**Digital Article 1: Ibrutinib Efficacy and Safety**
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Chronic Lymphocytic Leukemia (CLL) is a type of mature B-cell neoplasm. Several small-molecule immuno-oncologic agents that target various mechanisms of differentiation and growth of B cells have been developed for use in CLL.[NCCN,2021] These include anti-CD20 monoclonal antibodies (obinutuzumab, ofatumumab, and rituximab), phosphatidylinositol 3-kinase (PI3K) inhibitors (idelalisib and duvelisib), a B-cell lymphoma 2 (BCL-2) inhibitor (venetoclax) and Bruton's Tyrosine Kinase (BTK) inhibitors (ibrutinib, acalabrutinib, and zanubrutinib).[Sharma,2019][Jain,2015][Payandeh,2019][Woyach,2012]

BTK is an essential component of the B-cell receptor (BCR) signaling pathway required for proliferation, differentiation, development, trafficking, chemotaxis, adhesion, and cell survival[Ibrutinib_PI] Autophosphorylation of BTK on the BCR activates its kinase activity which subsequently sets in motion a cascade of downstream effects.[Li,2019;p269,col2,para1,ln7-11] The absence or inhibition of BTK has been correlated with a high rate of apoptosis in various B-cell lineages. Malignant B-cells, as in the setting of CLL, upregulate BTK expression, making BTK an actionable therapeutic target to initiate malignant B cell death.[Owen,2019;pg234,col2,para2,ln6-7][Li,2019;p270,col1,para1,ln1-3]

Ibrutinib is a first-generation BTK inhibitor that was approved for use in the second-line[illegible]g of CLL in February of 2014 and then approved for use in the first-line setting 2 years later, in M[illegible] 2016.[LymphomaResearchFoundation_FDAupdates,2021] Ibrutinib is taken orally, once daily, for[illegible]hronic lymphocytic leukemia (CLL) in adult patients.[Ibrutinib_PI] The recommended d[illegible]g per day.[Ibrutinib_PI] Ibrutinib covalently binds to cysteine-481 in the active site [illegible]main of BTK.[Seiler,2017][Kim,2019] In July of 2014, ibrutinib received approval for use s[illegible]ents with CLL who carry the deletion in chromosome 17 (del(17p)), which is cons[illegible]gnostic category.[LymphomaResearchFoundation_FDAupdates,2021][NCCN,2021]

Along with del(17p) status, the National Comprehensive[illegible]clines for CLL also recommend testing for other cytogenetic abnormalities for prognos[illegible]therapy determination. These include del(11q), del(13q), trisomy 12, *TP53* mut[illegible], and CpG-stimulated metaphase karyotyping.[NCCN,2021] Del(11q), del(17p), TP[illegible]ed IGHV, and complex karyotype as detected by CpG testing have all been inde[illegible]with poor prognosis in CLL.[NCCN,2021][Blanco,2016][Thompson,2015][Woyach,2017][LeBris,201[illegible]Thompson,2016] While del(17p) is usually associated with loss of the TP53 gene, mutatio[illegible]een observed in the absence of del(17p).[Dohner,2000][Hallek,2018] [Rossi,2009]

Key clinical trials that le[illegible]se in CLL include RESONATE-2, iLLUMINATE, and E1912 (use in the first-line s[illegible]L, RESONATE, and HELIOS (second- and subsequent-line settings).[Ibrutinib_PI][illegible]uch as ALLIANCE, have also been helpful in establishing the efficacy of ibrutinib for[illegible]

RESONATE-2 (NC[illegible]7) was an international, open-label, randomized, phase 3 trial comparing ibrutinib to chlorambucil in pati[illegible]s with treatment-naïve CLL/SLL who were age 65 years or older. Patients (N = 269) were randomly assigned 1:1 to either ibrutinib (420 mg/day taken orally) or chlorambucil (administered on days 1 and 15 of a 28-day cycle for up to 12 cycles). The primary efficacy endpoint, as assessed by an independent review committee (IRC), was progression-free survival (PFS). Those in the ibrutinib arm experienced a significantly prolonged median PFS compared to those in the chlorambucil arm (Not Reached [NR] vs 18.9 months, respectively; HR for progression or death, 0.16; 95% CI, 0.09-0.28), with an estimated PFS rate at 24 months of 98% vs 85%, respectively.[Burger,2015]

Results published in a 5-year follow-up analysis of RESONATE-2 demonstrated that the significant treatment benefit of ibrutinib was sustainable through at least 60 months. Median PFS remained Not Reached in the

ibrutinib arm and was 15 months in the chlorambucil arm (HR, 0.146; 95% CI, 0.098-0.218), with an estimated PFS rate at 60 months of 70% vs 12%, respectively.[Burger,2020] In addition, ibrutinib was associated with significantly improved PFS in a subgroup analysis of those with a high prognostic risk (defined as a TP53 mutation, 11q mutation, and/or unmutated IGHV). These patients were nearly 92% less likely to experience disease progression or death compared to those who received chlorambucil (HR, 0.083; 95% CI, 0.047-0.145).[Burger,2020;calculation:1-0.083=0.917*100=91.7%]

One of the limitations that has been noted with use of ibrutinib is the development of drug resistance mechanisms. Acquired mutations have been found in patients who have progressed after treatment with ibrutinib. Such mutations prevent the covalent binding of ibrutinib to its target (*BTK* Cys481 mutation), activate a phospholipase enzyme Cγ 2 (PLCγ2) downstream of BTK (the *PLCG2* mutation), result in haploinsufficiency of *TRAIL-R* (del(8p)), and/or other effects deleterious to the drug's mechanism of action (driver mutations in *EP300*, *MLL2*, and *EIF2A*).[Ahn,2017] In a study of heavily pre-treated patients with CLL (receipt of a median of 3 prior therapies) who were treated with single-agent ibrutinib (n = 237) or a regimen of ibrutinib + ofatumumab (n = 71), 46 patients who experienced relapse had samples available for deep sequencing. Of these 46 patients, 87% (n = 40) had *BTK* Cys481 and/or *PLCG2* mutations at the time of clinical relapse.[Woya…JClinOnc,2017]

Data from patients with CLL bearing TP53 aberrations or del(17p) who had receive… …ed therapy in the first-line setting (n = 89) was extracted out from 4 different studies and the fi… …at ASH last December 2020. The pooled analysis revealed that PFS and OS at 4 years wa… …ctively, which the investigators noted was highly promising for a population with… …omes.[Allan,2020] Median duration of ibrutinib-based treatment was 46 months, with 46… …g on ibrutinib at current follow-up. Adverse events of grade 3 or higher noted over… …overed across the 4 studies were infection (22%), hypertension (13%), atrial fibrill… …hemorrhage (7%) – all of which are consistent with the safety profile observed in oth… …tinib.[Strati,2019] In conclusion, these results are suggestive of ibrutinib's ability to offer… …hose with TP53 or del(17p) mutations.[Allan,2020]

Ibrutinib was the first BTK inhibitor to be ap… …and so therefore has been utilized in this setting the longest of all the BTK inhibito… …n the market for use in CLL. It appears to offer sustained efficacy and a consistent saf… …tial approval over 8 years ago in 2014.

## References


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