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# Imbruvica (ibrutinib) Capsules and Tablets
# Clinical Update

Clinical Update: FDA Approves Imbruvica (ibrutinib) Plus Rituximab for the Treatment of Patients with Chronic Lymphocytic Leukemia (CLL).
FDA approval date: April 21, 2020

Imbruvica is a once-daily, first-in-class Bruton's tyrosine kinase (BTK) inhibitor that is administered orally, and is jointly developed and commercialized by Pharmacyclics, LLC, an AbbVie Company and Janssen Biotech, Inc. The BTK protein sends important signals that tell B cells to mature and produce antibodies. BTK signaling is needed by specific cancer cells to multiply and spread. By blocking BTK, Imbruvica may help move abnormal B cells out of their nourishing environments in the lymph nodes, bone marrow, and other organs.

The approval is based on positive results from the landmark Phase 3 E1912 study, which was designed and conducted by the ECOG-ACRIN Cancer Research Group (ECOG-ACRIN) and sponsored by the National Cancer Institute (NCI), part of the National Institutes of Health (NIH). This is the third Phase 3 randomized study in the treatment of previously untreated CLL patients incorporated into the medicine's U.S. prescribing information.

The E1912 study demonstrated previously untreated patients (aged 70 or younger) with CLL lived longer without disease progression – as measured by statistically significant progression-free survival (PFS) – with Imbruvica plus rituximab compared to those treated with the potent chemoimmunotherapy regimen comparator of fludarabine, cyclophosphamide and rituximab (FCR). At a median follow-up of 37 months, Imbruvica plus rituximab significantly improved PFS compared to FCR (hazard ratio [HR] 0.34; 95% confidence interval [CI]: 0.22-0.52; p<0.0001). With a median follow-up time of 49 months, median overall survival was not reached with a total of 23 deaths: 11 (3%) in the Imbruvica plus rituximab and 12 (7%) in the FCR treatment arms. Extended follow-up results from the E1912 study were most recently presented in an oral session at the 2019 American Society of Hematology (ASH) Annual Meeting.

In the E1912 study, the most common adverse reactions (occurring in 30% or more of patients) of all Grades in patients treated with Imbruvica plus rituximab compared to patients treated with FCR were fatigue (80% vs. 78%), musculoskeletal pain* (61% vs. 35%), diarrhea (53% vs. 27%), rash* (49% vs. 29%), hypertension* (42% vs. 22%), arthralgia (41% vs. 10%), nausea (40% vs. 64%), headache (40% vs. 27%), bruising* (36% vs. 4%), cough (32% vs. 25%) and hemorrhage* (31% vs. 8%).

The Phase 3 E1912 study evaluated 529 previously untreated CLL patients ages 70 or younger (median age of 58) who were randomly assigned in a 2:1 fashion to receive Imbruvica plus rituximab (N=354) or the chemoimmunotherapy FCR (N=175). The primary endpoint was PFS. The study was led by ECOG-ACRIN with study site participation by groups in the NCI's National Clinical Trials Network (Alliance for Clinical Trials in Oncology, ECOG-ACRIN, NRG Oncology and SWOG), and was sponsored by the NCI. Pharmacyclics LLC supported the study through a Cooperative Research and Development Agreement with the NCI.

The recommended dosage of Imbruvica for CLL/SLL is 420 mg orally once a day until disease progression or unacceptable toxicity. For adults with CLL/SLL, Imbruvica can be administered as a single agent, in combination rituximab or obinutuzumab, or in combination with bendamustine and rituximab (BR). When administering Imbruvica in combination with rituximab or obinutuzumab, consider administering Imbruvica prior to rituximab or obinutuzumab when given on the same day.