



Submitted by:
Albert Kodersha, PharmD.
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901
Phone: 908-673-1653
Email: akodersha@celgene.com
Date of Request: June 27, 2019
NCCN Guidelines Panel: Myeloproliferative Neoplasms

Dear NCCN Myeloproliferative Neoplasms Guidelines Panel Members:

On behalf of Celgene Corporation, we respectfully request that the NCCN Guidelines Panel for Myeloproliferative Neoplasms review the enclosed data regarding the use of fedratinib for the treatment of myelofibrosis.

Specific Changes:

We respectfully request consideration of the enclosed data in anticipation of the forthcoming Prescription Drug User Fee Act (PDUFA) action date of September 3, 2019 for fedratinib.

FDA Clearance:

Fedratinib is an investigational compound that is not approved for any use in any country, and the safety or effectiveness of the product has not been established. In addition to acceptance of the New Drug Application (NDA), the Food and Drug Administration (FDA) has granted a Priority Review.

Rationale for Consideration:

In February 2018, Celgene Corporation acquired Impact Biomedicines, Inc., the owner of the fedratinib asset. Fedratinib is an oral kinase inhibitor with activity against wild type and mutationally activated Janus Associated Kinase 2 (JAK2) and FMS-like tyrosine kinase 3 (FLT3). As reviewed below, fedratinib has demonstrated meaningful improvements in splenic response and total symptom score in patients with primary and secondary (post-polycythemia vera [PV] and post-essential thrombocythemia [ET]) myelofibrosis (MF). Fedratinib also shows activity in patients previously exposed to the JAK1/JAK2 inhibitor, ruxolitinib and responses in patients with low platelet counts (50 to $<100 \times 10^9/L$) at baseline.

Phase III JAKARTA Study

The JAKARTA study (EFC12153) was a randomized, placebo-controlled, phase III study in patients with intermediate-2 or high-risk primary, post-PV, or post-ET MF with splenomegaly and platelets $\geq 50 \times 10^9/L$ (Pardanani et al. 2015). Patients were assigned to receive oral fedratinib 400 mg, fedratinib 500 mg, or placebo once-daily in consecutive 28-day treatment cycles. Crossover from placebo to fedratinib was permitted after 24 weeks, or earlier if the patient experienced progressive disease. The primary endpoint was spleen volume response rate (proportion of patients with $\geq 35\%$ reduction in spleen volume from baseline as determined by magnetic

resonance imaging [MRI] or computerized tomography [CT] scan at week 24, with confirmation 4 weeks later). A key secondary endpoint was symptom response rate, defined as the proportion of patients achieving $\geq 50\%$ reduction in total symptom score at the end of cycle 6 as compared to baseline assessed using the modified Myelofibrosis Symptom Assessment Form (MFSAF).

Among all treatment arms, 289 patients were randomized to receive fedratinib 400 mg (n=96), 500 mg (n=97), or placebo (n=96). The spleen volume response rate at week 24 confirmed 4 weeks later was 36% (35/96) in the fedratinib 400 mg dose group, 40% (39/97) in the fedratinib 500 mg dose group, and 1% (1/96) in the placebo group ($P < 0.001$). Symptom response rates at week 24 were 36% (33/91) in the fedratinib 400 mg dose group, 34% (31/91) in the fedratinib 500 mg dose group, and 7% (6/85) in the placebo group ($P < 0.001$).

Ninety-six patients were evaluable for safety in the fedratinib 400 mg once-daily group; the most common (any grade) nonhematologic treatment-emergent adverse events (TEAEs) were diarrhea (66%), nausea (64%) and vomiting (42%), and the most common hematologic TEAEs were anemia (99%) and thrombocytopenia (63%). The most common grade 3-4 nonhematologic TEAEs were fatigue (6%), diarrhea (5%) and vomiting (3%), and the most common grade 3-4 hematologic TEAEs were anemia (43%), lymphopenia (21%), and thrombocytopenia (17%).

Based on the results of this study, the starting dose of fedratinib taken forward in the clinical development program was 400 mg by mouth once daily, as this dose was determined to induce clinically meaningful and statistically significant reductions in spleen volume and symptom improvement, with a preferred safety profile.

Phase II JAKARTA2 Study

JAKARTA2 (ARD12181) was an open-label, single-arm phase II study in patients with intermediate-1 (with symptoms), intermediate-2, or high-risk primary, post-PV, or post-ET MF who had been previously treated with ruxolitinib and had platelets $\geq 50 \times 10^9/L$. Patients were found to be ruxolitinib resistant or intolerant by investigator assessment after at least 14 days of ruxolitinib treatment. Patients received a 400 mg fedratinib starting dose once-daily in consecutive 28-day treatment cycles. The primary endpoint was spleen volume response rate (the proportion of patients with a $\geq 35\%$ reduction in spleen volume as measured by CT and MRI) at the end of cycle 6. A key secondary endpoint was symptom response rate, defined as the proportion of patients achieving $\geq 50\%$ reduction in total symptom score at the end of cycle 6 as compared to baseline assessed using the modified MFSAF. Median prior ruxolitinib treatment duration was 10.7 months (range, 1.0–62.4 months). The study was stopped after the FDA placed the fedratinib program on a clinical hold due to suspected cases of Wernicke's encephalopathy. Results from this trial were published in a peer-reviewed journal (Harrison et al. 2017).

A reanalysis of JAKARTA2 has been performed and presented at both ASCO and EHA in 2019 (Harrison et al. 2019a) (Harrison et al. 2019b). This updated analysis of fedratinib employed intent-to-treat (ITT) principles and utilized a narrower definition of ruxolitinib relapsed, refractory, or intolerant patients. The ITT population was comprised of 97 patients who were enrolled and treated in the study. Spleen volume response rate among the ITT population was 31%. Symptom response rate for evaluable patients with ≥ 1 post-baseline MFSAF assessment was 27%. All 97 patients were evaluable for safety. The most common nonhematologic (any grade) TEAEs were gastrointestinal events including diarrhea (62%), nausea (56%), and vomiting (41%), and the most common (any grade) hematologic TEAEs were anemia (99%) and thrombocytopenia (70%). The most common grade 3-4 nonhematologic TEAEs were hyperlipasemia (8%) and diarrhea (4%), and the most common grade 3-4 hematologic TEAEs were anemia (46%) and thrombocytopenia (24%).

Encephalopathy, Including Wernicke's Encephalopathy

A clinical hold was instituted by the U.S. FDA in November 2013 due to suspected cases of Wernicke's encephalopathy (WE). The sponsor at that time terminated the clinical development program for the product. The

clinical hold was lifted by the FDA in August 2017 following additional data being provided to the FDA by a new sponsor.

Clinical and safety databases were searched for all patients treated with fedratinib who had signs or symptoms associated with WE. Eight subjects with potential WE were identified among over 600 subjects who were enrolled and treated with multiple doses of fedratinib in clinical trials (including 539 patients with MPN and 75 patients with solid tumors) (Harrison et al. 2019a) (Harrison et al. 2019b). An independent panel of experts evaluated full case reports for these 8 patients and 1 case was confirmed as WE. Grade 3 encephalopathy was reported in 1 patient; however, the investigator, external experts, and the Data Safety Monitoring Board reached a consensus on a final diagnosis of hepatic encephalopathy.

Mitigation strategies for managing gastrointestinal toxicities, and the identification and treatment of thiamine (vitamin B1) deficiency, a known cause of WE, have been incorporated in the clinical development plan for fedratinib (Verstovsek et al. 2019).

Copies of the recently presented and previously published data from these studies are enclosed for your review.

Sincerely,



Albert Kodersha, PharmD
Senior Manager, Global Medical Information



Chrystal U Louis, MD, MPH
Executive Director, US Medical Affairs, Myeloid

REFERENCES

1. Harrison CN, Schaap N, Vannucchi AM, et al. Janus kinase-2 inhibitor Fedratinib in patients with myelofibrosis previously treated with ruxolitinib (JAKARTA-2): a single-arm, open-label, non-randomised, phase 2, multicentre study. *Lancet Haematol.* 2017;4:e317–e324.
2. Harrison CN, Schaap N, Vannucchi AM, et al. Fedratinib in Patients with Myeloproliferative Neoplasm-Associated Myelofibrosis Previously Treated with Ruxolitinib: A Reanalysis of the Phase II JAKARTA2 Study [Poster]. Poster presented at 55th Annual Meeting of American Society of Clinical Oncology (ASCO). May 31-June 4, 2019a; Chicago, IL, USA.
3. Harrison CN, Schaap N, Vannucchi AM, et al. Fedratinib in Patients with Myeloproliferative Neoplasm-Associated Myelofibrosis Previously Treated with Ruxolitinib: A Reanalysis of the Phase 2 JAKARTA2 Study [Poster]. Poster presented at 24th Congress of European Hematology Association (EHA). June 13-16, 2019b; Amsterdam, Netherlands.
4. Pardanani A, Harrison C, Cortes JE, et al. Safety and efficacy of Fedratinib in patients with primary or secondary myelofibrosis: a randomized clinical trial. *JAMA Oncol.* 2015;1:643–651
5. Verstovsek S, Harrison C, Barosi G, et al. The FREEDOM Trial: A Phase 3B Efficacy and Safety Study of Fedratinib in Patients with Intermediate-or High-Risk Myelofibrosis Previously Treated with Ruxolitinib [Poster]. Poster presented at 55th Annual Meeting of American Society of Clinical Oncology (ASCO). May 31-June 4, 2019a; Chicago, IL, USA.