



INC018424, a Selective JAK1/2 Inhibitor, Significantly Improves the Compromised Nutritional Status and Frank Cachexia in Patients with Myelofibrosis (MF)

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Abstract

Background: MF is a progressive clonal disease associated with bone marrow disease, cachexia, and weight loss. *In vivo* studies have shown that JAK1/2 inhibition with INC018424 improves nutritional status and cachexia in MF patients. **Objective:** To evaluate the effect of INC018424 on body weight, spleen size, and cachexia in MF patients. **Design:** A phase III, randomized, controlled trial. **Setting:** Mayo Clinic, Rochester, Minnesota. **Participants:** 100 MF patients with a median age of 67 years, median BMI of 21.5 kg/m², and median spleen size of 10.5 cm. **Interventions:** Patients were randomized to receive either INC018424 25 mg BID or placebo. **Measurements and Main Results:** At baseline, patients had a median weight loss of 10.5 kg (range 0-25 kg) and a median spleen size of 10.5 cm (range 5-15 cm). After 24 weeks of treatment, the INC018424 group had a median weight gain of 5.5 kg (range 0-15 kg) and a median spleen size of 8.5 cm (range 5-12 cm), compared to a median weight loss of 2.5 kg (range 0-10 kg) and a median spleen size of 10.5 cm (range 5-15 cm) in the placebo group. **Conclusions:** Treatment with INC018424 significantly improved body weight and reduced spleen size in MF patients. **Keywords:** Myelofibrosis, cachexia, spleen, weight gain, JAK1/2 inhibitor.

Study Design / Methods

- Symptomatic patients with MF enrolled in a phase III trial with INC018424 (on the 25 mg BID cohort) were analyzed for the impact of therapy on nutritional status and cachexia¹
- Patients were assessed for
 - Changes in body mass index (BMI)
 - Serum cholesterol values
 - Spleen size
 - Patient reports of early satiety and anorexia
- Leptin, an adipose-derived protein hormone that plays a key role in regulating energy balance and circulates at levels proportional to body fat in health and disease,² was assessed serially.

The details of trial see www.clinicaltrials.gov, NCT02055911

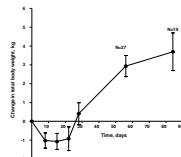
¹Source: Verstovsek et al. / *J Clin Oncol* 2019; 37: 406

Summary of Results (cont.)

- Cholesterol**
 - Hypocholesterolemia (total cholesterol < 150 or 100 mg/dL) is associated with decreased survival in MF patients, primarily from hypercatabolism and altered consumption of lipids (see panel 7)
 - At enrollment, median total cholesterol was 85 mg/dL, with 34% and 55% below 150 mg/dL and 100 mg/dL, respectively.
 - Following treatment with INC018424, median total cholesterol increased to 148 mg/dL (range 72-265 mg/dL) with 72% increasing to an improved range above that baseline (similar to the > 150 mg/dL or the > 100 mg/dL range) (see panel 7)
- Leptin**
 - At enrollment, MF patients had very low leptin levels (mean = 2.55 ng/mL with 50% below 1 ng/mL, a range of 0.12 ng/mL for normal elderly volunteers)
 - Cachectic MF patients have lower leptin levels than patients with GI cancer (see panel 8)
 - Low plasma leptin levels are associated with shortened survival in cancer patients
 - The plasma leptin levels increased 176% on average after 1 month of treatment with INC018424, continued to increase to levels matching healthy volunteers with time on study (mean = 17.04 ng/mL range 0.25 – 55 ng/mL) after 2 months on INC018424, and continued to weight increase (see panel 8)

¹Source: Mesa et al. / *Cancer* 2007; 109: 65

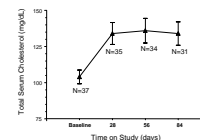
Effect of INC018424 on Body Weight



- Treatment with INC018424 25 mg BID results in improved body weight in MF patients

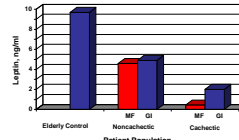
INC018424 and Serum Cholesterol

- Effect of INC018424 treatment on total serum cholesterol level over time



Leptin Levels in Cachectic MF Patients

- Plasma leptin levels in cachectic MF patients are lower than those in elderly controls and GI cancer patients with cachexia



Background

- Myelofibrosis (MF) is a progressive illness associated with cachexia and weight loss
 - These clinical signs, resulting from both hypercatabolism (secondary to increased pro-inflammatory cytokines) and MF-associated splenomegaly, are associated with decreased survival¹
- Currently, there is no therapy that decreases the progressive cachexia of MF
- INC018424 is a selective JAK1/2 inhibitor which has the potential to improve
 - the abnormal myeloproliferation in MF through decreasing constitutively active JAK-STAT signaling, and
 - nutritional status by decreasing both splenomegaly and the expression and signaling of pathologically increased cytokines.

¹Source: Mesa et al. / *Cancer* 2007; 109: 65

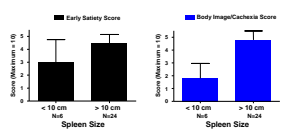
Patient Baseline Characteristics

Parameter	Value
N	47
Median age (range)	67.0 (42 to 80)
Male:female ratio	3:116
PMF	49%
Post-PMF	33%
Post-ETMF	18%
Median time on drug	9.7 months
Percentage with JAK2 mutation	84.5%
Baseline spleen size, cm	8
Median no. patients with splenomegaly/hepatomegaly	20
Median BMI (range)	25.1 (17.9 to 49.7)

¹Source: Cooper et al. / *Blood* 2008; 110: 13

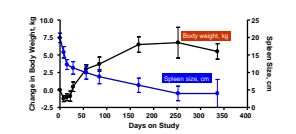
Splenomegaly, Satiety, and Cachexia

- Splenomegaly is associated with symptoms of early satiety and cachexia



Spleen Size and INC018424 Treatment

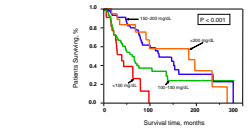
- Spleen size reduction correlates with body weight gain following treatment with INC018424



Note: Includes all subjects (N=47) with monitoring for dose change or dose interruption, but values after each time point.

Serum Cholesterol and Survival in MF

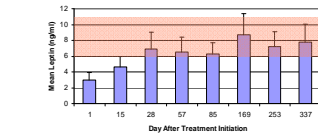
- Low serum cholesterol is associated with poor survival in patients with MF



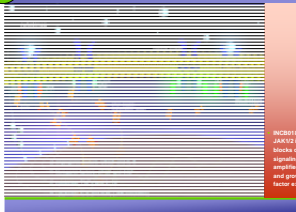
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INC018424 Normalizes Leptin Levels

- INC018424 raises abnormally low serum leptin levels into the normal range



INC018424 Mechanism of Action

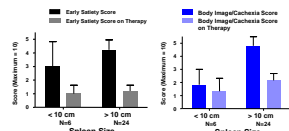


Summary of Results

- Patients
 - Thirty-four MF patients, treated for at least 2 months with INC018424 25 mg BID, were included in this analysis (for baseline data see panel 5)
- Improvements in appetite
 - At enrollment, a clearly positive correlation between the presence of anorexia and early satiety (by patient's report) and significant splenomegaly was observed
 - Treatment with INC018424 led to resolution of the symptoms of poor appetite and early satiety, along with the reduction in splenomegaly (see panels 6 and 7)
- Improvements in weight
 - MF patients on therapy initially lost weight, which reflects resolution of excess extracellular water (based on investigator-reported edema in peripheral edema, ascites, or splenomegaly) (see panels 6 and 7)
 - As the trial progressed, MF patients on INC018424 treatment progressively gained weight (mean increase of 10.5 kg at 1 month, 2.93 kg at 2 months, 3.70 at 3 months), and exhibited improved appetite
 - Weight gain was more consistent, of greater magnitude and more durable in patients who entered the study in the lowest quartile for BMI (see panel 8)

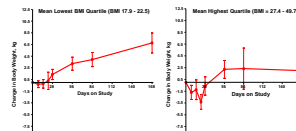
INC018424 and Symptoms of Splenomegaly

- Treatment with INC018424 25 mg BID resolves symptoms of splenomegaly



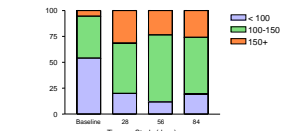
BMI and INC018424 Treatment

- Patients in lowest BMI quartile gained more weight over more time than patients in highest BMI quartile



INC018424 and Total Cholesterol

- Effect of INC018424 treatment on total serum cholesterol: categorical analysis



Conclusions

- Therapy with INC018424 improves the nutritional status of MF patients:
 - Pathologic weight loss
 - Hypercatabolism associated hypocholesterolemia
 - Pathologically decreased serum leptin
- Improved nutritional status of MF patients treated with INC018424 may reflect ability of JAK inhibition to target underlying pathophysiology of MF cachexia by
 - Reducing organomegaly
 - Reducing levels of pro-inflammatory cytokines
 - Reducing pro-inflammatory cytokine signaling

