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Advancements in chronic lymphocytic leukemia (CLL) treatment bring new hope to patients

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The treatment and management of blood cancers, in particular CLL, has advanced greatly in the last decade. Physicians and patients now have an armamentarium of targeted treatments to choose from to aid in the achievement of individual treatment goals.

The approval of rituximab in the late 90s, a chimeric anti-CD20 antibody, ushered in the era of chemoimmunotherapy (CIT) and culminated in the establishment of the fludarabine, cyclophosphamide, and rituximab (FCR) regimen as a gold standard for the first-line treatment of CLL.[1,2] However, the FCR combination is known to be significantly myelosuppressive and immunosuppressive, which can result in a heightened risk for opportunistic infections in some patients that could persist for several years following treatment.[3]

“Today, CIT is being rapidly displaced by oral targeted inhibitors such as Bruton’s tyrosine kinase inhibitors (BTKis), which have demonstrated significantly better efficacy than CIT.[4] Given the now consistent observations of improved progression free survival (PFS) and overall survival (OS) with the use of novel agents compared to CIT, regimens such as FCR are no longer recommended for the frontline management of CLL,[5]” said Frances Chang, Vice President, Medical Affairs, Pharmaceuticals, Janssen Asia Pacific.



The last few decades have been an exciting period of therapeutic transformation for CLL treatment. Credit: Image by Freepik

BTKis transformed the treatment paradigm for CLL

The introduction and subsequent approvals of oral kinase inhibitors signified a major milestone in the treatment of CLL. Ibrutinib, a first-in-class BTKi, was approved in 2014 and has significantly transformed the treatment regimen of CLL.[6]

“In the last decade, ibrutinib has had an unprecedented impact on both survival and quality of life for more than 290,000 patients. Ibrutinib is proven to deliver patients with treatment naïve CLL the chance of a similar life expectancy to that of the general population,[7]” said Chang.

Long-term follow-up from RESONATE-2 reported sustained benefit with first-line ibrutinib treatment for CLL, including for patients with high-risk genomic features (TP53 mutation, del[11q], and/or unmutated IGHV). Importantly, the long-term follow-up of RESONATE-2 observed that at 7 years, ibrutinib-randomized patients demonstrated an unprecedented OS rate of 78%, confirming the long-term value of first-line ibrutinib treatment, including for patients with high-risk disease features.[8] RESONATE-2 represents the longest phase 3 survival data ever reported for any BTKi in CLL. To date, ibrutinib is the only therapy to have demonstrated significant PFS and OS benefit for the first-line treatment of CLL across multiple randomized phase 3 studies.

“Ibrutinib is also the BTKi with the most extensively studied tolerability profile,” said Chang. “The primary results from the pivotal RESONATE-2 phase 3 study demonstrated the superior efficacy and tolerability of once-daily ibrutinib versus chlorambucil chemotherapy for the first-line treatment of patients with CLL.[9]”



Ibrutinib has had an unprecedented impact on both survival and quality of life for more than 290,000 patients. Credit: Getty Images Grandfather and grandson fishing stock photo (Getty #169279757)

BTKis as first-line CLL therapy

The European Society for Medical Oncology (ESMO) guidelines on CLL recommends the continuous use of BTKis such as ibrutinib for first-line therapy of CLL, until progression. These guidelines note that treatment decision should include an assessment of *IGHV* and *TP53* status, as well as patient-related factors such as comedication, comorbidities, preferences, drug availability and potential of treatment adherence.[10]

Similarly, the Japanese Society of Hematology's 2023 Practical Guidelines for Hematological Malignancies recommends the use of BTKis, such as ibrutinib, for the first-line treatment of symptomatic or active CLL, with or without the del(17p)/TP53 mutation. In the second-line setting, BTKis are also recommended in patients who had not received prior BTKi therapy.[11] The 2021 Chinese Society of Clinical Oncology (CSCO) diagnosis and treatment guidelines for malignant lymphoma noted that BTKIs are recommend in first-line therapy of CLL patients with or without the del(17p)/*TP53* mutation.[12]

Towards the next breakthrough

“BTKis have created a new era of chemotherapy-free treatment for CLL. At Janssen, while we are inspired by the progress to-date, we also have a singular focus – the elimination of cancer. With three decades of innovation in oncology, we are driven by the enormous global unmet medical needs that continue to persist in disease treatment,” said Chang. “No single company can solve the challenges of cancer. This is why Janssen continues to collaborate with experts from across academia and industry to advance science and deliver innovative therapies to patients in the region and around the world.”

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