

The JAK Inhibitor NCB018424 Demonstrates Durable and Marked Clinical Responses in Primary Myelofibrosis (PMF) and Post-Polycythemia/Essential Thrombocythemia Myelofibrosis (Post-PV/ET-MF)

S. Verstovsek,¹ H. M. Kantarjian,¹ A. D. Pardanani,² D Thomas,¹ J. Cortes,¹ R. A. Mesa,² W. J. Hogan,² J. R. Redman,³ S. Erickson-Viitanen,³ R. Levy,³ K. Vaddi,³ E. Bradley,³ J. Fridman,³ and A. Tefferi²

¹University of Texas M. D. Anderson Cancer Center, Houston, Texas, ²Mayo Clinic, Rochester, Minnesota, and ³Incyte Corporation, Wilmington, Delaware, USA

Abstract

Background: Myelofibrosis (MF) is characterized by progressive bone marrow dysfunction, extramedullary hematopoiesis, massive splenomegaly, elevated levels of inflammatory cytokines, severe constitutional symptoms, and premature death. NCB018424 is a potent, selective inhibitor of JAK1 and JAK2, which has demonstrated impressive clinical activity in the early portion of a phase 1/2 study in patients with Post-PV/ET-MF.

Methods: Following the initial dose escalation phase with a BID schedule (N=11) twice daily (10 mg BID to 25 mg BID, N=10) and once daily (10 mg QD to 200 mg QD, N=37) dose regimens were explored. Endpoints included spleen size assessed by manual palpation, constitutional symptoms assessed using the Modified Symptom Assessment Form (MSAF), and JAK2 kinase levels. Extensive safety data were collected using the NCI Common Data Elements, and body mass and composition are being assessed using standard methods. Safety was assessed by collection of adverse events using the Modified Toxicity Symptom Assessment Form (M-TSAP).

Results: Overall 100 patients are currently enrolled in the study, with a mean age of 70 years. Twenty percent of patients have received NCB018424 for >3 months. NCB018424 is associated with a rapid reduction in splenomegaly in over 93% of patients from mean baseline spleen size >20 cm, with 50% or greater reduction being observed in 50% of patients dosed with 10 mg QD or 50 mg QD, and 59% of patients dosed with 25mg BID regimens. These declines nearly always occur within the first month of therapy, with further, slower decreases often observed thereafter.

NCB018424

- Potent and selective ATP competitive JAK1 and JAK2 inhibitor
 - > 80-fold selective against JAK3 and panel of non-JAK kinases
- Inhibits signaling through mutant JAK2 and MPL pathways
 - Highly active in cell assay systems driven by JAK2 V617F
 - IC50 = 127 nM
 - Selective inhibition of V617F-driven EEC colony formation
- Inhibits pro-inflammatory cytokine expression and signaling in MF
 - Down-regulates cytokines and fibrogenic/angiogenic growth factors that play a potentially causal role in the pathogenesis of myelofibrosis
 - Inhibits the signaling of cytokines such as IL-6 which are known to be responsible for debilitaing constitutional symptoms such as systemic inflammatory state and weight loss

NCB018424-251: Patient Characteristics

Parameter	10 mg BID	15 mg BID	25 mg BID	50 mg BID
N	22	25	20	47
Median age (range)	65.5 (59-80)	58 (50-79)	65 (40-78)	67 (42-80)
Male:female ratio	10:12	15:10	13:7	31:16
PMF	14 (63.6%)	9 (36.0%)	12 (60.0%)	22 (46.8%)
Post-PV/ET	4 (18.2%)	4 (16.0%)	4 (20.0%)	17 (36.2%)
Post-ETMF	4 (18.2%)	4 (16.0%)	2 (10.0%)	8 (17.0%)
Median time on drug	7.3 months	6.7 months	2.4 months	9.7 months
Prevalence with JAK2 mutation	83.6%	96.7%	85.0%	94.3%
Baseline spleen size, cm	20.2	20.2	17.2	19.8
Median (N with splenomegaly)	(N=21)	(N=23)	(N=20)	(N=35)
Baseline platelet count, K/cuL (range x 10 ⁹)	359 ± 272	333 ± 200	429 ± 186	346 ± 253
Percentage transfusion dependent	56%	52%	15%	38%

Include only dose groups with at least 20 patients.

NCB018424-251: Blood Counts

CTCAE grade	10 mg BID			15 mg BID			25 mg BID			50 mg BID		
	Hgb†	Platelets†	WBC†	Hgb†	Platelets†	WBC†	Hgb†	Platelets†	WBC†	Hgb†	Platelets†	WBC†
3	5 (16)	5 (16)	1 (3)	1 (4)	1 (4)	0	7 (21)	11 (33)	7 (21)	7 (21)	3 (9)	3 (9)
4	0	0	0	0	0	0	3 (9)	3 (9)	3 (9)	4 (12)	4 (12)	1 (3)

†Includes only subjects who were transfusion independent at entry.

NCB018424 Treatment Results in Marked and Durable Improvement in Splenomegaly

Overall daily activity in 9 subjects was assessed using an accelerometer (pedometer) worn for 1-week periods of time at pre-dose and post 1 month dosing at 15 mg BID NCB018424

Data reflects the difference in the average steps/day after 1 month therapy compared to baseline

Mean = 43 ± 12%
Median = 41%

NCB018424 Treatment Results in Marked Increase in Overall Daily Activity Level

Overall daily activity in 9 subjects was assessed using an accelerometer (pedometer) worn for 1-week periods of time at pre-dose and post 1 month dosing at 15 mg BID NCB018424

Data reflects the difference in the average steps/day after 1 month therapy compared to baseline

Mean = 43 ± 12%
Median = 41%

Abstract (cont.)

Results (cont.): In responding patients, spleen size reduction persists for the duration of therapy (currently up to one year follow-up). Constitutional symptoms are reported with high frequency in the study population as assessed by the MSAF; night sweats, pruritis and fatigue were reported by >60%, >45% and >50% of patients respectively. Improvements in self-assessed symptoms (mean % improvement of 40% to 80%) occurred by the first assessment at week 2. Activity limitations are also reported by a high proportion of MF patients; 70% of respondents reported impaired ability to exercise at all levels, with a mean score of 1.0 on the 1-point MFI scale. NCB018424 therapy was associated with weight (mean 2 weeks) and retained 40% or more improvement in self-assessed scores. There was a dose-dependent weight gain, most pronounced in patients with the lowest body mass index (BMI) values at baseline. Profound reductions in inflammatory cytokines were observed by the first evaluation at week 2 in patients with elevated cytokine levels at baseline. NCB018424 is generally well tolerated with the primary toxicity being dose-dependent grade 3 or 4 reversible thrombocytopenia which occurred in 0%, 18% and 32% of patients dosed with 10 mg BID, 50 mg QD or 25 mg BID.

Conclusions: NCB018424 shows unprecedented and durable clinical efficacy in reducing spleen size and improving constitutional symptoms in patients with MF. Results from phase 1/2 dose modification regimens, assessments of exercise capacity, MRI based spleen volume assessment and body composition determination will be presented.

NCB018424 Mechanism of Action

NCB018424 is a JAK1/JAK2 inhibitor blocks cytokine signaling and growth factor expression

Study NCB018424-251: Disposition of Patients

Dose	N	Remains on study	Lack of response	Discontinued Progression or toxicity	Other
10 mg BID	25	18	2	4	1
15 mg BID	20	20	0	0	0
25 mg BID	47	39	0	6	2
50 mg QD	5	2	0	2	1
25 mg QD	6	2	0	1	3
50 mg QD	22	18	1	1	2
100 mg QD	6	6	0	0	0
200 mg QD	3	3	0	0	0

- Most patients (108/134 patients) remain on study with a median duration on drug of 6.8 months

NCB018424-251: Safety Summary

- NCB018424 is generally well tolerated, with few adverse events other than mechanism-based effects on hematology
 - 108/134 patients remain on study with a median duration of ~7 months
- Reductions in platelet and Hgb counts are readily reversible with dose interruption and/or dose reduction while patients maintain clinical improvement
- Three transfusion-dependent MF patients in the study have achieved durable transfusion independence on NCB018424 therapy: one for > 1 year and 2 for > 6 months

NCB018424 Improves Splenomegaly Independent of JAK2 Mutation Status or Diagnosis

NCB018424 improves splenomegaly independent of JAK2 mutation status or diagnosis

NCB018424 Treatment Results in Rapid Improvement in Constitutional Symptoms

Improvements in symptoms were seen at the first on-treatment evaluation (2 weeks)

Myelofibrosis Symptom Assessment Form (MSAF) was used (N = 55 respondents)

Hyperactivation of JAK/STAT signaling is pathogenic in MPDs

- An activating mutation in the pseudokinase domain of JAK2 known as V617F is present in
 - > 95% of polycythemia vera (PV)
 - > 50% of essential thrombocythemia (ET)
 - > 50% of primary myelofibrosis (PMF)
- Additional mutations that result in hyperactivation of JAK/STAT signaling include
 - Exon 12 mutations in JAK2
 - Mut (TPD receptor) mutations - V615L, etc.
 - JAK2/JAK3 mutations alone are causal in producing MPD phenotype in mice
 - V617F allele burden in myelofibrosis correlates with
 - Poor survival
 - Increased leukemic transformation
 - Constitutional symptoms

NCB018424-251: Phase I/II Study of NCB018424 in Myelofibrosis

- Phase I dose escalation study of NCB018424 in PMF, post-PV MF and post-ET MF (ASH 2007)
 - Identified the starting dose of 25 mg BID as a highly effective dose in reducing splenomegaly and constitutional symptoms
 - Identified 25 mg BID as maximum tolerated dose (MTD), with reversible thrombocytopenia as the dose-limiting toxicity
- Expansion Cohort:
 - Safety and durability of efficacy upon long-term dosing
 - Evaluation of additional doses
 - Lower BID doses - 10 and 15 mg BID
 - Once daily doses - 25, 50, 100 and 200 mg
 - Evaluation of spleen size reduction by Magnetic Resonance Imaging
 - Prospective evaluation of improvement in constitutional symptoms associated with MF
 - Evaluation of functional end points of clinical efficacy

NCB018424-251: Adverse Events of at Least Moderate Intensity, All Causality

Adverse event	Number (%) of subjects reporting			
	10 mg BID (N=23)	15 mg BID (N=20)	25 mg BID (N=47)	50 mg QD (N=22)
Arthralgia	1 (4.3)	2 (10.0)	0	0
Diarrhea	1 (4.3)	0	1 (2.1)	1 (4.5)
Fatigue	2 (8.7)	0	1 (2.1)	0
Pruriginous rash	1 (4.3)	0	2 (4.3)	1 (4.5)
Pyrexia	0	0	2 (4.3)	1 (4.5)
Dyspnea	0	0	1 (2.1)	2 (9.1)
Cytopaenia	0	0	2 (4.3)	2 (9.1)

- Reported by at least 2% of the patients enrolled

NCB018424 Treatment Reduces Elevated Leukocytes and CD34+ Progenitor Cells

- Myelofibrosis is characterized by high levels of circulating CD34+ cells, which correlate with the stage of disease
- NCB018424 treatment resulted in reduced circulating CD34+ cells
- NCB018424 (25 mg BID) reduces leukocytosis, an adverse prognostic factor, in MF patients*

Objective Measurement by MRI Mirrors Spleen Size Reduction by Palpation After NCB018424 Treatment

37% decrease in spleen volume

NCB018424-251: Summary

- NCB018424 treatment results in significant clinical benefits in myelofibrosis patients which include:
 - Decreased splenomegaly
 - Improvement in constitutional symptoms
 - Significant reduction in inflammatory cytokines (ASH Abstract # 2804)
 - Improvement of body weight (ASH Abstract # 1780)
 - Improvement of overall daily activity
- NCB018424 is very well tolerated
 - Median duration of therapy - 7 months
- NCB018424-251 results to date suggest that NCB018424 treatment results in significant clinical benefits to myelofibrosis patients, and represents a major advance as a therapy for this disease