Safety Overview of Phase 1-2 Studies of Pacritinib, a Non-Myelosuppressive JAK2/FLT3 inhibitor, in Patients with Hematological Malignancies

Srdan Verstovsek[1], Paul Cernohous[2], Rami Komrokji[3], Ruben Mesa[4], John F Seymour[5], James P Dean[2], Lixia Wang[2], Jack Singer[2], Han Myint[2], Anas Younes[6]

1.MD Anderson Cancer Center, Houston, TX, USA; 2. Cell Therapeutics, Inc. Seattle, WA, USA; 3. Moffitt Cancer Center, Tampa, Florida, USA; 4. Mayo Clinic, Scottsdale, AZ, USA; 5. Peter McCallum Cancer Center & University of Melbourne, Melbourne, Australia; 6. Department of Lymphoma/Myeloma, University of Texas-MD Anderson Cancer Center, Houston, TX, USA

BACKGROUND

- Pacritinib is a novel orally active once-daily dual JAK2/FLT3 inhibitor.
- The major signaling pathway for erythropoietin and MPL is through receptor activation of JAK2 and subsequent phosphorylation of STAT proteins. Inhibition of JAK2 therefore is expected to be associated with anemia and thrombocytopenia through inhibition of normal EPO and MPL signaling and both have been observed with current JAK inhibitors.
- In preclinical models of myeloproliferative diseases in a $JAK2^{V617F}$ dependent SET-2 xenograft model, treatment with pacritinib was not associated with cytopenias at optimal effective dosing of 150mg/kg (human equivalent dose 840mg) given orally, twice daily, despite JAK2-STAT3 and 5 pathway inhibition.

AIMS

- This present integrated analysis was performed to quantify clinical toxicities of pacritinib, with a focus on hematologic effects.

METHODS

- We reviewed the safety database which included 4 clinical studies: a phase 1/2 study in advanced myeloid malignancies, a phase 1 and a phase 2 study in advanced lymphoid malignancies, and a phase 1/2 study in myelofibrosis.

RESULTS

- In phase 1 and 2 clinical trials, a total of 191 patients (pts) were treated with pacritinib: 129 with advanced myeloid malignancies including 122 myelofibrosis pts [primary 72/122 (59%)] and 7 AML pts; and 62 with advanced lymphoid malignancies, including 38 NHL pts & 24 Hodgkin lymphoma pts.
- The median age was 65 years and the median time from initial diagnosis was 3.8 years. 44% of pts with myeloid disorders had baseline platelet counts <100,000/μL.
- Pacritinib was dosed from 100 to 600 mg daily during phase 1 and at 400 mg during phase 2. One hundred and forty six (76%) patients received dosage ≥400mg daily. The median dose delivered was 98% of intended.
- The most common adverse events (AEs) were gastrointestinal (GI) (all grades/grade 3-4): diarrhea (73%/8%), nausea (48%/1%), vomiting (30%/1%), constipation (24%/0%) and abdominal pain (21%/4%). Most pts had no decline in hemoglobin or platelet count. There were no late toxicities noted in the 2 pts treated beyond 3 years.

Patient Demographics

	Advanced Myeloid Malignancies (n=129)	Advanced Lymphoid Malignancies (n=62)
Median age, years (range)	68 (44 – 86)	56 (20 – 91)
Sex, n (%)		
Female, n (%)	42 (33%)	19 (31%)
Male, n (%)	87 (67%)	43 (69%)
Diagnosis, n (%)		
AML	7 (5%)	
Primary or secondary myelofibrosis	122 (95%)	
Non-Hodgkin lymphoma		38 (61%)
Hodgkin lymphoma		24 (39%)
Duration of treatment, n (%)		
< 6 months	50 (39%)	49 (79%)
6 to < 12 months	23 (18%)	10 (16%)
≥ 12 months	56 (43%)	3 (5%)
Median duration of treatment, days (range)	306 (2-1210)	90.5 (1-631)

Summary of Efficacy in Patients with Myelofibrosis

Study name	Intent-to-treat population	Disease diagnosis	# of patients with ≥50% spleen reduction by physical exam
SB1518-001 Phase 1	43	MF =36 AML=7	11 (26%)
SB1518-001 Phase 2	31	Primary MF=17 PPV-MF=11 PET-MF=3	12 (39%)
SB1518-003 Phase 1	20	Primary MF=8 PPV-MF=5 PET-MF=5 MDS=1 MF-unspecified=1	2 (10%)
SB1518-003 Phase 2	34	Primary MF=23 PPV-MF=5 PET-MF=6	14 (41%)

Summary of Efficacy in Patients with Advanced Lymphoid Malignancies

Open-label Phase 1 study (SB1518-2007-002) (n=35)

Disease Subtype	# of patients
Hodgkin lymphoma (HL)	15
Follicular lymphoma (FL)	10
Diffuse large B-cell lymphoma (DLBCL)	4
Mantle cell lymphoma (MCL)	5
Small lymphocytic lymphoma (SLL)	1

Of 31 patients with at least one follow-up tumor assessment:
- 4 had partial responses (2 patients with MCL at 300 and 400 mg/d doses and 2 with FL at 400 and 600 mg/d doses)
- 17 had stable disease (7 with FL, 7 with HL, 2 with MCL, and 1 with SLL.)
- 13 of 17 patients with stable disease had tumor mass reductions of 4-45%.

Open-label Phase 2 study (SB1518-2007-005) (n=28)

Disease Subtype	# of patients
Hodgkin lymphoma (HL)	10
Mantle cell lymphoma (MCL)	8
Indolent FL	10

Of 24 patients with at least one follow-up tumor assessment:
- 1 patient with FL had PR and 1 with HL had CR.
- 17 had SD (5 patients with HL, 4 with MCL, and 8 with FL).
- 4 of 16 patients with SD had tumor mass reductions of >50% from baseline

Hemoglobin and Platelet Shift From Baseline to Last Assessment in Patients from All Studies

Safety population (n=189)* (> 1 post-baseline value)	Hemoglobin shift from baseline to last value	Platelet shift from baseline to last- value
No shift	101 (53.4%)	108 (57.1%)
Cytopenia Improvement		
1 grade improvement	28 (14.8%)	17 (9%)
2-4 grade improvement	6 (3.2%)	2 (1.1%)
Cytopenia Decline		
1 -2 grade decline	51 (27%)	52 (27.5%)
3-4 grade decline	1 (0.5%)	8 (4.2%)

*Note: 2 patients did not have CTC grades at baseline or post-baseline due to missing laboratory normal ranges.

Hematological Safety (See figures)

- There was no clinically significant decline in mean hemoglobin or platelet count from baseline values.
- Of the 30 patients with myeloid disorders with baseline platelet counts <50,000/μL, the median decline in platelet count observed at the end of study was 3,000/μL.
- In the 11 patients with myelofibrosis with baseline platelet counts <50,000/μL enrolled in phase II studies, no dose reductions were required for worsening thrombocytopenia.

Overview of Adverse Events in All Pacritinib Studies

	Advanced Myeloid Malignancies (n=129)	Advanced Lymphoid Malignancies (n=62)	Overall (n=191)
Adverse events	128 (99.2%)	59 (95.2%)	187 (97.9%)
Grade 3/4 adverse events	99 (76.7%)	24 (38.7%)	123 (64.4%)
Serious adverse events	54 (41.9%)	17 (27.4%)	71 (37.2%)
Deaths	16 (12.4%)	6 (9.7%)	22 (11.5%)

AEs Related Dose Interruption/ Reduction or Discontinuation in All Pacritinib Studies

	Advanced Myeloid Malignancies (n=129)	Advanced Lymphoid Malignancies (n=62)	Overall (n=191)
Dose Interruption/ Reduction			
Any AEs	56.6%	33.9%	49.2%
GI AEs	31.8%	12.9%	25.7%
AEs that led to study drug discontinuation			
Any AEs	20.9%	16.1%	19.4%
GI AEs	3.9%	0	2.6%

Adverse Events (AEs)

- The most common AEs were gastrointestinal (GI).
- Time to onset of diarrhea was ≤30 days in 89% of those affected but rarely caused drug discontinuation (1.0%).
- Anti-diarrheal prophylaxis was not used routinely in these early studies.
- Cumulative toxicities have not been noted in patients treated beyond 3 years.

Serious Adverse Events (SAEs)

- SAEs were reported in 41.9% of the myeloid patients and 27.4% of the lymphoid patients.

The most frequently reported (≥2%) SAEs included:
- pneumonia (4.7%)
- anemia (3.1%)
- abdominal pain (2.1%)
- acute myeloid leukemia (2.1%)
- cardiac failure congestive (2.1%)
- sepsis (2.1%)
- subdural hematoma (2.1%)

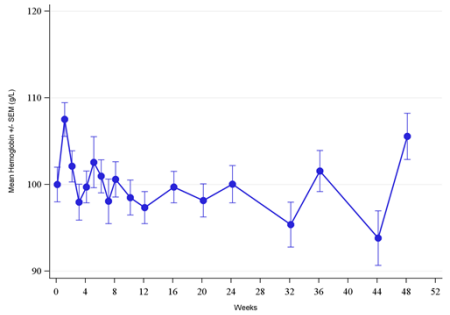
Twenty-two deaths (11.5%) reported as treatment emergent AEs with a fatal outcome occurred during the studies: 16 in the myeloid studies (12.4%) and 6 in the lymphoid studies (9.7%).
- Twenty-one patients died of non-drug related causes.
- One patient died of a possibly drug-related subdural hematoma.

Most Common Adverse Events

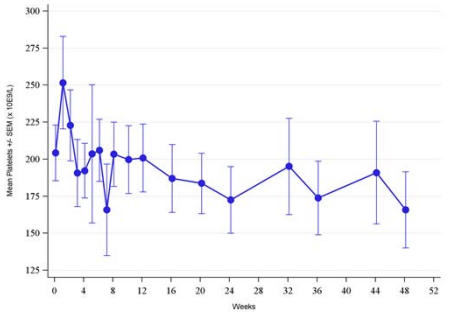
	All Grades (n=191)	Grade 3/4 (n=191)
Diarrhea	139 (72.8%)	15 (7.9%)*
Nausea	92 (48.2%)	2 (1.0%)
Fatigue	72 (37.7%)	17 (8.9%)
Vomiting	57 (29.8%)	1 (0.5%)
Anemia	47 (24.6%)	32 (16.8%)
Constipation	46 (24.1%)	0
Abdominal pain	40 (20.9%)	7 (3.7%)
Edema peripheral	38 (19.9%)	4 (2.1%)
Thrombocytopenia	37 (19.4%)	23 (12.0%)
Pyrexia	33 (17.3%)	3 (1.6%)
Dyspnea	28 (14.7%)	2 (1.0%)
Pruritis	27 (14.1%)	2 (1.0%)
Cough	26 (13.6%)	0
Dizziness	24 (12.6%)	1 (0.5%)
Insomnia	24 (12.6%)	0
Anorexia	23 (12.0 %)	0
Headache	22 (11.5%)	1 (0.5%)
Abdominal distension	20 (10.5%)	1 (0.5%)
Asthenia	20 (10.5%)	3 (1.6%)

* No Grade 4 GI Toxicities

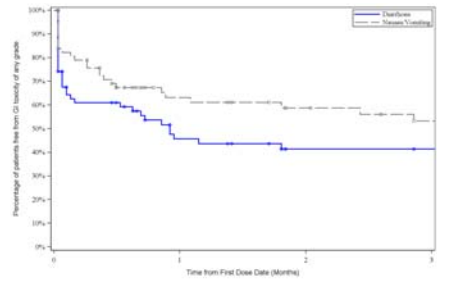
Mean Hemoglobin Results (Safety Populations) in MF Studies SB1518-001 and SB1518-003



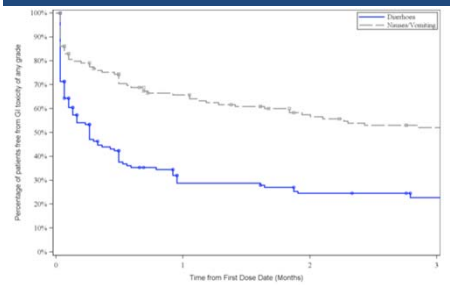
Mean Platelet Count Results (Safety Populations) in MF Studies SB1518-001 and SB1518-003



Time to First Gastrointestinal Event (Safety Populations) in Lymphoid Studies SB1518-002 and SB1518-005



Time to First Gastrointestinal Event (Safety Populations) in MF Studies SB1518-001 and SB1518-003



DISCUSSION

- Pacritinib is an active agent in patients with myeloid or lymphoid disorders with minimal marrow suppression.
- Patients with initial platelet counts <50,000/μL tolerated therapy, maintained stable platelet counts and did not require dose reductions.
- Ongoing phase 3 studies of pacritinib in myelofibrosis do not restrict study entry due to thrombocytopenia or anemia and allow enrollment of platelet and RBC transfusion dependent patients.
- GI events, particularly diarrhea, were the most common AEs. Most of these were grade 1 or 2. Time to onset of diarrhea was within the first 30 days in the majority of those affected but only 1% led to drug discontinuation. Anecdotal data from treating physicians suggest toxicity is readily controlled with early administration of standard anti-diarrheal agents.
- The relative lack of bone marrow suppression also suggests that pacritinib could be used without added myelotoxicity in combination with marrow suppressive therapies in patients whose neoplasms are associated with activation of JAK2 or FLT3.