

Ibrutinib in CLL/SLL: From bench to bedside (Review)

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Abstract. B-cell receptor (BCR) signaling is important for the development and maturation of normal B-cells and plays a key role in B-cell malignancies. Bruton's tyrosine kinase (BTK), a crucial terminal kinase enzyme in BCR signaling, has emerged as an attractive target and has been successfully applied in the treatment of hematological malignancies. Ibrutinib, a BTK inhibitor, has demonstrated marked efficacy and tolerability in treatment-naïve, relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and mantle cell lymphoma (MCL). Ibrutinib has been approved by the Food and Drug Administration (FDA) for the treatment of CLL/SLL, MCL, marginal zone lymphoma and Waldenström macroglobulinemia and by the China FDA for the treatment of CLL/SLL and MCL. Clinical trials of ibrutinib, as a single agent or combined with chemoimmunotherapy and other promising novel agents in the treatment of B-cell malignancy therapy, such as diffuse large B-cell lymphoma, follicular lymphoma, multiple myeloma, primary and secondary CNS lymphoma and acute lymphoblastic leukemia, T-cell lymphoma and myelodysplastic syndrome, are ongoing (<https://clinicaltrials.gov/>). The aim of the present review was mainly to cover the clinical developments regarding the use of ibrutinib in the treatment of CLL/SLL, as well as its safety and toxicity profile.

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1. Introduction

The B-cell receptor (BCR) signaling pathway plays an important role in maintaining cellular functions such as proliferation, selection, maturation, apoptosis and differentiation of normal B lymphocytes (1,2). Aberrant activation of the BCR signaling pathway is a common hallmark of several B-lymphoid malignancies. Bruton's tyrosine kinase (BTK), a non-receptor tyrosine kinase that belongs to the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family of kinases, is a crucial terminal kinase enzyme in the BCR signaling pathway (3). This downstream signal transduction protein acts as an important effector molecule in governing B-cell development, differentiation, survival and function. Recently, BTK has emerged as a novel target in the treatment of B-cell malignancies (4).

Ibrutinib, a potent, orally administered BTK inhibitor, has demonstrated promising effectiveness in several B-cell malignancies and autoimmune diseases in preclinical models and clinical trials (5). Ibrutinib has been approved by the Food and Drug Administration for mantle cell lymphoma (MCL) in November 2013, for chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) in July 2014, and for Waldenström macroglobulinemia (WM) in January 2015 (6-8). The present review includes three main topics: i) The BCR/BTK signaling pathway in B-cell malignancies; ii) the clinical application of ibrutinib in CLL/SLL; and iii) the side effects of ibrutinib and their management.

2. BCR/BTK signaling pathway in B-cell malignancies

The BCR signaling pathway plays an important role in the development and maturation of B cells. The BCR consists of membrane-bound immunoglobulin (mIg) non-covalently associated with a heterodimer of CD79a (Igα) and CD79b (Igβ), which contains the immunoreceptor tyrosine-based activation motif (ITAM) (9). Following binding of the mIg, signals are transduced across the plasma membrane, leading to phosphorylation of the ITAM primarily by Src-family tyrosine kinases (SFKs), such as Lyn. Phosphorylated ITAM leads to SFK binding by Src-homology 2 (SH2) domains (9). This binding, results in the activation and phosphorylation of spleen tyrosine kinases (SYKs) (10). Once Syk is activated, the BCR signal is transduced through a group of proteins associated with the adaptor protein, such as B-cell adaptor for phosphoinositide-3-kinase (BCAP), B-cell linker (Blnk) and its downstream

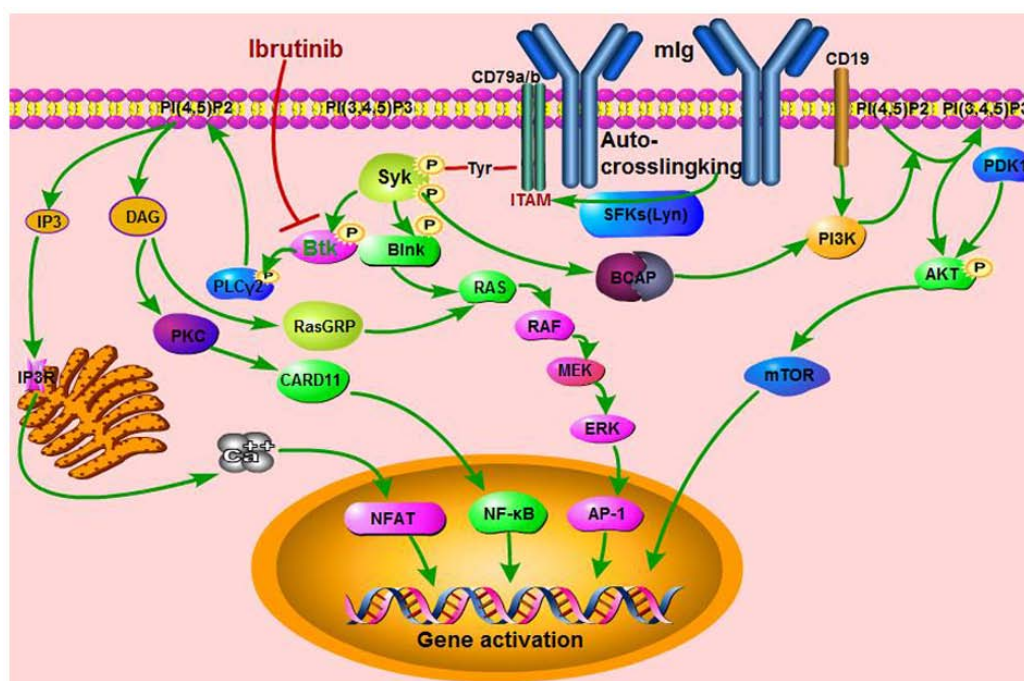


Figure 1. The pathways of BCR/BTK signaling cascade. BCR, B-cell receptor; BTK, Bruton's tyrosine kinase.

signaling components, BTK and phospholipase $C\gamma 2$ (PLC $\gamma 2$) (2,9). When phosphorylated by Syk, Blnk recruits BTK and PLC $\gamma 2$. After their recruitment, Btk phosphorylates PLC $\gamma 2$, which then cleaves the phosphoinositide phosphatidylinositol 4,5-bisphosphate [PI(4,5)P $_2$], generating inositol triphosphate (IP $_3$) and diacylglycerol (DAG) (2,9,10). IP $_3$ binds to the IP $_3$ receptor (IP $_3$ R) in the membrane of the endoplasmic reticulum to facilitate the mobilization of calcium ions, which leads to the activation of nuclear factor for activated T-cells (NF-AT) (2,9). DAG activates protein kinase C (PKC) and its downstream substrates caspase recruitment domain 11 protein (CARD11) and subsequently initiates NF- κ B signaling (2,10). In addition, DAG also binds to Ras guanyl nucleotide-releasing protein (RasGRP) and activates the RAS/RAF/MEK/ERK signaling pathway (9-11). With the assistance of PI3K, the activity of which is localized to the plasma membrane by a lipid-binding domain or by recruitment to CD19 or BCAP, PI(4,5)P $_2$ generates phosphatidylinositol 3,4,5-triphosphate [PI(3,4,5)P $_3$], which subsequently activates protein kinase B (AKT) and causes upregulation of mammalian target of the rapamycin (mTOR) pathway (10,11). PI(3,4,5)P $_3$ in turn recruits BTK, PLC $\gamma 2$, and 3-phosphoinositide-dependent protein kinase 1 (PDK1) (10,12). The pathways of the BCR/BTK signaling cascade are depicted in Fig. 1.

BTK was first revealed to be defective in the primary immunodeficiency X-linked agammaglobulinemia (XLA), which was initially described by Dr Ogden Carr Bruton in 1952 (13,14). It is encoded by the XLA gene that is located on chromosome Xq21.3-22 and has a length of 37.5 kb (15,16). BTK is a non-receptor tyrosine kinase that belongs to the TEC family kinases (TFKs), which has five members (BTK, TEC, ITK, BMX and RLK/TXK) (17,18). BTK carries a conserved cysteine residue adjacent to an ATP-binding site, which is critical for inhibition by tyrosine kinase inhibitors (17,19).

BTK has five domains: Pleckstrin homology (PH), Tec homology (TH), two Src homology domains (SH2 and SH3), and tyrosine kinase or Src homology 1 domain (TK or SH1, respectively) (18,20). The expression of BTK is restricted to B lymphocytes, myeloid cells, erythroid cells, platelets, mast cells, macrophages, natural killer (NK) cells and myeloid-derived suppressor cells (20-23). BTK is crucial for B-cell development, function of mature B cells, proliferation and survival of B-cells (20, 24). Constitutive-activation or mutation of the BTK pathways has been implicated in maintaining the malignant phenotype in a wide variety of B-cell malignancies, such as CLL, MCL and WM (25-27), and acute lymphoblastic leukemia (ALL) (28). BTK has been recognized as a therapy target for B-cell malignancies (4,29).

Ibrutinib (formerly referred to as PCI-32765) is a first-in-class, orally bioavailable, small-molecule covalent inhibitor of BTK, which selectively and irreversibly inhibits BTK (19,26,30). Ibrutinib selectively binds to the cysteine residue at position 481 (Cys-481) in the allosteric inhibitory segment of BTK (TK/SH1 domain), which blocks adenosine triphosphate (ATP) from binding, thereby preventing Btk phosphorylation and activation (19). The domain structure of BTK, the C481 binding site of ibrutinib and the chemical structure of ibrutinib are presented in Fig. 2. As a small-molecule inhibitor, kinase selectivity is a factor important for the efficacy and safety of ibrutinib. However, other kinases also have a cysteine residue in the ATP-binding site, such as TFK members, EGFR family kinases, BLK and JAK3 (31). Therefore, this on-target or off-target effect of ibrutinib may be used in other diseases or may cause adverse events (AEs). Recently, ibrutinib has also been used as a novel anticancer drug for several solid tumors and hematological malignancies, such as breast, ovarian, gastric and lung cancer, glioma, glioblastoma, CD117 $^+$ acute myeloid leukemia and BCR $^+$ ALL (32-39).

Table I. Commonly used CYP3A4 inhibitors and inducers with ibrutinib.

Drug classification	Drugs
Strong CYP3A4 inhibitors	
Antifungal drugs	Ketoconazole, voriconazole, posaconazole
Antibiotics	Clarithromycin, telithromycin
Antivirals	Indinavir, nelfinavir, ritonavir, saquinavir
Antidepressants	Nefazodone
Others	Cobicistat, buprenorphine/naloxone
Moderate CYP3A4 inhibitors	
Anti-arrhythmic drugs	Amiodarone, diltiazem, verapamil, dronedarone
Antifungal drugs	Fluconazole, itraconazole
Antibiotics	Erythromycin, ciprofloxacin
Antivirals	Amprenavir, atazanavir, darunavir, fosamprenavir
Anti-emetics	Aprepitant
Antineoplastic agents	Crizotinib, imatinib
Mild CYP3A4 inhibitors	
Antibiotics	Azithromycin
Psychotropic drugs	Fluvoxamine
Other	Grapefruit juice, Seville oranges
Strong CYP3A4 inducers	
Antituberculosis drugs	Rifampin
Psychotropic drugs	Carbamazepine, phenytoin
Moderate CYP3A4 inducers	
Anti-HIV drugs	Efavirenz
Others	St John's wort

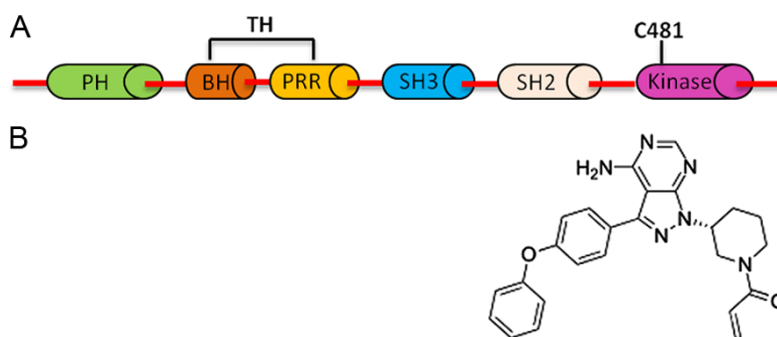


Figure 2. Structure of BTK, the C481 binding site of ibrutinib and the chemical structure of ibrutinib. (A) Domain structure of BTK and the C481 binding site of ibrutinib. (B) Chemical structure of ibrutinib. PH, pleckstrin homology; TH, TEC homology; BH, BTK homology; BTK, Bruton's tyrosine kinase; PRR, proline rich domain; SH2/SH3, SRC homology domains 2 and 3; kinase, tyrosine kinase domain or Src homology 1 domain.

3. Drug-drug interactions (DDIs)

Ibrutinib is primarily metabolized in the liver and is eliminated predominantly by cytochrome P450 enzyme 3A4 (CYP3A4) and less by CYP2D6 (40,41). Caution must be exercised regarding the co-administration of ibrutinib with strong or moderate CYP3A4 inhibitors and inducers. Recently, in an analysis of 118 ibrutinib-treated patients with CLL, 75 patients (64%) were on medications that could increase ibrutinib toxicity and 4 (3%) were receiving drugs that could decrease ibrutinib efficacy (42). A previous study revealed that ketoconazole (a strong CYP3A4 inhibitor) increased the ibrutinib area

under the curve (AUC) by 24-fold, while rifampin (a strong CYP3A4 inducer) decreased the ibrutinib AUC by 10-fold (41). Thus, co-administration of ibrutinib with CYP3A4 inhibitors or inducers should be avoided. If co-administration of strong CYP3A4 inhibitors or inducers is necessary, ibrutinib dosage modifications may be required. The CYP3A4 inhibitors and inducers commonly used with ibrutinib are summarized in Table I.

There is *in vitro* evidence to demonstrate that ibrutinib inhibits P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), although it is not a P-gp or BCRP substrate (43). To minimize the risk of interactions, it is recom-

mended that co-administration of ibrutinib and P-gp or BCRP substrates with a narrow therapeutic range should occur at least 6 h before or after ibrutinib (44). In addition, ibrutinib has a pH-dependent solubility, with lower solubility at higher pH. Although, co-administration of ibrutinib with omeprazole leads to the lower C_{max} of ibrutinib, medicinal products that increase gastric pH have been used without restrictions in clinical trials (44).

4. Application of ibrutinib in CLL/SLL

A series of *in vitro* and mouse xenograft model preclinical studies have investigated the activity of ibrutinib against CLL (45-47).

Treatment-naïve (TN) CLL/SLL. In an open-label phase 1b/2 trial (NCT01105247 and PCYC-1102) (48), previously untreated CLL/SLL patients who required therapy and were aged at least 65 years were enrolled. A total of 15 patients (48%) had unmutated immunoglobulin heavy-chain variable region (IGHV), 2 (6%) had del(17p13.1), 1 (3%) had del(11q22.3), 17 (55%) had del(13q14), and 8 (26%) had trisomy 12. The patients received 28-day cycles of once-daily ibrutinib 420 mg (n=27) or 840 mg (n=4). The primary endpoint was safety and the severity of AEs for all patients. Toxicity (such as diarrhea, nausea and fatigue) was mainly of mild-to-moderate severity (grade 1-2). A total of 3 (10%) patients developed grade 3 infections, 1 patient developed grade 3 neutropenia, and 1 developed grade 4 thrombocytopenia. The median time to initial response, best response and complete response (CR) was 1.9, 5.9 and 12.4 months, respectively. After a median follow-up of 22.1 months, 22 (71%) patients achieved an objective response (OR), and 4 patients (13%) had a CR. For all 31 patients at 24 months, the Kaplan-Meier estimate of progression-free survival (PFS) was 96.3% and the overall survival (OS) was 96.6%. This phase 1b/2 trial suggested that ibrutinib was well-tolerated and effective in a previously untreated population of elderly patients with CLL/SLL (48).

RESONATE-2 was an international, open-label, randomized phase 3 trial that evaluated the efficacy of ibrutinib (at a dose of 420 mg once daily) and chlorambucil in previously untreated patients with CLL or SLL aged ≥ 65 years and without chromosome 17p13.1 deletion (49). Of the patients, 70% (189/269) were aged at least 70 years, 45% (122/269) had advanced-stage disease (Rai stage III or IV), and 20% (54/269) had chromosome 11q22.3 deletion. The primary endpoint was PFS. At a median follow-up of 18.4 months, ibrutinib resulted in a significantly longer PFS compared with chlorambucil (median, not reached vs. 18.9 months, respectively) and resulted in a reduction of 84% in the risk of progression or death (hazard ratio = 0.16; $P < 0.001$). At 18 months, the PFS was 90% in the ibrutinib group and 52% in the chlorambucil group. The 2-year OS rate in the ibrutinib group and chlorambucil groups was 98 and 85%, respectively. The overall response rate (ORR) was 86 vs. 35% ($P < 0.001$) in the ibrutinib and chlorambucil groups, respectively. Approximately 20% of the patients in the ibrutinib group suffered from AEs of any grade: 4 patients (3%) in the ibrutinib group had grade 3 hemorrhage and 1 (1%) had grade 4 hemorrhage (49).

Recently, a randomized phase 3 study (NCT02048813) on ibrutinib-based therapy compared with standard fludarabine/cyclophosphamide/rituximab (FCR) chemoimmunotherapy (CIT) in treatment-naïve patients with CLL aged < 70 years and without deletion 17p- was reported (50). The study revealed that the ibrutinib with rituximab (IR) group was superior to the FCR group independently of age, sex, performance status, disease stage or the presence/absence of del11q23, with fewer grade 3 and 4 treatment-related AEs (58 vs. 72%, respectively). IR was also superior to FCR for IGHV unmutated but not IGHV mutated patients. Another phase 3 trial (NCT01886872) enrolled 547 untreated CLL patients aged ≥ 65 years to evaluate the efficacy of ibrutinib-based therapy compared with CIT (51). The 2-year PFS was 74% with bendamustine plus rituximab (BR), 87% with ibrutinib alone and 88% with ibrutinib plus rituximab (IR). There was no significant difference in OS among the three treatment groups with a median follow-up of 38 months. The rate of grade ≥ 3 hematological AEs was 61% in the BR group, 41% in the ibrutinib group and 39% in the IR group. The grade ≥ 3 non-hematological AEs were 63% in the BR group, 74% in the ibrutinib group and 74% in the IR group (51).

iLLUMINATE (NCT02264574) is a multicentre, randomized, open-label, phase 3 trial comparing the efficacy of the combination of ibrutinib plus obinutuzumab (IO) with chlorambucil plus obinutuzumab (CO) (52). A total of 229 patients were enrolled (aged ≥ 65 years or < 65 years) with previously untreated CLL/SLL (52). The estimated 30-month PFS was 79% in the IO group and 31% in the CO group. The grade 3-4 AEs in both groups were neutropenia and thrombocytopenia. Serious AEs occurred in 65 out of 113 patients (58%) treated with IO and in 40 out of 115 patients (35%) treated with CO.

Relapsed or refractory CLL/SLL. In a multi-institutional phase 1 dose-escalating study, two dosing schedules of ibrutinib were analyzed in patients with relapsed or refractory CLL/SLL (R/R CLL/SLL) and other B-cell malignancies (FL, MCL, MZL, DLBCL and WM) (53). A total of 56 patients received ibrutinib at doses of 1.25 (n=7), 2.5 (n=9), 5.0 (n=6), 8.3 (n=8), or 12.5 (n=7) mg/kg/day on a 28-day on/7-day off schedule (35-day cycle), or continuous dosing of 8.3 mg/kg/day or 560 mg/day until development of progressive disease (PD) or unacceptable toxicity. The results favored 12.5 mg/kg/day without reaching the maximum tolerated dose (MTD). The majority of AEs were grade 1 and 2 and self-limited. In the 50 patients evaluated for response, the objective response rate was 60%, including a CR rate of 16%. The median PFS in all patients was 13.6 months. Another phase 1b/2 trial (NCT01105247, PCYC-1102) assessed the safety, efficacy, pharmacokinetics, and pharmacodynamics of ibrutinib in patients with R/R CLL or SLL (54). A total of 85 patients, 65% of whom were considered to have advanced-stage disease, were stratified into two treatment groups of once-daily ibrutinib 420 mg (n=51) or 840 mg (n=34) until development of PD or unacceptable toxicity. There was no difference in the time to peak ibrutinib concentration in the blood of the two groups. Toxic effects included transient diarrhea, fatigue and upper respiratory tract infection, which were predominantly grade 1 or 2, without the need for treatment suspension. A total of 2 patients in the 420-mg cohort (4%) and 4 patients

in the 840-mg cohort (12%) suffered from SAEs that led to discontinuation of treatment. The overall response rate was the same in the two groups (71%). An additional 20 and 15% of the patients in the 420 and 840 mg cohorts, respectively, had a partial response (PR), with lymphocytosis. The response was irrelevant to the clinical and genomic risk factors present pre-treatment, such as advanced-stage disease, number of previous treatments and the 17p13.1 deletion. At 26 months, the PFS was 75% and the OS was 83% (54).

In the first randomized phase 3 RESONATE study (PCYC-1112), 391 elderly patients with R/R CLL/SLL were randomized to receive either ibrutinib (at a dose of 420 mg once daily) or ofatumumab (55). The primary endpoint was PFS. During a median follow-up of 9.4 months, the median PFS was not reached in the ibrutinib cohort compared with 8.1 months in the ofatumumab cohort. Ibrutinib also significantly improved OS (1-year OS rate 90% vs. 81%, respectively) and overall response rate (42.6% vs. 4.1%, respectively) (55).

In 2015, the 3-year follow-up data from PCYC-1102 and the ongoing long-term extension study PCYC-1103 in 132 patients (85 patients with R/R CLL/SLL, 31 patients with TN, and 16 patients with ≥ 2 prior therapies) revealed that prolonged treatment with ibrutinib ameliorated the quality of response over time, with durable remissions and acceptable toxicity (56). In 2017, the authors reported the safety and efficacy outcomes with continued follow-up (up to 44 months) of patients in the phase 1b/2 study (PCYC-1102) and extension study (PCYC-1103) receiving ibrutinib 420 mg once-daily until progression (57). A total of 94 CLL/SLL patients (27 with TN and 67 with R/R) were treated with ibrutinib. The best overall response was 85% in TN patients and 94% in R/R patients. The median PFS was not reached in either group and the 30-month PFS rate was 96 and 76% for TN and R/R patients, respectively (57). Recently, O'Brien *et al* reported 5-year follow-up data from the PCYC-1102 and PCYC-1103 studies on ibrutinib monotherapy for TN ($n=31$) and R/R ($n=101$) CLL/SLL (58). With a 5-year follow-up, ibrutinib yielded an overall response rate of 89%, with CR of 29% in TN and 10% in R/R patients. The 5-year PFS rate was 92 and 44% in TN and R/R patients, respectively. The median PFS in R/R patients was 51 months. Subgroup analysis demonstrated that the median PFS in those with del(11q), del(17p), and unmutated IGHV was 51, 26 and 43 months, respectively. A total of 45% of TN patients and 72% of R/R patients discontinued treatment, with the most common reasons being AEs (19% TN and 21% R/R) and disease progression (6% TN and 33% R/R). The most common grade ≥ 3 AEs in TN and R/R patients were hypertension (32% TN and 25% R/R), pneumonia (10% TN and 27% R/R), neutropenia (3% TN and 21% R/R), thrombocytopenia (3% TN and 11% R/R), and atrial fibrillation (AF; 6% TN and 9% R/R) (58).

CLL patients with 17p deletion (del17p) have poor responses and survival after CIT. A phase 2, single-arm trial of ibrutinib for previously untreated and R/R CLL patients with TP53 aberrations demonstrated that 32 (97%) of 33 previously untreated patients and 12 (80%) of 15 R/R CLL patients achieved an objective response (59). The study revealed that the activity and safety profile of ibrutinib in CLL with TP53 aberrations are encouraging. Recently, the 5-year follow-up of this study was reported (60). The overall response rate at 6 months was

95.8% (CR, 29.2%) for the TP53 cohort and 93.9% (CR, 27.3%) for the elderly cohort. The 5-year PFS was 74.4% and 19.4% in TN-CLL and RR-CLL in the TP53 cohort, respectively, and the OS was 85.3 vs. 53.7%, respectively. The 5-year PFS and OS in RR-CLL were 64.8 and 71.6% in the elderly cohort, respectively. AF occurred in 18 (20.9%) patients, and there was no reported serious bleeding. Another phase 2, open-label, multicentre, single-arm study (RESONATE-17) with R/R del17p CLL/SLL patients received ibrutinib 420 mg/day until PD or unacceptable toxicity (61). A total of 83% patients (119/144) had an overall response according to investigator assessment. The 2-year PFS and OS were 63% and 75%, respectively. Grade 3-4 bleeding occurred in 13 patients. Forty-three patients suffered from grade 3 or worse infections, including 19 patients with pneumonia (61). Recently, a pooled analysis from 3 clinical trials (PCYC-1102/1103, PCYC-1112 and PCYC-1117) evaluated 230 R/R CLL patients with del17p (62). With a median follow-up of 28 months, the overall response rate was 85%. The estimated PFS rate at 12, 24 and 30 months was 80, 65 and 57%, respectively. The estimated OS rate at 12, 24 and 30 months was 85, 77 and 69%, respectively. Subgroup analysis revealed that the overall response rate was the same for patients with and without complex karyotype (86% for both). However, patients with complex karyotype had a worse estimated median PFS (26 vs. 52 months) and OS (32 months vs. not reached). Grade ≥ 3 AEs occurring in $\geq 5\%$ of patients included neutropenia, pneumonia, hypertension, thrombocytopenia, anemia and urinary tract infection.

All these clinical trials suggested that ibrutinib is well tolerated and effective in the treatment of newly diagnosed and R/R CLL, including patients with del17p.

Real-world studies. In a real-world study of ibrutinib in R/R CLL patients (65% with del17p/TP53 mutations) from the Swedish Chronic Lymphocytic Leukemia Group, the response rate was 84% and the PFS was 77% at a median follow-up of 10.2 months (63). Patients with del17p/TP53 mutations had shorter PFS and OS (63).

The data on practice patterns following ibrutinib discontinuation are limited. Mato *et al* conducted a multicenter, retrospective analysis on 178 patients with CLL (ibrutinib $n=143$; idelalisib $n=35$) who discontinued BTK inhibitor therapy (64). The most common reasons for BTK inhibitor discontinuation were toxicity (51%), disease progression (29%), and Richter transformation (RT) (8%). The reported overall response rate was 58% (15% CR; 22% stable disease and 20% partial response) in the ibrutinib cohort. The median PFS and OS for the entire cohort ($n=178$) from BTK inhibitor initiation were 10.5 and 29 months, respectively. The median PFS in BTK inhibitor-intolerant patients treated with an alternative BTK inhibitor was not reached vs. 7 months for patients with CLL progression on the first BTK inhibitor, and who were subsequently treated with an alternative BTK inhibitor. Therefore, BTK inhibitor-intolerant patients without CLL progression, may be successfully treated with different BTK inhibitors (64).

The real-world results of ibrutinib in R/R CLL patients with poor prognosis (92.9% of patients had advanced Binet stage B/C, 45.1% had del17p and/or TP53 mutation, and 54.2% had at least one significant comorbidity) previously treated

with FCR, R-bendamustine, chlorambucil ± steroids ± R, ofatumumab, alemtuzumab ± steroids, R-CHOP and transplantation in France revealed that the best overall response rate was 88.5% (65). The authors also evaluated the safety of ibrutinib, with 73.4% of patients experiencing ≥1 AEs of mild-to-moderate severity and 33.2% experiencing ≥1 SAEs, confirming the good safety and efficacy of ibrutinib in a real-world setting. In the largest real-world experience of novel agents in CLL, ibrutinib appears to be superior to idelalisib as first kinase inhibitors (KI) (66).

Recently, the largest named patient program (NPP), which was compared with the phase 3 RESONATE (PCYC-1112) study, was conducted across 30 countries and 2,908 patients with R/R CLL were enrolled (67). The estimated proportion of patients on treatment at 12 months was 77.3 and 81.5% in the NPP and RESONATE study, respectively (67). In the NPP, 332 patients (11.4%) discontinued ibrutinib (mostly due to death, n=123; PD, n=55; AEs, n=50), whereas in RESONATE, the discontinuation rate due to AEs was 4% of the patients (67). In a subset of the UK/Ireland NPP patients (n=315), the 1-year OS rate was 83.8%, with 73.7% of patients still receiving therapy at 1 year (68). Using univariate analysis, the NPP analysis by the UK CLL Forum demonstrated that OS and discontinuation-free survival (DFS) were not associated with the number of prior lines of therapy or 17p deletion, while, with multivariate analysis revealed that older patients with del17p had inferior survival when treated with ibrutinib (68). With multivariate analysis in the international NPP study, time-on-treatment was significantly longer for patients who were younger (67). This NPP study suggested that ibrutinib is effective and well-tolerated in the real-world setting, with similar time-on-treatment to the RESONATE (PCYC-1112) study (67).

What is the relationship of dose intensity (DI) and response? Barr *et al* evaluated the effect of ibrutinib dose adherence on patient outcomes in the phase 3 RESONATE trial (69). This study demonstrated that patients with higher ibrutinib DI experienced longer median PFS, independent of del17p or TP53 mutation. Patients missing ≥8 consecutive days of ibrutinib had a shorter median PFS vs. those missing <8 days (10.9 months vs. not reached).

Combination therapy of ibrutinib with other agents. Despite the promising therapeutic efficacy of ibrutinib in CLL, CR is infrequent, and acquired resistance to ibrutinib has been reported. Combination therapy may increase the rate of CR and overcome resistance to ibrutinib.

An *in vitro* study reporting that ibrutinib can interfere with the cell-mediated antitumor activities of therapeutic CD20 antibodies provided grounds for combination therapy (70). Another *in vitro* and mouse model study demonstrated that the XPO1 inhibitor selinexor exerted a synergistic effect with ibrutinib in primary CLL cells and increased OS compared with ibrutinib alone (71).

The results of previous clinical studies reported a good response with good tolerability when ibrutinib was used in combination with chemoimmunotherapy, anti-CD20 antibodies (rituximab, ofatumumab, obinutuzumab and TG-1101), or Bcl-2 inhibitors (ABT-199) (72-78).

A single-arm, phase 2 study evaluated the safety and activity of ibrutinib plus rituximab for patients with high-risk

CLL (73). The 18-month PFS in all patients was 78.0%, whereas in those with a del17p or TP53 mutation, it was 72.4%. The 18-month OS in all patients was 83.8%, whereas in those with del17p or TP53 mutation, it was 78.4%. Toxicity was mainly mild to moderate in severity (grade 1-2), with 5 patients (13%) experiencing grade 3 infections, and there were no grade 4 or 5 infections (73). Another phase 1b/2 study assessed the safety and activity of ibrutinib in combination with the anti-CD20 antibody ofatumumab in R/R CLL (including prolymphocytic leukemia, or Richter's transformation) (74). A total of 71 patients were treated, including 66 CLL/SLL patients. The trial was divided into 3 groups: Ibrutinib lead-in (group 1, n=27), concurrent start (group 2, n=20), or ofatumumab lead-in (group 3, n=24). Of the 71 patients, 68 (96%) were evaluable for response. The overall response rates among patients with CLL/SLL patients were 100%, 78.9% and 70.8% in groups 1, 2 and 3, respectively. The median PFS had not yet been reached at a median time on study of 12.5 months. The estimated 12-month PFS was 88.7%, 85% and 75%, in groups 1, 2 and 3, respectively. The estimated 12-month OS was 92.3%, 85% and 87.5% in groups 1, 2 and 3, respectively (74). Ublituximab (TG-1101), a novel glycoengineered anti-CD20 antibody, was also evaluated in combination with ibrutinib in R/R CLL in a phase 2 study (76). Combination therapy resulted in an overall response rate of 88% at 6 months, with 2 subjects (5%) achieving a CR and 34 subjects (83%) a PR. In the high-risk CLL population (n=20), the overall response rates were 95%, with 10% CR and 85% PR. The most common AEs were infusion-related reaction (IRR), diarrhea, fatigue, nausea and rash (76). All these clinical trials suggested that ibrutinib in combination with anti-CD20 antibodies can be used as a treatment option for CLL/SLL.

A phase 1b clinical trial (PCYC-1108) evaluated the safety and efficacy of ibrutinib in combination with CIT in patients with R/R CLL (78). The study enrolled patients into 2 parallel cohorts, bendamustine, rituximab plus ibrutinib (BR-ibrutinib, n=30) and fludarabine, cyclophosphamide, rituximab plus ibrutinib (FCR-ibrutinib, n=3). CIT was up to 6 cycles and ibrutinib was administered daily at a dose of 420 mg after CIT infusions until disease progression or unacceptable toxicity. With a median treatment duration of 15.7 months, the estimated 6- and 12-month PFS of the BR-ibrutinib cohort was 93.1% and 85.9%, respectively. The overall response rate with BR-ibrutinib was 93.3%, and with FCR-ibrutinib it was 100%. Safety was as expected with either CIT or single-agent ibrutinib, with the majority of treatment-related AEs being grade 1 or 2. A total of 6 SAEs in the BR-ibrutinib cohort (1 event of tumor lysis, 2 events of cellulitis, 1 event of dehydration, 2 events of febrile neutropenia) and 1 SAE in the FCR-ibrutinib cohort (gastrointestinal bleeding) were reported. This PCYC-1108 study demonstrated that ibrutinib may enhance CIT efficacy without additive toxicities (78).

A randomized, double-blind, placebo-controlled, phase 3 study (HELIOS) evaluated ibrutinib in combination with bendamustine plus rituximab compared with placebo, bendamustine, and rituximab for CLL/SLL patients who had received one or more prior systemic therapies (79). The investigator-assessed overall response rates were 86% (249/289) of patients in the ibrutinib group compared with 69% (199/289) of patients in the placebo group. At a median follow-up of

17 months, the PFS was significantly improved (not reached in the ibrutinib group vs. 13.3 months in the placebo group). PFS at 18 months was 79% in the ibrutinib group and 24% in the placebo group (79). There was no statistically significant difference in OS between the two groups. However, after adjusting for crossover (90 out of 289 patients from the placebo group crossed over to receive ibrutinib after disease progression), patients in the ibrutinib group had a significantly better OS compared with those in the placebo group (79). The frequency of infections was similar between the ibrutinib and placebo groups (all-grade: 70% vs. 70%). Major hemorrhage was more frequent in the ibrutinib group compared with the placebo group (4% vs. 2%, respectively) (79).

A phase 1 trial evaluated the safety and efficacy of the triplet combination of ibrutinib with a novel anti-CD20 mAb (ublituximab) and a PI3K δ inhibitor (TGR-1202) in patients with R/R B-cell malignancies (80). A total of 38 patients were enrolled: 20 CLL/SLL, 6 FL, 6 DLBCL, 4 MCL and 2 MZL cases. The overall response rates of 36 evaluable patients were CLL/SLL 100% (CR 3, PR 16), MCL 100% (CR 1, PR 3), FL/MZL 86% (CR 2, PR 4) and DLBCL 17% (CR 0, PR 1).

Recently, a phase 1 study of lenalidomide and ibrutinib in combination with rituximab in R/R CLL was reported (81). The study demonstrated that the overall response rate was 67% and the combination of ibrutinib, lenalidomide and rituximab did not appear to be more effective compared with the rituximab-lenalidomide doublet or single-agent ibrutinib with sustained grade 4 neutropenia (81). Table II summarizes the completed clinical trials of ibrutinib in CLL/SLL malignancies.

5. Ibrutinib resistance and management

As described above, ibrutinib alone or as part of combination therapies has achieved remarkable responses in treatment-naïve patients or those with R/R B-cell malignancies. However, several patients developed PD during ibrutinib treatment. Recently, Hershkovitz-Rokah *et al* reviewed 5 published studies including 539 patients in total (82). They found that primary resistance ranged from 10.2% to 35% and acquired resistance ranged from 17.5% to 54% (82).

A 49-year-old woman enrolled in a phase 1 study of ibrutinib exhibited a rapidly rising lymphocyte count and progressive lymphadenopathy at month 21 (53). RNA sequencing revealed a thymidine-to-adenine mutation at nucleotide 1634 of the BTK complementary DNA (83). This mutation leads to a substitution of serine for cysteine at residue 481 (C481S), which disrupts covalent binding of ibrutinib to the sulfhydryl group of C481 of BTK in the active site and leads to a loss of inhibition of BTK enzymatic activity (83).

Another study demonstrated that BTKCys481 and PLC γ 2 mutations appear early and have the potential to be used as biomarkers for future relapse in CLL patients (84). Ahn *et al* reported a prognostic scoring system in CLL patients treated with single-agent ibrutinib on an investigator-initiated phase 2 trial (85). With median follow-up of 34 months, 17.9% patients (15/84) progressed. Most cases of ibrutinib-resistant CLL were due to mutations in BTK and/or PLCG2. Using high-sensitivity testing could detect mutations up to 15 months before manifestation of clinical progression (85). Long-term follow-up results and validation of the prognostic models in a large inde-

pendent cohort of patients with CLL was reported (86). They determined that with BTK and/or PLCG2 mutations heralded ibrutinib resistance.

A study that evaluated prolonged use of ibrutinib in a real-life setting from the French Innovative Leukemia Organization (FILO) Group was reported in an ASH meeting (87). This real-life study also highlighted the onset of BTK and PLC γ 2 mutations before any evidence of disease progression.

Except BTK, PLC γ 2 and CARD11 mutation-mediated ibrutinib resistance, nurse-like cells (NLC) in the tumor microenvironment (TME) may play a role in ibrutinib resistance (88). It has been demonstrated that ibrutinib may impair the phagocytosis of rituximab-coated leukemic cells from CLL patients by human macrophages and antagonize rituximab-dependent NK cell-mediated cytotoxicity (89,90). These results suggested that the sequential administration, but not the concurrent treatment, with these agents may enhance their antitumor activity.

A preclinical study demonstrated that HSP90 inhibitors can overcome ibrutinib resistance *in vitro* and *in vivo* by the degradation of both BTK and I κ B kinase, with downstream loss of MAPK and non-classical NF- κ B signaling (91). Srour *et al* reported that a chemotherapy-free combination that includes dexamethasone, rituximab, lenalidomide and bortezomib (DR2IVE) can overcome resistance in heavily treated ibrutinib-resistant MCL patients, achieving an optimal response (92). Other resistance mechanisms and how to overcome ibrutinib resistance was summarized in a review by Hershkovitz-Rokah (82) and is investigated in ongoing clinical trials (Clinical trial information: NCT02912754, NCT03513562, NCT02973399, NCT02914327).

6. Side effects and management

AF. One study demonstrated that the incidence of AF was ~5% in the ibrutinib group in CLL (55). Another study including 4 RCTs (RESONATE, RESONATE-2, HELIOS and RAY) reported that the AF incidence was 6.5% for the ibrutinib group at 16.6 months and 10.4% at 36 months of follow-up (93). Univariate analyses identified prior history of AF, ibrutinib exposure, age \geq 65 years, hypertension, and hyperlipidemia as significant risk factors for developing AF. However, the effect of prior coronary artery disease, valvular heart disease and diabetes were not identified as significant risk factors. Multivariate analyses revealed that prior history of AF, ibrutinib exposure and age \geq 65 years were independent predictors of AF. Gustine *et al* identified 112 patients with WM and revealed that 12 (10.7%) patients were diagnosed with AF, of whom 6 (50%) had a prior history of AF (94). The median time to AF was 3.9 months vs. 33.4 months in patients with a prior history of AF compared with patients without a history of AF, respectively (94). The incidence may increase with the duration of the medication (up to 16% in longer-term follow-up) (95). A systematic review and meta-analysis suggested that ibrutinib consistently increases the risk of AF compared with control. The authors advised that patient exposure to ibrutinib should be closely monitored (96). Although BTK and TEC protein kinases are expressed in cardiac tissue and inhibited by ibrutinib, the mechanism of AF remains elusive and requires further investigation. A preclinical mouse model suggested

Table II. Finished clinical trials of ibrutinib in CLL/SLL malignancies.

Patient population/numbers	Therapeutic regimen	Phase	Efficacy	≥Grade 3 adverse events (AE)	Ref.
R/R B-Cell malignancies (56)	Ibrutinib	1	ORR (60%), CR (16%) MCL:ORR (78%), CR (33%), PR (44%), SD (11%)	Hematologic toxicities, Nonhematologic toxicity (diarrhea, dyspepsia, fatigue, pain)	(53)
TN CD20+ B-NHL (33)	Ibrutinib and R-CHOP	1b	ORR (94%)	Neutropenia, thrombocytopenia, anemia	(72)
TN CLL (31) (NCT01105247)	Ibrutinib	1b/2	ORR (71%), CR (13%) 24 months PFS (96.3%) 24 months OS (96.6%)	Infections, neutropenia, thrombocytopenia	(48)
TN CLL (269) (RESONATE-2)	Ibrutinib vs. chlorambucil	3	ORR (86% vs. 35%) 18 months PFS (90% vs. 52%) 24 months OS (98% vs. 85%)	Hemorrhage, diarrhea, hypertension, atrial fibrillation	(49)
TN CLL (529) (NCT02048813)	Ibrutinib vs. IR vs. FCR	3	NA	Neutropenia	(50)
TN CLL (547) (NCT01886872)	Ibrutinib (182) vs. IR (182) vs. BR (183)	3	2 years PFS (87% vs. 88% vs. 74%)	NA	(51)
TN CLL (229) (NCT02264574)	Ibrutinib+obinutuzumab (113) vs. chlorambucil+obinutuzumab (116)	3	30 months PFS (79% vs. 31%)	Neutropenia, thrombocytopenia	(52)
R/R CLL (85) (NCT01105247)	Ibrutinib	1b/2	ORR (71%), PR (20%)	Neutropenia, sinusitis, hypertension, pyrexia, fatigue	(54)
R/R CLL (391) (RESONATE, PCYC-1112)	Ibrutinib vs. ofatumumab	3	ORR (42.6% vs. 4.1%) 12 months OS (90% vs. 81%)	Neutropenia, thrombocytopenia, pneumonia	(55)
CLL with TP53 aberrations (51)	Ibrutinib	2	ORR (TN: 97%; R/R: 80%)	Neutropenia, anemia, thrombocytopenia, pneumonia, rash	(59)
CLL (TP53 cohort vs. elderly cohort)	Ibrutinib	2	ORR (95.8 vs. 93.9%) CR (29.2 vs. 27.3%) TP53 cohort: 5-year PFS: TN-CLL, 74.4%; RR-CLL, 19.4% OS: 85.3 vs. 53.7% Elderly cohort: 5-year PFS: RR-CLL, 64.8% OS:71.6%	Neutropenia, anemia, thrombocytopenia, infection, atrial fibrillation, diarrhea, rash, arthritis	(60)
R/R CLL with 17p deletion (145) (RESONATE-17)	Ibrutinib	2	ORR (83%) 24-months PFS:63% 24-months OS:75%	Bleeding, pneumonia, sepsis, acute myocardial infarction, abnormal hepatic function	(61)
R/R CLL (40)	Ibrutinib and rituximab	2	18 months PFS (78%)	Infections, subdural hematoma, neutropenia, mucositis	(73)

Table II. Continued.

Patient population/numbers	Therapeutic regimen	Phase	Efficacy	≥Grade 3 adverse events (AE)	Ref.
R/R CLL (71)	Ibrutinib and ofatumumab	1/1b	ORR (83.3%), 12-months PFS (83.1%), 2-months OS (88.6%)	Pneumonia, atrial fibrillation, bleeding	(74)
R/R CLL (45)	Ibrutinib and ublituximab	1	ORR (88%),	Anaemia, neutropenia, IRRs, thrombocytopenia	(76)
R/R CLL (33) (PCYC-1108)	Ibrutinib+BR, Ibrutinib+FCR	2 1b	ORR (93.1%; I+FCR:100%)	Tumorlysis, cellulitis, dehydration, febrile neutropenia, gastrointestinal bleeding	(78)
R/R CLL (289 in each group) (HELIOS)	Ibrutinib+bendamustine+rituximab	3	ORR (86% vs. 69%) 18-months PFS (79% vs. 24%)	Neutropenia, thrombocytopenia	(79)
R/R CLL (12)	(BR) vs. placebo+BR Ibrutinib, lenalidomide, and rituximab	1	ORR (67%), 12-months PFS (77.9%)	Neutropenia, thrombocytopenia, hemolytic anemia, febrile neutropenia, infection, abdominal pain, myalgia/arthritis	(81)

ORR, objective response rate or overall response rate; CBR, clinical benefit rate. NA, not available.

that ibrutinib-related AF may be mediated through inhibition of PI3K/Akt signaling (97).

In an international retrospective study, Thompson *et al* reported that median time to onset AF was 3.8 months. AF was persistent in 65% (35/56) cases despite treatment and ibrutinib was permanently discontinued in 46% (26/56) cases (98).

Since bleeding is another common side effect and several anticoagulants and anti-arrhythmic drugs (e.g. verapamil, amiodarone) interact with ibrutinib (99,100), managing AF is particularly challenging due to the increased bleeding risk of anticoagulation for AF stroke prophylaxis. Wang *et al* reported that MCL patients who suffered from AF were controlled with β -blockers and/or antiarrhythmics (amiodarone, dronedarone), and 1 patient underwent ablation therapy. Half of the patients who suffered from AF were treated with anticoagulants (warfarin and low-dose heparin), and no patients discontinued therapy as a result of AF (101). Brown *et al* revealed that 49.0% (24/49) of the patients with AF in the ibrutinib group and 33.3% (4/12) in the comparator were managed without any interruption or modification of the study drug. Patients with ibrutinib dose interruption for ≥ 7 days vs. those for < 7 days exhibited no statistically significant difference in the 18-month PFS (93). Also in this study, the author summarized that 34.7% (17/49) of patients of the ibrutinib group who had an AF event were receiving antiplatelet medications and 8.2% (4/49) were taking an anticoagulant. The most commonly used antiplatelet and anticoagulant agents were aspirin and low-molecular-weight heparin, respectively (93). Most scholars advised avoiding P-glycoprotein substrates (e.g., digoxin) and CYP3A4 inhibitors (e.g., verapamil, amiodarone, diltiazem) to control the ibrutinib-related AF (IRAF) and propose deciding whether to prescribe anticoagulation according to the CHA₂DS₂-VASc (the risk of stroke) and HAS-BLED (the risk of bleeding) scoring methods to decide whether to give anticoagulation or not (102-104). If CHA₂DS₂-VASc \leq HAS-BLED, there is no need to prescribe an anticoagulant agent and ibrutinib therapy may continue (102,104). In a secondary analysis of data from the phase 2 PCYC-1102 study and phase 3 PCYC-1112 study, the use of antithrombotic agents was common, with $\geq 50\%$ of patients on ibrutinib receiving an anticoagulant, antiplatelet, or a combination of both (105). Recently, Gribben *et al* provided detailed recommendations on how to prescribe anticoagulation (apixaban and dabigatran) and antiplatelet (aspirin and clopidogrel) therapy (106).

Bleeding. The other important AE is bleeding (56,101). Studies demonstrated that ibrutinib selectively inhibits collagen and von Willebrand factor (vWF)-mediated platelet activation (107-109). The platelet function assay revealed impaired aggregation at baseline after ibrutinib treatment increased from 22/85 to 41/85 (108). Brown *et al* summarized 4 RCTs (RESONATE, RESONATE-2, HELIOS and RAY) and revealed that the incidence of bleeding events was 38.8% (293/756) and 17.2% (129/749) in the ibrutinib group and comparator groups, respectively; the majority of events were grade 1 or 2 (91.5 and 88.3%, respectively) (93). In a phase 3 trial enrolling 280 patients with R/R MCL (ibrutinib group: n=139; temsirolimus group: n=141), a major bleeding event

was reported in 14 (10%) patients in the ibrutinib group and in 9 (6%) in the temsirolimus group (110). A systematic review confirmed an increased incidence of any-grade bleeding, with a 2.93-fold increase in the ibrutinib group compared with the control group, with the risk of major bleeding also increased (111).

Several patients treated with ibrutinib have comorbidities such as cardiovascular disease, warranting antiplatelet or anticoagulant therapy for primary or secondary prevention. Based on the observation of occasional severe hemorrhage, including subdural hematoma and post-traumatic surgical hemorrhage, the safety issue of combination therapy with ibrutinib and antiplatelet/anticoagulant drugs was proposed, but the information on ibrutinib in combination with anticoagulant or antiplatelet treatment was not released (101,112). At present, few data are available on the safety of concomitant ibrutinib with warfarin/other vitamin K antagonist, as patients requiring anticoagulant therapy with warfarin/other vitamin K antagonist were excluded from subsequent trials (55,73). In the HELIOS study, 6 out of 11 patients with major hemorrhage in the ibrutinib group were taking a concomitant anticoagulant or antiplatelet treatment (79). In the RESONATE study, the authors excluded patients requiring warfarin, but not those requiring other forms of anticoagulation. The major hemorrhage incidence was similar in the two study groups (2 patients in the ibrutinib group and 3 patients in the ofatumumab group), while bleeding-related AEs of any grade were more common in the ibrutinib group compared with the ofatumumab group (44% vs. 12%, respectively) (55). Data from the PCYC-1104-CA trial suggest that the combination of antiplatelet agents and ibrutinib increases the risk of bleeding (101). Another study revealed that grade ≥ 3 bleeding occurred in $\sim 3\%$ in patients without concomitant anticoagulant/antiplatelet therapy (105). A real-world study reported no increased incidence of bleeding in 19 patients who received concomitant low-molecular-weight heparin and 5 patients who received aspirin or clopidogrel (63). Similarly, in a report of patients on concomitant directly acting oral anticoagulant (DOAC) therapy, none of the 15 patients developed major bleeding (98). Experience with ibrutinib in combination with both antiplatelet and anticoagulant agents is limited. A meta-analysis demonstrated that dual antiplatelet therapy with aspirin and a P2Y₁₂ antagonist (clopidogrel, prasugrel or ticagrelor) increases the risk of major bleeding by 40–50% compared with single-agent antiplatelet therapy (113). Adding ibrutinib to dual antiplatelet therapy (DAPT) is likely to further increase this risk. Based on the available data, Shatzel *et al* reviewed patients taking ibrutinib with concomitant antiplatelet and anticoagulant agents; more information may be found in that review (114).

Bleeding events in patients receiving ibrutinib are usually mild, mostly grade 1 and 2, and do not require dose modification/interruption. In the case of serious bleeding, platelet transfusion is recommended, regardless of the platelet count. Antifibrinolytic drugs, such as tranexamic acid, may be prescribed if bleeding persists after platelet transfusion. Additionally, *in vitro* studies demonstrated that platelet aggregation is fully restored within 5–7 days after ibrutinib cessation (107,109). It was recommended that ibrutinib should be withheld for 3–7 days before and after any surgical or invasive procedures (112).

Infection. B-cell malignancies are characterized by immune dysregulation, with associated hypogammaglobulinemia and recurrent infections. Considering that ibrutinib plays important roles in both normal and malignant B lymphocytes, the effect of ibrutinib on infection risk and immunoglobulin levels in B-cell malignancies should be assessed. Apart from BTK, ibrutinib is also an irreversible inhibitor of interleukin-2-inducible T-cell kinase (ITK), which plays an important role in inflammatory responses and T-cell maturation (115). Without ITK, CD4⁺ T cells do not effectively differentiate into Th2 effector cells and cannot elicit protective responses to pathogens, which increases the risk of severe and opportunistic infections, such as *Candida* species, *Pneumocystis jirovecii*, Epstein-Barr virus and varicella zoster virus (VZV) (115,116). Byrd *et al* had revealed that the most common AEs of grade ≥ 3 of ibrutinib included pneumonia (12%) (54). O'Brien *et al* also reported that $\sim 10\%$ of the patients developed grade 3 infections (48). Some case reports and retrospective cohort studies also demonstrated that ibrutinib was associated with serious pneumonia and opportunistic infections, such as pneumocystosis, aspergillosis, herpes simplex virus, VZV, cytomegalovirus, cryptococcal meningitis, candidiasis, fusarium and other invasive mold infections (117–119). A previous study demonstrated that 5 cases (5.2%) of *Pneumocystis jirovecii* pneumonia (PJP) were identified in 96 patients with CLL treated with ibrutinib (120). Furthermore, the authors revealed that all patients had a CD4 T-cell count $>500/\mu\text{l}$ and IgG >500 mg/dl at the time of PJP, indicating that PJP may be linked to ibrutinib (120). Lionakis *et al* reported that 39% (7/18) patients with primary CNS lymphoma (PCNSL) who received ibrutinib combination therapy developed invasive aspergillosis (121). Diamantopoulos *et al* reported a 72-year-old man with stage IV MCL (122). After receiving ibrutinib for 5 months, he developed *Staphylococcus aureus* meningitis. A systematic review demonstrated that $\sim 56\%$ of patients on single-agent ibrutinib and 52% of those on combination therapy developed infectious complications, and grade 3–4 infectious AEs occurred in 26 and 20%, respectively (123). Aspergillus, VZV and *Pneumocystis* were the most common opportunistic pathogens (123). Recently, Varughese *et al* reviewed 378 patients with lymphoid malignancies, and revealed that 43 of the patients suffered from serious infection, of whom 37.2% (16/43) developed invasive fungal infections (IFIs) (124). Ghez *et al* reported the results of a retrospective survey in France, and identified 33 cases of IFIs in patients receiving ibrutinib alone or in combination (125). Most of IFIs occurred within a median of 3 months after starting ibrutinib. Invasive aspergillosis (IA) accounted for the majority of IFIs (27/33), including 40.7% (11/27) with CNS localizations (125). Tuberculosis infection after ibrutinib should also be taken into consideration (126).

However, a different sensitivity of malignant and normal B cells to ibrutinib may potentially restore immune system function. Sun *et al* assessed humoral immunity and B-cell subsets in 86 patients with TN or R/R CLL who had received ibrutinib for at least 12 months (127). They, consistently with other researchers, found that there was a decrease in serum IgG and IgM levels and an increase in serum IgA level (48,54,127). Yin *et al* noted elevated peripheral blood CD4⁺ and CD8⁺ T-cell numbers and T-cell-related cytokine levels (128). Studies have

also reported that the infection rate declined by more than 50% after 6 months of ibrutinib therapy (56,127). This may be due to the partial reconstitution of humoral immunity and cellular immunity (127,128).

Secondary primary malignancies (SPMs). Another less reported but important AE of ibrutinib are SPMs. The overall incidence of other malignancies was 5% in clinical trials, including skin cancers (4%) and other carcinomas (1%) (101).

Hepatitis B virus (HBV) reactivation. Certain therapies for hematological malignancies are associated with increased risk of HBV reactivation in previously infected patients (129,130). De Jesus Ngoma *et al* reported the first case of HBV reactivation in an 80-year-old CLL patient receiving ibrutinib, suggesting that such treatment must be associated with HBV screening (131). In 2017, Herishanu *et al* reported a 79-year-old HBsAg-negative, anti-HBs- and anti-HBc-positive CLL patient who suffered from severe HBV reactivation 1 year after starting ibrutinib (132). However, Tedeschi *et al* revealed that 18% (7/38) of CLL patients were determined to be HbsAg-negative/anti-Hbc-positive with undetectable HBV DNA before starting ibrutinib (133). After a median follow-up of 25 months, none of the patients exhibited HBV reactivation, suggesting that any recommendation that prophylaxis during ibrutinib treatment should be administered to anti-Hbc-positive patients was not enough. Thus, further systematic studies are warranted to assess the risk of HBV reactivation during ibrutinib therapy to provide appropriate recommendations.

Other side-effects. In published studies, rash or pruritic rash occurs at a frequency of 13-27% with single-agent ibrutinib (48,54,134). The combination therapy of ibrutinib with rituximab and lenalidomide is associated with a high incidence of all-grade rash, up to 82% (grade 3, 36%) (135). Mannis *et al* reported the case of a 67-year-old man with del17p CLL who developed non-pruritic, edematous papules after 2 weeks of ibrutinib treatment, characterized by peripheral-to-central spread (136). Jensen *et al* reported the case of a 79-year-old man with WM who developed a painless, slightly pruritic rash starting from the groin and wrists and subsequently spreading to the trunk and extremities after 12 weeks of ibrutinib treatment (137).

Iberri *et al* defined the clinicopathological characteristics and management of patients with ibrutinib-associated rash (138). They observed two distinct rash subtypes: i) A non-palpable, largely asymptomatic petechial rash and ii) a palpable eruption characterized by pruritic, non-blanching, violaceous papules. Most non-palpable rashes were grade 1-2 and required no dose interruptions or delays of ibrutinib. Patients with palpable rash all received topical corticosteroids and oral antihistamines, with (grade 3) or without (grade 1-2) interruption of ibrutinib (138).

Neffendorf *et al* had reported that an 80-year-old woman with CLL who had received ibrutinib had a 1-month history of deteriorating vision and bilateral cataracts (139). As tyrosine kinase receptors, such as EPHA2, are known to be key regulators in lens clarity and organization, the authors raised the possibility that a tyrosine kinase mechanism may be implicated in the cataracts. They also advised that old patients

who receive ibrutinib should have baseline and repeated visual acuity testing, as well as ophthalmological assessment in case of visual deterioration (139). Wallace *et al* reported the case of a 78-year-old man with a history of MCL who experienced new-onset cardiomyopathy and ventricular tachycardia after 4 months of ibrutinib therapy (140). Finally, a case report indicated that a CLL patient on ibrutinib suffered from progressive multifocal leukoencephalopathy (141).

7. Conclusion

Ibrutinib, alone or as combination therapy, is effective and well-tolerated in patients with CLL. The safety profile of ibrutinib is manageable. Single-agent or combination therapies can significantly improve outcomes in patients with high-risk disease. In clinical trials and real-world experience, AF, bleeding and infection have emerged as the most challenging complications associated with the use of ibrutinib. Collaboration from multidisciplinary experts (cardiologists, epidemiologists and hepatologists) should be considered to deal with ibrutinib-associated AF, bleeding, infections and HBV reactivation, among others. Candidates for ibrutinib treatment should be provided with an adequate program of surveillance to avoid SAEs and unnecessary discontinuation.

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Authors' contributions

FZ initiated the study and wrote the manuscript. LY revised it critically for important intellectual content. QS and AT gave important advice concerning the literature research. JC approved the version to be published. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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