Ibrutinib in primary central nervous system diffuse large B-cell lymphoma

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The standard regimen for the treatment of newly diagnosed primary CNS lymphoma (PCNSL) remains regimens that contain high-dose methotrexate (MTX). While these regimens can provide control for some patients, there is a dearth of options for the treatment of patients with PCNSL who cannot tolerate MTX-containing regimens, or whose cancers are refractory to MTX. In this article, we review a promising new option; ibrutinib, a Bruton tyrosine kinase inhibitor, for patients with relapsed and refractory PCNSL.

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Primary CNS lymphoma (PCNSL) is a rare form of extranodal lymphoma in the CNS without evidence of systemic involvement at presentation. They comprise only about 2% of all primary brain tumors [1]. Ocular involvement in PCNSL is common (about 20% [2]) although spread outside of the CNS is rare [3]. Approximately 80–90% of PCNSL cases are diffuse-large B-cell lymphomas (DLBCL). Efforts to treat PCNSL similarly to systemic lymphoma have generally been unsuccessful. Extranodal lymphomas are generally highly radiosensitive [4]; however, early attempts to treat PCNSL with whole-brain radiotherapy resulted in poor long-term survival following a robust but transient treatment response [5]. Additionally, cognitive side effects, particularly in the elderly and those on concurrent methotrexate (MTX) therapy, significantly affect the quality of life of this modality [6,7]. Standard chemotherapy for systemic DLBCL, such as cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP)-based regimens, are also ineffective for PCNSL, probably due in part to poor penetration of the blood–brain barrier (BBB) [8]. Instead, high-dose IV MTX, which does cross the BBB, prolongs overall survival and now forms the backbone of PCNSL therapy [9]. Retrospective analysis has shown improved response rates when MTX is combined with rituximab, which targets the CD-20 B-cell marker [10]. However, rituximab does not appear to cross the BBB and the benefit of adding rituximab to MTX-containing regimens has yet to be definitively demonstrated in prospective trials. Its role in the treatment of PCNSL thus remains a topic of active debate [11].

Despite these advances, recurrence with MTX and rituximab-based regimens is common and long-term survival remains poor, with data from the Central Brain Tumor Registry of the United States (IL, USA) showing a 5-year survival of only 29–37% [12,13]. Several groups have studied the addition of various chemotherapeutic agents with or without radiation therapy to MTX and rituximab, including vincristine and procarbazine [14], cytarabine and thiopeta [15], temozolomide, among others. However, no regimen was clearly superior and few direct comparisons have been made, making the choice of treatment regimen largely dependent on institutional preferences [16]. Furthermore, treatment options for recurrent disease are also limited and consensus is lacking on their optimal treatment. Hence there remains a critical need for novel, effective therapeutics for recurrent and refractory PCNSL.

Dependence of PCNSL on the B-cell receptor pathway

Insights into the molecular pathogenesis and genomic landscape of DLBCL and PCNSL have motivated the exploration of several new therapeutic avenues. Outside the CNS, DLBCL arises in the germinal centers of secondary lymphoid organs. Beginning in the germinal center dark zone, mature B cells undergo proliferation,
somatic hypermutation and class-switch recombination to enable efficient production of more effective antibodies in response to antigenic stimulation. This process is stimulated by the expression of transcription factors, such as NF-κB and MYC, and is downregulated by BCL-6. B cells subsequently migrate from the dark zone to the light zone where activation of the cell-surface B-cell receptor (BCR) upregulates mediators of cell survival and proliferation, in particular NF-κB. Dysregulation of these processes is integral to the pathogenesis of B-cell malignancies, including DLBCL.

While initially described based on characteristic histopathologic features, DLBCL actually comprises distinct molecular subgroups that likely reflect differing pathogenic paradigms and phenotypes. Germinal center DLBCLs are thought to arise from normal germinal center B cells in the dark zone and commonly contain translocations of chromosomes 14 and 18 that result in overexpression of the anti-apoptotic factor BCL-2. On the other hand, nongerminatal center (also known as activated B-cell-like) forms arise from post-germinatal center B cells in the light zone and carry a worse prognosis than germinal center DLBCL [17]. The overwhelming majority (>85%) of PCNSL are of the nongerminatal center subgroup [18].

**Targeting the BCR pathway through bruton tyrosine kinase inhibition**

The dependence of nongerminatal center DLBCL on the BCR pathway has motivated the development of inhibitors of key components of this pathway. Activation of the transmembrane BCR triggers a variety of downstream signaling cascades, including phospholipase C-γ2, PI3K and Bruton tyrosine kinase (BTK) [19]. BTK is a nonreceptor protein kinase that is critical for amplification of B-cell signaling; its mutation results in X-linked (Bruton's) agammaglobulinemia. The key role of BTK in B-cell signal amplification makes it an attractive target in the treatment of B-cell malignancies [20].

Initially designed as a potential novel therapeutic for rheumatoid arthritis, ibrutinib was the first BTK inhibitor developed [21]. Ibrutinib is a small molecule that covalently binds to a critical cysteine residue (C481) at the BTK active site with nanomolar affinity. This results in irreversible inhibition of BTK and attenuation of downstream signaling. Initial clinical studies showed an overall response rate of 60% when ibrutinib monotherapy was used in relapsed and refractory B-cell lymphoma and chronic lymphocytic leukemia (CLL) [22]. Subsequent Phase III clinical trials have demonstrated an overall response rate of 63% for CLL/SLL [23] and 72% for mantle cell lymphoma [24]. Ibrutinib can lead to response rates of >90% for previously treated Waldenström macroglobulinemia [25]. Lower response rates are seen in relapsed/refractory follicular zone lymphoma (38%) [26] and marginal zone lymphoma (48%) [27]. In systemic DLBCL, a Phase I/II study showed an overall response rate of 37% [28]. Ibrutinib is now US FDA approved for relapsed/refractory mantle cell lymphoma, Waldenström macroglobulinemia, marginal zone lymphoma, and as both first and second-line therapy for CLL/SLL.

In these studies, ibrutinib monotherapy appears to be relatively well tolerated [29]. Common early adverse effects include diarrhea (50–60%), nausea (40–50%) and upper respiratory infections (30–40%). These adverse events were typically self-limited. An increase in the lymphocyte count is commonly seen and is thought to be related to redistribution of lymphoma cells from lymph nodes to blood [30]. The most common serious adverse events include cytopenias, atrial fibrillation (6–16%) [31] and bleeding (3–5%). Of the cytopenias, neutropenia was the most common (10–15%), followed by thrombocytopenia (5–8%) and anemia (6–8%). At long-term follow-up of patients with CLL treated with single-agent ibrutinib, 13% had discontinued therapy due to adverse events [32].

As a small molecule, ibrutinib rapidly penetrates the BBB and preclinical mouse work has demonstrated a brain-to-plasma ratio of 0.7 with the orally administered drug [33]. Initial clinical studies have shown promising results in treating CNS mantle cell lymphoma, a disease with a median survival of only 3.7 months after diagnosis of CNS metastasis [34]. In this review, we will discuss recent efforts to use ibrutinib and ibrutinib-containing chemotherapy regimens for the treatment of PCNSL.

**Response of PCNSL to ibrutinib therapy**

Investigators are now studying ibrutinib alone and in combination with chemotherapy for the treatment of PCNSL (summarized in Table 1). Chamoun and colleagues reported a retrospective case series of 14 patients who had failed high-dose MTX-based chemotherapy [35]. Seven patients (50%) responded to therapy, of whom three achieved complete responses and the remaining four exhibited partial responses. Partial response was short-lived, with median duration to treatment cessation due to disease progression being 3 months. At last follow-up (median 8 months after initiation of ibrutinib therapy), five patients had died, six were alive with active disease and three patients were alive without active disease.
| Study         | Study type | Number of patients | Regimen                                      | Overall response | Ref.   |
|---------------|------------|--------------------|----------------------------------------------|------------------|--------|
| Chamoun et al.| Retrospective | 14                 | Ibrutinib monotherapy                        | 7 (50%)          | [35]   |
| Soussain et al.| Phase II | 52                 | Ibrutinib monotherapy                        | 31 (60%)         | [36]   |
| Grommes et al.| Phase I  | 13 with PCNSL       | Ibrutinib monotherapy                        | 10 (77%)         | [18]   |
| Lionakis et al.| Phase I | 18 (13 with relapsed/refractory PCNSL, 5 treatment-naive) | Ibrutinib monotherapy followed by temozolomide, etoposide, liposomal doxorubicin, dexamethasone, ibrutinib and rituximab with intraventricular cytarabine | 12 (67%) | [37]   |

PCNSL: Primary CNS lymphoma.

Soussain et al. recently published the results of their open-label Phase II study of ibrutinib monotherapy for patients with relapsed or refractory PCNSL or primary vitreo-retinal lymphoma of the DLBCL subtype [36]. A total of 52 patients across France were recruited. All patients had previously been treated with high-dose MTX and seven had additionally received autologous stem cell transplantation. The primary end point was disease control (defined as any response except for progressive disease) after 2 months of treatment. By this end point, eight patients had ended treatment due to disease progression (n = 7) or toxicity (n = 1), yielding 44 evaluable patients. Out of these patients, 31/44 (70%) had achieved disease control. Serious adverse events included two patients with ventricular hemorrhages, two with intraocular hemorrhages, two with atrial fibrillation and two who developed pulmonary aspergillosis, of whom one died.

In a Phase I clinical trial, Grommes et al. investigated ibrutinib monotherapy in 20 patients with relapsed or refractory primary or secondary CNS lymphoma [18]. 13 of the 20 patients had PCNSL and the authors were able to evaluate responses to treatment in 12 (one patient discontinued the medication early by choice). Out of these 12 patients, five had complete responses and five had partial responses. The median progression-free survival was 4.6 months, while the median overall survival was 15 months.

Lionakis and colleagues explored the use of ibrutinib in combination with chemotherapy in PCNSL [37]. Treatment in this study included ibrutinib monotherapy followed by a regimen comprising temozolomide, etoposide, liposomal doxorubicin, dexamethasone, ibrutinib and rituximab (DA-TEDDi-R) with intraventricular cytarabine. 18 enrolled subjects received initial ibrutinib monotherapy. Thirteen of the enrolled patients were previously treated with high dose MTX while five were treatment naive. Therapy was discontinued in two patients who developed aspergillosis infections after ibrutinib induction. Out of the remaining 16 patients who continued to the DA-TEDDi-R chemotherapy phase, two additional patients died of causes deemed unrelated to treatment. 12 of the remaining 14 patients (67% of the initial 18 enrolled) achieved a complete response and one patient achieved a partial response. At final follow-up (range 8 to 27 months, median 15.5 months), eight patients remained progression-free.

**Toxicity & tolerability**

Grommes et al. investigated ibrutinib monotherapy toxicity in a dose-escalation study where the recommended dose of 560 mg was increased to 840 mg after 28 days [18]. No dose-limiting toxicity was reported at the dose of 560 mg. The dose of 840 mg was reduced to 560 mg in one patient who developed colitis. The most common adverse effects were neutropenia and lymphopenia. Treatment had to be discontinued in one patient due to pulmonary aspergillosis.

In the Leonakis study, in which ibrutinib monotherapy induction was followed with chemotherapy, seven out of 18 patients (39%) developed pulmonary and cerebral aspergillosis [37]. Out of these seven patients, two developed aspergillosis during the ibrutinib monotherapy phase while in the other five aspergillosis was detected after the DA-TEDDi-R regimen was initiated. A significant percentage of patients (5/18, 28%) died during treatment. The aspergillosis rates in the Leonakis study (7/18 = 39%) were much higher than those observed in the Soussain study (2/44 = 5%) and the Grommes study (1/20 = 5%).

Several mechanisms could potentially explain an increased susceptibility to fungal infections in patients on ibrutinib therapy. These include B-cell inhibition secondary to BTK inhibition, off target effects of ibrutinib on homologous kinases and the combined immunodeficiency of ibrutinib with other immunosuppressive chemotherapeutics in the context of the inherent immunodeficiency of PCNSL. Interestingly, invasive fungal infections are...
enrichment of PI3K mechanisms to activate downstream cell growth factors. Indeed, through RNA expression analysis, they showed ibrutinib could induce cell death.

In the recent reports of ibrutinib therapy for PCNSL, the overall response rates (7/14 in the Chamoun study [35], 31/52 in the Soussain study [36], 10/13 in the Grommes study [18] and 12/18 in the Lionakis study [37]) were much higher than for systemic DLBCL, where the ORR has been reported as 25% [28]. Grommes et al. explored the gene expression profiles of cancer-associated genes from 177 human PCNSL biopsies [18]. In agreement with prior data [52], the majority of PCNSL samples (157/177, 89%) belonged to the nongerminal center DLBCL subgroup, which is more dependent on BCR pathway activation than the germinal center subgroup, providing a plausible explanation for the better ibrutinib response rates seen with PCNSL versus systemic DLBCL.

Sequencing analysis of the sole patient who demonstrated complete primary resistance to ibrutinib therapy revealed an R179Q mutation in CARD11, a known ibrutinib resistance mutation that is thought to allow BTK-independent activation of the NF-kB pathway. Patients with CD79B mutations responded only partially to ibrutinib therapy. The Y196D point mutation in the CD79B ITAM has previously been shown to attenuate BCR downregulation [53]. Grommes et al. hypothesized that CD79B mutant tumors could use BTK-independent mechanisms to activate downstream cell growth factors. Indeed, through RNA expression analysis, they showed enrichment of PI3K/mTOR pathway mediators in CD79B-mutant PCNSL tumors. In cell lines created from CD79B-mutant patient-derived xenograft models, they showed that the combination of PI3K inhibitors and ibrutinib could induce cell death.

Resistance to ibrutinib monotherapy could potentially be overcome by combination regimens with chemotherapy and/or targeted biologic agents. The anti-CD20 antibody rituximab is widely used in the treatment of both systemic and primary CNS lymphoma and its use with ibrutinib is the subject of several investigations. Interestingly, however, ibrutinib covalently binds off-target to ITK, a key receptor expressed on natural killer (NK) cells. Activated NK cells are integral to antibody-dependent cellular cytotoxicity (ADCC) that is critical for rituximab therapy. Indeed, in vitro data show a significant reduction in CD20 levels upon exposure to ibrutinib [54]. Such studies raise concern that ibrutinib may antagonize the therapeutic effect of rituximab. Paradoxically, however, initial clinical studies with rituximab and ibrutinib combination therapies have yielded promising results [55]. Skarzynski et al. [56] showed that CD55, which downregulates the complement cascade, is also inhibited by ibrutinib, suggesting that ibrutinib’s effect on rituximab therapy may be both inhibitory (via CD20 antagonism and ADCC downregulation) and
stimulatory (via CD55 antagonism and complement upregulation). Intriguingly, these contrasting effects may be manipulated by appropriately timing co-administration of anti-CD20 antibodies and ibrutinib. Administration of single-agent ibrutinib, followed by concurrent administration of ibrutinib with the anti-CD20 agent ofatumumab was more effective than concurrent administration with prior ibrutinib monotherapy [57].

In CLL, Waldenström macroglobulinemia and mantle cell lymphoma, resistance to ibrutinib is most commonly acquired by mutation of the active site C481 residue that replaces the nucleophilic target with serine [58–60]. This has motivated the development of noncovalent BTK inhibitors whose binding is not dependent on C481 [61]. Several noncovalent inhibitors have nanomolar affinity and high specificity against both wild-type and C481S mutant BTK in vitro, in cell culture and in animal models [62–64].

Future perspective
In summary, these recent studies have shown high overall treatment response rates with ibrutinib therapy. The DA-TEDDi-R regimen trial of Leonakis et al. reported a remarkably durable treatment response with a median progression-free survival of greater than 15.5 months [37]. Unfortunately, this combination regimen resulted in a high rate of *Aspergillus* infections, motivating further study into a potential role for fungal prophylaxis and alternative chemotherapy regimens. Indeed, the combination of ibrutinib and high-dose MTX with or without rituximab is currently being studied for recurrent/refractory primary and secondary CNS lymphoma [65]. Additionally, the clinical significance of off-target inhibition of NK-dependent ADCC and the implications for combination therapies involving rituximab remain intriguing areas of active research.

While all three trials demonstrated favorable initial response to ibrutinib monotherapy, secondary resistance rates were high. The genomic analyses of Grommes et al. provide insight into ibrutinib resistance mechanisms and have future implications for optimized individual treatment [18]. Pretreatment sequencing could identify patients with *CARD11* R179Q mutant tumors that are unlikely to respond to ibrutinib treatment. Those with *CD79B* mutant tumors are at risk for secondary resistance via the PI3K/mTOR pathway and may benefit from combination therapies that target PI3K/mTOR. Efforts are ongoing to develop more specific BTK inhibitors with similar potency but fewer off-target effects than ibrutinib. Additionally, in preclinical studies, noncovalent BTK inhibitors have demonstrated efficacy against both wild-type BTK and its most common C481S escape mutant. Collectively, these studies demonstrate a promising novel role for ibrutinib and other BTK inhibitors in the treatment of PCNSL, especially for relapsed/refractory cases.

Executive summary

- **Primary CNS lymphoma** predominantly comprises the nongerminal center diffuse large B-cell lymphoma subgroup present in the CNS.
- Diffuse large B-cell lymphoma depend on upregulation of B-cell receptor pathway components.
- Inhibitors of Bruton’s tyrosine kinase (BTK), a key component of the B-cell receptor pathway, are in development for a number of hyperproliferative disorders.
- The irreversible BTK inhibitor ibrutinib has shown promising results in Phase II clinical studies trials of relapsed and refractory primary CNS lymphoma.
- Ibrutinib was generally well-tolerated, although invasive *Aspergillus* infection rates were high, particularly when ibrutinib was combined with certain chemotherapy regimens.
- Current research focuses on the development of more specific BTK inhibitors, noncovalent BTK inhibitors and optimal combination regimens.

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References

1. Ostrom QT, Gittleman H, De Blank PM et al. American Brain Tumor Association adolescent and young adult primary brain and central nervous system tumors diagnosed in the United States in 2008–2012. *Neuro Oncol.* 18(Suppl. 1), 1–150 (2016).

2. Jahnke K, Korfel A, Komm J et al. Intracranial lymphoma 2000–2005: results of a retrospective multicentre trial. *Graefes Arch. Clin. Exp. Ophthalmol.* 244(6), 663–669 (2006).

3. Booman M, Douwes J, Glas AM et al. Preirradiation chemotherapy with cyclophosphamide, doxorubicin, vincristine, and dexamethasone for primary CNS lymphomas: initial report of radiation therapy oncology group protocol 88-06. *J. Clin. Oncol.* 14(2), 556–564 (1996).

4. Batchelor T, Carson K, O’Neill A et al. Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96-07. *J. Clin. Oncol.* 21(6), 1044–1049 (2003).

5. Nelson DF, Martz KL, Bonner H et al. Radiation therapy for localized low-grade non-Hodgkin’s lymphomas. *Radiology* 231(1), 3–17 (2004).

6. Holdhoff M, Ambady P, Abdelaziz A et al. High-dose methotrexate with or without rituximab in newly diagnosed primary CNS lymphoma. *Neurology* 83(3), 235–239 (2014).

7. Lukas RV, Stupp R, Gondi V, Raizer JJ. Primary central nervous system lymphoma – Part 1: epidemiology, diagnosis, staging, and prognosis. *Oncology* 32(1), 17–22 (2018).

8. Morris PG, Correa DD, Yahalom J et al. Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. *J. Clin. Oncol.* 31(31), 3971–3979 (2013).

9. Ferreri AJ, Cwyarnski K, Pulczynski E et al. Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) Phase II trial. *Lancet Haematol.* 3(5), e217–e227 (2016).

10. Ostrom QT, Cioffi G, Gittleman H et al. CBTRUS Statistical Report: primary brain and other central nervous system tumors diagnosed in the United States in 2012–2016. *Neuro Oncol.* 21(Suppl. 5), v1–v100 (2019).

11. Advani RH, Bugg JC, Sharman JP et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. *J. Clin. Oncol.* 31(1), 88–94 (2013).

12. Byrd JC, Brown JR, O’Brien S et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N. Engl. J. Med.* 371(5), 213–223 (2014).

13. Woyach JA, Johnson AJ, Byrd JC. The B-cell receptor signaling pathway as a therapeutic target in CLL. *Cancer Discov.* 7(9), 1018–1029 (2017).

14. Woyach JA, Johnson AJ, Byrd JC. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. *Proc. Natl Acad. Sci. USA* 107(29), 13075–13080 (2010).

15. Honigberg LA, Smith AM, Sirisawad M et al. Discovery of selective irreversible inhibitors for Bruton’s tyrosine kinase. *ChemMedChem* 2(1), 58–61 (2007).
25. Treon SP, Tripsas CK, Meid K et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. *N. Engl. J. Med.* 372(15), 1430–1440 (2015).

26. Bartlett NL, Costello BA, Laplant BR et al. Single-agent ibrutinib in relapsed or refractory follicular lymphoma: a Phase II consortium trial. *Blood* 131(2), 182–190 (2018).

27. Noy A, De Vos S, Thieblemont C et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. *Blood* 129(16), 2224–2232 (2017).

28. Wilson WH, Young RM, Schmitz R et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. *Nat. Med.* 21(8), 922–926 (2015).

29. Kaur V, Swami A. Ibrutinib in CLL: a focus on adverse events, resistance, and novel approaches beyond ibrutinib. *Ann. Hematol.* 96(7), 1175–1184 (2017).

30. Rossi D, Gaidano G. Lymphocytosis and ibrutinib treatment of CLL. *Blood* 125(12), 1772–1774 (2014).

31. Reda G, Fattizzo B, Cassin R et al. Ibrutinib brain distribution: a preclinical study. *Cancer Chemoth. Pharmacol.* 81(4), 783–789 (2018).

32. Byrd JC, Furman RR, Coutre SE et al. Ibrutinib monotherapy in relapsed/refractory CNS lymphoma: a retrospective case series. *Neurology* 88(1), 101–102 (2017).

33. Soussain C, Choquet S, Blonski M et al. Ibrutinib monotherapy for relapse or refractory primary CNS lymphoma and primary vitreoretinal lymphoma: final analysis of the Phase II ‘proof-of-concept’ iLOC study by the Lymphoma study association (LYSA) and the French oculo-cerebral lymphoma (LOC) network. *Eur. J. Cancer* 117, 121–130 (2019).

34. Lionakis MS, Dunleavy K, Roschewski M et al. Inhibition of B cell receptor signaling by ibrutinib in primary CNS lymphoma. *Cancer Cell* 31(6), 833.e5–843.e5 (2017).

35. Tisi MC, Hohaus S, Cuccaro A et al. Acalabrutinib (ACP-196): a selective second-generation BTK inhibitor with a differentiated selectivity and potency profile. *J. Pharmacol. Exp. Ther.* 363(2), 240–252 (2017).

36. McHale E, Do PL, Stoner FK et al. Acalabrutinib (ACP-196): a covalent bruton tyrosine kinase inhibitor with a differentiated selectivity and potency profile. *J. Pharmacol. Exp. Ther.* 363(2), 240–252 (2017).

37. Lionakis MS, Dunleavy K, Roschewski M et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. *Blood* 129(16), 2224–2232 (2017).

38. Jongco AM, Gough JD, Sarnataro K et al. Activity of ibrutinib in mantle cell lymphoma patients with central nervous system relapse. *Blood* 126(14), 1695–1698 (2015).

39. Kaur V, Swami A. Ibrutinib in CLL: a focus on adverse events, resistance, and novel approaches beyond ibrutinib. *Ann. Hematol.* 96(7), 1175–1184 (2017).
52. Camilleri-Broet S, Criniere E, Broet P et al. A uniform activated B-cell-like immunophenotype might explain the poor prognosis of primary central nervous system lymphomas: analysis of 83 cases. *Blood* 107(1), 190–196 (2006).
53. Davis RE, Ngo VN, Lenz G et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. *Nature* 463(7277), 88–92 (2010).
54. Bojarczuk K, Siernicka M, Dwojak M et al. B-cell receptor pathway inhibitors affect CD20 levels and impair antitumor activity of anti-CD20 monoclonal antibodies. *Leukemia* 28(5), 1163–1167 (2014).
55. Burger JA, Keating MJ, Wierda WG et al. Safety and activity of ibrutinib plus rituximab for patients with high-risk chronic lymphocytic leukemia: a single-arm, Phase II study. *Lancet Oncol.* 15(10), 1090–1099 (2014).
56. Skarzynski M, Niemann CU, Lee YS et al. Interactions between ibrutinib and anti-CD20 antibodies: competing effects on the outcome of combination therapy. *Clin. Cancer Res.* 22(1), 86–95 (2016).
57. Jaglowski SM, Jones JA, Nagar V et al. Safety and activity of BTK inhibitor ibrutinib combined with ofatumumab in chronic lymphocytic leukemia: a Phase Ib/II study. *Blood* 126(7), 842–850 (2015).
58. Woyach JA, Furman RR, Liu TM et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N. Engl. J. Med.* 370(24), 2286–2294 (2014).
59. Zhang SQ, Smith SM, Zhang SY, Lynn Wang Y. Mechanisms of ibrutinib resistance in chronic lymphocytic leukemia and non-Hodgkin lymphoma. *Br. J. Haematol.* 170(4), 445–456 (2015).
60. Xu L, Tsakmaklis N, Yang G et al. Acquired mutations associated with ibrutinib resistance in Waldenstrom macroglobulinemia. *Blood* 129(18), 2519–2525 (2017).
61. Kim HO. Development of BTK inhibitors for the treatment of B-cell malignancies. *Arch. Pharm. Res.* 42(2), 171–181 (2019).
62. Johnson AR, Kohli PB, Katewa A et al. Battling Btk mutants with noncovalent inhibitors that overcome Cys481 and Thr474 mutations. *ACS Chem. Biol.* 11(10), 2897–2907 (2016).
63. Asami T, Kawahara W, Kashimoto S, Sawa M. Abstract B152: CB1763, a highly selective, novel non-covalent BTK inhibitor, targeting ibrutinib-resistant BTK C481S mutant. *Mol. Cancer Ther.* 17(Suppl. 1), B152 (2018).
64. Brandhuber B, Gomez E, Smith S et al. LOXO-305, A next generation reversible BTK inhibitor, for overcoming acquired resistance to irreversible BTK inhibitors. *Clin. Lymphoma Myeloma Leuk.* 18(Suppl. 1), S216 (2018).
65. Grommes C, Tang SS, Wolfe J et al. Phase Ib trial of an ibrutinib-based combination therapy in recurrent/refractory CNS lymphoma. *Blood* 133(5), 436–445 (2019).