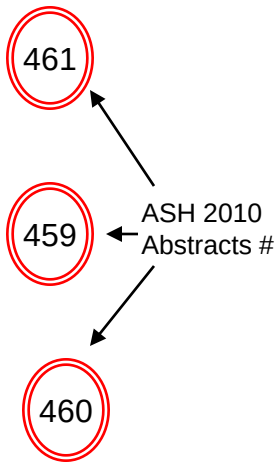
JAK inhibitor ATP mimetics in clinical trials for myelofibrosis at Mayo

	Anti-JAK2 IC50 (JAK1/JAK3 selectivity)	**Non-JAK kinase targets**
INCB018424 (Phase 1/2 study) N=153-51	5.7 nM (x1.0/x98)	None of ~28 kinases evaluated
TG101348 (Phase 1/2 study) N=59-15	3 nM (x35/x332)	FLT3 RET
CYT387 (Phase 1/2 study) N~160-100	18 nM (x0.6/x8.6)	JNK1 CDK2



CYT387 in myelofibrosis

- N = 60
- Age = 65 years (34 – 85); male 65%
- Diagnosis
  - PMF = 68%
  - PPMF = 20%
  - PTMF = 12%
- DIPSS-Plus category: Int-1 - 5%; Int-2 - 65%; High - 30%
- *JAK2*V617F = 75%
- Red cell transfusion-dependent, n=33 (55%)
- Palpable splenomegaly >10 cm, n=48 (80%)
- INCB018424 failures, n=11 (18%)
- TG101348 failures, n=3 (5%)
- Pomalidomide failures, n=13 (22%)

Study design

- ☑ Dose escalation (n = 21)
- ☑ Dose confirmation (n = 39)

Dose-escalation phase

- Starting dose levels
  - 100 (n=3), 150 (n=3), 200 (n=3), 300 (n=6), and 400 (n=6) mg/day
- DLT (2 of 6 subjects at 400 mg/d)
  - asymptomatic reversible Gr 3 hyperlipasemia (n=1), and Gr 3 headache (n=1)
- MTD = 300 mg/day

Subject disposition

- All patients have now been followed for a minimum of 5 months (median = 8 months) and 90% of subjects remain on study drug
- Treatment discontinuation in 6 patients was because of death from unrelated causes (*n*=4), choice to proceed with transplant after 8 months of therapy (*n*=1) or lack of response after completing the study period of 9 months (*n*=1)

Treatment-emergent non-hematologic adverse events

at least possibly-related to study drug, N = 60

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	15%-20%			
Diarrhea	12%-20%			
Abdominal pain	7%			
Vomiting	3%			
Increased transaminases	20%-25%		3%	
Increased bilirubin	16%			
Increased lipase	7%-20%		5%	
Increased amylase	5%-20%	5%		
Increased Alk Pase	7%-15%	3%		
Increased creatinine	5%-20%			
Numbness	5%-20%			
Headache	10%-20%		3%	
Prolonged QTc	3%			
Dry mouth	3%			

TG101348

70%

64%

34%

27%

27%

24%

Dry/skin Exfoliation 14%

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About half of the patients experienced transient and non-recurrent first dose effect
Lightheadedness
Drop in blood pressure

Treatment-emergent hematologic adverse events

at least possibly related to study drug

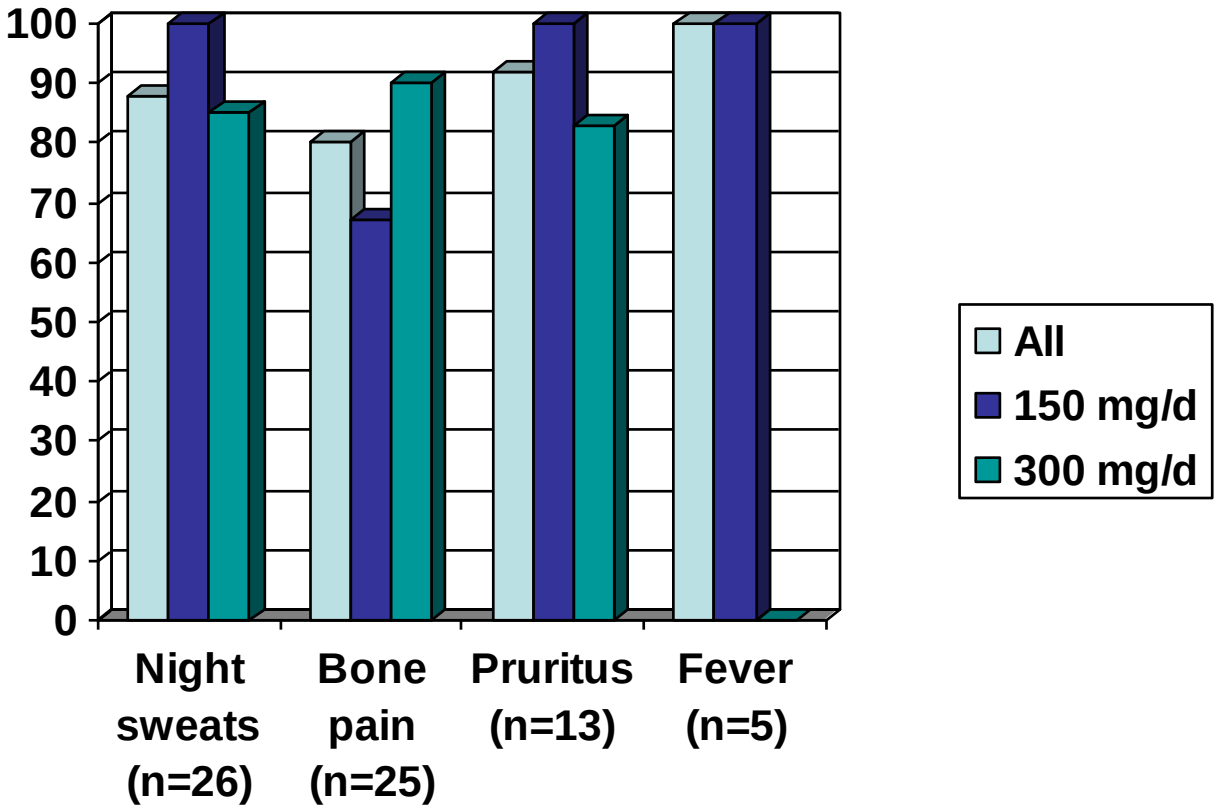
Adverse events	Grades 1/2	Grade 3	Grade 4
Anemia	7%	7%	
Thrombocytopenia	42%	18%	8%
Neutropenia	2%		5%

Platelet inclusion criteria: INCB018424: 100k ; TG101348: 50K; CYT387: 50k

	Gr 3/4 thrombocytopenia	Gr 3/4 anemia
INCB018424	**20%**	**23%**
TG101348	**24%**	**35%**
CYT387	**27%**	**7%**

Verstovsek S et al. N Engl J Med 2010;363:1117
Pardanani A et al. JCO in press, ASH 2010 abstract #459
Pardanani A et al. ASH 2010 abstract #460

Control of constitutional symptoms



Pruritus	
INCB018424	82%
TG101348	100%
CYT387	92%

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

Pardanani A et al. JCO in press

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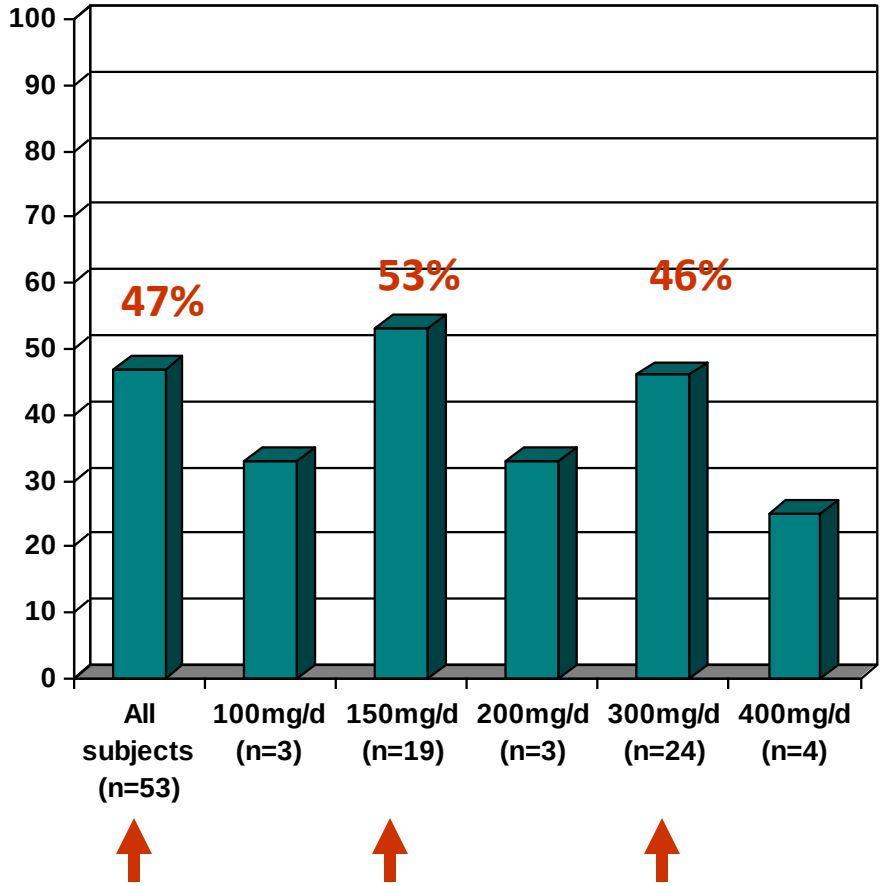
Spleen response ‘CI’ by ITT, IWG

Stratified by *starting* dose

N =53 (Splenectomy=4, not palpable=2, <5 cm=1)



Median (range) time to response = 2 weeks (1-16)

Median (range) duration of response = 2+ months (2-12)

Spleen response by IWG	
INCB018424	44%
TG101348	47%
CYT387	47%

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

Pardanani A et al. JCO in press

Pardanani A et al. ASH 2010 abstract #460

SAR302503
Phase 3 myelofibrosis trial design

SAR302503 Phase 3 Study Design – 1/2

STUDY CONCEPT:

- Randomized, placebo controlled 3-arm trial of SAR302503 in patients with myelofibrosis who are either Intermediate-2 or High Risk by IWG-MRT criteria
- 3-arms: placebo, 400 mg qd and 500 mg qd
- Randomized 1:1:1
- Sample size: 75 patients per group (225 total)

Study Design:

- SAR302503 or placebo taken daily until response assessed at 6 months

Primary end point: RR

- Response Rate: Proportion of patients who have 35% reduction in volume of spleen size at 24 weeks (6 months) measured by MRI compared to baseline

Secondary endpoints

- **Accelerated approval:**
  - Symptom improvement (MPN-SAF score)
  - Duration of response
- **Full Approval:**
  - Progression-free survival (PFS)
  - Overall survival (OS)

Proposed Revised Phase 3 Study Design – 2/2

- **Statistical design:**
  - Randomization: 1:1:1 (placebo: 400 mg dose cohort: 500 mg dose cohort).
  - Time of primary analysis: The RR will be analyzed when the last randomized subject has received 24 weeks of treatment with placebo,
  - Crossover: Eligible patients in placebo arm may cross over to receive SAR302503 open label at the completion of 6 months of treatment.

- **Planned Study start:** September 2011 (~ 100 sites in US, EU, Asia)