Phase 1/2, dose-escalation study of oral NS-018 in patients with primary myelofibrosis (PMF), post-polycthemia vera MF (post-PV MF), or post-essential thrombocythemia MF (post-ET MF)

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INTRODUCTION

JAK2/STAT signaling in MF, most commonly as a result of the hyperactivating JAK2 V617F mutation, underpins disease pathogenesis1,2; inhibition of JAK-STAT signaling is a key target for the treatment of MF.3

Avoidance of JAK2/STAT signaling in MF might be achieved by treating with a potent and specific inhibitor of JAK2.

METHODS

This is a multicenter, Phase 1/2, 3+3 dose-escalation study of once-daily (QD) or twice-daily (BID) oral NS-018 in patients with primary MF, post-PV MF, or post-ET MF.4

The study was conducted according to the International Conference on Harmonization (ICH) guidelines and was reviewed and approved by the institutional review board at each center. Patients provided written informed consent.

Inclusion criteria included adult patients with MF, post-PV MF, or post-ET MF who had received ≥1 prior JAK2 inhibitor and had ≥1 symptom or ≥1 physical manifestation of MF based on the Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, age ≥18 years, and adequate organ function. Patients were excluded if they had prior allogeneic hematopoietic stem cell transplantation, were pregnant, and had a primary skin MF.

Patients were screened for prior JAK2 inhibitor exposure for at least 12 weeks before the first dose of study treatment. Patients were treated until disease progression or unacceptable toxicity, following informed consent to use blood donations at centers in the European Union (EU) for follow-up disease status, or withdrawal of consent to participate in the study.

Patients were randomized to 1 of 3 dose levels within a dose cohort, with 3–8 patients/dose cohort: (1) NS-018, given in 28-day cycles, in patients with primary MF, post-PV MF, or post-ET MF, beginning at 100 mg QD or BID; (2) NS-018, given in 28-day cycles, in patients with primary MF, post-PV MF, or post-ET MF, beginning at 200 mg QD; (3) NS-018, given in 28-day cycles, in patients with primary MF, post-PV MF, or post-ET MF, beginning at 300 mg QD.

Patients were eligible for dose escalation to the next dose level if they had no serious adverse events (AEs) or death of any grade associated with NS-018 treatment, no new or progressive ≥3-grade AEs, no ≥5-grade AEs, no >50% increase in tumor markers, and no treatment-related deaths.

The median age (range) was 69.5 (38–83) years (Table 2) and 23 patients had received previous JAK2 inhibitor treatment.

The proportion of patients with ≥50% reduction in spleen size was observed in 36% (13/36) of patients. Among evaluable patients, ≥50% improvement in spleen size was observed in 47% (17/36) of patients (Table 3).

RESULTS

Adverse events (AEs) were graded according to the common toxicity criteria for adverse events (CTCAE) version 4.0.

In all dose levels, the most frequent ≥3-grade AEs were nausea, fatigue, and myalgia. Between 25% and 50% of patients experienced grade 3 myalgia, nausea, fatigue, temperature increase, and headache. In general, all ≥3-grade AEs were observed over multiple dose levels (Table 3).

The proportion of patients with ≥50% reduction in their Worst pain score was observed in 75% (27/36) of patients (Table 3).

The proportion of patients with ≥75% improvement in 50% reduction in individual symptoms across all dose cohorts for (A) all evaluable patient population and (B) patients who had received previous JAK2 inhibitor treatment.

REFERENCES


CONCLUSIONS

Despite initially promising clinical benefit, the study was discontinued, with ongoing patient enrollment for Phase 2 part of the study.

Safety assessments

Patients without previous JAK2 inhibitor treatment were included in the Phase 1 dose-escalation study (Phase 1/2, 3+3 dose-escalation study of oral NS-018 for patients with MF, post-PV MF, or post-ET MF), and patients with previous JAK2 inhibitor treatment were included in the Phase 2 part of the study.

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No relevant conflicts of interest to disclose.

DISCLOSURES

No relevant conflicts of interest to disclose.