Therapy with the Histone Deacetylase Inhibitor Pracinostat (SB939) in Patients with Myelofibrosis

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Abstract

Background — The discovery of the JAK2V617F mutation has triggered the development of agents that target the activity of this mutant enzyme. It has been recently shown that both wild-type JAK2 and JAK2V617F kinases translocate to the nucleus of various human leukemic cell lines and primary CD34+ hematopoietic progenitors and phosphorylate histone H3, resulting in loss of affinity for the transcriptional repressor heterochromatin protein 1α (HP1α), which in turn, it causes aberrant gene expression. These results provide the rationale to use histone modifying agents for the treatment of MF. SB939 is a small molecule (dialkyl benzimidazole) competitive inhibitor of histone deacetylase (HDAC) that has >1000-fold selectivity for HDAC Class 1 and 2 *versus* Class 3. We are conducting a study of SB939 in pts with MF.

Methods — This is a phase 2, prospective, open-label study to determine the efficacy and safety of SB939 in subjects with MF (primary or post-ET or –PV) with intermediate-1, intermediate -2 or high risk disease according to the IWG prognostic scoring system, and for those with low risk and symptomatic splenomegaly ≥5 cm below left costal margin. Initial SB939 dose was 60mg every other day three times weekly for three weeks. Response is assessed using the International Working Group (IWG) criteria. After 22 pts started SB939, the study was put on hold to assess toxicity with a provision of terminating the trial if ≤4 pts responded after being treated for 6 months.

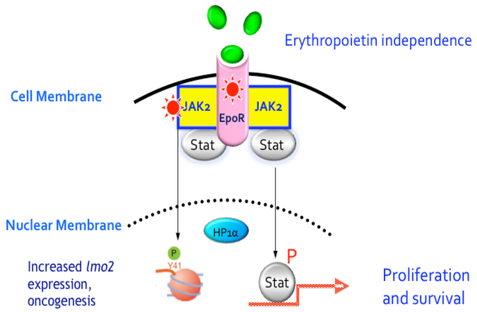
Results — 23 pts were accrued (77% male, 81% JAK2V617F-positive). Median age was 67 years (range, 51-74), WBC 13x10^9/dL (1.2-103.2), Hg 9g/dL (6-26.6), platelets 143x10^9/dL (21-572). Eighteen (82%) pts carried the JAK2V617F mutation, with a median allele burden of 59.6% (19.9-94.95%). Seven (33%) pts had abnormal cytogenetics. Ninety-one percent of pts were symptomatic at study entry with a performance status of 0 (n=5%), 1 (73%), or 2 (22%). Ninety-five percent had splenomegaly with a median spleen size of 13cm (range, 0-29cm). Twenty-two pts are assessable for response and toxicity. Six (27%) pts experience a decrease in spleen size (median 3 cm, range 1-4). Two pts had anemia clinical improvement by IWG criteria (Hg increased from 9.1g/dL at baseline to 11.1g/dL at last follow-up and from 7.9g/dL to 15.3g/dL). Five (50%) of 10 pts with hepatomegaly reduced their liver size (median 3cm, range, 1-6cm). Three (17%) of 18 JAK2V617F-positive pts had reductions of allele burden (median 11.4%). The most frequent side effect was fatigue, which occurred in 20 (91%) pts: grade 1 (n=17) and grade 2 (n=3). Other toxicities included pain (n=5), peripheral edema (n=4), and diarrhea (n=3), all grade 1. Rates of grade 3-4 neutropenia, anemia, and thrombocytopenia were 13%, 0%, and 21%, respectively. No pt has died during the conduction of the study and 3 remain on the study receiving SB939 at 60mg (n=1) or 50mg (n=2); 19 pts are off study due to lack of response (n=9), disease progression (n=4), pt's request (n=2), unrelated medical problems (n=3, surgery for aortic aneurism, prostate cancer, infection), fatigue (n=1).

Conclusion — SB939 has modest activity as single agent in pts with MF. Most responses consisted of reductions in spleen and/or liver size with minimal activity on anemia. Combination studies at lower doses are planned with JAK2 inhibitor

Background

- The discovery of the JAK2V617F mutation has triggered the development of agents that target the activity of this mutant enzyme.
- Inhibition of the JAK2/STAT pathway has proven very effective as treatment of MPNs
- However, JAK2 inhibitors fail to decrease JAK2V617F mutant allele burden, increase hemoglobin levels, or improve fibrosis in the bone marro
- In addition, JAK2 inhibitors cared

JAK2 & JAK2^{V617F}-mediated signaling



JAK2^{V617F} is constitutively active

- It has been recently shown that both wild-type JAK2 and JAK2V617F kinases translocate to the nucleus of various human leukemic cell lines and primary CD34+ hematopoietic progenitors
- There, JAK2 phosphorylates histone H3, resulting in loss of affinity for the transcriptional repressor heterochromatin protein 1α (HP1α), which in turn, it causes aberrant oncogenice expression (e.g. *Imo*).

Pracinostat (SB939) Therapy

- Pracinostat is a novel orally bioavailable inhibitor of class 1, 2 and 4 histone deacetylases that inhibits proliferation and promotes apoptosis of human tumor cell lines with an IC_{50} of 0.1 – 1.3mM.
- Pracinostat was tested in a phase I study involving 44 patients with advanced hematologic malignancies using dose levels from 10mg to 120mg
- The phase II recommended dose was 100mg
- DLTs included prolonged QTc at 40 mg and neutropenic sepsis at 120 mg
- At 100mg, grade 3-4 adverse events included thrombocytopenia (39%), anemia (23%), pneumonia (23%), febrile neutropenia (20%), fatigue (16%), hypokalemia (11%), and neutropenic sepsis (11%)

Garcia-Manero et al. ASH 2010 (abstract 3292)

- Based on the toxicity profile of pracinostat, which involves fatigue, the initial dose for the present phase II study in MF was set at 60mg

Methods

- This is an ongoing phase 2, prospective, open-label clinical trial whose main objective is to determine the efficacy and safety of pracinostat in patients with MF (primary or post-ET or –PV) with intermediate-1, intermediate -2 or high risk disease
- Risk was stratified prior to enrollment according to the International Working Group (IWG) prognostic scoring system
- Patients with low risk MF and symptomatic splenomegaly ≥5 cm below left costal margin were also eligible for this study
- The initial pracinostat dose was 60mg every other day three times weekly for three weeks
- Response was assessed using the IWG criteria.
- After 22 pts were started on pracinostat, the study was put on hold to assess toxicity with a provision of terminating the trial if ≤4 pts responded after being treated for at least 6 months

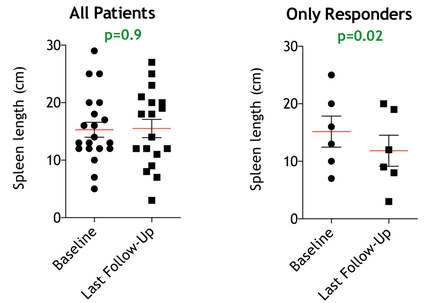
Patient Characteristics (n=22)

Characteristic	Median (range)	No. (%)	Percentage
Age (median)	67 (51-74)		
Sex - Male		17	77
- Female		5	23
Race - Caucasian		20	91
- Other		2	9
Hb (median,range)	9.4 (8.4-14.3)		
WBC (median,range)	12.25 (2-46.4)		
PLT (median,range)	146 (21-572)		
No. JAK2 V617F+ (%)		18	82
% JAK2 V617F allele burden (median,range)		59.66 (19.85-94.95)	
Symptoms	Yes	20	91
	No	2	9
Splenomegaly (%)	Yes	21	95
	No	1	5
Median (range) size (cm)	13 (5-29)		
Performance status	0	1	5
	1	16	73
	2	5	22
Cytogenetics (%)	Diploid	14	64
	Abnormal	7	32
	IM	1	4

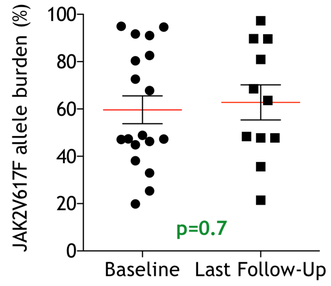
Response to Pracinostat

- Twenty-two pts are assessable for response and toxicity
- Six (27%) pts experienced a decrease in spleen size (median 3 cm, range 1-4)
- One pt had splenomegaly clinical improvement by IWG criteria (spleen sized reduced from 7cm to 3cm)
- Two pts had anemia clinical improvement by IWG criteria (Hg increased from 9.1g/dL at baseline to 11.1g/dL at last follow-up and from 7.9g/dL to 15.3g/dL)
- Five (50%) of 10 pts with hepatomegaly reduced their liver size (median 3cm, range, 1-6cm)
- Three (17%) of 18 JAK2^{V617F}-positive pts had reductions of allele burden (median 11.4%).

Dynamics of spleen reduction



Cohort dynamics of JAK2V617F allele burden



Adverse events on study

- The median number of pracinostat cycles was 3
- Eight patients required at least 1 dose reduction to 50mg
- One patient required 2 dose reductions to 40mg
- Six patients required dose increase due to lack of efficacy
- Eight patients continued therapy at 60mg

Adverse events on study

- The most frequent side effect was fatigue, which occurred in 20 (91%) pts: grade 1 (n=17) and grade 2 (n=3)
- Other toxicities included pain (n=5), peripheral edema (n=4), and diarrhea (n=3), all grade 1
- Rates of grade 3-4 neutropenia, anemia, and thrombocytopenia were 13%, 0%, and 21%, respectively
- No pt has died during the conduction of the study
- 3 remain on the study receiving SB939 at 60mg (n=1) or 50mg (n=2)
- 21 pts are off study due to lack of response (n=9), disease progression (n=6), pt's request (n=2), unrelated medical problems (n=3, surgery for aortic aneurism, prostate cancer, infection), fatigue (n=1).

Conclusions

- Single agent pracinostat therapy has modest activity in pts with MF
- Most responses consisted of reductions in spleen and/or liver size with minimal activity on anemia
- No significant effects were observed in reduction of JAK2V617F mutant allele burden
- Combination studies at lower doses are planned with JAK2 inhibitors

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