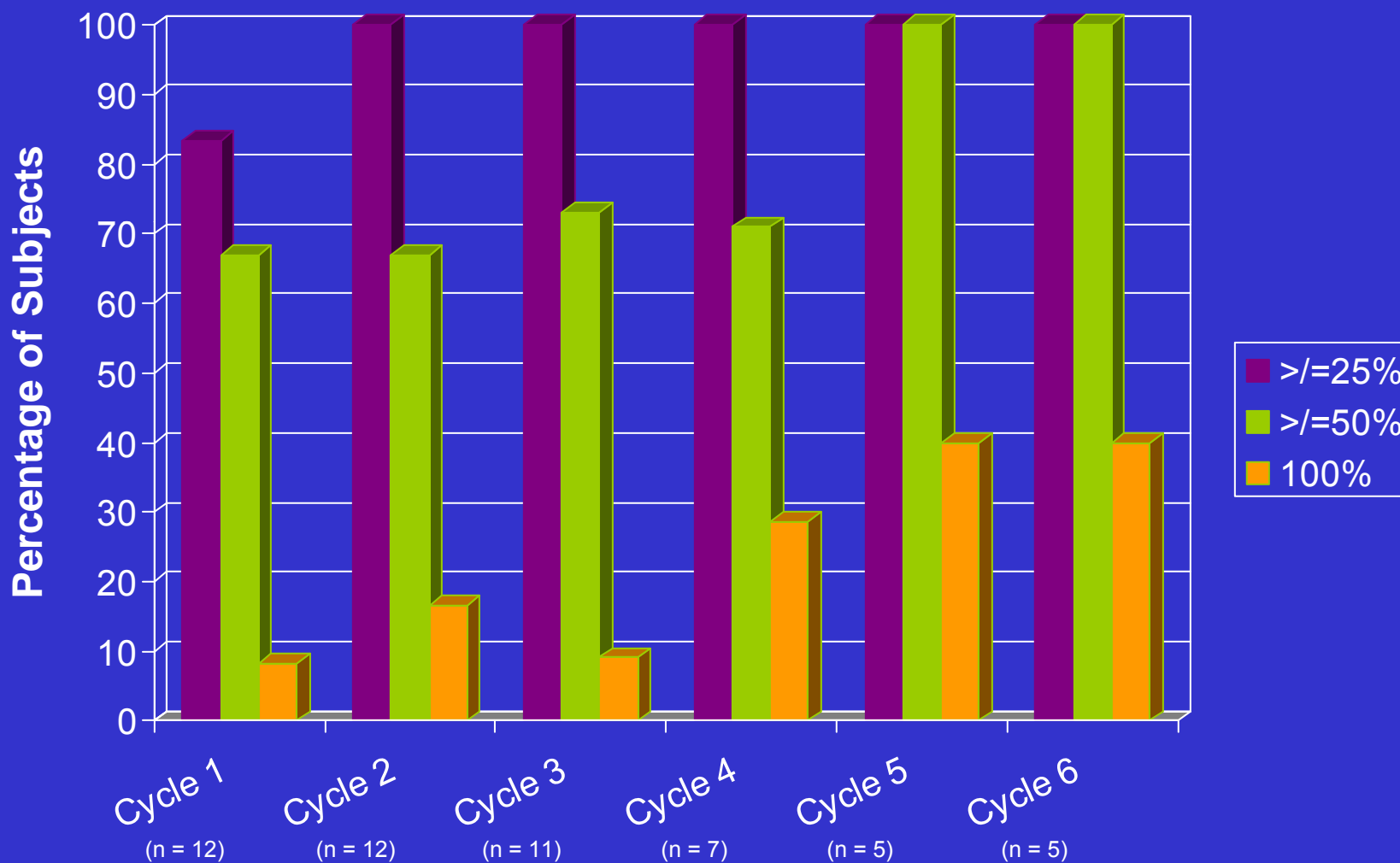
Finding	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine increased	15 (54%)	10 (36%)	5 (18%)	0	0
AST increased	14 (50%)	11 (39%)	0	3 (11%)	0
ALT increased	10 (36%)	3 (11%)	5 (18%)	2 (7%)	0
Lipase increased	7 (25%)	5 (18%)	1 (4%)	0	1 (4%)
Amylase increased	5 (18%)	2 (7%)	1 (4%)	1 (4%)	1 (4%)

Grade 3 & 4 Hematologic Toxicities

	Neutropenia (N = 28)		Thrombocytopenia (N = 28)		Anemia (N = 19)*
	Grade 3	Grade 4	Grade 3	Grade 4	≥ 2 g/dL Decrease in Hemoglobin
Overall	3 (11%)	1 (4%)	2 (7%)	5 (18%)	9 (47%)
Dose at Time of Observation					
30-120 mg/day	0	0	0	0	1
240-360 mg/day	1	0	1	2	4
520-800 mg/day	2	1	1	3	4

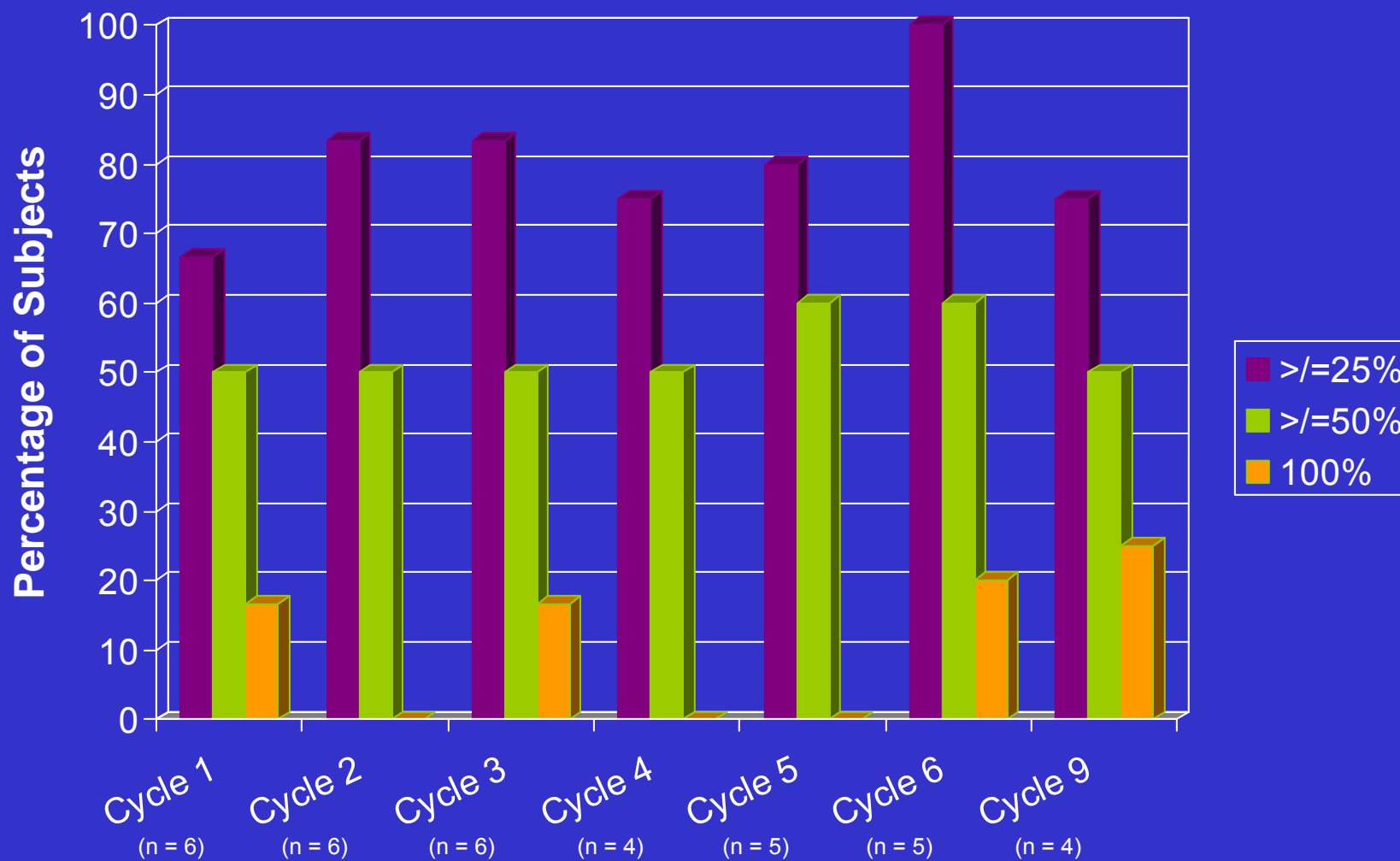
*Patients who were not transfusion dependent at baseline.

Decrease in Palpable Spleen Size by Cycle 520-800 mg/day* TG101348 (N = 12)



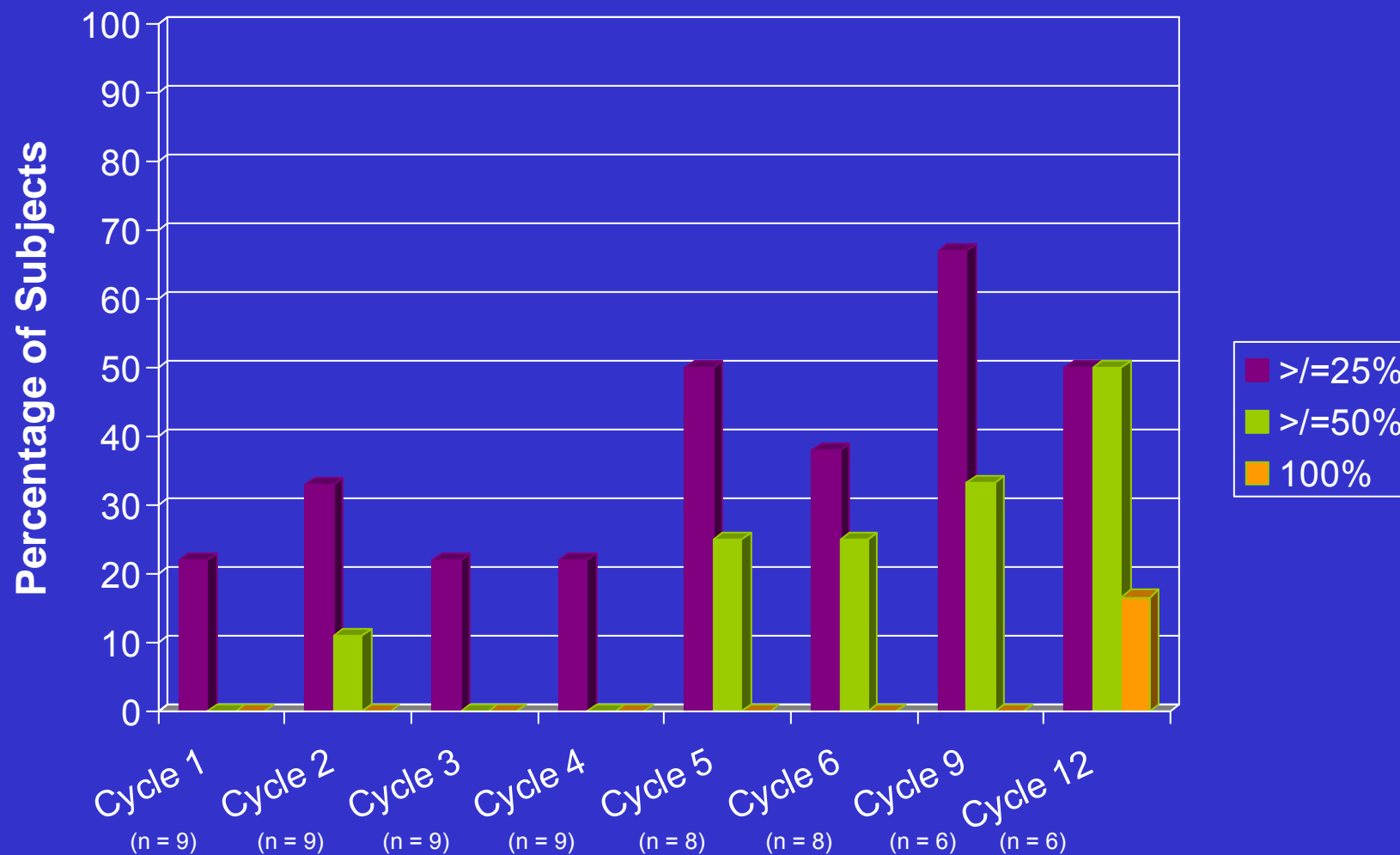
*Starting dose. Doses (mg/day) Cycle 1, 680-800; Cycles 2-5, 520-680; Cycle 6, 680.

Decrease in Palpable Spleen Size by Cycle 240-360 mg/day* TG101348 (N = 6)



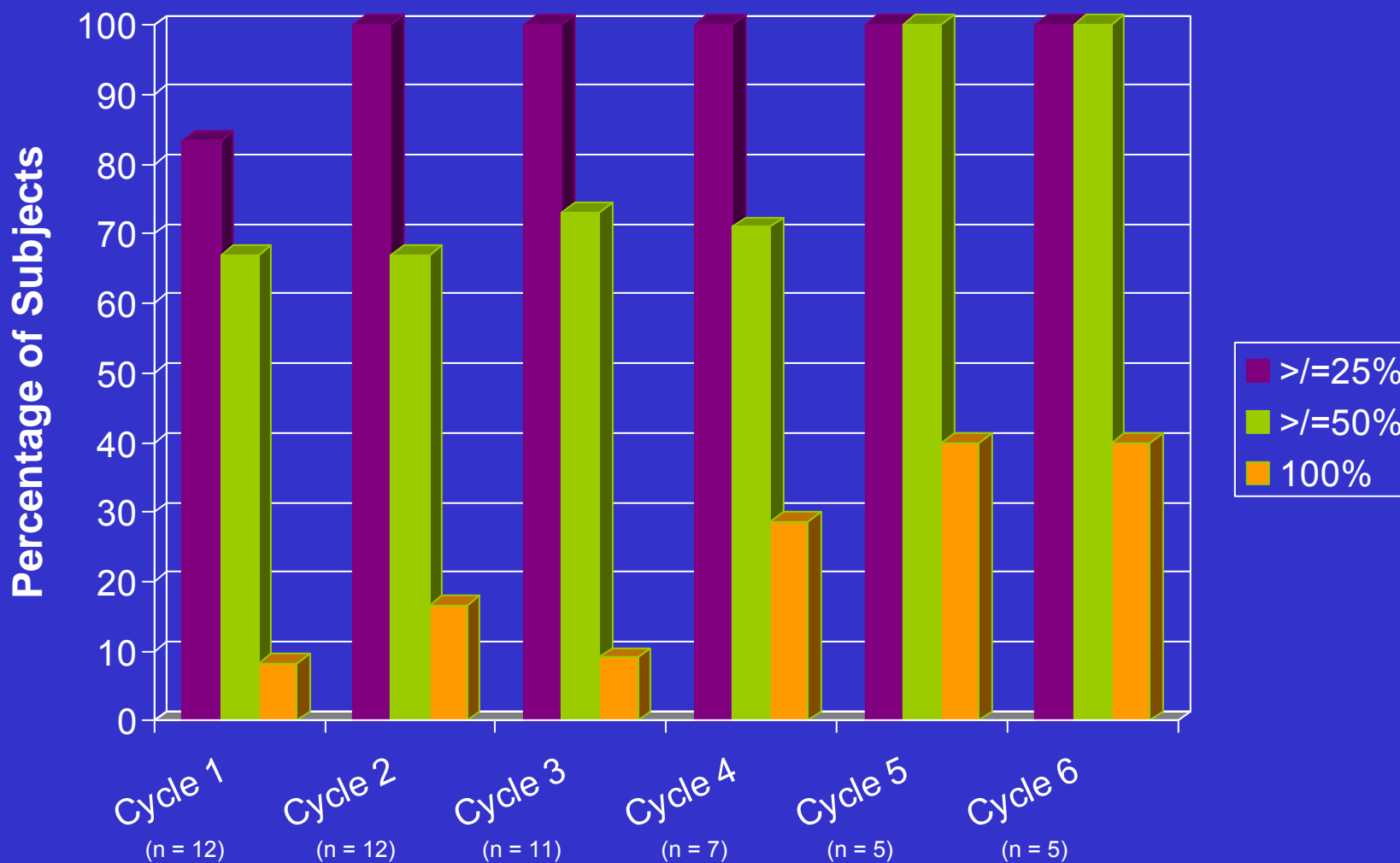
*Starting dose (Cycles 1-3). Doses (mg/day) Cycles 4 & 5, 240-520; Cycles 5, 6 & 9, 240-680.

Decrease in Palpable Spleen Size by Cycle 30-120 mg/day* TG101348 (N = 9)



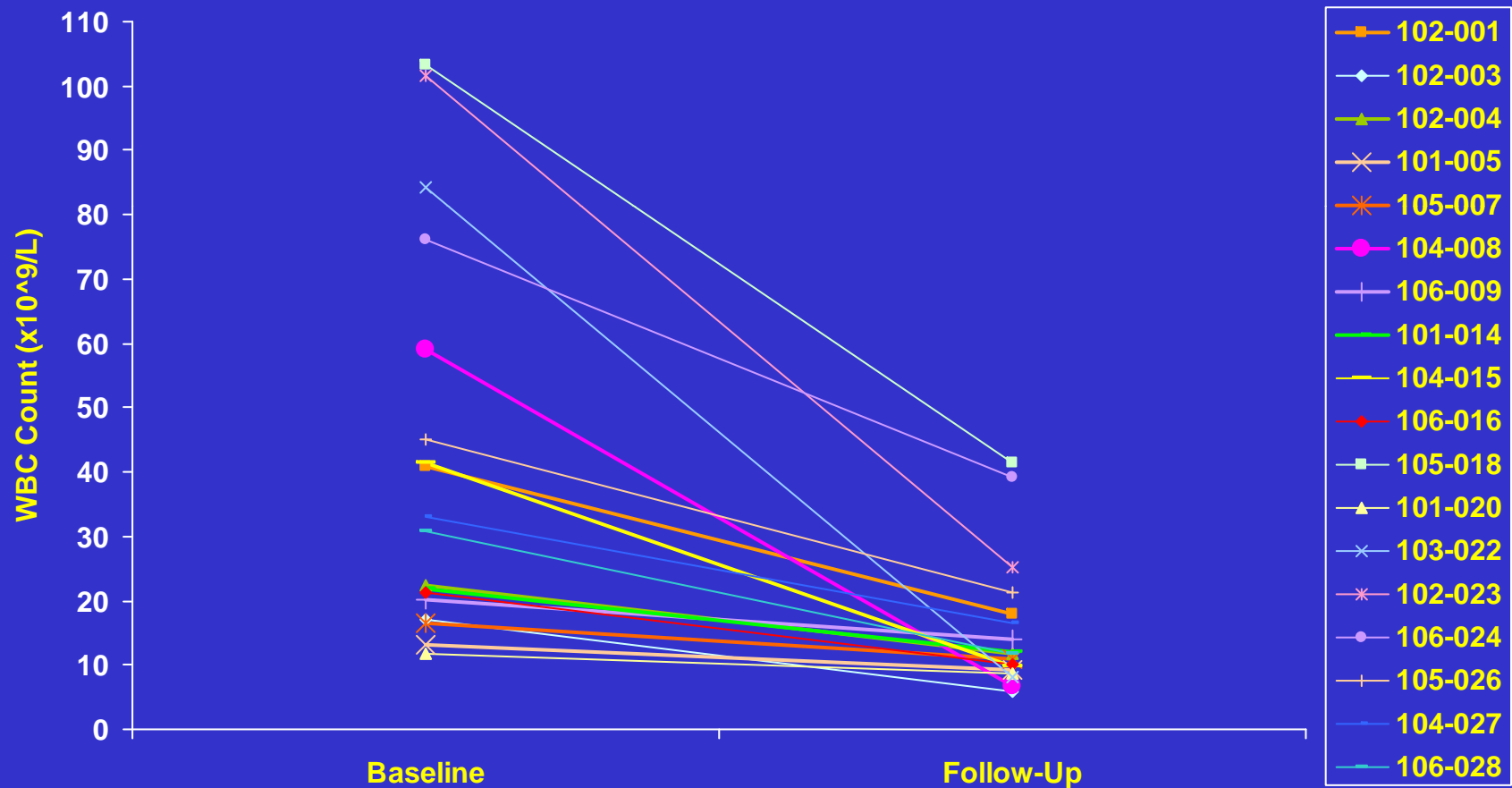
*Starting dose (Cycles 1-3). Doses (mg/day) Cycle 4, 30-240; Cycle 5, 60-240; Cycle 6, 120-360; Cycles 9 & 12, 360-680.

Decrease in Palpable Spleen Size by Cycle 520-800 mg/day* TG101348 (N = 12)



*Starting dose. Doses (mg/day) Cycle 1, 680-800; Cycles 2-5, 520-680; Cycle 6, 680.

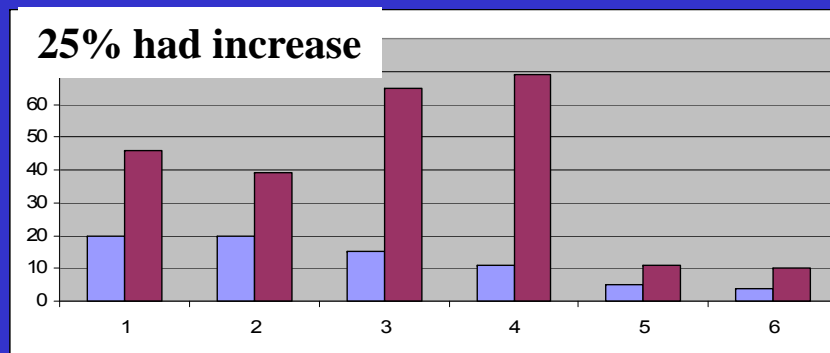
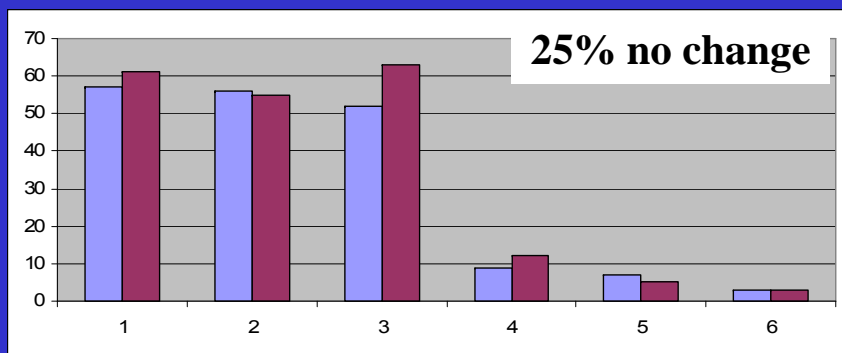
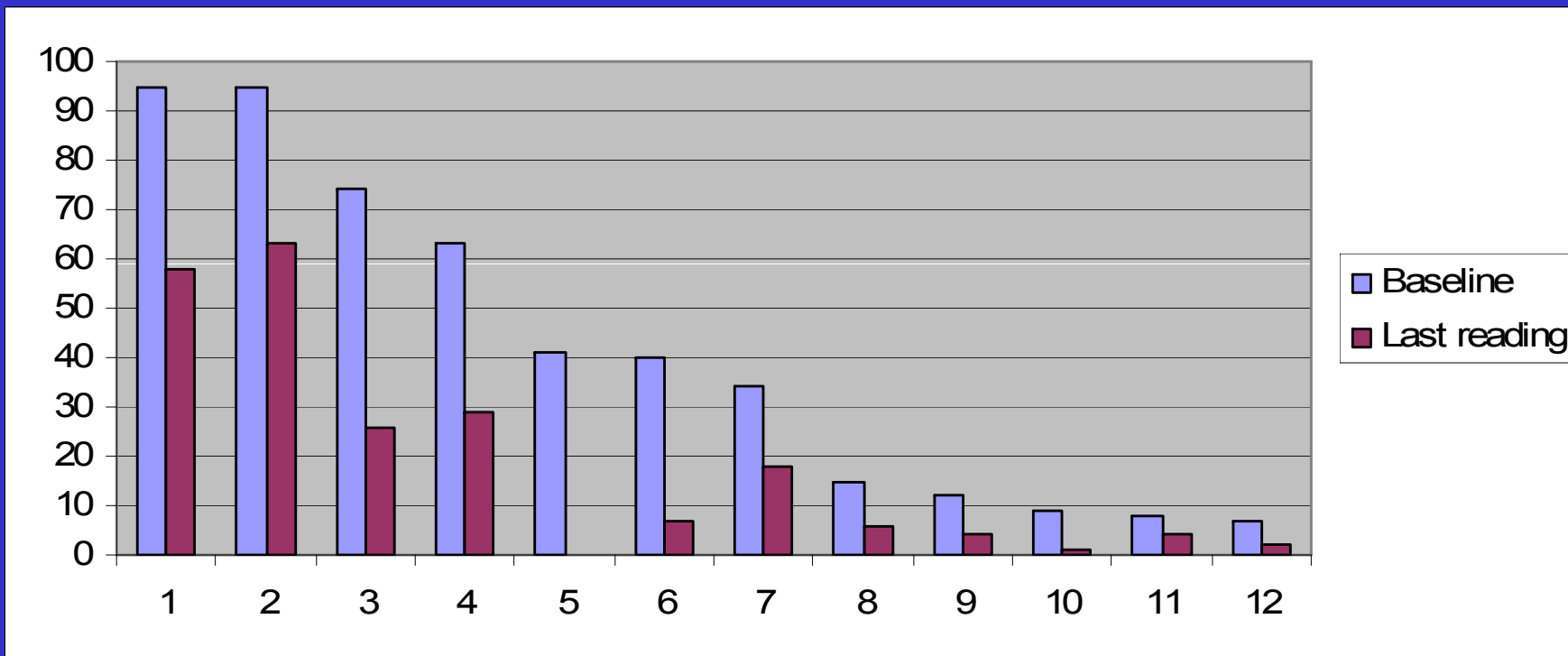
Effect of TG101348 in Patients With Leukocytosis (WBC >11 x10⁹/L)



N = 18. Median treatment duration 30 weeks (range 10-64 weeks). Doses at follow-up 240-680 mg/day.

JAK2V617F allele burden (N=24)

Intent to treat population that are mutation-positive
50% of treated patients achieved more than 30% reduction in allele burden



Another patient of mine with JAK2V617F-positive PMF started at 680 mg/day (TG101348)

	Day -8	Screen -1	C1D8	C1D15	C1D22	C2D1	C2D15	C3D1
Hgb (g/dL)	8.5	10.6	11.3	11.4	10.2	8.9		
WBC (x 10 ⁹ /L)	8.2	13.7	20.8	10.1	6.3	6.1		
Meta	6	-				3		
Myelo	8	9				4		
Blasts	-	2				2		
nuRBC	4	7				-		
Plt (x 10 ⁹ /L)	166	150	233	186	103	73		
LDH U/L	771	816	922	689	510	500		

Spleen ————— **25 cm below LCM
9 cm right from mid-abdomen** ————— **0 cm
0 cm**

V617F allele burden ————— **100%** ————— **40%**

Conclusions

regarding the use of TG101348 at MTD
TOXICITY

- 1.** The drug is safe and well tolerated.
- 2.** Grade 3 or 4 non-hematologic toxicity is infrequent.
- 3.** Grade 1 or 2 non-hematologic toxicity is limited to nausea, diarrhea or increased transaminases or serum creatinine; all were transient and easily manageable.
- 4.** No neurologic toxicity that could be clearly attributed to drug.
- 5.** Grade 4 neutropenia was rare. Grade 4 thrombocytopenia was infrequent (< 20%). Grade 4 anemia was also rare whereas 47% experienced a > 2 g/dL decrease in hemoglobin, an expected on-target effect of the drug.

Conclusions

regarding the use of TG101348 at MTD

EFFICACY

1. Virtually all patients experienced a more than 50% reduction in spleen size. Half of these patients had a complete resolution of splenomegaly.
2. Virtually all patients had complete resolution of leukocytosis.
3. Most patients with constitutional symptoms, including pruritus or night sweats experienced complete resolution.
4. We are encouraged by the preliminary findings of marked reduction in JAK2V617F allele burden that is already being observed in approximately 50% of the patients despite short follow up. We are also intrigued by resolution of leukoerythroblastosis in some patients.