A Phase 2, Multicenter, Open-Label Study of the Safety and Efficacy of Luspatercept in Subjects With Myeloproliferative Neoplasm (MPN)-Associated Myelofibrosis and Anemia With or Without RBC Transfusion Dependence

Ruben A. Mesa1, Giovanni Barosi1, Claire N. Harrison2, Jean-Jacques Kiladjian3, Robert Peter Gale4, Abderrahmane Laadem5, Torsten Gerike6, Peter G. Linde7, Matthew L. Sherman8, Joseph Pariseau9, Srdan Verstovsek10

1. UT Health San Antonio Cancer Center, San Antonio, TX, USA; 2. RCCS Policlinico San Matteo, Pavia, Italy; 3. Guy’s and St Thomas’ NHS Foundation Trust, London, UK; 4. Hôpital Saint-Louis and Université Paris Diderot, Paris, France; 5. Celgene Corporation, Summit, NJ, USA; 6. Acceleron Pharma, Cambridge, MA, USA; 7. MD Anderson Cancer Center, Houston, TX, USA

BACKGROUND

• Myeloproliferative neoplasm (MPN)-associated myelofibrosis (MF) is a clonal myeloid neoplasm characterized by bone marrow fibrosis, defective bone marrow function, extramedullary hematopoiesis, a propensity for transformation to blast phase, and inflammation1

• Anemia is an important complication of MPN-associated MF, eventually developing in all patients1,2

• Anemia and red blood cell (RBC) transfusion dependence (TD) are independent adverse prognostic and predictive variables for survival among these patients1,4

Luspatercept

• Luspatercept is a recombinant fusion protein consisting of a modified activin receptor type IIb linked to the Fc domain of human immunoglobulin G1 (IgG1) (Figure 1)5,6

• Luspatercept acts as an erythroid maturation agent by binding specific transforming growth factor-β (TGF-β) superfamily ligands such as growth differentiation factor-11 (GDF11), blocking their inhibitory effect, and leading to up-regulation of the transcription factor CCAAT/enhancer-binding protein β (C/EBPβ), increased erythroid progenitor survival and proliferation, and increased erythroid differentiation1,2,7

OBJECTIVE

• To evaluate the efficacy and safety of luspatercept for the treatment of anemia in patients with MPN-associated MF with or without RBC-TD

STUDY DETAILS

STUDY DESIGN AND TREATMENT

• The study comprises 3 periods (Figure 2):

  • Screening period
  • Treatment period (primary phase, disease response assessment at day 169, and extension phase)
  • Post-Treatment Follow-up Period

• This is an ongoing, multicenter, open-label, phase 2 study

STUDY POPULATION

• Inclusion criteria:
  - Age ≥ 18 years
  - MPN-associated MF (primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF)
  - Anemia, defined as:
    - Cohorts 1 and 3a: ≥ 3 hemoglobin (Hb) levels ≤ 9.5 g/dL or ≥ 3 days (including day of dosing), with no RBC transfusions in the 84 days prior to cycle 1 day 1 (C1D1); ≥ 42 days between measurements will be excluded
    - Cohorts 2 and 3b: average RBC transfusion frequency of 2–4 RBC units/28 days over ≥ 84 days prior to C1D1, with an interval ≥ 42 days without ≥ 2 RBC transfusion; Hb < 13 g/dL on C1D1 prior to luspatercept administration
  - Eastern Cooperative Oncology Group performance status ≤ 2

STUDY DESIGN AND TREATMENT

• The study comprises 3 periods (Figure 2):
  - Screening period
  - Treatment period (primary phase, disease response assessment at day 169, and extension phase)
  - Post-treatment follow-up period

SCREENING PERIOD

• All screening procedures are conducted ≤ 28 days prior to enrollment

TREATMENT PERIOD

• All patients will receive luspatercept 1 mg/kg subcutaneously on day 1 of each 21-day cycle

• Patients will be enrolled in cohorts according to RBC transfusion requirement:
  - Cohorts 1 and 3a (anemia only)
  - Cohorts 2 and 3b (RBC-TD)

• Best supportive care may be used in combination with study treatment

• Disease response assessment should be completed at day 169 following the first dose of study treatment
  - Responders may continue treatment for up to an additional 1.5 years
  - Non-responders will discontinue treatment

ENDPOINTS

• Primary and secondary endpoints are listed in the Table

• Exploratory endpoints include treatment exposure-response, biomarkers, and mutational analyses

• All efficacy analyses will be performed primarily on the intent-to-treat population, defined as all patients enrolled

• Confirmatory efficacy analyses will be performed on the efficacy-evaluable population, defined as all patients who:
  - Received ≥ 3 cycles of study treatment and remain on study for ≥ 21 days after the third study dose OR
  - Achieved Hb > 13 g/dL in < 3 cycles

• Safety analyses will be performed on all patients receiving ≥ 1 study treatment dose

• Adverse events and laboratory abnormalities are classified according to the NCI-CTCAE version 4.03

• Pharmacokinetic analyses will be based on all patients who have evaluable concentration data to determine the pharmacokinetic parameters

POST-TREATMENT FOLLOW-UP PERIOD

• After treatment discontinuation, follow-up safety data will be collected up to 42 days after the last dose of study treatment

• Safety data will then be collected every 3 months for up to 3 years after the last dose of study treatment or until death, consent withdrawal, or loss to follow-up

STUDY DETAILS (cont.)

POSTER TPS7083

Figure 2. Study Design

Primary Phase

- Day 169 disease assessment
- If clinical benefit: Continue for up to an additional 1.5 years
- If clinical benefit: Discontinue treatment

Secondary Phase

- Time to anemia response
- Duration of anemia response
- Frequency of RBC transfusions (mean RBC units/4 weeks)
- Symptom response improvement (defined as ≥ 50% reduction in fatigue symptoms or ≥ 50% reduction in total symptom score by MF-SAF or MPN-SAF)
- HRQoL improvement
- Safety
- Pharmacokinetics
- Antidrug antibodies

Table. Study Endpoints

Endpoints Cohorts 1 and 3a (Anemia Only) Cohorts 2 and 3b (RBC-TD)

Primary

- ≥ 1.5 g/dL Hb increase from baseline over any consecutive 84-day period without an RBC transfusion

Secondary

- Time to anemia response
- Duration of anemia response
- Frequency of RBC transfusions (mean RBC units/4 weeks)
- Symptom response improvement (defined as ≥ 50% reduction in fatigue symptoms or ≥ 50% reduction in total symptom score by MF-SAF or MPN-SAF)
- HRQoL improvement
- Safety
- Pharmacokinetics
- Antidrug antibodies

 aftermath: treatment discontinuation (QR) Code are for personal use only

REFERENCES


ACKNOWLEDGEMENTS AND DISCLOSURES

This study was sponsored by Celgene Corporation, Summit, NJ, USA. The authors received editorial assistance and printing support in the preparation of this poster from Excerpta Medica (Daniel Gimlin), PhD, supported by Celgene Corporation. The authors are fully responsible for all content and editorial decisions.


Correspondence

Ruben A. Mesa, rmesa@Upstate.edu

Presented at the 2018 Annual Meeting of the American Society of Clinical Oncology (ASCO); June 1–5, 2018; Chicago, IL, USA.