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10 years journey of Inrebic

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The journey of Celgene's Inrebic (fedratinib), which received the go-ahead from US FDA in August 2019 for the treatment of myelofibrosis started in 2001 at TargeGen

Celgene Corporation's INREBIC (fedratinib) became the first drug to be approved by the U S Food and Drug Administration (FDA) in nearly a decade for the treatment of myelofibrosis. The drug is used for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis. Prior to Inrebic (fedratinib), the only FDA approved drug for myelofibrosis was Incyte Corporation's Jakafi (ruxolitinib) which was approved by the US regulatory body in 2011.

The approval of Fedratinib is not the only regulatory win for Celgene this year. In June, the firm received FDA approval for Otezla (apremilast) for the treatment of oral ulcers associated with Behçet's disease. In May, FDA approved its Revlimid (Lenalidomide) in combination with rituximab for the treatment of adult patients with previously treated follicular lymphoma or marginal zone lymphoma.

A long regulatory battle

Fedratinib was originally discovered at TargeGen, a California based biopharmaceutical company, founded in 2001. In 2010, French drug maker, Sanofi-Aventis acquired TargeGen for $560 million and continued development of fedratinib until 2013.

In 2013, the development of fedratinib was discontinued by Sanofi after the FDA issued a clinical hold subsequent to reports of a few potential cases of Wernicke's encephalopathy (WE), an acute neurological condition usually indicative of a vitamin B deficiency, in patients participating in fedratinib clinical trials.

In 2016, San Diego based startup Impact Biomedicines acquired the rights to fedratinib from Sanofi. Following a Type A meeting and review of additional data, the FDA concluded that Impact provided the necessary documentation to support lifting the clinical hold opening the path for Impact's continued development of fedratinib for the treatment of myelofibrosis, after the FDA lifted the hold in 2017.

In January 2018, Celgene acquired Impact in a deal worth $7 billion and got rights to the drugs. Now, Bristol-Myers Squibb (BMS) is set to acquire Celgene. In January 2019, BMS and Celgene Corporation have announced that they have entered into a definitive merger agreement under which BMS will acquire Celgene in a cash and stock transaction with an equity value of approximately $74 billion.

Approval of fedratinib

Inrebic (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). Inrebic is a JAK2-selective inhibitor with higher potency for JAK2 over family members JAK1, JAK3 and TYK2. Abnormal activation of JAK2 is associated with myeloproliferative neoplasms, including myelofibrosis and polycythemia vera.

The approval of Inrebic for intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis was based on the results of a clinical trial where 289 patients with myelofibrosis were randomized to receive two different doses (400 mg or 500 mg daily by mouth) of fedratinib or placebo. The clinical trial showed that 35 of 96 patients treated with the fedratinib 400 mg daily dose (the dose recommended in the approved label) experienced a significant therapeutic effect (measured by greater than or equal to a 35 per cent reduction from baseline in spleen volume at the end of cycle 6 (week as measured by an MRI or CT scan with a follow-up scan four weeks later). As a result of treatment with Inrebic, 36 patients experienced greater than or equal to a 50 per cent reduction in myelofibrosis-related symptoms, such as night sweats, itching, abdominal discomfort, feeling full sooner than normal, pain under ribs on the left side, and bone or muscle pain.

The efficacy of the drug was investigated in JAKARTA (NCT01437787), a double-blind, randomized, placebo-controlled trial in 289 patients with intermediate-2 or high-risk MF, post-polycythemia vera MF, or post-essential thrombocythemia MF with splenomegaly.

Patients were randomized to receive either Inrebic 500 mg (N=97), 400 mg (n=96) or placebo (n=96) once daily for at least 6 cycles.

The primary efficacy outcome was the proportion of patients achieving ?35 per cent reduction from baseline in spleen volume at the end of cycle 6 measured by MRI or CT with a follow-up scan 4 weeks later. Of the 96 patients treated with the recommended dose (400 mg) of fedratinib, 35 (37 per cent) achieved a ? 35 per cent reduction in spleen volume, compared with 1 of 96 patients who received placebo ($p<0.0001$). The median duration of spleen response was 18.2 months for the fedratinib 400 mg group. In addition, 40 per cent of patients who received 400 mg experienced a ? 50 per cent reduction in myelofibrosis-related symptoms, whereas only 9 per cent of patients receiving placebo experienced a decline in these symptoms.

However, the prescribing information for fedratinib includes a Boxed Warning to advise health care professionals and patients about the risk of serious and fatal encephalopathy, including Wernicke’s encephalopathy. Health care professionals are advised to assess thiamine levels in all patients prior to starting fedratinib, periodically during treatment, and as clinically indicated. If encephalopathy is suspected, fedratinib should be immediately discontinued and parenteral thiamine initiated.

The most common adverse reactions (? 20 per cent) in patients who received fedratinib were diarrhea, nausea, anaemia, and vomiting. The recommended fedratinib dose is 400 mg orally once daily with or without food for patients with a baseline platelet count of greater than or equal to 50 x 109/L. Reduce dose for patients taking strong CYP3A inhibitors or for patients with severe renal impairment.

The approval of Inrebic was granted under Priority Review. Inrebic also received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases