RESPONSE is a pivotal Phase III, global, randomized, open-label study of Jakavi® (ruxolitinib) compared to best available therapy in patients with polycythemia vera (PV) resistant to or intolerant of hydroxyurea.

PV is a rare and incurable blood cancer typically associated with an elevated hematocrit, which can lead to an increased risk of blood clots.

PV patients with resistance to or intolerance of hydroxyurea are considered to have uncontrolled disease, which may be characterized by:
- Hematocrit levels greater than 45% and/or elevated white blood cell count
- Need for frequent phlebotomy to keep hematocrit less than 45%
- Treatment-related adverse reactions
- Burdensome symptoms

**Trial Design**

- Jakavi in patients with PV resistant to or intolerant of hydroxyurea
- 222 PV patients at more than 90 clinical trial sites worldwide
- Study duration = 80 weeks

- Patients randomized 1:1
  - 110 patients randomized to Jakavi (starting dose of 10 mg BID)
  - 112 patients randomized to best available therapy (dosing N/A)
    (defined as investigator selected monotherapy or observation only)

At or subsequent to week 32, patients on best available therapy were eligible to cross over if they did not have a response or if they met criteria for progression. 86% of patients crossed over to Jakavi treatment. Patients who received benefit from Jakavi at week 80 were eligible for an extension study.

**Primary Objective**: Proportion of patients whose hematocrit was controlled without phlebotomy eligibility from week 8 through 32 (with no more than one phlebotomy eligibility between randomization and week 8) and whose spleen volume was reduced by 35% or more from baseline as assessed by imaging at week 32.

**Additional Objectives**: Durable primary response, complete hematological remission, safety and symptom improvement.

Primary endpoint and additional objectives were assessed after all patients completed the week-48 visit or discontinued treatment.

**Definitions**

- **Hematocrit** is a measure of the volume percentage of red blood cells in whole blood
- **Phlebotomy** is a procedure to remove blood from the body to reduce the concentration of red blood cells

RESPONSE (Randomized Study of Efficacy and Safety in Polycythemia Vera with JAK Inhibitor Ruxolitinib Versus Best Available Care) is the first Phase III study to evaluate a JAK inhibitor (ruxolitinib) in treating PV.

Jakavi is approved by the European Commission for the treatment of adult patients with PV who are resistant to or intolerant of hydroxyurea. Jakavi is also currently approved in more than 80 countries for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis.

See important safety information on reverse side.
About Jakavi

Jakavi (ruxolitinib) is an oral inhibitor of the JAK 1 and JAK 2 tyrosine kinases. Jakavi is approved by the European Commission for the treatment of adult patients with polycythemia vera (PV) who are resistant to or intolerant of hydroxyurea and for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis. Jakavi is approved in more than 80 countries for patients with myelofibrosis, including countries in the European Union, Canada, Japan and some countries in Asia, Latin and South America. Additional worldwide regulatory filings are underway in myelofibrosis and PV.

Novartis licensed ruxolitinib from Incyte Corporation for development and commercialization outside the United States. Jakavi is marketed in the United States by Incyte Corporation as Jakafi® for the treatment of patients with PV who have had an inadequate response to or are intolerant of hydroxyurea and for the treatment of patients with intermediate or high-risk myelofibrosis.

The recommended starting dose of Jakavi in PV is 10 mg given orally twice daily. The recommended starting dose of Jakavi in myelofibrosis is 15 mg twice daily for patients with a platelet count between 100,000 cubic millimeters (mm³) and 200,000 mm³, and 20 mg twice daily for patients with a platelet count of >200,000 mm³. Doses may be titrated based on safety and efficacy. There is limited information to recommend a starting dose for myelofibrosis and PV patients with platelet counts between 50,000/mm³ and <100,000/mm³. The maximum recommended starting dose in these patients is 5 mg twice daily, and patients should be titrated cautiously.

Jakavi is a registered trademark of Novartis AG in countries outside the United States. Jakafi is a registered trademark of Incyte Corporation. The safety and efficacy profile of Jakavi has not yet been established outside the approved indications.

Jakavi Important Safety Information for Treatment of Myelofibrosis (MF) and Polycythemia Vera (PV)

Jakavi can cause serious side effects, including a decrease in blood cell count and infections. Complete blood count monitoring is recommended. Dose reduction or interruption may be required in patients with any hepatic impairment or severe renal impairment or in patients developing hematologic adverse reactions such as thrombocytopenia, anemia and neutropenia. Dose reductions are also recommended when Jakavi is co-administered with strong CYP3A4 inhibitors or fluconazole. Use of Jakavi during pregnancy is not recommended, and women should avoid becoming pregnant during Jakavi therapy. Women taking Jakavi should not breast feed. Progressive multifocal leukoencephalopathy (PML) has been reported. Physicians should be alert for neuropsychiatric symptoms suggestive of PML. Hepatitis B viral load (HBV-DNA titer) increases have been reported in patients with chronic HBV infections. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. Non-melanoma skin cancer (NMSC) has been reported in Jakavi treated patients. Periodic skin examination is recommended. Very common adverse reactions in MF (>10%) include urinary tract infections, anemia, thrombocytopenia, neutropenia, hypercholesterolemia, dizziness, headache, alanine aminotransferase increased, aspartate aminotransferase increased, bruising and weight gain. Common adverse reactions in MF (1 to 10%) include herpes zoster and flatulence. Uncommon adverse reactions in MF include tuberculosis. Very common adverse reactions in PV (>10%) include anemia, thrombocytopenia, hypercholesterolemia, hypertriglyceridemia, dizziness, alanine aminotransferase increased and aspartate aminotransferase increased. Common adverse reactions in PV (1 to 10%) include urinary tract infections, herpes zoster, weight gain, constipation and hypertension.

References