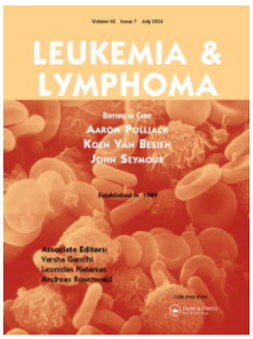

Leukemia & Lymphoma

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ilal20

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To cite this article: Lauren Schaff, Lakshmi Nayak & Christian Grommes (2024) Bruton's tyrosine kinase (BTK) inhibitors for the treatment of primary central nervous system lymphoma (PCNSL): current progress and latest advances, Leukemia & Lymphoma, 65:7, 882-894, DOI: 10.1080/10428194.2024.2333985

To link to this article: https://doi.org/10.1080/10428194.2024.2333985

Published online: 10 Apr 2024.

LEUKEMIA & LYMPHOMA
2024, VOL. 65, NO. 7, 882–894
https://doi.org/10.1080/10428194.2024.2333985

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REVIEW ARTICLE

Bruton's tyrosine kinase (BTK) inhibitors for the treatment of primary central nervous system lymphoma (PCNSL): current progress and latest advances

Lauren Schaff[a,b], Lakshmi Nayak[c] and Christian Grommes[a,b]

[a]Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [b]Department of Neurology, Weill Cornell Medical Center, New York, NY, USA; [c]Center for Neuro-Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

ABSTRACT

The incidence of primary central nervous system lymphoma (PCNSL) has steadily increased, particularly in elderly patients. Although highly responsive to first-line chemotherapy and radiotherapy, approximately 50% of patients relapse or become refractory within 1 year. Prognosis following relapse is dismal and no standard salvage therapy exists. Bruton's tyrosine kinase (BTK), a key regulator of the B-cell receptor (BCR) pathway, has emerged as a promising therapeutic target. The first BTK inhibitor ibrutinib has been evaluated in the relapsed/refractory PCNSL setting, with overall response rates of 51.9%–89.0% and median progression-free survival of 4.6–4.8 months. However, ibrutinib inhibits several kinases in addition to BTK, leading to off-target effects. Second-generation BTK inhibitors have since been developed, which afford greater selectivity for BTK and fewer off-target effects. We review current practices in the diagnosis and evaluation of PCNSL, as well as clinical trials of BTK inhibitors in PCNSL and future developments in PCNSL treatment.

ARTICLE HISTORY
Received 10 December 2023
Revised 7 March 2024
Accepted 18 March 2024

KEYWORDS
Acalabrutinib; ibrutinib; orelabrutinib; primary central nervous system lymphoma; tirabrutinib; zanubrutinib

Introduction

Primary central nervous system lymphoma (PCNSL) is a highly aggressive non-Hodgkin lymphoma (NHL) restricted to the brain, meninges, spinal cord, and eyes and is histopathologically predominantly classified as diffuse large B-cell lymphoma (DLBCL) (90%). In immunocompetent patients, advancing age is a primary risk factor for PCNSL, with a median age at diagnosis of 65 years, and approximately one-third of patients aged ≥70 years [1]. PCNSL is considered a relatively rare tumor, accounting for 4%–6% of all extranodal lymphomas in the USA [2,3]. However, epidemiological data shows that the incidence of PCNSL has been steadily rising in recent decades in parallel with the burgeoning aging population. In an analysis of data from the Central Brain Tumor Registry of the USA and the Surveillance, Epidemiology, and End Results registry, the incidence of PCNSL rose from 0.1 patients per 100,000/years in the 1970s to 0.4 patients per 100,000/years in 2013 [4]. Of these, elderly patients were disproportionately affected, with an incidence rate of 4.32 per 100,000/years in patients aged 70–79 years in the USA [4].

High-dose methotrexate (HD-MTX)-based regimens are considered the standard of care for newly diagnosed PCNSL [5]. Although PCNSL is highly responsive to chemotherapy and radiation therapy in the first-line setting [5], median time to relapse is 10–18 months and most relapses occur within 2 years [3]. The prognosis for patients with relapsed/refractory (r/r) PCNSL is dismal, with a median overall survival (OS) of 8.4 months despite salvage therapy [6]. Furthermore, many elderly patients are not able to tolerate intensive treatments due to poor performance status, impaired renal function (CCr < 50 ml/min), and other comorbidities, and are particularly susceptible to treatment-associated toxicity [7]. Whole-brain radiotherapy (WBRT) has traditionally been used as consolidation following HD-MTX-based chemotherapy but is associated with a significant risk of permanent and irreversible neurotoxicity, particularly in patients aged ≥60 years [8].

Bruton's tyrosine kinase (BTK) is a key regulator of the B-cell receptor (BCR) pathway and a promising target in the treatment of lymphomas with constitutive activation of the nuclear factor kappa β (NF-κB)

CONTACT Christian Grommes grommesc@mskcc.org Department of Neurology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA

pathway. Due to the central role of the BCR signaling pathway in B-cell survival and proliferation, BTK represents an attractive molecular target for the treatment of B-cell NHL, and PCNSL in particular. Characterized by DLBCL, PCNSL exhibits diverse molecular features, including alterations in key genes associated with B-cell lymphomas. MYD88 (primarily L265P) and CD79B (primarily Y196) are the most frequently mutated genes in DLBCL [9], which lead to constitutive activation of the BCR pathway, including NF-κβ and downstream signals responsible for the activation, proliferation, and survival of B-cell lymphomas (Figure 1) [9,10]. Over 75% of patients with PCNSL possess mutations in one or both of these genes [11]. In recent genomic analyses, PCNSL also frequently exhibits 9p24.1/PD-L1 (programmed cell death-ligand 1)/PD-L2 (programmed cell death-ligand 2) copy number alterations and translocations, which are likely genetic bases of immune evasion. In a small case series of 21 patients with PCNSL, 67% had 9p24.1/PD-L1/PD-L2 copy gain and copy number-associated increased expression of the 2 ligands [12]. Another study reported that only 4% of PCNSL tissue specimens had PD-L1-positive tumor cells; however, 52% of the samples had PD-L1-positive cells in the tumor microenvironment [13]. Mutations in TP53, PIM1, and IRF4 are also frequently reported in PCNSL and may play a role in disease development and progression [14]. However, it should be noted that no known molecular signature to predict therapy failure/resistance.

In this review, we summarize recent progress and the latest advances in the development of BTK inhibitors for the treatment of PCNSL.

BTK inhibitors for the treatment of PCNSL

To date, five BTK inhibitors – ibrutinib, acalabrutinib, zanubrutinib, tirabrutinib, and orelabrutinib – have been approved for the treatment of hematological malignancies, all of which are covalent and irreversible inhibitors of BTK activity (Table 1). BTK inhibitors act by binding to the active site of BTK, cysteine-481 (Cys-481) to inhibit the overexpression and phosphorylation of tyrosine-223 and aberrant activation of the NF-κβ pathway.

BTK kinase selectivity and safety profile of existing BTK inhibitors

Each BTK inhibitor possesses its own unique safety profile, with differences in kinase selectivity believed to be largely responsible for the variations observed

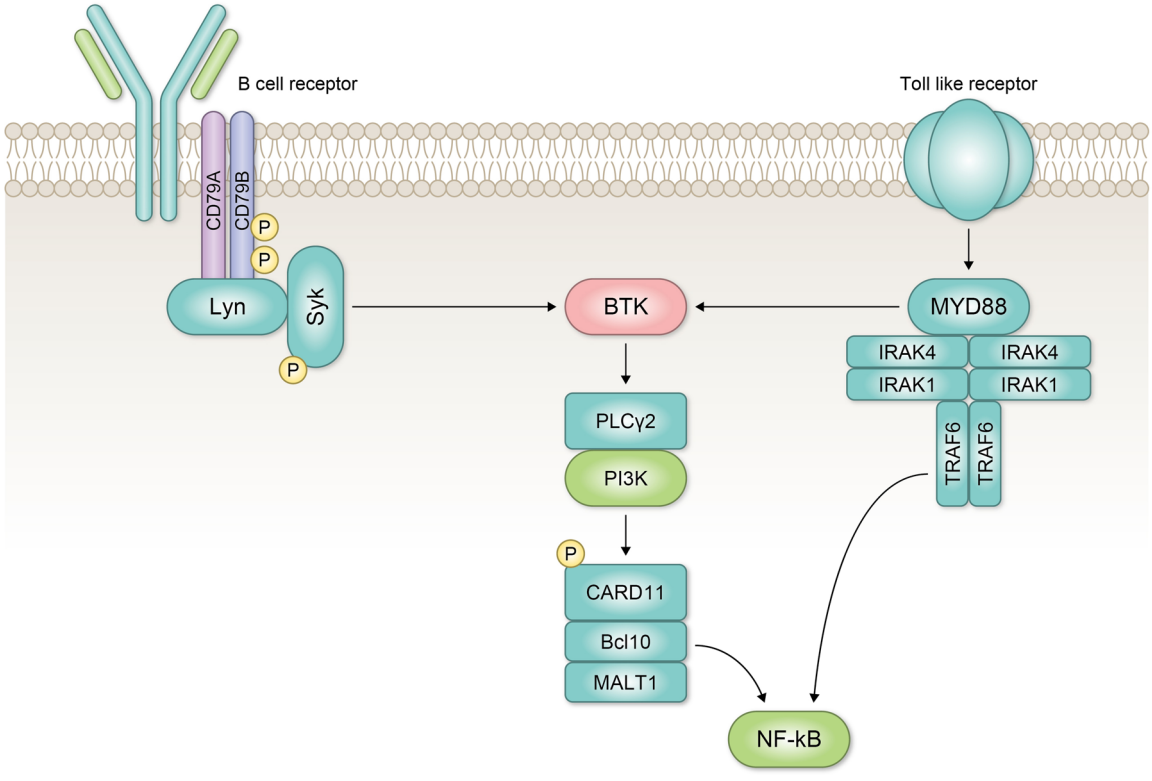

Figure 1. Overview of the BTK signaling pathway.
BTK: Bruton's tyrosine kinase.

Table 1. Summary of approved BTK inhibitors.

Inhibitor	Generation	Binding mechanism	Dosage studied	Approval status	Reference
Ibrutinib	First	Irreversible, covalent binding to Cys481	420/560 mg, QD	CLL/SLL, GVHD, WM, r/r MCL[a], and r/r PCNSL[b]	Leukemia. 2021;35(2):312–32.
Acalabrutinib	Second	Irreversible, covalent binding to Cys481	100 mg BID	CLL and R/R MCL	Target Oncol. 2022;17(1):69–84, Blood Lymphat Cancer 2022;12:81–98.
Zanubrutinib	Second	Irreversible, covalent binding to Cys481	160 mg BID, or 320 mg QD	R/R MCL, WM, and R/R MZL	Drugs. 2020;80(1):91–97, Target Oncol. 2022; 17(1): 69–84
Orelabrutinib	Second	Irreversible, covalent binding to Cys481	150 mg QD	r/r MCL[c] and r/r CLL[c]	Target Oncol. 2022; 17(1): 69–84, Drugs. 2021;81(4):503–7.
Tirabrutinib	Second	Irreversible, covalent binding to Cys481	480 mg QD	r/r PCNSL[d] and WM[e]	Target Oncol. 2022; 17(1): 69–84, Int J Hematol 2023;117:553–562.

BTK: Bruton's tyrosine kinase; CLL: chronic lymphocytic leukemia; SLL: small lymphocytic leukemia; WM: Waldenstrom macroglobulinemia; MCL: mantle cell lymphoma; PCNSL: primary central nervous system lymphoma; MZL: marginal zone lymphoma; r/r: relapsed/refractory; NCCN: National Comprehensive Cancer Network; QD: daily; GVHD: Graft Versus Host Disease; BID: twice daily.
[a] Ibrutinib (560 mg) was approved for the treatment of r/r MCL.
[b] NCCN guideline recommended for the treatment of r/r PCNSL.
[c] Orelabrutinib was approved for the treatment of r/r MCL and r/r CLL in China.
[d] Tirabrutinib was approved for the treatment of r/r PCNSL in Japan, Korea, and Taiwan.
[e] Tirabrutinib was approved for the treatment of WM in Japan.

in adverse event (AE) profiles [15]. In addition to BTK, ibrutinib has been shown to irreversibly inhibit the activity of several important kinases, including epidermal growth factor receptor (EGFR), which is associated with severe skin toxicities [16], IL-2-inducible T-cell kinase (ITK), an important regulator of natural killer cell-mediated cytotoxicity [17], and other members in the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family of kinases (such as bone marrow tyrosine kinase gene on chromosome X [BMX]), which are involved in diverse biological processes related to cell survival and differentiation [18]. In contrast, *in vitro* kinase assays demonstrate that the second-generation BTK inhibitors, tirabrutinib, acalabrutinib, and zanubrutinib, possess more selective kinase binding compared with ibrutinib and thus fewer off-target effects (Figure 2) [19]. In a study evaluating half-maximal inhibitory concentrations (IC_{50}) of BTK inhibitors against BTK and 13 kinases, the IC_{50} of the second-generation inhibitors was considerably higher than ibrutinib against all kinases tested, and there were 5 kinases that ibrutinib inhibited to a similar degree as BTK (IC_{50} within 10-fold of BTK) compared with only 2–3 kinases with the second-generation BTK inhibitors (Table 2) [19].

BTK inhibitor common AEs

Ibrutinib is generally well tolerated but carries a clinically significant risk of cardiovascular events, bleeding, infection, diarrhea, and dermatological AEs, which often lead to dose reductions and treatment discontinuation [20]. Cardiovascular AEs are perhaps the most notable off-target effect associated with ibrutinib treatment, with an increased risk of new or worsening hypertension (78.3%), atrial fibrillation (AF) (4%–13%), and minor (16%–55%) and major (2%–6%) bleeding reported across clinical studies [20–22]. In contrast, fewer cardiovascular events are reported with the second-generation BTK inhibitors, acalabrutinib (hypertension: 9%; AF: 3%–7%; major bleeding: 6%) [23,24], zanubrutinib (hypertension: 12%; AF: 3%; major bleeding: 4%) [25], and tirabrutinib (hypertension: 0%–3.7%; AF: 0%–7%; major bleeding: 0%) [15,26].

Compared with second-generation BTK inhibitors, ibrutinib is a more potent inhibitor of human epidermal growth factor 2 (HER2) and 4 (HER4) [15], and inhibition of HER2/HER4 expression in cardiomyocytes by ibrutinib is widely considered to be the mechanism responsible for the increased incidence of cardiovascular events observed [15]. In a review of studies evaluating kinase activity of BTK inhibitors, ibrutinib was found to inhibit all kinases implicated in causing cardiovascular AEs, namely HER2, HER4, and TEC [15]. Conversely, acalabrutinib was found to inhibit HER4, and only slightly TEC, but not HER2, zanubrutinib inhibited TEC and HER4, but not HER2, and tirabrutinib inhibited TEC but not HER2 or HER4. More recently, C-terminal Src kinase (CSK) has emerged as another potential molecular target underlying AF after it was identified on a short list of candidate kinases, and cardiac symptoms were reproduced in cardiac-specific CSK knockout mice [27]. Consistent with the low incidence of cardiovascular events, zanubrutinib demonstrates less inhibition of CSK compared with ibrutinib and acalabrutinib does not inhibit Src family kinases [28,29]. The cumulative incidence of new or worsened hypertension in patients treated with ibrutinib at 1.8 months was also reported to be 50%, and the cardiovascular effects of long-term use should be considered [22].

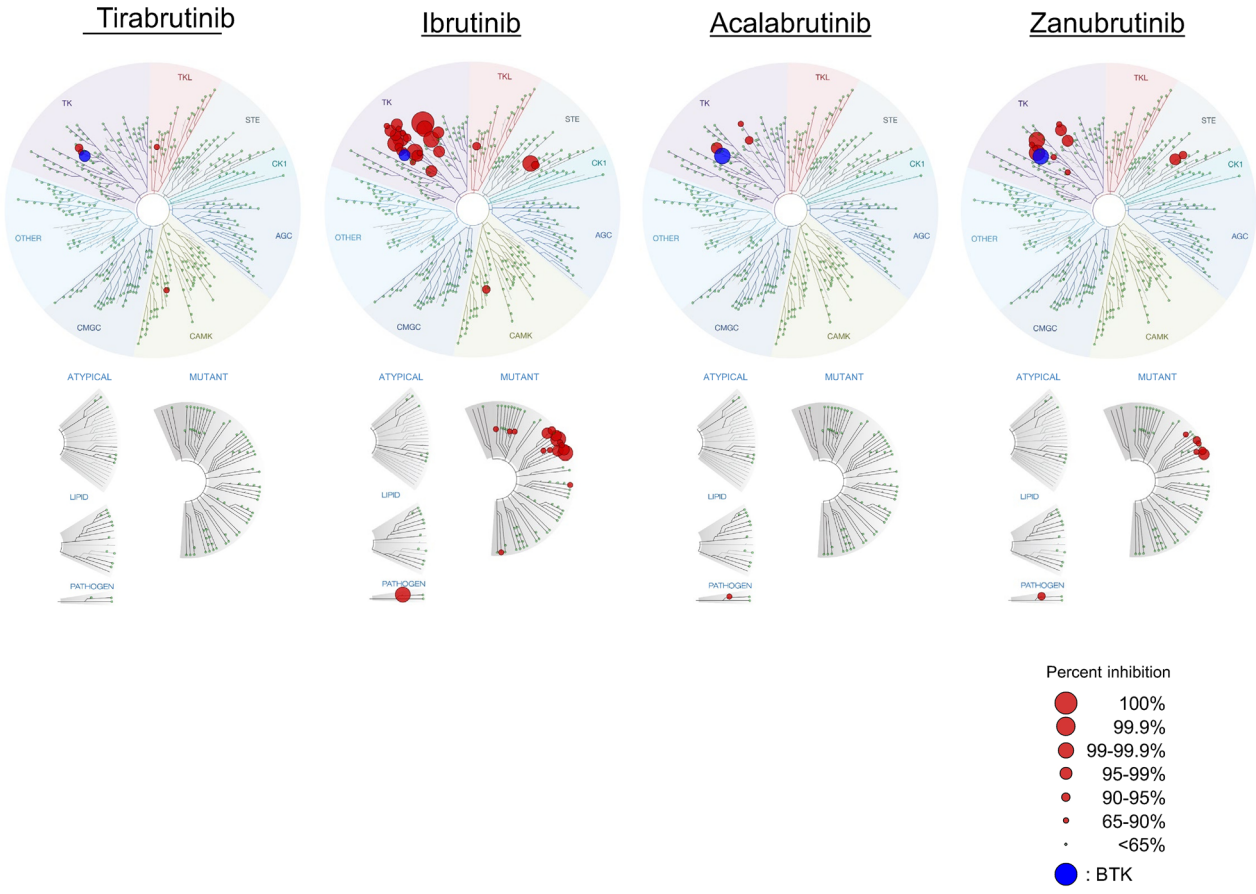

Figure 2. Kinome profiling using the KINOMEscan assay for the first- and second-generation BTK inhibitors[a].
BTK: Bruton's tyrosine kinase.
[a]Reproduced from Kozaki et al. [19].

Table 2. Selectivity of first- and second-generation BTK inhibitors targeting 14 kinases.

	Tirabrutinib		Ibrutinib		Acalabrutinib		Zanubrutinib	
	IC_{50} (nM)	Selectivity	IC_{50} (nM)	Selectivity	IC_{50} (nM)	Selectivity	IC_{50} (nM)	Selectivity
BTK[a]	2.78	1	0.256	1	4.95	1	0.285	1
FYN	2220	799	55.0	215	>10,000	>2020	1659	5821
LYN[a]	3490	1255	17.8	70	>10,000	>2020	734	2575
LCK	788	283	5.87	23	5204	1051	369	1293
BLK	1280	460	0.155	0.6	2270	459	1.71	6
BMX	3.16	1	0.747	3	45.1	9	1.26	4
EGFR	>10,000	>3597	1.71	7	>10,000	>2020	10.7	38
ERBB2	8610	3097	3.01	12	370	75	34.8	122
ERBB4	177	64	0.325	1	30.1	6	2.63	9
ITK	>10,000	>3597	21.9	86	>10,000	>2020	346	1214
JAK3	>10,000	>3597	14.5	57	>10,000	>2020	811	2846
TXK	54.5	20	4.89	19	273	55	4.59	16
TEC	9.92	4	1.37	5	13.9	3	4.47	16
CSK	449	162	10.7	42	6653	1344	194	680

BTK: Bruton's tyrosine kinase; BMX: bone-marrow tyrosine kinase gene on chromosome X; EGFR: epidermal growth factor receptor; ITK: IL-2-inducible T-cell kinase; TEC: tyrosine kinase expressed in hepatocellular carcinoma; CSK: C-terminal Src kinase; IC_{50}: half-maximal inhibitory concentration; LYN: Lck/Yes novel tyrosine kinase; LCK: lymphocyte-specific protein tyrosine kinase; BLK: B-cell lymphocyte kinase; ERBB2: v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2; ERBB4: v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 4; JAK3: Janus kinase 3; TXK: Tyrosine-protein kinase.
[a]BTK was used as the reference kinase for calculating the selectivity of the other 13 kinases evaluated.
Reproduced from Kozaki et al. [19].

Dermatological reactions and diarrhea are among the most commonly experienced AEs with ibrutinib, most of which are grade 1–2 in severity and occur within the first 6 months to 1 year of treatment [30,31]. In a recent review evaluating the relative incidence of dermatological AEs in phase 2/3 studies with BTK inhibitors, rash occurred at a similar rate between patients treated with ibrutinib (13%–27%; grade ≥3: 0%–3%), acalabrutinib (15%–18%), and zanubrutinib (13%–18%) [31]. However, in the Phase 1/2 trial of tirabrutinib in

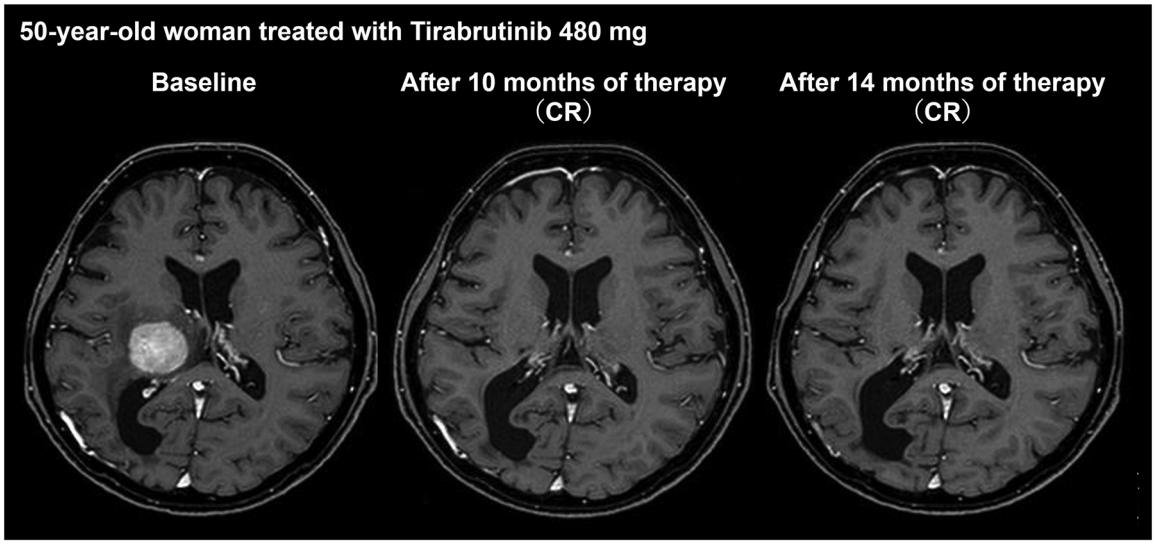

Figure 3. MRI image of patient who responded to BTK inhibitors (tirabrutinib, ONO-4059-02 trial) in PCNSL.
MRI: magnetic resonance imaging; PCNSL: primary central nervous system lymphoma.

Japanese patients with r/r PCNSL (ONO-4059-02), a relatively high incidence of skin disorders was reported, including rash (31.8%; grade ≥3: 2.3%), erythema multiforme (11.4%; grade ≥3: 6.8%), drug eruption (9.1%; grade ≥3: 4.5%), and maculo-papular rash (6.8%; grade ≥3: 2.3%) [32]. Diarrhea is reported in approximately 50% of patients during ibrutinib treatment (grade ≥3: 5%–7%) [33,34], which is a similar frequency to that reported during acalabrutinib (35%–52%), and tirabrutinib (25%–44%) treatment, although severity is lower with the newer agents (grade ≥3 events: 0%–5% vs. 0%–7%, respectively) [35–38].

Dermatological reactions and diarrhea are generally thought to occur with BTK inhibitors as a result of off-target inhibition of EGFR. Gastrointestinal and dermatological AEs are well-recognized class effects with EGFR inhibitors [39], and cutaneous manifestations with ibrutinib closely resemble those experienced with EGFR inhibitors [40]. The incidence of dermatological reactions and diarrhea reported with second-generation BTK inhibitors, which have a relatively low potency for EGFR inhibition, suggest that other mechanisms distinct from EGFR may be at play and warrant further investigation.

Although considered to be less immunosuppressive than conventional immunochemotherapy, several cases of invasive fungal infections have been reported in clinical trials of BTK inhibitors in PCNSL [32,41]. Ghez et al. reported on 33 patients who developed invasive fungal infections during ibrutinib treatment, the majority of which were invasive aspergillosis [42]. However, the majority of patients also had at least one additional factor that increased their risk for fungal infections, including chemotherapy within the last 6 months, neutropenia, or corticosteroid use. Second-generation BTK inhibitors such as acalabrutinib and zanubrutinib possess greater binding selectivity and fewer off-target effects compared to ibrutinib but disseminated fungal infections have still been reported, albeit less frequently [32,41]. In a Phase 1/2 study of tirabrutinib in R/R PCNSL, grade ≥3 bronchopulmonary aspergillosis, pneumonia, and *Pneumocystis jirovecii* pneumonia occurred in 1 of 44 patients (2.3%) each [32]. In a phase 2 study of orelabrutinib in combination with an anti-PD-1 monoclonal antibody in R/R PCNSL ($n = 13$), 1 patient experienced a grade 3 AE of interstitial pneumonitis-related *Pneumocystis jirovecii* infection [41]. These findings indicate that susceptibility to invasive fungal infection and pneumocystis pneumonia is not merely a consequence of off-target effects on T cell response and suggests a greater role of B-cell pathways in antifungal immunity, although the exact mechanism/s by which BTK inhibitors raise the risk of these events are still under investigation. Given that corticosteroid use is common in the treatment of PCNSL and the risk of invasive fungal infections and pneumocystis pneumonia appears higher in this cohort compared with other non-central nervous system (CNS) lymphomas and chronic lymphocytic leukemia (CLL), caution is warranted in those patients.

Penetration of BTK inhibitors across the blood–brain barrier

Given that PCNSL is restricted to the brain, eyes, meninges, and other structures of the CNS, drugs that

are capable of crossing the blood–brain barrier (BBB) to deliver sufficient cytotoxic doses to malignant cells and tissues in the CNS are necessary to achieve durable responses. However, the vast majority of chemotherapeutic agents that are effective in other systemic lymphomas have limited penetration of the BBB. For example, standard doses of MTX do not cross the BBB, necessitating administration of high doses and/or rapid infusion, which increase the risk of systemic and neurological toxicity.

BTK inhibitors are small molecules that have been shown to readily cross the BBB, with a cerebrospinal fluid (CSF) to total plasma concentration ratio of 1%–7% for ibrutinib [43], 0.61%–5.83% for zanubrutinib [44], and 13%–18% for tirabrutinib [32]. The timing of pharmacokinetics (PK) evaluations differed (2–4 h ibrutinib/zanubrtinitb, 24 h tirabrutinib), limiting direct comparison.

Drug–drug interaction with methotrexate

A lack of high-quality data exists regarding a potential interaction between MTX and BTK inhibitors in the literature. However, when BTK inhibitors are used in combination with high-dose MTX-based therapy, pharmacokinetic interactions *via* CYP3A4 are a concern and should be considered with caution [45,46]. In a phase 1b study evaluating ibrutinib in combination with HD-MTX and rituximab (RTX) in patients with r/r CNS lymphoma, the ibrutinib dose was reduced due to a drug interaction with the CYP3A inhibitor, amlodipine, which was initiated to control AF [47]. However, no dose-limiting toxicities (DLTs), treatment-related deaths, or cases of aspergillosis were observed and all grade 4 AEs were seen in patients treated with RTX, HD-MTX, and ibrutinib (840 mg, $n = 2$; 560 mg, $n = 2$). Similarly, most (62%) grade 3 AEs were seen in patients treated with this combination. Using a rat model of collagen-induced arthritis, potential drug–drug interactions between HM71224, a BTK inhibitor, and MTX were explored. HM71224 in combination with MTX was found to decrease the arthritis score, bone erosion, synovitis, and cartilage degradation without apparent interaction [48].

Efficacy and safety of BTK inhibitors for PCNSL in clinical trials

Ibrutinib

To date, two prospective clinical studies have been conducted evaluating the efficacy and safety of ibrutinib monotherapy for the treatment of r/r PCNSL (Table 3). In an open-label, Phase 1 dose escalation study evaluating 560 mg and 840 mg of ibrutinib, 77% (10/13) achieved a clinical response (5 each with a complete response [CR] and partial response [PR]), and the median progression-free survival (PFS) was 4.6 months [9]. In a phase 2 study of 52 patients receiving ibrutinib 560 mg once daily for r/r PCNSL and primary vitreoretinal lymphoma, a CR rate of 19% (10/52 patients) and a PR rate of 33% (17/52 patients) was achieved, and the median PFS was 4.8 months [49]. Grommes et al. reported that while PCNSL patients with MYD88/CD79B co-mutations that activate BCR signaling were expected to respond better to ibrutinib than wild-type patients, there was no apparent response differentiation between patients with or without the co-mutations [9]. In the phase 1 study, hyperglycemia (95%), thrombocytopenia (70%), anemia (70%), and hypertriglyceridemia (70%) were the most common AEs, however, in the above two studies three patients experienced pulmonary aspergillosis, with a favorable ($n = 1$) and fatal ($n = 2$) outcome [49]. Based on the results of the aforementioned studies, ibrutinib monotherapy is listed in the NCCN guidelines as a treatment option for r/r PCNSL [50].

More recently, ibrutinib has been investigated in combination with other therapies for the treatment of r/r PCNSL (Table 3). In a phase 1 study of ibrutinib in combination with HD-MTX and RTX in patients with r/r CNS lymphoma, an overall response rate (ORR) of 89%

Table 3. Clinical trials of BTK inhibitors for r/r PCNSL.

Reference	Agent/s	Origin	Phase	Patients, *N*	ORR (%)	Median PFS, months	Median OS, months
Grommes et al. 2017 [9]	Ibrutinib	USA	1	13	10/13 (76.9)	4.6	15
Sousain et al. 2019 [49]	Ibrutinib	France	2	52	27/52 (51.9)	4.8	19.2
Grommes et al. 2019 [47]	Ibrutinib, MTX, and RTX	USA	1b	15 (PCNSL 9)	8/9 (88.9)	NR	NR
Lionakis et al. 2017 [11]	Ibrutinib monotherapy; ibrutinib + chemotherapy	USA	1b	18	13/14 (92.9)	15.3	NR
Narita et al. 2020 [32]	Tirabrutinib	Japan	1/2	44	28/44 (63.6)	2.9	NR
Song et al. 2022 (interim analysis) [51]	Zanubrutinib, lenalidomide, TMZ, RTX ± MTX	China	2	24	19/24 (79.2)	NR	NR
Zhang et al. 2022 [41]	Orelabrutinib + sintilimab	China	2	13 (interim)	8/13 (61.5)	NR	NR

BTK: Bruton's tyrosine kinase; r/r: relapsed/refractory; PCNSL: primary central nervous system lymphoma; ORR: overall response rate; PFS: progression-free survival; OS: overall survival; MTX: methotrexate; RTX: rituximab; NR; not reported; TMZ: temozolomide.

(8/9 patients) was achieved and the median PFS was not reached in the PCNSL cohort [47]. The most common AEs were anemia, thrombocytopenia, alanine aminotransferase/aspartate aminotransferase elevation, and lymphopenia. No DLTs, treatment-related death, or cases of aspergillosis were observed. A phase 1b study has also been conducted of ibrutinib monotherapy followed by ibrutinib plus chemotherapy (DA-TEDDi-R) in patients with PCNSL and CD79B and/or MYD88 mutations, in which 18 patients were treated with ibrutinib monotherapy, 16 patients started TEDDi-R treatment and 14 were evaluated [11]. A total of 94% of patients showed tumor reductions with ibrutinib alone, and 12 (86%) achieved a complete remission with DA-TEDDi-R. However, the combination of ibrutinib with chemotherapeutic agents was associated with invasive aspergillosis in 7/18 patients (39%), three of which were related, one was probably related, and three were possibly related.

Tirabrutinib

A phase 1/2 study (ONO-4059-02) has been conducted of tirabrutinib in 44 Japanese patients with r/r PCNSL using three dosing regimens (320 mg, 480 mg, and 480 mg in the fasting state) (Table 3) [32]. During the 9-month follow-up period, the ORR was 63.6% (28/44 patients) in the overall population, and 60.0% (12/20 patients) in the 320 mg group, 100% (7/7 patients) in the 480 mg group, and 52.9% (9/17 patients) in the 480 mg fasted group. CR was achieved in 9.1% (4/44 patients), unconfirmed complete response (CRu) in 25% (11/44 patients), and PR in 29.5% (13/44 patients) of patients. Figure 3 shows the MRI image of a patient with PCNSL who responded to tirabrutinib in the ONO-4059-02 trial. No notable differences in ORR were observed between patients receiving tirabrutinib with gene mutations versus those without gene mutations in the phase 1/2 study (ONO-4059-02), including CARD11 (58.8% [10/17] vs. 66.7% [18/27]), MYD88 (59.4% [19/32] vs. 75.0% [9/12]), and CD79B (50.0% [9/18] vs. 73.1% [19/26]) mutations [32]. The median PFS was 2.9 months (95% confidence interval [CI]: 1.8–11.1) in the overall population, 2.1 months (95% CI: 1.8–not evaluable [NE]) in the 320 mg group, 11.1 months (95% CI: 1.4–NE) in the 480 mg group, and 5.8 months (95% CI: 1.0–5.8) in the 480 mg fasted group. No DLTs were observed in this study. AEs occurred in 38 of the 44 patients (all grades), and grade ≥3 AEs occurred in approximately 50% of patients. The most common AEs were skin disorders (31.8%), leukopenia (18.2%), and lymphopenia (15.9%), and the most common grade ≥3 AEs were neutropenia (9.1%), lymphopenia, leukopenia, and erythema multiforme (6.8% each). If administration of tirabrutinib was interrupted in response to a skin disorder, prophylactic use of antiallergic drugs or corticosteroids at the resumption of administration was considered [32]. Skin disorders resolved after treatment with an antihistamine or corticosteroid, which facilitated continued tirabrutinib administration. There were no cardiovascular-related AEs of any grade, including AF or hypotension. The final 3-year follow-up data have now been published for the entire 44 patients [52]. The ORR was 63.6%, including 36.4% of patients who achieved a CR, the median duration response was 9.2 months, and the median PFS was 2.9 months. No new grade 5 AEs nor new safety profiles were observed since the last data cutoff.

A prospective, noninterventional, multicenter, observational post-marketing all-case surveillance study (JRCT ID: jRCT2011210002) has since been conducted to evaluate adverse drug reactions (ADRs) and the ORR of tirabrutinib in r/r PCNSL in Japan [53]. During an interim analysis (data cutoff date: 31 October 2020), 140 patients who received tirabrutinib treatment were analyzed for safety, and data from 127 of those patients were analyzed for effectiveness. The most common ADRs were skin and subcutaneous tissue disorders (30.7%), and no new safety concerns were identified compared with those reported in the phase 1/2 study. No instances of cardiovascular ADRs or grade 5 ADRs were observed. Furthermore, the ORR was 63.0% and the rate of CR or CRu response (37% each) was similar to that achieved in the 480 mg fasted group in the phase 1/2 ONO-4059-02 study [32]. By the end of the 52 weeks, 73 patients (52.1%) were still alive, 46 (32.9%) had died, and the status of 21 (15.0%) was unknown.

Zanubrutinib

Zanubrutinib in combination with lenalidomide, temozolomide (TMZ), and RTX, with or without methotrexate (RLZT ± MTX) has been shown to be an effective and safe treatment option in the first-line setting for patients with PCNSL (Table 3). In a prospective, open-label study, the efficacy and safety of RLZT + MTX were compared against RLZT alone in newly diagnosed patients with PCNSL [51]. At data cutoff (30 June 2022), 24 patients were enrolled in the study, including 12 patients each in the RLZT + MTX and RLZT groups, respectively. The ORR in the overall population was 79.2%, including 9 (37.5%) patients with CR and 10 (41.7%) patients with PR; 2 (8.3%) patients had SD, and 3 (12.5%) patients had progressive disease (PD). The ORR was 66.7% (CR: 16.7%; PR: 50%) in the RLZT + MTX

group and 91.7% (CR: 58.3%; PR: 33.3%) in the RLZT group. Median PFS and OS were not achieved in the overall population, and the estimated 18-month OS and PFS were 95.8% and 78.2%, respectively. Overall, 50% of patients experienced hematologic toxicity. The incidence of non-hematologic toxicity was 50% and included gastrointestinal reactions, rash, and liver and kidney damage. Only one patient experienced grade ≥3 rash. However, pneumonia was reported in 16.7% (4/24) of patients.

Orelabrutinib

Preliminary results have recently been published from an ongoing prospective, multicenter, single-arm phase 2 study evaluating orelabrutinib with the programmed cell death protein 1 (PD-1) inhibitor, sintilimab, for r/r PCNSL [41]. Thirteen patients were enrolled from March 2021 to January 2022, with a median follow-up of 7.0 (1.5–10.5) months. At data cutoff, the ORR was 61.5%; 4 (30.7%) achieved CR, 1 (7.7%) achieved CRu, and 3 (23.1%) achieved PR, and the estimated 1-year PFS rate was 67.7%. Ten patients completed 4 cycles of the combination regimen, while 3 patients discontinued treatment in the first 2 cycles due to PD. Aside from one grade 3 AE of interstitial pneumonitis-related *Pneumocystis jirovecii* infection, no other grade 3–4 hematological or non-hematological AEs were reported, and toxicities were mild.

Despite these promising results, it should be noted that cohorts of PCNSL patients are extremely challenging to collect given the relative rarity of the disease, and many of the clinical trials included ≤20 patients, thus making new interventions incredibly difficult to assess.

Future directions for BTK inhibitors

Future directions

Development status of BTK inhibitors for PCNSL

Currently, there are several BTK inhibitors in development for the treatment of PCNSL, and their use in combination with chemotherapy, molecular targeted drugs, and immune checkpoint inhibitors is also being explored (Table 4). Newer BTK inhibitors such as pirtobrutinib and vecabrutinib are also under investigation in hemato-oncology, with the possibility for expansion into PCNSL in the future (Table 5).

Table 4. Development status of BTK inhibitors for PCNSL.

Study identifier	Agent/s	Indication	Phase
NCT02623010	Ibrutinib	Newly diagnosed PCNSL	2
NCT04129710	Ibrutinib + MTX + RTX + etoposide	r/r PCNSL	2
NCT03703167	Ibrutinib + lenalidomide + RTX	r/r PCNSL	1b
NCT03581942	Ibrutinib + copanlisib	r/r PCNSL or SCNSL	1b/2
NCT02315326	Ibrutinib + HD-MTX Ibrutinib + RTX + HD-MTX Ibrutinib + R-MPV	Newly diagnosed or r/r PCNSL	1/2
NCT04421560	Ibrutinib + pembrolizumab + RTX	PCNSL, NHL	1b/2
NCT04514393	Ibrutinib + MTX + TMZ	Newly diagnosed PCNSL	2
NCT04446962	Ibrutinib + R-MPV	Newly diagnosed PCNSL	1b/2
NCT03770416	Ibrutinib + nivolumab	r/r PCNSL	2
NCT04947319	Tirabrutinib Tirabrutinib + MTR or R-MPV	Newly diagnosed or r/r PCNSL	2
jRCT2031200383	Tirabrutinib	Primary intraocular lymphoma	2
NCT05549284	Orelabrutinib + RTX + MTX	Newly diagnosed PCNSL	2
NCT05390749	Orelabrutinib + RTX + MTX after pomalidomide + orelabrutinib + RTX	Newly diagnosed PCNSL	2
NCT04899427	Orelabrutinib + sintilimab or tislelizumab	r/r PCNSL	2
NCT05334238	Orelabrutinib after ASCT	PCNSL	3
NCT04831658	Orelabrutinib + PD-1 + fotemustine	Treatment-naïve PCNSL	1/2
NCT05209620	Orelabrutini + pemetrexed	PCNSL or SCNSL	2
NCT05242146	GB5121	r/r PCNSL	1b/2
NCT04548648	Acalabrutinib + isavuconazole	PCNSL	2
NCT04462328	Acalabrutinib + durvalumab	PCNSL	1
NCT04906902	Acalabrutinib	r/r CNSL	1/2
NCT04938297	Zanubrutinib + RTX + lenalidomide followed by lenalidomide or zanubrutinib Zanubrutinib + RTX + lenalidomide followed by lenalidomide	PCNSL r/r PCNSL, large B-cell lymphoma with CNS invasion	2
NCT05117814	Zanubrutinib	r/r PCNSL or r/r SCNSL	–
NCT05398224	Zanubrutinib + HD-MTX + RTX followed by zanubrutinib maintenance	r/r SCNSL	2
NCT03740529	Pirtobrutinib + venetoclax + RTX	r/r CLL/SLL or NHL	1/2

BTK: Bruton's tyrosine kinase; r/r: relapsed/refractory; PCNSL: primary central nervous system lymphoma; MTX: methotrexate; RTX: rituximab; HD: high dose; R-MPV: RTX, MTX, procarbazine, vincristine; NHL: non-Hodgkin lymphoma; TMZ: temozolomide; ASCT: autologous stem cell transplantation; SCNSL: secondary CNS lymphoma; CNS: central nervous system; CLL: chronic lymphocytic leukemia; SLL: small lymphocytic leukemia.

Table 5. Next-generation BTK inhibitors.

Study identifier	Agent/s	Indication	Phase
NCT04728893	ArQule 531 (ARQ 531)	CLL, SLL, MZL, MCL, FL and WM	2
NCT03740529	Pirtobrutinib (LOXO-305)	CLL, SLL and NHL	1/2
NCT04666038		CLL and SLL who received BTK inhibitor therapy	3
NCT04662255		MCL	3
NCT05131022	NX-5948	Advanced B-cell malignancies (including PCNSL)	1
NCT03037645	Vecabrutinib (SNS-062)	CLL, SLL, MCL, WM, DLBCL, FL, MZL and lymphoplasmacytoid lymphoma	1b/2

BTK: Bruton's tyrosine kinase; CLL: chronic lymphocytic leukemia; SLL: small lymphocytic leukemia; MZL: marginal zone lymphoma; MCL: mantle cell lymphoma; FL: follicular lymphoma; WM: Waldenstrom macroglobulinemia; NHL: non-Hodgkin lymphoma; PCNSL: primary central nervous system lymphoma; DLBCL: diffuse large B-cell lymphoma; MS: multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

Treatment of newly diagnosed treatment-naïve PCNSL

HD-MTX-based chemotherapy regimens are recommended as first-line treatment for newly diagnosed PCNSL. However, toxicity and the need for frequent hospitalizations are a concern. Initiation of BTK inhibitors prior to recurrence might further optimize patient outcomes (Table 4). It has been reported that synergistic effects can be expected when HD-MTX and BTK inhibitors are used in combination. Currently, ibrutinib is also being studied as an add-on chemotherapy regimen with RTX, MTX, procarbazine, and vincristine (R-MPV) to further improve first-line therapy for PCNSL (Table 4; NCT02315326). The results of the Phase 1b LOC-R01 study (NCT04446962) of ibrutinib added to R-MPV in France have been reported, with 3/11 evaluable patients achieving CR/CRu and 7/11 achieving PR in the ibrutinib group [54]. A Phase 2 study of tirabrutinib in patients with r/r and untreated PCNSL is ongoing in the USA (PROSPECT study Part B). In patients with untreated PCNSL, the safety and efficacy of tirabrutinib added to either MTX, TMZ, and RTX or R-MPV is being evaluated (Table 4; NCT04947319). The efficacy of orelabrutinib, which is under development in China, is also being investigated in a Phase 2 study in combination with RTX and MTX for the treatment of newly diagnosed PCNCL (Table 4; NCT05549284). These results suggest that BTK inhibitors are an attractive add-on to existing chemotherapy regimens.

Secondary CNS lymphoma

Secondary CNS lymphoma (SCNSL) refers to lymphoma that has metastasized to the CNS during or after systemic therapy. Relapse outside of the CNS, including at extranodal sites, is observed in approximately 16% of patients [55]. SCNSL, which is classified into DLBCL, is a highly malignant tumor like PCNSL and early diagnosis is therefore necessary to achieve optimal therapeutic effects and improved prognosis. There is no standard treatment for SCNSL and prognosis is extremely dismal (median OS of 1.5 months) [56]. Conventional PCNSL treatment with MTX or cytarabine chemotherapy is the treatment strategy of choice for SCNSL but is often inactive against primary chemorefractory disease [57]. As is the case with PCNSL, BTK inhibitors are also expected to demonstrate a therapeutic effect in SCNSL. In a phase 2 study in 44 patients with r/r CNS lymphoma (PCNSL; $n=29$, SCNSL; $n=15$), treatment with ibrutinib was associated with an ORR of 69% in patients with SCNSL [58] which is in contrast to the less impressive efficacy in non-CNS lymphomas, where only 37% responded [59]. That being said, the proportion of MYD88 mutations is lower in SCNSL than in PCNSL [60], and further investigation is therefore required to evaluate whether a similar level of efficacy observed with PCNSL may also be achieved with SCNSL. Combination regimens utilizing BTK inhibitors and other novel agents currently being investigated for SCNSL are presented in Table 4.

Next-generation BTK inhibitors

First- and second-generation BTK-targeting agents have shown impressive clinical responses in PCNSL; however, reports detailing the development of acquired resistance to ibrutinib have been published and are of concern [61]. Mutations in the active site of BTK have been identified as the main mechanism of acquired resistance to ibrutinib in CLL and mantle cell lymphoma (MCL), with the most common mutation sites being C481S/F/T/R, as well as less frequent variants at T474I/S/M, R490H, Q516Km, L528W, and V537I [62]. However, the mechanism of resistance in PCNSL is not currently clear and remains speculative.

The rise of mutations that are refractory to current therapies has presented a need for new therapeutic approaches in PCNSL. To address the problem of acquired resistance, next-generation BTK inhibitors, which are potent inhibitors of BTK as well as different variants of the BTK C481 mutation, are being developed for use in patients with CLL and MCL refractory to first- or second-generation BTK inhibitors (Table 5) [63]. Pirtobrutinib, a highly selective reversible inhibitor that acts on both wild-type and C481 mutant BTK [64], is currently being developed, as are dual BTK-based inhibitors designed to overcome acquired resistance. Development of a novel BTK inhibitor with efficacy in patients with PCNSL despite acquired

resistance to first- and second-generation BTK inhibitors is eagerly anticipated [65]. Recently, protein degraders have been developed that target and degrade the BTK protein for BTK inhibition, with several molecules in Phase 1 clinical trials for various B-cell malignancies (Beigene [NCT05006716]; Nurix [NCT04830137, NCT05131022]; Haisco [NCT04861779]) and promising preliminary efficacy observed.

Conclusion

Although PCNSL is highly responsive to chemotherapy and radiation therapy in the first-line setting, the recurrence rate remains unacceptably high and prognosis is extremely poor. New treatment strategies with novel mechanisms of action distinct from conventional therapies are therefore of interest. PCNSL is associated with constitutive activation of BCR signaling, and BTK plays an important role in oncogenic signal transduction downstream of BCR, making it an attractive molecular target. Following the efficacy of the first-generation BTK inhibitor ibrutinib for the treatment of PCNSL, second-generation BTK inhibitors tirabrutinib, zanubrutinib, and orelabrutinib, have subsequently been developed, which possess greater selectivity for BTK and thus fewer off-target effects. These agents have delivered impressive treatment responses in the relapsed/refractory setting with acceptable safety. The expansion of these BTK inhibitors to newly diagnosed PCNSL, and potentially SCNSL, and the development of next-generation BTK inhibitors are expected to revolutionize the treatment landscape for PCNSL.

Acknowledgments

All authors participated in the writing, editing, and critical revision for intellectual content, and approval of the final version of this manuscript. All authors met ICMJE authorship criteria and agreed to be accountable for all aspects of the work.

Author contributions

CG developed the concept for the review and assisted in performing the literature search. All authors critically reviewed, edited, and revised the manuscript, and approved the final draft for submission.

Disclosure statement

LRS: grant support from the National Institutes of Health (P30-CA008748). Support for manuscript preparation received from ONO. Advisory Board fees from BTG Speciality Pharmaceuticals. Consultation fees from BTG Speciality Pharmaceuticals and ONO. Research support from BTG. Patent pending for low-dose glucarpidase. LN: support for manuscript preparation received from ONO. Grant support from the Leukemia and Lymphoma Society and the National Institutes of Health. Royalties or license fees received from Wolters Kluwer (UpToDate Inc). Consultation fees from ONO, BraveBio, and Genmab. Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events received from ONO. Support for attending meetings and/or travel received from ONO. Participation on a Data Safety Monitoring Board or Advisory Board from ONO and Kite/Gilead. CG: grant support from the National Institutes of Health (P30-CA008748). Consultation fees from BTG Speciality Pharmaceuticals, Roche, and ONO. Support for manuscript preparation received from ONO. Payment or honoraria for lectures, presentations, and speakers' bureaus received from ONO. Support for attending meetings and/or travel received from ONO. Participation on an Advisory Board from ONO.

Funding

Medical writing support was provided by Jordana Campbell, BSc, CMPP of inScience Communications, Springer Healthcare. This medical writing assistance was funded by ONO Pharmaceutical Co., Ltd.

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