388 Rusfertide (PTG-300) Controls Hematocrit Levels and Essentially Eliminates Phlebotomy Requirement in Polycythemia Vera Patients

Authors: Ronald Hoffman, Marina Kremyanskaya, Yelena Ginzburg, Andrew T. Kuykendall, Naveen Pemmaraju, Abdulraheem Yacoub, Jay Yang, Suneel Gupta, Frank Valone, Sarita Khanna, Srdan Verstovsek

Background:

To reduce the incidence of thrombotic events, polycythemia vera (PV) patients are treated with periodic therapeutic phlebotomy (TP) alone or in combination with either hydroxyurea (HU), ruxolitinib (RUX) or interferon (IFN) to maintain hematocrit (HCT) levels below 45% as per NCCN guidelines. Since patients are seen periodically, PV patients spend significant time with HCT levels above 45%, thereby increasing their risk of thrombosis [Marchioli NEJM 2013]. PV is also associated with systemic symptoms with fatigue found to be the most prevalent and severe symptom in an international survey among PV patients [Scherber Cancer 2016]. Symptomatic iron deficiency represents an unaddressed clinical challenge to PV patients as most PV patients present with iron deficiency at diagnosis due to increased iron utilization [Ginzburg Leukemia 2018] which worsens after repeated TP. Ultimately, this leads to suppression of hepcidin, the body's main negative regulator of iron metabolism, resulting in increased iron absorption and iron recycling, fueling expanded erythropoiesis resulting in a continued need for TP and exacerbating patients' iron deficiency. Thus, we hypothesized that the therapeutic administration of a hepcidin mimetic agent would be useful in achieving HCT control in PV patients. The current report summarizes data after completion of accrual to a Phase 2 clinical trial of 63 PV patients who have been dosed with rusfertide for 8-92 weeks.

Methods:

PTG-300-04 (NCT04057040) is a Phase 2 trial consisting of three phases: (1) a 28-week dose-finding; (2) a 12-week blinded randomized withdrawal (1:1) rusfertide vs placebo; and (3) a 52-week open label extension (Figure 1). Eligibility criteria include PV diagnosis (by 2016 WHO criteria) and ≥3 phlebotomies with or without concurrent cytoreductive therapy to maintain HCT below 45% in the 24 weeks prior to enrollment in Part 1. Rusfertide doses of 10-120 mg were self-administered subcutaneously by patients and adjusted to consistently maintain HCT below 45%. The primary endpoint for randomized withdrawal phase is the comparison of proportion of subjects who maintain hematocrit control without phlebotomy eligibility during the 12 weeks of double-blind treatment.

Results:

Sixty-three subjects were enrolled in this trial. 71% patients were male, and 44% of all patients were low-risk. TP alone was the most common treatment (n=30) and was combined with HU in 18 patients, IFN in 10 patients, RUX in 3 patients, a combination of RUX and HU in 1 patient, a combination of IFN and HU in 1 patient, and a combination of IFN and RUX in 1 patient. Median number of TP in the 28 weeks prior to enrollment varied was 4 with maximum of 10. Seven patients dropped out of the trial: 1 due to asymptomatic thrombocytosis. Remaining withdrawals were due to subject decision. Following initiation of rusfertide therapy, TP was essentially eliminated in all sub-groups (Figure 2). HCT was maintained consistently below 45% and there was a decrease in red blood

cell (RBC) counts and an increase in both mean corpuscular volume and mean corpuscular hemoglobin Values. Prior to treatment, these mean iron-related parameters were consistent with systemic iron deficiency as previously reported in PV patients. PV patients on rusfertide demonstrated progressively increased serum ferritin levels approaching the normal range indicating a reversal of systemic iron deficiency. Lastly, a third of the subjects have a reduction of at least a 40% in Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) Total Symptom Scores from baseline at week 28. After 8 weeks of treatment, 69% of patients reported improvement in the Patient Global Impression of Change compared to baseline. During this relatively short follow-up period, no significant increases in JAK2 V617F variant allele frequency were observed and none of the treated PV patients suffered from a thrombotic event. The most frequent adverse events were injection site reactions reported following injections. These were transient in nature and generally managed by antihistamines. Most of the adverse events were grade 1-2 and there were no drug-related serious adverse events or grade 3 or 4 adverse reactions.