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The regulatory saga of fedratinib.

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Fedratinib is an oral Janus Associated Kinase 2 (JAK2) inhibitor that became the second-ever drug to gain FDA approval for treatment of myelofibrosis (MF) in August of 2019. Specifically, fedratinib gained approval in patients with intermediate-2 or high-risk primary or secondary myelofibrosis. Ruxolitinib is the first JAK2 inhibitor that gained approval for this indication in November 2011. The sequence of events for approval of fedratinib, raises concerns about the appropriateness of controls in clinical trials. The purpose of this paper is to discuss the timeline for approval of each of these agents for myelofibrosis.

Ruxolitinib was compared to placebo in the COMFORT-I trial, showing $\geq35\%$ reduction of spleen volume in 65 of 155 (41.9\%) patients compared with 0.7\% in the placebo group ($p<0.001$). Ruxolitinib also achieved $\geq50\%$ reduction in total symptom score in 45.9\% of patients, versus 5.3\% in the placebo group ($p<0.001$). Ruxolitinib was then compared to the standard of care at the time (i.e., hydroxyurea, glucocorticoids) in the COMFORT-II trial. Positive results of the COMFORT-I and COMFORT-II trials were announced in press releases in December 2010 and March 2011 respectively, which eventually led to its approval for treatment of MF in November 2011 (Figure 1).

One month later enrollment for JAKARTA began in December 2011. Fedratinib received approval for treatment of MF based on the results of the JAKARTA study, a phase III trial that showed fedratinib was able achieve a $\geq35\%$ reduction in spleen volume in 35 of 96 (36\%) patients compared to 1 of 96 (1\%) patients in the placebo group ($p<0.001$). It also yielded a $\geq50\%$ reduction in total modified Myelofibrosis Symptom Assessment Form symptom score in MF patients over placebo. Common adverse events included anemia, gastrointestinal symptoms, and increased levels of liver transaminases, serum creatinine, and pancreatic enzymes.

That the JAKARTA trial lead to FDA approval of fedratinib as a first-line agent for MF without an active comparator speaks to the ongoing issue of the use of substandard control arms in trials testing new anticancer medications. In a recent analysis of control arm quality in randomized controlled trials leading to anti-cancer drug approvals between 2013 and 2018, Hilal et al. found that 16 of 95 (17\%) trials were conducted using suboptimal control arms. With regard to fedratinib, an appropriate control arm would have been the active treatment ruxolitinib, whose results were known and approval granted prior to enrollment. It can be argued that randomizing to placebo was in fact unethical. This is especially concerning given the toxicities of
Fedratinib, including the serious and potentially fatal Wernicke’s encephalopathy.1

Fedratinib was also studied in ruxolitinib-resistant or ruxolitinib-intolerant patients in JAKARTA-2, an open-label, single-arm trial.7 Of note, the original analysis did not use a standard definition of ruxolitinib intolerance or resistance. Therefore, a re-analysis was performed using a standard definition confirming the benefit of fedratinib in this population.8 Given the lack of treatment options following ruxolitinib failure, this is a large area of unmet need for MF patients. While the primary endpoint of ≥35% reduction in spleen volume was reached in JAKARTA-2, the authors concluded that the use of fedratinib in this population requires further study due to potential toxicity such as Wernicke’s encephalopathy (WE).7 Fedratinib was placed on clinical hold in 2013 for this very reason, when seven patients were found to have suspected cases of Wernicke’s encephalopathy. The hold was later lifted in 2017, following a retrospective analysis of the eight WE cases in fedratinib-treated patients that suggested they may have been due to multi-factorial causes including exacerbation of malnutrition due to poor management of GI side effects, rather than a direct effect of the drug.1,8,9

The role of fedratinib in the treatment of myelofibrosis is yet to be elucidated. Given that the trial that led to the approval of fedratinib showed efficacy against placebo rather than the current standard of care in the front-line setting, it is difficult to ascertain fedratinib’s true place in therapy. It is questionable then as to how this drug was able to gain approval for front-line treatment of intermediate or high-risk primary or secondary MF without answering the important clinical question of whether or not it is superior or at least non-inferior to ruxolitinib. With the potential risk of Wernicke’s encephalopathy and lack of data to establish superiority or non-inferiority to ruxolitinib, we would suggest that fedratinib not be considered as a first-line option until further data is acquired. Finally, a potential for treatment in ruxolitinib-resistant or intolerant patients was identified, but again requires further study.

Declaration of Conflicting Interests
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