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A phase 1 study of the Janus kinase 2 (*JAK2*)^{V617F} inhibitor, gandotinib (LY2784544), in patients with primary myelofibrosis, polycythemia vera, and essential thrombocythemia

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Abstract

Mutations in Janus kinase 2 (*JAK2*) are implicated in the pathogenesis of Philadelphia-chromosome negative myeloproliferative neoplasms, including primary myelofibrosis, polycythemia vera, and essential thrombocythemia. Gandotinib (LY2784544), a potent inhibitor of *JAK2* activity, shows increased potency for the *JAK2*^{V6l7F} mutation. The study had a standard 3 + 3 dose-escalation design to define the maximum-tolerated dose. Primary objectives were to determine safety, tolerability, and recommended oral daily dose of gandotinib for patients with *JAK2*^{V617F}-positive myelofibrosis, essential thrombocythemia, or polycythemia vera. Secondary objectives included estimating pharmacokinetic parameters and documenting evidence of efficacy by measuring clinical improvement. Thirty-eight patients were enrolled and treated (31

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.leukres.2017.08.010.

Conflict of interest

Li Li, Celine Pitou, Fabio P. Nunes, Gregory L. Price, Jennifer L. Giles, and Richard Walgren are employees of Eli Lilly and Company. Deborah D'Souza is an employee of inVentiv Health Clinical, LLC. Srdan Verstovsek received research support for conduct of this clinical study. Mohamed Salama received research support for pathology studies. Josef T. Prchal received research support for conduct of this clinical study. Ruben Mesa receives research support from Incyte, Gilead, CTI, Genentech, Lilly, Promedior, NS Pharma and is a consultant for Novartis and Shire.

myelofibrosis, 6 polycythemia vera, 1 essential thrombocythemia). The maximum-tolerated dose of gandotinib was 120 mg daily, based on dose-limiting toxicities of blood creatinine increase or hyperuricemia at higher doses. Maximum plasma concentration was reached 4 h after single and multiple doses, and mean half-life on day 1 was approximately 6 h. Most common treatment-emergent adverse events were diarrhea (55.3%) and nausea (42.1%), a majority of which were of grade 1 severity. Best response of clinical improvement was achieved by 29% of myelofibrosis patients. A ≥ 50% palpable spleen length reduction was observed at any time during therapy in 20/32 evaluable patients. Additionally, ≥ 50% reduction in the Total Symptom Myeloproliferative Neoplasm Symptom Assessment Form Score was seen in 11/21 (52%) and 6/14 patients (43%) receiving ≥ 120 mg at 12 and 24 weeks respectively. Gandotinib demonstrated an acceptable safety and tolerability profile, and findings at the maximum-tolerated dose of 120 mg supported further clinical testing. Clinicaltrials.gov identifier: NCT01134120.

Keywords

Myeloproliferative; Neoplasm; JAK-2; Gandotinib; Dosage

1. Introduction

The classic chronic myeloproliferative neoplasms (MPNs) are a group of hematologic malignancies characterized by the clonal proliferation of one or more myeloid lineages and include myelofibrosis occurring either *de novo* as primary myelofibrosis (PMF), or as a transformation from other classic MPNs, polycythemia vera (PV) or essential thrombocythemia (ET) [1]. Signs and symptoms of myelofibrosis include anemia, splenomegaly, bone marrow fibrosis, fatigue, weakness, night sweats, and weight loss [2–4], among others.

The mutation in the pseudokinase domain of Janus kinase 2 (*JAK2*); i.e., $JAK2^{V617F}$ is present in many patients with PMF, ET, and PV [5–7] and results in constitutive activation of *JAK2.* It is found in most patients with PV (≥ 95%) and in approximately two thirds of patients with ET and PMF [8–11]. Since wild-type *JAK2* plays a central role in multiple stages of hematopoiesis, it would be desirable to treat $JAK2^{V617F}$-positive cases by preferentially inhibiting $JAK2^{V617F}$ while minimizing inhibition of wild-type *JAK2.* Janus kinase *(JAK)* inhibitors can modulate *JAK* signal transducer and activator of transcription (STAT) signaling in MPNs [12,13], and they offer clinical benefits to patients with MPNs [14–18]. In addition to *JAK2* mutations, in view of growing evidence of interaction of inflammatory and coagulation pathways and the purported reduction of inflammatory response by *JAK2* inhibitors, we selected, among other markers, the changes of plasma levels of C4B binding protein (C4BP) after gandotinib therapy. C4b protein has a known role in complement activation and also binds protein C [19]. Protein C is the principal negative regulator of coagulation factors Va and Villa. C4BP is an important binding partner to vitamin K-dependent protein S in circulation. The high-affinity binding of protein S to C4BP serves the purpose of localizing complement regulatory activity close to the phospholipid membranes [20,21], affecting the regulation of blood coagulation [22]. Therefore, we assessed if C4BP levels correlate with the occurrence of thrombotic events

during the study, and performed *ad hoc* analysis to compare C4BP levels with different parameters of clinical response.

Gandotinib (LY2784544) is a potent inhibitor of *JAK2*^{V617F} [23]. Inhibition of the constitutive activity of the mutant *JAK2* could have a significant impact on the course of disease, disease complication rates, survival, and quality of life for patients with BCR-ABL1-negative classic MPN.

This phase 1 study evaluated the safety, tolerability, and pharmacokinetic parameters of gandotinib, and explored the potential efficacy of this study drug in patients with non-chronic myelogenous leukemia MPN harboring the *JAK2*^{V617F} mutation.

2. Materials and methods

2.1. Study population

Patients had a diagnosis of PV, ET, or myelofibrosis, as defined by the World Health Organization diagnostic criteria for MPNs [24]; detailed inclusion/exclusion criteria are described in the supplement.

2.2. Study design

This study was performed in accordance with the principles of good clinical practice to ensure compliance with appropriate ethical and quality standards. This was a multicenter, nonrandomized, open-label, phase 1 study of gandotinib that included a dose-escalation part followed by a maximum tolerated dose (MTD) dose-confirmation part (Fig. 1).

A 3 + 3 dose-escalation paradigm was used (further details of the study design are provided in the supplement). To evaluate the safety of a dose level, all subjects in a cohort must have received 1 cycle (28 days) of therapy. Part A1 was used to define the MTD of gandotinib at a fixed daily dose. As the predicted efficacious human exposure target was not reached at 120 mg (Supplementary Table S1 and Supplementary Fig. S1A), the study was amended after identification of dose-limiting toxicity (DLT) chemistry changes suggesting potential tumor lysis and renal function impairment at doses ≥120 mg. The amendment used a lead-in period where patients received 120 mg daily for 14–28 days prior to increasing to higher doses in an attempt to avoid the previously observed chemistry changes. In part Al, cycles 1 and beyond consisted of 28 days. In part A2, which tested the lead-in strategy, cycle 1 could be 42–56 days, depending on the length of the lead-in period (i.e., a 14 or 28 day lead in plus 28 day DLT period for the higher dose). Dose escalation was based primarily on safety with attention to signs of toxicity including tumor lysis syndrome [25,26]. If evidence of tumor lysis syndrome was observed, the patient was to be managed and re-evaluated appropriately. To prevent and manage potential tumor lysis syndrome, allopurinol could be administered based on MPN subtype and investigator discretion.

Patient-reported quality-of-life measures were assessed by the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) [27] and the European Organization for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire (QLQ-C30) [28]. Patient-reported outcomes (PRO) data were collected at baseline, approximately every

other cycle for the first year of therapy, quarterly after year 1, and at the post-therapy follow-up visit.

To explore safety and tolerability, the putative recommended phase 2 daily dose was explored during the dose-confirmation portion of the study (part B). Patients in part B were treated at doses no greater than the defined MTD from part A2. Part B was intended to target an enrollment of 10 patients.

2.3. Statistical methods

The analysis for this study was primarily descriptive and details are provided in the supplement. Data analysis was provided by received dose groups and for all study patients combined wherever appropriate. For continuous variables, summary statistics included number of patients, mean, median, standard deviation, minimum, and maximum. Categorical endpoints were summarized using frequency and percentages. Missing data were not imputed.

3. Results

3.1. Patient disposition

Of the 47 patients that entered the study, 38 were enrolled and received at least 1 dose of the study treatment. Of the 38 treated patients, 36 had discontinued treatment and 2 patients remained on treatment at the time of the database lock for this report (Supplementary Fig. S2). Across all cohorts, the most common reasons for discontinuation from study treatment were physician decision (n = 17), adverse events (n = 11), patient decision (n = 4), and progressive disease (n = 3). The most frequent adverse event that resulted in treatment discontinuation was renal failure (n = 4).

3.2. Patient demographics and baseline characteristics

The majority of patients were Caucasian (97.4%) and non-Hispanic (89.5%). Of 38 patients, 21 (55.3%) were male. The median body mass index (BMI) was 26 kg/m^2 (range: 18–41), and the mean and standard deviation of the baseline characteristic was 26.6 ± 5.24 kg/m^2 which makes the overall population BMI relatively consistent. The majority of patients had myelofibrosis followed by PV and ET (Table 1). The clinic-pathologic diagnosis in all patients was confirmed according to 2008 World Health Organization criteria [24]. Thirty-three patients (86.8%) reported receiving prior systemic therapies before enrollment into the study. The most commonly received prior therapy was hydroxyurea. On study, the most frequendy used concomitant drugs were allopurinol (27 patients [71.1%]) and aspirin (18 patients [47.4%]). Median time from diagnosis to study therapy was 438.5 days (range: 21–5498); the median regimen number of prior systematic treatments was 2 (range: 1–8).

3.3. Dose-limiting toxicity and maximum tolerated dose

This study sequentially tested daily oral administration of gandotinib at 30, 60, 120, 240, and then an intermediate dose of 200 mg. Table 2 summarizes the observed DLTs by received dose during cycle 1. No DLTs were seen at the first 3 tested doses. At 240 mg, one DLT was observed, and subsequently at 200 mg, 3 DLTs were observed. The protocol was

subsequently amended to include a lead-in period at 120 mg before escalation to a higher dose so as to facilitate reaching the targeted predicted efficacious exposure level. In total, 9 patients had a DLT. The most commonly reported DLTs were increased blood creatinine (5 patients), and hyperuricemia (2 patients). The MTD was determined to be 120 mg as this was the highest study dose level at which < 33% of patients experienced a DLT in cycle 1. In addition, the use of a 120-mg lead-in dose did not facilitate a transition to higher doses with acceptable tolerability.

3.4. Safety

3.4.1. Extent of exposure—For the study population, the median number of cycles completed was 6 (range: 1–44). The median duration of treatment exposure for all 38 patients was 170 days (range 2–1350).

3.4.2. Treatment-emergent adverse events—Of 38 patients who received at least 1 dose of study therapy, 34 (89.5%) reported ≥1 treatment-emergent adverse event (TEAE) that was possibly related to study drug (Supplementary Table S2). The most common TEAEs were diarrhea (21 patients [55.3%]) and nausea (16 patients [42.1%]). The majority of these events were of grade 1 severity.

3.4.3. Serious adverse events and deaths—During the study, 9 patients (23.7%) reported ≥ 1 serious adverse event (SAE) that was possibly related to study therapy (Table 3). Of the 9 patients, 7 had myelofibrosis, while there was 1 each with ET and PV. One patient in cohort 3 died during the study due to bilateral pneumonia which was assessed as not related to the study drug.

3.4.4. Clinical laboratory evaluation—Using the definitions of Cairo and Bishop [25,26], laboratory tumor lysis syndrome (LTLS) was defined as either a 25% change or level above or below normal for any 2 or more serum values of uric acid (≥ 476 μmol/L), potassium (≥ 6.0 mmol/L), phosphorus (≥ 1.45 mmol/L in adults), and calcium (≤ 1.75 mmol/L) within 3 days before or 7 days after initiation of chemotherapy. Clinical tumor lysis syndrome (CTLS) was defined as the presence of LTLS and any 1 or more of the following criteria, creatinine (≥1.5 times the upper limit of normal), cardiac arrhythmia/sudden death, and seizures. Two patients reported CLTS and LTLS events. Five patients reported 8 LTLS events. Six patients reported 8 CTLS events (6 were grade 2 CTLS events and 2 were grade 3 CTLS events).

3.5. Pharmacokinetics

The maximum plasma concentration (C_{max}) was reached, on average, 4 h after single and multiple doses. The mean gandotinib half-life on day 1 across all doses was ~ 6 h, with a coefficient of variation (CV) of 43%. This terminal elimination half-life ($t_{1/2}$) value was associated with gandotinib being rapidly cleared (mean value of 80.7 L/h for the apparent clearance (CL/F) with a CV of 68) with an extensive distribution into the body (mean value of 682 L for the apparent volume of distribution (Vz/F) with a CV of 58). Supplementary Table S1 represents the pharmacokinetic parameters of interest. Supplementary Fig. S1A represents the individual area under the plasma concentration-time curve from time 0–8 h

[$AUC_{(0–8h)}$] and Supplementary Fig. S1B represents individual C_{max} on cycle 1 day 1. A definitive statement on dose proportionality could not be made based on these data due to high variability and available sample size. However, both C_{max} and exposures appeared to increase with an increase in dose. The influence of the individual baseline BMI and weight values was assessed on the dose normalized maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) values and no specific trend was detected from the visual representation.

From a toxicity-versus-exposure relationship perspective, daily administration of dose levels above 120 mg once daily was associated with several cases of renal adverse events. There is a clear exposure difference between the 120-mg dose and higher doses (such as 200 mg). Hence, one plausible reason for the toxicity observed is the increased exposure at doses of 200 mg or above, even if, at the patient level and within a dose level, this trend is less apparent. It is also important to note that the predicted daily human exposure target of 6920 ng*h/mL was not reached at 120 mg.

3.6. Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) and European Organization for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire (EORTC QLQ-C30)

A total of 38 patients contributed PRO data from 238 visits (35 baseline visits, 182 on-therapy visits, and 21 post-therapy follow-up visits). PRO data was reported for 87% of the visits where PRO data was requested.

For all doses at weeks 16 and 32, no statistically significant deterioration in functioning or QOL was observed from patient-reported EORTC data (cognitive, emotional, physical, role, social and global health status/QOL). A numerical improvement at week 16 was observed in physical and social functioning (Supplementary Table S3).

In the same cohort of 21 patients with a starting dose of ≥120 mg, no statistically significant deterioration or improvement was observed from baseline in EORTC scores either at week 16 or at week 32.

For the MPN-SAF scores, among patients who received a starting dose of ≥120 mg at 12 weeks, 11 of 21 patients had a ≥ 50% reduction in Total Symptom Score. At 24 weeks, 6 of 14 patients had a ≥50% reduction in Total Symptom Score (Fig. 2).

3.7. Efficacy

Among 31 patients with myelofibrosis, 9 (29%) patients achieved a best response of clinical improvement. Investigator International Working Group (IWG) responses were seen in the first dose (30 mg) level tested. Efficacy was documented by measuring clinical improvement as defined by the IWG criteria, and the European Leukemia Net response criteria for PV and ET [29,30]. The duration of best response for these 9 patients ranged from 1 to 18 cycles. Across all cohorts, 20 of 32 evaluable patients had a palpable spleen length reduction of ≥ 50% at any time during therapy. Of the 6 patients with PV, 3 (2 in cohort 6 and 1 in cohort 7) had a clinic-hematologic partial response that varied in duration (range: 3–16 cycles). The

remaining 3 PV patients had no clinic-hematologic response. One patient with ET had a partial response.

Changes in the *JAK2*^{V617F} allele mutation burden across the 3 MPN subtypes of patients showed a heterogeneous trend (Supplementary Fig. S3). Across all cohorts, 5 of 36 evaluable patients had an allele burden reduction of ≥50% at any time. Among all the laboratory markers studied, coagulation marker C4BP showed potential for being a biomarker for spleen size reduction. A longitudinal review of the relationship between C4BP and spleen size for different doses of gandotinib, showed an inverse correlative trend for many patients in the myelofibrosis subtype and this trend was further confirmed by plotting the maximum reduction in spleen size from baseline versus C4BP for various doses of gandotinib (Supplementary Fig. S4). The reduction in spleen size corresponded with an increase in C4BP compared at various doses of gandotinib. At the maximum dose of 300 mg, increased C4BP corresponded with a maximum percent change in spleen size from baseline. In the scatter plot of C4BP versus total protein S at baseline, myelofibrosis patients had a positive correlation of 0.7. Over the short follow-up of this study there was no clear trend seen in terms of bone marrow myelofibrosis grading for myelofibrosis patients, however, this potentially could be related to the fact that many patients lacked enough data points.

4. Discussion

In this phase 1 dose-escalation study in patients with *JAK2*^{V617F}-mutation positive MPN, a recommended phase 2 dose of 120 mg given once daily by mouth with food was identified as the MTD. Treatment with gandotinib at a daily oral dose of 120 mg or lower was associated with an acceptable safety and tolerability profile. Clinical improvements were observed in MPN patients at this dose.

While the majority of the 38 patients enrolled and treated in the study had myelofibrosis (81.6%), 15.8% of patients had a diagnosis of PV and 1 patient (2.6%) had ET. At the time of the final study report, 36 (94.7%) had discontinued study treatment while 2 (5.3%) remained on study treatment. The most common reason for early discontinuation from study treatment was physician decision. Case report forms collected additional explanation details to support this decision. In a majority of cases, the explanations were related to challenges in implementation of the response criteria which did not reflect the need to account for discontinuation due to a lack of initial response/failure to respond or a loss of response. Of the 17 patients who discontinued due to physician decision, 7 did so for a lack/loss of efficacy (verbatim terms from the investigators), 4 due to lost response to medication/lack/loss of response (verbatim terms from the investigators), and 1 each for no evidence of specific response per investigator, suboptimal response to study medication, relapse, patient lost response due to dose reduction, loss of control of the disease sign and symptoms, and not responding to treatment.

Other reasons for discontinuation included adverse events, patient decision, and progressive disease. One patient died during the course of the study due to bilateral pneumonia. Nineteen patients reported at least 1 SAE and 11 patients discontinued the study treatment

due to adverse events. The most frequent adverse event that resulted in treatment discontinuation was renal failure. At 120 mg, the most frequently reported treatment-related adverse events were diarrhea and nausea.

Previous studies with other *JAK2* inhibitors have also reported common gastrointestinal side effects such as nausea and diarrhea suggesting the possibility there may be a class effect in the gastrointestinal tract or a relationship to a treatment effect on disease specific gastrointestinal involvement [16,18,31,32]. During the study the observed increases in serum creatinine were handled as potential renal toxicities. In the majority of patients with an increase in serum creatinine the increase was small, without progression, and resolved after drug discontinuation. While gandotinib has not been tested against transporters involved in creatinine disposition, the results of studies with INCB039110 suggest that the conclusions drawn from the use of serum creatinine as a marker of renal function should be made with caution, acknowledging the possibility of artifactual increases resulting from modulation of transporters involved in creatinine clearance [33].

Approximately 29% (9/31) of patients with myelofibrosis achieved a best response of clinical improvement. Across cohorts, 20 of 32 evaluable patients had a palpable spleen length reduction of ≥ 50% at any time. We report here a strong inverse correlation between reduction of spleen size and C4BP protein; however, the validity of this observation and its biological significance will need to be elaborated by future laboratory as well as clinical studies. Approximately 52% of patients who received a starting dose of ≥120 mg at 12 weeks (43% at 24 weeks) had a ≥ 50% reduction in Total Symptom Score.

The $JAK2^{V617F}$ allele mutation burden across the MPN subtypes of patients showed a heterogeneous trend, 5 of 36 evaluable patients had an allele burden reduction of ≥ 50% at any time. Previous studies have shown that although patients may experience improvements in splenomegaly and symptoms with *JAK2* inhibitors, the $JAK2^{V617F}$ allele burden may not change with treatment [16,18,32]. Consistent with the findings of this study, the relationship between clinical benefit and reduction in the $JAK2^{V617F}$ allele burden has not yet been demonstrated [34]. It is possible that the $JAK2^{V617F}$ allele burden did not change significantly, because the optimal efficacy AUC was not reached. Patients with myelofibrosis had a positive correlation of 0.7 in the scatter plot of C4BP versus total protein S at baseline. C4B binding protein is known to inhibit the classic complement cascade by blocking the formation and promoting the decay of the C3 convertase, C4b, C2a. Protein S is a cofactor for the anticoagulant effects of activated protein C. About 60% of protein S is complexed to C4BP, and therefore the positive correlation is expected between C4BP and protein S. C4B binding protein and protein S were initially assessed in this study to determine a possible correlation between the circulating levels of these proteins and the occurrence of thrombotic events in patients with myelofibrosis. Although we did not see any correlation between C4B binding protein and the very few observed thrombotic events in this study (data not shown) we did identify as part of an *ad hoc* analysis that baseline levels of C4B binding protein were correlated with better responses, particularly in patients receiving the higher doses of gandotinib (Supplementary Fig. S4). It is unclear at this time what the underlying mechanism for this association is, and whether high C4B binding protein levels at baseline is a good prognostic factor in myelofibrosis, or if it could be a predictive marker for *JAK*

inhibitor treatments in myelofibrosis. Additional studies in larger cohorts are necessary to answer these questions.

Gandotinib pharmacokinetic parameters showed high variability; although a statistical analysis could not conclude dose proportionality, both C_{max} and AUC increased with dose. Gandotinib appeared to be eliminated rapidly, with a $t_{1/2}$ of approximately 6 h.

In conclusion, gandotinib was generally well tolerated in the enrolled MPN patients, and the recommended phase 2 dose of 120 mg daily was associated with clinical improvements.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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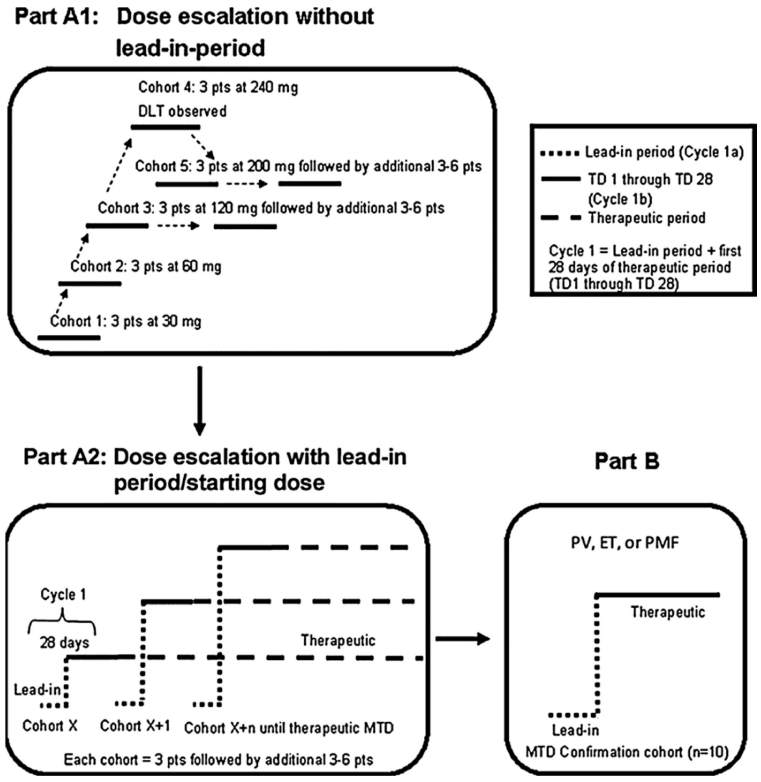

Fig. 1.

Study design. Part A1. Dose-escalation without lead-in period. Part A2. Dose-escalation with lead-in period. Starting dose for lead-in was 120 mg. After the lead-in period doses of 200 and 300 mg were tested. Part B. Dose-confirmation portion of the study; For Part B, a dose of 120 mg was used. Abbreviations: DLT = dose-limiting toxicity; ET = essential thrombocythemia; MTD = maximum tolerated dose; PMF = primary myelofibrosis; pts = patients; PV = polycythemia vera; TD = therapeutic day.

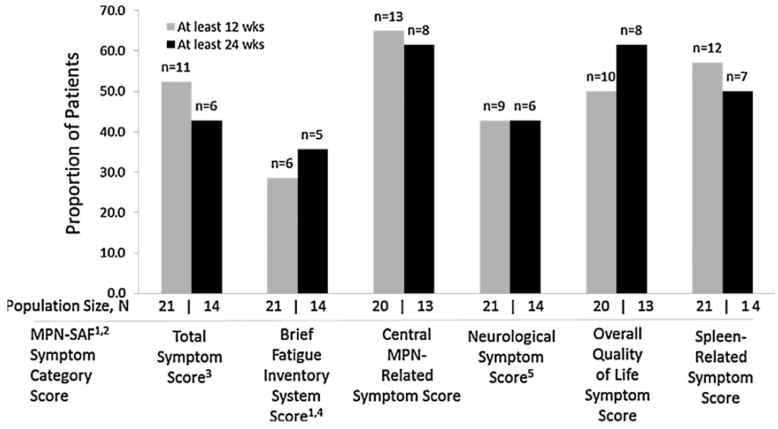

Fig. 2.

Number of patients with a ≥50% reduction in MPN-SAF scores among patients receiving starting dose ≥ 120 mg. References: [1]Mesa RA, et al. *Leuk Res* 2009;33:1199–1203; [2]Mesa RA, et al. *Cancer* 2007;109:68–76; [3]Mesa RA, Cortes J. *J Hematol Oncol* 2013;6:79; [4]Mendoza TR, et al. *Cancer* 1999;85:1186–1196; [5]Scherber R, et al. *Blood* 2011;118:401–408. Abbreviations: MPN-SAF = Myeloproliferative Neoplasm-Symptom Assessment Form; wks = weeks.

Table 1

Patient demographics and baseline characteristics.

Characteristic	Total (N = 38)
Age (years), mean (SD)	66.3 (10.1)
Thrombotic events in last 12 months, n (%)	3 (7.9)
RBC Transfusions in last 2 months, n (%)	8 (21.1)
Phlebotomies, n (%)	2 (5.3)
JAK2^{V617F} burden, mean%, (SD)	61.5 (32.0)
Spleen size[a]	13.0 (7.3)
Total protein S (%), mean (SD)	90.7 (24.2)
Free protein S (%), mean (SD)	65.7 (23.2)
C4B binding protein, mean (SD)	101.7 (28.4)
Leukocyte alkaline phosphatase, mean (SD)	112.8 (29.2)
Bone marrow biopsy: total cell count, mean (SD)	318.1 (170.4)
ECOG Performance Status, n (%)	
0	3 (7.9)
1	30 (78.9)
2	3 (7.9)
Bone Marrow Fibrosis, n (%)	
Grade 0	1 (2.6)
Grade 1	6 (15.8)
Grade 2	14 (36.8)
Grade 3	10 (26.3)
No bone marrow fibrosis[b]	7 (18.4)
Basis of Initial Pathological Diagnosis	
PMF	31 (81.6)
PV	6 (15.8)
ET	1 (2.6)
Spleen Size, Frequency (%)	
≤ 5 cm	6 (15.8)
> 5, ≤ 10 cm	6[c] (15.8)
> 10 cm	22 (57.9)
Missing	4 (10.5)

[a] This study did not use imaging, and this was a measurement from the costal margin.

[b] All patients with either PV or ET have no value for bone marrow fibrosis.

[c] 1 (100.0%) in cohort L (patients withdrawn in the leading phase – never assigned to a cohort).

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ET = essential thrombocythemia; n = number of patients; PMF = primary myelofibrosis; PV = polycythemia vera; RBC = red blood cell; SD = standard deviation.

Table 2

Summary of dose-limiting toxicities by received dose during cycle 1.[a]

Cohort	1	2	3	4	5	6		7		L[b]	Total
Dose (mg)	30	60	120	240	200	120 (Cycle la)	200 (Cycle 1b)	120 (Cycle 1a)	300 (Cycle 1b)	120	
Population	N = 3	N = 3	N = 10	N = 3	N = 3	N = 8	N = 7	N = 6	N = 5	N = 1	N = 37
Patients with DLT, n (%)	0	0	0	1 (33.3)	3 (100)	3 (37.5)	3 (42.9)	0	2 (40.0)	0	9 (24.3)
Blood creatinine increased	0	0	0	0	1 (33.3)	3 (37.5)	3 (42.9)	0	1 (20.0)	0	5 (13.5)
Hyperuricemia	0	0	0	1 (33.3)	1 (33.3)	0	0	0	0	0	2 (5.4)
Hyperkalemia	0	0	0	0	1 (33.3)	0	0	0	0	0	1 (2.7)
Renal failure acute	0	0	0	0	0	0	0	0	1 (20.0)	0	1 (2.7)

[a]Per protocol, dose-limiting toxicities were those events that occurred within the first cycle of treatment in dose-escalation stage (Part A).

[b]Cohort L = Patients withdrawn in the lead-in phase – never assigned to a cohort.

Abbreviations;: DLT = dose-limiting toxicity; N = total population size; n = number of patients.

Table 3

Serious adverse events possibly related to study drug treatment.

	30 mg (N = 3) n%	60 mg (N = 7) n%	120 mg (N = 34) n%	200 mg (N = 15) n%	240 mg (N = 3) n%	300 mg (N = 5) n%	Total[a] (N = 38)	Grade 3 and above, Total[a]	Grade 4 and above, Total[a]
Patients with ≥ 1 SAE[b]	0	0	0	4 (26.7)	1 (33.3)	1 (20.0)	9 (23.7)	6 (15.8)	2 (5.3)
Anemia	0	0	0	1 (6.7)	0	0	1 (2.6) MF	1 (2.6)	0
Blood creatinine increased	0	0	0	3 (20.0)	1 (33.3)	0	5 (13.2) MF	1 (2.6)	0
Hyperuricemia	0	0	0	1 (6.7)	0	0	2 (5.3) MF	2 (5.3)	2 (5.3)
Hyperkalemia	0	0	0	0 (0.0)	0	0	1 (2.6) MF	0	0
Renal failure, acute	0	0	0	1 (6.7)	0	1 (20.0)	4 (10.5) [2 MF, 1 ET, 1 PV]	2 (5.3)	0

[a]The total column includes events for which the study drug dose that the patients were taking could not be determined;

[b]Three patients reported SAEs while on the study but not receiving treatment. These SAEs were blood creatinine increased, hyperuricemia, hyperkalemia, and renal failure acute.

Abbreviations;: ET = essential thrombocythemia; MF = myelofibrosis; N = total safety population at each received dose or total; n = number of received dose patients with at least one SAE; PV = polycythemia vera; SAE = serious adverse event.