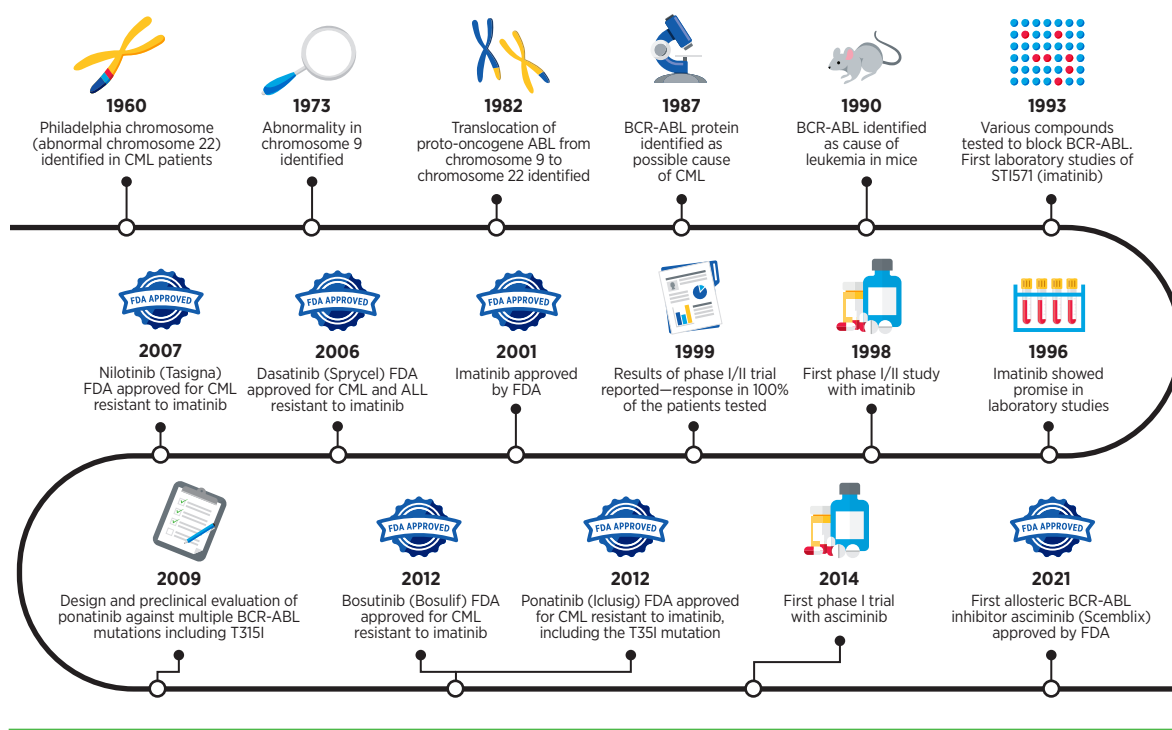


FIGURE 9

The Pathway to Progress Against Chronic Myelogenous Leukemia



Development of the first molecularly targeted therapy approved by the U.S. Food and Drug Administration (FDA)—imatinib (Gleevec)—was the culmination of numerous groundbreaking discoveries. The story began in 1960, when a multi-institutional collaborative team of researchers noted that the majority of patients with chronic myelogenous leukemia (CML) had an abnormal chromosome 22, which was called the Philadelphia chromosome (named because it was discovered at research institutes located in Philadelphia, Pennsylvania). In 1973, the abnormal chromosome 9 was discovered and, in 1980, it was discovered that two chromosomes traded pieces to generate an entirely new protein, BCR-ABL, the activity of which was later found to cause CML. As a result, drugs that shut off the BCR-ABL functions by blocking the most active sites within the protein were developed.

Clinical trials for many of the drugs, including imatinib, began in 1998, subsequently resulting in FDA

approval of imatinib for the treatment of Philadelphia chromosome-positive CML in 2001. Subsequently, identification of imatinib-resistant patients led to the development and FDA approval of dasatinib (Sprycel) in 2006, nilotinib (Tasigna) in 2007, and bosutinib (Bosulif) in 2012. However, none of these drugs were effective against the T315I BCR-ABL mutation. In late 2012, the FDA approved ponatinib (Iclusig) for the treatment of T315I-mutant CML. Since its approval, ponatinib has benefited many patients; however, its success in treating patients whose CML cells have acquired the highly resistant T315I BCR-ABL mutation has been greatly varied.

In October 2021, FDA approved asciminib (Scemblix), the first BCR-ABL inhibitor that binds to a different active site of the protein than any of the drugs indicated above, and persistently blocks the activity of the mutated form of BCR-ABL.