

## Introduction of novel agents in the treatment of primary CNS lymphoma

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### Abstract

Novel insights into the pathophysiology of primary central nervous system lymphoma (PCNSL) have identified the B-cell receptor and Toll-like receptor pathway as well as immune evasion and suppressed tumor immune micro-environment as a key mechanism in the pathogenesis of PCNSL. Small molecules and novel agents targeting these aberrant pathways have been introduced into clinical trials targeting the recurrent or refractory PCNSL patient population. Agents like the Bruton tyrosine kinase (BTK) inhibitor ibrutinib or immunomodulatory drugs (IMiDs) like pomalidomide and lenalidomide have shown promising high response rates in the salvage setting. Here, we give an overview about the recent, exciting developments in PCNSL and summarize the results of clinical trials using novel agents in the recurrent and refractory salvage setting, which include immune checkpoint inhibitors, IMiDs, as well as BTK, phosphatidylinositol-3 kinase, and mammalian target of rapamycin inhibitors.

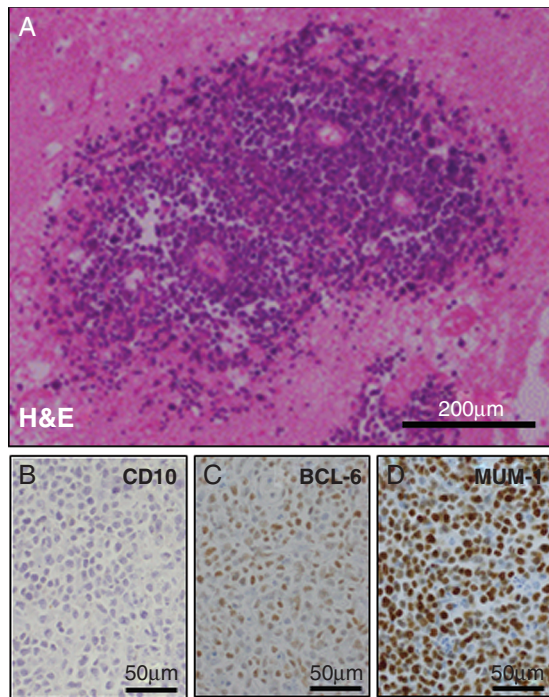
### Keywords

BTK | immune checkpoint inhibition | IMiD | PCNSL | targeted agents

For decades, there has been limited insight into the pathophysiology of primary central nervous system lymphoma (PCNSL), mainly due to the absence of comprehensive, multidimensional data, small clinical trials, and lack of correlation of histologic/genetic data with clinical outcomes. Moreover, tissue availability has been limited, since most patients undergo stereotactic biopsy at first diagnosis rather than surgical resection and the tumor tissue is often exhausted for histopathological diagnosis. Recently, there has been a surge of novel insights based on large-scale genomic investigations using archival tissue banks. These studies have identified novel drivers of PCNSL and these alterations are now being targeted with small molecular inhibitors and immune checkpoint inhibitors in clinical trials for patients with refractory and relapsed disease for which treatment options have been limited.

### Pathophysiology of PCNSL

Pathologic review of PCNSLs reveals a diffuse large B-cell lymphoma (DLBCL) in most of the cases (90%). On rare occasions, Burkitt, low-grade, or T-cell lymphoma are observed.<sup>1</sup> PCNSL cells are highly proliferative and grow in a perivascular growth pattern diffusely infiltrating the brain parenchyma (Fig. 1A). Gene expression profiling of systemic DLBCL tissue samples has established 3 molecular subgroups: (i) germinal center B-cell-like (GCB), (ii) activated B-cell-like (ABC)/nongerminal center (NGC), and (iii) type 3 subgroups.<sup>2</sup> Immunohistochemical (IHC) markers (cluster of differentiation 10 [CD10], B-cell lymphoma 6 protein [BCL6], and multiple myeloma oncogene 1 [MUM1], also called interferon regulatory factor 4 [IRF4]) have been used to distinguish these DLBCL subtypes in



**Fig. 1** Histologic Features of PCNSL. (A) Hematoxylin/eosin (H&E) staining demonstrating the typical perivascular growth of PCNSL. (B–D) Diffuse large B-cell lymphoma subgroup determination using 3 immunohistochemical markers (CD10, BCL6, and MUM1) and applying the Hans algorithm.<sup>3</sup> The majority of PCNSLs are classified as nongerminal center/activated B-cell subtype and display a similar staining pattern as displayed in (B) CD10 negative, (C) BCL-6 positive, and (D) MUM1 positive.

tissue samples.<sup>3</sup> Applying these markers on PCNSL specimens (Fig. 1B–D) demonstrates that the majority (>85%) of PCNSLs can be classified as NGC subtype,<sup>4,5</sup> even though gene expression studies have identified an activated germinal center signature.<sup>6</sup> Systemically, the NGC/ABC subtype is associated with inferior clinical outcome and frequent mutations within the B-cell receptor (BCR) pathway.<sup>7</sup> Recently a large methylation study involving 95 PCNSLs, 73 systemic DLBCLs, and 7 DLBCLs with CNS involvement identified a significantly larger number of methylated cytosine-phosphate-guanine sites in PCNSL than in systemic DLBCL. Unsupervised clustering did not entirely separate PCNSL from DLBCL samples, but this study suggests that PCNSL might be a biologically distinct entity.

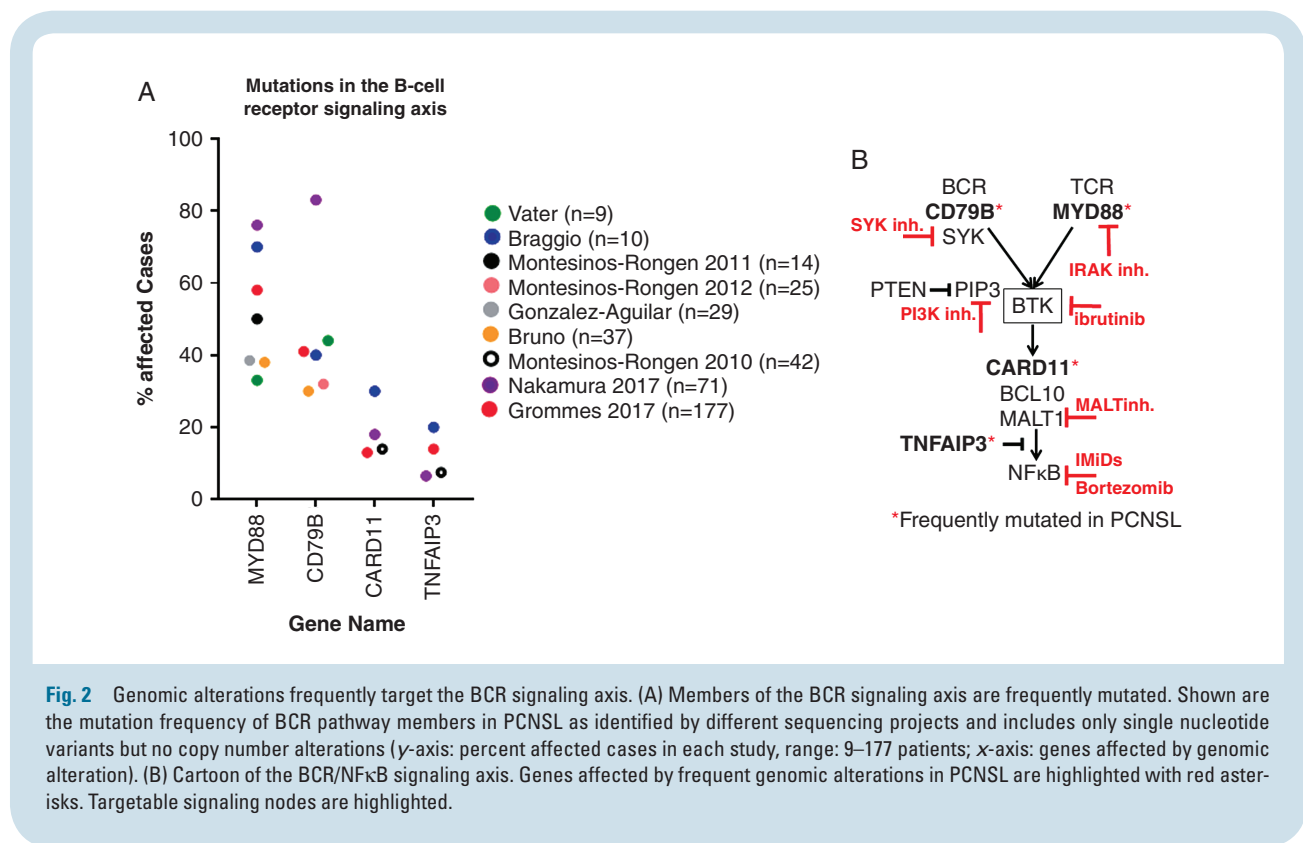
## Novel Insights

In PCNSL cohorts<sup>5,8–14</sup> the BCR signaling axis, particularly *MYD88*, *CD79B*, and less frequently *CARD11* and *TNFAIP3* (Fig. 2A) are frequently affected by recurrent genomic alterations. The Toll-like receptor (TLR) signaling pathway is constitutively activated by *MYD88* mutations.<sup>15</sup> The BCR signaling pathway is activated by *CD79B*<sup>16</sup> and *CARD11*<sup>17</sup>

mutations. Activation of both the TLR and BCR pathways leads to robust nuclear factor kappaB (NFκB) activity. Moreover, a negative regulator of NFκB, tumor necrosis factor alpha induced protein 3 (*TNFAIP3*) (also known as A20), is inactivated due to deletion or mutation, further amplifying NFκB activity.<sup>18</sup> *MYD88* and *CD79B* mutations are enriched in ABC/NGC PCNSLs and are more frequently observed than in ABC DLBCL outside the CNS.<sup>19</sup> Therefore, PCNSL more closely resembles lymphomas found in other immune-privileged organs like the testes, in which *MYD88* and combined *MYD88/CD79B* mutations are reported in >70% of samples.<sup>20,21</sup> Of note, *MYD88* and/or *CD79B* mutations were also identified in PCNSL of the GCB subtype.<sup>5,22</sup> *MYD88* and *CD79B* mutations are characterized as missense mutations and mainly found at hotspot locations (*MYD88* at L265P and *CD79B* at Y196). IHC staining for MUM1, a transcriptional target of NFκB, is positive in 70–95%<sup>1,5,23</sup> of PCNSL tissue samples, further suggesting that aberrant activation of the BCR signaling axis is a significant driver of PCNSL pathophysiology. The BCR signaling pathway can potentially be targeted at different signaling nodes (Fig. 2B). Upstream inhibition could target the spleen tyrosine kinase, phosphatidylinositol-3 kinase (PI3K), Bruton tyrosine kinase (BTK) or interleukin 1 receptor-associated kinase. Downstream, the pathway could be inhibited by immunomodulatory drugs (IMiDs) like thalidomide and its analogues lenalidomide and pomalidomide, which inhibit IRF4, or inhibitors of mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1). NFκB transcription factors are retained in cytoplasm by inhibitory kappaB (IκappaB). IκappaB kinase phosphorylates IκappaB, which then is degraded by proteasome. This allows NFκB transcription factors to enter the nucleus, resulting in alteration of gene expression. The proteasome-mediated hydrolysis of IκappaB, therefore, might be another aspect of the BCR signaling axis that could be targeted by proteasome inhibitors like bortezomib. Activity of current proteasome inhibitors might be limited due to poor CNS penetration, but novel agents with better blood–brain barrier penetration might be active in PCNSL.

Investigations in copy number variations have been completed in cohorts of up to 22 PCNSL patients and reported chromosomal losses at 6q and gains at 12q, 18q, 19q, and 22q.<sup>24–28</sup> *TNFAIP3* is located on chromosome 6q, and the frequent loss of this genomic region might further lead to NFκB activation. Frequent copy number gains at chromosome 9p24.1, which includes the programmed death ligand 1 and 2 (*PD-L1/PD-L2*) locus, have been observed.<sup>29</sup> Moreover, the investigators identified novel chromosomal translocation involving the *PD-L1* and *PD-L2* loci in PCNSL samples, suggesting that immune evasion may play a role in PCNSL. A recent French study identified a novel recurrent gene fusion, E26 transformation-specific translocation variant 6–immunoglobulin heavy chain (*ETV6-IgH*) in 13 of 72 (18%) PCNSL samples and the gene fusion was associated with prolonged survival.<sup>30</sup>

Moreover, aberrant somatic hypermutation (aSHM), which has been found to be a prominent feature in systemic DLBCL, has also been identified in PCNSL.<sup>8,31,32</sup> Aberrant SHM has been characterized by mutations within the first 2000 base pairs of the transcription start site that occur within a WGYR motif. The aSHM causes



**Fig. 2** Genomic alterations frequently target the BCR signaling axis. (A) Members of the BCR signaling axis are frequently mutated. Shown are the mutation frequency of BCR pathway members in PCNSL as identified by different sequencing projects and includes only single nucleotide variants but no copy number alterations (y-axis: percent affected cases in each study, range: 9–177 patients; x-axis: genes affected by genomic alteration). (B) Cartoon of the BCR/NFκB signaling axis. Genes affected by frequent genomic alterations in PCNSL are highlighted with red asterisks. Targetable signaling nodes are highlighted.

mainly transition (change from purine nucleotide to another purine) versus transversion (change from a purine to pyrimidine or vice versa) mutations and more frequently C/T versus A/G mutations. Aberrant SHM frequently affects PIM1, XBP1, BTG2, PRDM1, NFKBIE, TOX, and IRF4 in PCNSL.<sup>5,22</sup> The common occurrence of aSHM, perhaps causing an increase in the mutational load, in combination with frequent copy number gain at chromosome 9p24.1 might increase the susceptibility of PCNSL to immune checkpoint inhibitors like pembrolizumab and nivolumab.

An additional molecular feature described in PCNSL is the frequent inactivation of *CDKN2A* through mutations or deletion.<sup>12,13,33</sup> This genomic alteration could potentially be exploited therapeutically through cyclin-dependent kinase inhibitors (CDKs), like abemaciclib, which has been FDA approved for the treatment of hormone-positive, human epidermal growth factor receptor 2–negative advanced or metastatic breast cancer.

By using IHC, 41.8–93% of PCNSLs are found to express B-cell lymphoma 2 (BCL-2).<sup>1,23,34</sup> One study suggests that high BCL-2 expression in PCNSL is associated with a poor prognosis.<sup>34</sup> BCL-2 can be targeted by the small molecule venetoclax, a highly selective BCL-2 inhibitor that has been FDA approved for the treatment of chronic lymphocytic leukemia (CLL). Of note, response to venetoclax is not necessarily dependent on the degree of BCL-2 expression. Even though BCL-2 expression is higher in follicular lymphoma than in CLL, venetoclax treatment leads to better responses in CLL. In animal models, venetoclax seem to have limited CNS penetration.<sup>35</sup>

## Current Salvage Therapy Options

Treatment of refractory and relapsed PCNSL has largely been based on the experience gathered in numerous small retrospective studies (Table 1). Whole brain radiation therapy (WBRT), in previously unirradiated patients, and high-dose methotrexate (HD-MTX) rechallenge have been used successfully. Rechallenging recurrent PCNSL with HD-MTX led to an overall response rate (ORR) of 85–91%,<sup>36,37</sup> associated with a median overall survival (OS) of 41–62 months. A high ORR of 74–79% was also observed after salvage WBRT with a median OS of 10–16 months.<sup>38,39</sup> Salvage WBRT might therefore be a treatment option for those recurrent PCNSLs that have not received radiation as a part of the initial treatment regimen. The clinical efficacy of HD-MTX rechallenge or WBRT has not been evaluated in prospective clinical trials. However, HD-MTX rechallenge is frequently used in relapsed PCNSL patients, especially if the time period between remission after initial HD-MTX therapy and recurrence is >1 year and the patient has responded well to the initial HD-MTX chemotherapy regimen. A French registry for PCNSL demonstrated that recurrent PCNSL have a better response to salvage therapy and improved OS if they had a good performance status (KPS ≥ 70), had been sensitive to the first-line treatment, had a longer than 1-year duration of first remission, and received salvage therapy at recurrence.<sup>40</sup> In some centers, a high-dose ifosfamide-based chemotherapy regimen (ifosfamide, carboplatin, etoposide [ICE])<sup>41</sup> or rituximab, ifosfamide, etoposide [R-IE])<sup>42</sup> has been used at first

recurrence. The R-IE combination led to an ORR of 41% in a multicenter series including 22 patients.<sup>42</sup>

A prospective French multicenter trial of high-dose etoposide/cytarabine followed by high-dose chemotherapy with autologous stem cell therapy (HDC-ASCT) demonstrated a median PFS of 11.6 months and 2-year OS of 45%.<sup>43</sup> Moreover, patients rechallenged with methotrexate-based chemotherapy in a retrospective case series who achieved a partial and complete response were treated with HDC-ASCT consolidation and had an excellent outcome with a 3-year PFS of 93%.<sup>44</sup> The age of HDC-ASCT recipients was limited to <65 years in both series, therefore limiting the applicability of this treatment approach to younger patients.

A limited number of prospective clinical trials have investigated single agents such as pemetrexed,<sup>45</sup> topotecan,<sup>46,47</sup> temozolomide,<sup>48</sup> and rituximab<sup>49,50</sup> (Table 1). These trials have demonstrated only modest response rates of 31–55%

with associated limited median progression-free survival (PFS) of 1.6–5.7 months. An optimal salvage regimen has not been established for relapsed or refractory PCNSL patients. The choice of therapy in the salvage setting is dependent on the first-line regimen used (inclusion of WBRT), age, performance status, and duration of prior response. Hopefully, additional data from ongoing clinical trials and future, ideally randomized, clinical trials will identify the optimal salvage strategy for the refractory/relapsed PCNSL population.

Randomized trials have not been conducted so far in the salvage setting. In general, prospective trial in recurrent/refractory PCNSL patients have been challenging due to the limited pathophysiologic insights of this disease identifying suitable drug targets and a heterogeneous patient population with different anatomical sites of relapse (brain, CSF, eyes, or multiple sites), multiple prior relapses, and age at relapse.

**Table 1** Salvage regimen in PCNSL

Author	Agents	# of Patients	ORR (PR+CR)	Median PFS, mo	Median OS, mo
<b>Retrospective</b>					
Herrlinger et al <sup>31</sup>	PCV	7	6/7 (86%)	NR	39
Arellano-Rodrigo et al <sup>32</sup>	eto+ifos+AraC	16	6/16 (37%)	4.5	6
Wong et al <sup>33</sup>	Ritux+temozolomide	7	7/7 (100%)	6	8
Enting et al <sup>34</sup>	Ritux+temozolomide	15	8/15 (53%)	2.2	13.6
Plotkin et al <sup>36</sup>	HD-MTX	22	20/22 (91%)	25.8	61.9
Nguyen et al <sup>39</sup>	WBRT	27	20/27 (74%)	9.7	10.9
Hottinger et al <sup>38</sup>	WBRT	48	38/48 (79%)	10	16
Makino et al <sup>34</sup>	Temozolomide	17	8/17 (47%)	1.9	6.7
Wong et al <sup>55</sup>	Temozolomide	7	1/7 (14%)	2	4
Zhang et al <sup>56</sup>	Pemetrexed	30 (18 PCNSL)	18/30 (60%)	4.1	22.6
Pentsova et al <sup>37</sup>	HD-MTX	39	33/39 (85%)	16	41
Chamberlain <sup>57</sup>	Bendamustine	12	6/12 (50%)	3.5	5
Houillier et al <sup>58</sup>	Lenalidomide	6	3/6 (50%)	1.5	2.5
Chamberlain <sup>59</sup>	AraC	14	5/14 (36%)	3	12
Chamoun et al <sup>60</sup>	Ibrutinib	14 (13 PCNSL)	7/14 (50%)	NR	NR
<b>Prospective</b>					
Fischer et al <sup>46</sup>	Topotecan	27	9/27 (33%)	2	8.4
Voloschin et al <sup>47</sup>	Topotecan	15	6/15 (40%)	2 (60 d)	32.7
Reni et al <sup>48</sup>	Temozolomide	36	11/36 (31%)	2.8	3.9
Soussain et al <sup>43</sup>	CYVE+SCT	43	20/40 (50%)	11.6	18.3
Batchelor et al <sup>49</sup>	Ritux	12	5/12 (42%)	1.9 (57 d)	20.9
Raizer et al <sup>45</sup>	Pemetrexed	11	6/11 (55%)	5.7	10.1
Rubenstein et al <sup>61</sup>	IT Ritux+ IT M	14 (6 PCNSL)	6/14 (43%)	1.2	NR
Nayak et al <sup>50</sup>	Ritux+temozolomide+pred	16	5/14 (36%)	1.6 (7 wk)	NR
Korfel et al <sup>62</sup>	Temozolomide	37	20/37 (54%)	2.1	3.7
Grommes et al <sup>5</sup>	Ibrutinib	20 (13 PCNSL)	10/13 (77%)	4.6	15 (PCNSL)
Rubenstein et al <sup>70</sup>	Lenalidomide	14	9/14 (64%)	6	NR
Tun et al <sup>71</sup>	Pomalidomide	25	12/25 (48%)	5.3	NR

AraC: cytarabine; CYVE: cytarabine + etoposide; eto: etoposide; HD-MTX: high dose methotrexate; ifos: ifosfamide; IT Ritux: intrathecal rituximab, IT M: intrathecal methotrexate; PCV: procarbazine, CCNU, vincristine; pred: methylprednisolone; Ritux: rituximab; SCT: stem cell transplant; WBRT: whole brain radiation; NR: not reported; ORR: overall response; CR: complete response; PR: partial response.

## The Use of Small Molecules and Immune Checkpoint Inhibitors in PCNSL

Based on the recent molecular insights into the underlying genomic alterations driving PCNSL, clinical trials for refractory or relapsed PCNSL assessing the efficacy of small molecules have been established. These agents mainly target the PI3K/mammalian target of rapamycin (mTOR) and BCR/TLR pathways as well as immune evasion and suppressed tumor immune microenvironment using IMiDs.

### PI3K/mTOR Pathway

The first targeted agent ever used as salvage treatment was the mTOR inhibitor temsirolimus in a multicenter German phase II study.<sup>62</sup> The investigators observed a response in 54% of patients, but median PFS was limited to only 2.1 months. An even lower response rate of 25% was seen in a clinical trial targeting the PI3K/mTOR axis using the pan-PI3K inhibitor buparlisib.<sup>63</sup> A limited blood-brain barrier penetration by buparlisib might be the possible explanation for the low response rate and lack of clinical response. Pharmacokinetic assessments in blood and CSF demonstrated plasma concentrations that are similar to those reported in the literature,<sup>64</sup> whereas the drug concentration in the CSF was below the half maximal inhibitory concentration needed to induce cell death in lymphoma cell lines. The use of PI3K inhibition in PCNSL is still under investigation in a multicenter phase I/II trial using the dual pan-PI3K/mTOR inhibitor PQR309 (NCT02669511).

### BCR/TLR Pathway

The BCR has been identified as a central signaling pathway in PCNSL.<sup>5</sup> The central signaling molecule BTK has been targeted with single-agent ibrutinib in a French retrospective case series reporting responses in 50% of patients leading to 2 investigator-initiated clinical trials which showed promising results in the recurrent/refractory setting. Fifty-two patients with refractory and relapsed PCNSL or ocular lymphoma were enrolled in a French study using 560 mg of daily dosed ibrutinib (NCT02542514). The investigators observed a radiographic response in 50% of patients after the first 2 cycles of ibrutinib.<sup>65</sup> In the second study, ibrutinib was dosed at 840 mg daily in refractory and relapsed PCNSL and secondary CNS lymphoma (SCNSL) (NCT02315326). Twenty patients were treated and a radiographic response rate of 75% (77% in PCNSL and 71% in SCNSL) with a median PFS of 4.6 months in PCNSL has been reported.<sup>5</sup> Finally, a study conducted by the National Cancer Institute (NCI) demonstrated that 15/18 (83%) PCNSL patients showed a radiographic response after 2 weeks of single-agent ibrutinib administration in a “window” study prior to the use of additional chemotherapy.<sup>66</sup> The results of the latter study are difficult to interpret due to the inclusion of newly diagnosed PCNSL patients (5/18), the addition of multiple other chemotherapy agents after the initial 2 weeks of single-agent ibrutinib (rituximab,

temozolomide, etoposide, doxorubicin, dexamethasone, and intrathecal cytarabine), and a much higher frequency of infectious complications (39% *Aspergillus* infections) than in single-agent ibrutinib studies (eg, 2/52 [3.8%] in 560 mg and 1/20 [5%] in the 840 mg study). The efficacy of ibrutinib is remarkable, with high response rates and a PFS that is promising. Remarkably, the response to ibrutinib observed in the brain is substantially higher<sup>5</sup> than in patients with systemic DLBCL (25% ORR to single-agent ibrutinib; PFS: 2 mo<sup>67</sup>). This remarkable difference in response needs to be further investigated to better define the underlying differences between BCR activation and inhibition in the CNS and outside the CNS. This difference is also likely related to significant difference in incidence of *MYD88* L265P mutation in CNS versus systemic lymphomas. Moreover, even patients without genomic alterations in the BCR pathway responded to ibrutinib.<sup>5</sup> In contrast to systemic DLBCL, where those tumors with both *CD79B* and *MYD88* mutations had a better response to ibrutinib,<sup>67</sup> *CD79B* mutations in PCNSL seem to provide redundant survival signals potentially promoting ibrutinib resistance.<sup>5</sup> Based on these results the updated National Comprehensive Cancer Network (NCCN) 2018 guidelines for the treatment of recurrent/refractory PCNSL now include the use of ibrutinib. The ibrutinib resistance mechanism, causing the limited PFS, needs to be further investigated. Ibrutinib-based combination therapy trials are enrolling including HD-MTX (NCT02315326) and other targeted agents, like PI3K inhibitors (NCT03581942).

### Immunomodulatory Drugs

The IMiDs lenalidomide and pomalidomide have been used in clinical trials for recurrent/refractory PCNSL patients alone or combined with rituximab. IMiDs inhibit NF $\kappa$ B<sup>68</sup> but also block the PI3K/AKT pathway<sup>69</sup> and therefore represent promising agents. Both agents have been demonstrated to cross the blood-brain barrier and have been measured in the CSF.<sup>70,71</sup> In preclinical model systems, pomalidomide was shown to have higher CNS penetration than lenalidomide (~40%<sup>72</sup> vs 11%,<sup>73</sup> respectively), but phase I pharmacokinetic data demonstrated that CNS penetration appears to be about the same for both agents.<sup>74</sup>

The third-generation IMiD, pomalidomide, has been tested in a phase I clinical trial.<sup>71</sup> The trial is based on a preclinical study in which pomalidomide was shown to have significant therapeutic activity in 2 murine CNS lymphoma models.<sup>72</sup> Therapeutic activity of IMiDs consists of direct cytotoxicity to lymphoma cells and indirect therapeutic activity via modulation of the lymphoma immune microenvironment. In particular, pomalidomide modulates tumor associated macrophages by converting their polarization status from M2 to M1. The trial consisted of a dose-escalation phase to determine the maximum tolerated dose (MTD) of pomalidomide and cohort expansion at the MTD. Twenty-nine patients were enrolled and 25 patients were eligible for assessment. The treatment consists of pomalidomide daily for 21 days every 28 days and dexamethasone 40 mg once a week. After the first 2 cycles, pomalidomide was continued alone until

progression, intolerance, or patient's withdrawal. The MTD of pomalidomide was determined to be 5 mg daily for 21 days every 28 days. The ORR for the study (10/25) was 40%. The ORR (whole study) was 48% (12/25; 95% CI: 27.8%, 68.7%) with 6 complete responses (CR), 2 complete responses–unconfirmed (CRu), and 4 partial responses (PR). ORR (MTD cohort) was 50% (8/16; 95% CI: 24.7%, 75.4%) with 5 CR, 1 CRu, and 2 PR. Pseudoprogression was seen in 1 patient after 4 cycles of treatment. Median PFS was 5.3 months for the whole study and 9 months for responders. Overall, grade 3/4 toxicity included hematologic (neutropenia 21%, thrombocytopenia 8%) and nonhematologic events (lung infection 12%, fatigue 8%, syncope 4%, sepsis 4%, respiratory failure 8%, and rash 4%).

In a phase I study the MTD for single agent lenalidomide<sup>70</sup> was defined as 15 mg daily dosing for 21 days out of 28. The radiographic response to single-agent lenalidomide was 64%, with a median PFS of 6 months. In a second study conducted in France, lenalidomide was combined with rituximab in a multicenter phase II trial for recurrent/relapsed PCNSL or ocular lymphoma.<sup>75</sup> Lenalidomide was dosed at 20 mg daily for 21 days out of 28 and combined with rituximab given at 375 mg/m<sup>2</sup> at day 1. This treatment was followed by single-agent lenalidomide in those who responded to maintenance therapy at 10 mg. Forty-five patients have been enrolled and the investigators observed a radiographic response rate to the lenalidomide/rituximab combination in 63% of patients, with a PFS of 8.1 months. Based on these results the updated NCCN 2018 guidelines for the treatment of recurrent/refractory PCNSL now include the use of single-agent lenalidomide or the combination rituximab/lenalidomide.

### Immune Checkpoint Blockade

The use of immune checkpoint inhibitors in PCNSL might represent another promising treatment approach. In an immunocompetent preclinical model, immune checkpoint inhibition by anti-PD1 monoclonal antibodies had significant therapeutic activity against CNS lymphoma.<sup>76</sup> Moreover, Nayak et al reported long-term responses in a small retrospective study<sup>77</sup> of 4 patients with PCNSL. This observation in conjunction with the knowledge of 9p24.1 copy number alterations observed in PCNSL samples<sup>29</sup> resulted in a multicenter trial investigating single-agent nivolumab in PCNSL and testicular lymphoma (NCT02857426). Moreover, a single institution trial using pembrolizumab (NCT02779101) is ongoing to further investigate the concept of immune evasion and PD-1 blockade in PCNSL. Additional clinical trials are planned combining checkpoint inhibitors with targeted agents, like ibrutinib or IMiDs.

### Future Directions

Significant advances have been made in the treatment of PCNSL over the past decades. Novel insights into the pathophysiology of PCNSL led to the introduction of targeted agents into clinical trials in the salvage setting, which have shown

**Table 2** Ongoing salvage trials

Agents	ClinicalTrials.gov ID	Date Opened
Pembrolizumab	NCT027791014	5/2016
PQR309 (dual PI3K/mTOR inhibitor)	NCT03127020	4/2017
Abemaciclib	NCT03220646	6/2017
R-CHOP preceded by blood–brain barrier permeabilization by t-NGR necrosis factor	NCT03536039	5/2018
Rituximab+lenalidomide+nivolumab	NCT03558750	6/2018
Copanlisib+ibrutinib	NCT03581942	9/2018
Rituximab+lenalidomide+ibrutinib	NCT03703167	10/2018

promising clinical responses. Some of these agents have now been included in the NCCN guidelines for the treatment of recurrent/refractory PCNSL and will be more frequently used in the future. To overcome resistance to those agents, combination trials are on the way and hopefully will be able to overcome the limited PFS time observed with single-agent small inhibitors (Table 2). The role of immune checkpoint inhibition is not yet clearly defined but will be addressed by ongoing clinical studies in the salvage setting. Chimeric antigen receptor (CAR) T-cell therapy, which has recently been approved for the treatment of recurrent/refractory systemic DLBCL, hopefully will also be evaluated in PCNSL soon. CART cells have been found to penetrate the CNS, and responses have been observed in secondary CNS lymphoma patients.<sup>78</sup> In the next years, we hopefully see the integration of small molecules into first-line treatment regimens and the emergence of additional maintenance treatment concepts, hopefully to reduce the number of refractory patients, further increase response rates, increase remission times, and further increase treatment options for recurrent patients who have a particularly poor clinical outcome. Small molecules might also help to improve outcomes in the elderly PCNSL population by reducing treatment associated comorbidities more commonly seen with conventional chemotherapy regimens.

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