Novel agents for primary central nervous system lymphoma: evidence and perspectives

Gerald Illerhaus,1 Elisabeth Schorb,2 and Benjamin Kasenda1,3,4

1Department of Hematology/Oncology and Palliative Care, Klinikum Stuttgart, Stuttgart, Germany; 2Department of Hematology, Oncology and Stem Cell Transplantation, Faculty of Medicine, University of Freiburg, Freiburg, Germany; and 3Department of Medical Oncology and 4Institute for Clinical Epidemiology & Biostatistics, University Hospital Basel, Basel, Switzerland

Primary central nervous system lymphoma (PCNSL) is a rare aggressive extranodal non-Hodgkin lymphoma. Although high remission rates can be achieved with high-dose methotrexate–based immunochemotherapy, risk of relapse and associated death is still substantial in at least a third of patients. Novel agents for treating lymphoid malignancies have substantially enriched treatment options for PCNSL. We herein systematically review the existing clinical evidence of novel agents in treatment of PCNSL, summarize ongoing studies, and discuss perspectives. The body of evidence for novel agents is still limited to noncomparative studies, but the most promising approaches include Bruton kinase inhibition with ibrutinib and immunomodulatory treatment (eg, with lenalidomide). Targeting the mammalian target of rapamycin pathway does not seem to have a meaningful clinical benefit, and evidence of checkpoint inhibition with nivolumab is limited to anecdotal evidence. Future studies should embrace the concept of induction and maintenance therapy as well as the combination of drugs with different mechanisms of action. Selection of patients based on molecular profiling and relapse patterns should be another aspect informing future comparative trials, which are urgently needed to improve prognosis for patients with PCNSL. (Blood. 2018;132(7):681-688)

Introduction

Primary central nervous system lymphoma (PCNSL) is an aggressive extranodal non-Hodgkin lymphoma that exclusively invades the central nervous system (CNS). The annual incidence is estimated at 0.48/100,000 per year (1.41 in patients ≥65 years). Induction treatment with high-dose methotrexate (HD-MTX)–based immunochemotherapy is a widely accepted approach. For consolidation, whole-brain radiotherapy, nonmyeloablative chemotherapy, and high-dose chemotherapy with autologous stem cell support (HCT-ASCT) are options depending on center expertise and patient eligibility. With conventional HD-MTX–based chemotherapy, ~50% of patients are still at risk for progression or relapse. Also, patients achieving a complete remission (CR) after HCT-ASCT are still at risk of relapse 5 years after treatment. There is no standard for second-line treatment, but several studies suggest that HD-MTX–free salvage regimens are effective, including HCT-ASCT. However, many patients are not eligible for HCT-ASCT at relapse, and prognosis remains poor. PCNSL shares characteristics with systemic diffuse large B-cell lymphoma (DLBCL) but is a unique World Health Organization entity. Moreover, PCNSL cannot be categorized into germinal center B (GCB) and activated B-cell (ABC) subtypes as it is for systemic DLBCL. PCNSL is typically characterized by pan-B-cell markers such as CD20, CD19, CD22, and CD79a. In addition, many also express BCL-6 (a marker of GCB cells) and IRF4/MUM1 (a marker of late GCB and plasma cells). High proliferative activity (Ki67 ≥90%) is another striking feature. Other typical characteristics include immunoglobulin M expression, lack of class-switch recombinations, and activation of the NF-κB pathway; at the same time, high immunoglobulin gene mutation frequency with ongoing somatic hypermutations are frequently observed. Proteins of the NF-κB pathway family, such as myeloid differentiation primary response 88 (MYD88) and CD79B, have been identified as the most frequent mutations in PCNSL underlining the dependency on B-cell receptor (BCR) signaling. Alterations in the MYD88 protein, which links interleukin-1 and Toll-like receptors with the NF-κB pathway, may especially serve as predictive markers for BTK inhibition. Recently gained insights into the mutational and signaling landscape of PCNSL hold promise to identify druggable targets and conduct clinical trials with novel agents to improve prognosis, particularly for patients with relapsed/refractory (r/r) PCNSL.

Methodology

We conducted a systematic MEDLINE search (via PubMed, with a filter for human studies and a time period of 1 January 2007 to 22 October 2017) using the following search terms: “pcnsl” OR “primary cns lymphoma” OR “primary central nervous system lymphoma.” We included prospective studies and retrospective case series (at least 5 patients) that reported clinical outcome data of PCNSL patients being treated with single drugs alone or in combination with cytotoxic chemotherapy; studies only reporting treatments with cytotoxic chemotherapy were excluded. We received 925 hits; after removal of duplicates, we screened titles and abstract of 757 potential articles. To identify
<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Type of publication</th>
<th>NCT identifier</th>
<th>Study design</th>
<th>Sample size</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>2017</td>
<td>Article</td>
<td>NCT02315326</td>
<td>Prospective, single center, no RCT</td>
<td>20</td>
<td>r/r PCNSL and SCNSL</td>
<td>Ibrutinib</td>
<td>77% ORR, median PFS 4.6 mo, median OS 15 mo</td>
<td>First full publication on single-agent ibrutinib in r/r PCNSL and SCNSL and comprehensive analyses on mutational landscape in PCNSL</td>
</tr>
<tr>
<td>28</td>
<td>2017</td>
<td>Article</td>
<td>NCT02203526</td>
<td>Prospective, single center, no RCT</td>
<td>18</td>
<td>De novo PCNSL, r/r PCNSL and SCNSL</td>
<td>Ibrutinib + chemotherapy (TEDDI-R)</td>
<td>89% ORR, median PFS 15.3 mo, median OS not reached</td>
<td>Novel polyimmunochemotherapy combined with ibrutinib, high morbidity rate, especially fungal infections</td>
</tr>
<tr>
<td>51</td>
<td>2017</td>
<td>Abstract</td>
<td>Unclear</td>
<td>Prospective, single center, no RCT</td>
<td>9</td>
<td>r/r PCNSL and SCNSL</td>
<td>Lenalidomide + rituximab maintenance</td>
<td>NA</td>
<td>Small series on lenalidomide maintenance after HD-MTX-based induction</td>
</tr>
<tr>
<td>52</td>
<td>2017</td>
<td>Abstract</td>
<td>NCT01722305</td>
<td>Prospective multicenter, no RCT</td>
<td>25</td>
<td>r/r PCNSL and IOL</td>
<td>Pomalidomide + dexamethasone followed by pomalidomide maintenance</td>
<td>43% ORR, PFS and OS not reported yet</td>
<td>First study investigating pomalidomide in r/r PCNSL; full study publication needs to be awaited regarding appraisal of long-term remissions</td>
</tr>
<tr>
<td>31</td>
<td>2017</td>
<td>Abstract</td>
<td>NCT02315326</td>
<td>Prospective bicentric, no RCT</td>
<td>6</td>
<td>r/r PCNSL and SCNSL</td>
<td>Ibrutinib + HD-MTX + rituximab</td>
<td>Four of 6 patients showed a response</td>
<td>Study investigating ibrutinib in combination with HD-MTX and rituximab in r/r CNS lymphoma</td>
</tr>
<tr>
<td>50</td>
<td>2016</td>
<td>Abstract</td>
<td>NCT01542918</td>
<td>Prospective, single center, no RCT</td>
<td>13</td>
<td>r/r PCNSL and SCNSL</td>
<td>Lenalidomide</td>
<td>8 of 13 achieved a response</td>
<td>Study showing activity of lenalidomide in r/r PCNSL</td>
</tr>
<tr>
<td>26</td>
<td>2016</td>
<td>Abstract</td>
<td>NCT02542514</td>
<td>Prospective multicenter, no RCT</td>
<td>52</td>
<td>r/r PCNSL and IOL</td>
<td>Ibrutinib</td>
<td>50% ORR, median PFS 8.1 mo, median OS 19.2 mo</td>
<td>Largest prospective study investigating ibrutinib single agent in r/r PCNSL; benchmark for future ibrutinib studies</td>
</tr>
<tr>
<td>36</td>
<td>2016</td>
<td>Article</td>
<td>NCT00942747</td>
<td>Prospective multicenter, no RCT</td>
<td>37</td>
<td>r/r PCNSL</td>
<td>Temsirolimus</td>
<td>54% ORR, PFS and OS not reported</td>
<td>Only prospective study that investigated mTOR inhibition in PCNSL, but results are not promising</td>
</tr>
<tr>
<td>49</td>
<td>2016</td>
<td>Abstract</td>
<td>NCT01956695</td>
<td>Prospective multicenter, no RCT</td>
<td>50</td>
<td>r/r PCNSL and IOL</td>
<td>Lenalidomide + rituximab</td>
<td>67% ORR, median PFS 8.1 mo, median OS 19.2 mo</td>
<td>Largest prospective study investigating this combination with promising activity, benchmark for future lenalidomide containing approached in r/r PCNSL</td>
</tr>
<tr>
<td>37</td>
<td>2016</td>
<td>Abstract</td>
<td>NCT02301364</td>
<td>Prospective single center, no RCT</td>
<td>4</td>
<td>r/r PCNSL and SCNSL</td>
<td>Buparlisib single agent</td>
<td>One patient with PR</td>
<td>Buparlisib did not reach meaningful concentrations in the CNS</td>
</tr>
</tbody>
</table>

IOL, intraocular lymphoma; NA, not applicable; ORR, overall response rate; RCT, randomized clinical trial; SCNSL, secondary CNS lymphoma.
ongoing eligible studies, we searched clinicaltrials.gov using the above-mentioned keywords. We also used Google Scholar to screen conference abstracts of ongoing studies. Identified prospective studies are summarized in Table 1.

**BTK inhibition**

In systemic DLBCL of the ABC subtype, activated NF-κB signaling is associated with lymphoma cell survival. Several activating mutations can target genes encoding subunits of the BCR such as CD79A/B, the BCR pathway adaptor CARD11, and MYD88; by this, chronic stimulation of the BCR signaling is maintained, promoting lymphoma cell survival and proliferation.21,22 Downstream of the BCR, Bruton tyrosine kinase (BTK) integrates BCR and Toll-like receptor signaling.23 In a single-arm study including 80 patients with r/r systemic DLBCL, inhibition of BTK with ibrutinib was associated with higher response rates in patients with the ABC subtype compared with the GCB subtype.24 However, patients not harboring mutations in BCR signaling also achieved responses, suggesting that oncogenic BCR signaling does not necessarily require BCR mutations and might be initiated by other mechanisms.24 PCNSL cannot be categorized into ABC or GCB subtypes; however, because MYD88 and CD79B are by far the most frequent mutations observed,25 BTK inhibition is an interesting treatment concept in PCNSL.

The largest study of ibrutinib in r/r PCNSL was conducted by the French LYSARC group;26 it was a multicenter, single-arm, phase 1 study enrolling 52 patients (median age, 70 years; 70% with relapse; 14 with primary intraocular lymphoma only) between September 2015 and July 2016. All patients were treated with single-agent ibrutinib (560 mg/d) until disease progression or toxicity. An interim analysis was presented at the 2016 annual meeting of the American Society of Hematology. On the first scan (after 2 months), a CR was observed in 10 patients (19%) and a partial remission (PR) was observed in 16 patients (31%) patients; 4 patients (8%) achieved stabilization of disease, and 13 patients (25%) progressed. Progression-free survival (PFS) and overall survival (OS) have not been reported, but after a median follow-up of 9.2 months, 32 of 52 patients (62%) terminated treatment (25 due to progressive disease, 3 due to toxicities, and the remaining for other reasons). Besides the known side effects of ibrutinib, there were 2 cases of pulmonary Aspergillus infection (1 resolved and 1 had a fatal outcome).26

Grommes and colleagues reported a nonrandomized, single-center, dose-escalation study designed to establish the maximum tolerated dose of single-agent ibrutinib in r/r PCNSL (n = 13) and secondary CNS lymphoma (n = 7).19 Ibrutinib was given until disease progression or intolerable toxicity starting at 560 mg/day. Dose escalation followed a “3+3” design (maximum dose, 840 mg). Pharmacokinetic data from the cerebrospinal fluid (CSF) were available in 18 of 20 patients and showed dose-dependent, meaningful ibrutinib concentrations in the CSF. There were no unexpected safety signals, but 1 patient developed a fungal infection (on steroids for 17 weeks prior to study enrollment) leading to termination of ibrutinib. In the PCNSL cohort (n = 13), overall response was 77% (5 complete and 5 PRs); 2 out of 13 patients showed stable and progressive disease, and in 1 patient, the response was not evaluated. Median PFS was 4.6 months, and median OS was 15 months (7 out of 13 patients are still alive).19 In the one patient with progressive disease under treatment with ibrutinib, a missense mutation within the coiled-coil domain of CARD11 (R179Q) was observed, which is a possible mechanism that has been observed in patients with ibrutinib resistance in systemic DLBCL and mantle cell lymphoma.24,27

In another dose-finding study, Lionakis and colleagues enrolled 18 patients (median age 66): Five patients with newly diagnosed and 13 with relapsed (n = 2) or refractory (n = 11) disease.28 In contrast to the study by Grommes and colleagues,19 they embedded ibrutinib into a dose-adjusted immune polychemotherapy protocol with temozolomide, etoposide, liposomal doxorubicin, dexamethasone, rituximab, and intrathecal cytarabine (DA-TEDDI-R). However, they allowed for a 14-day window with single-agent ibrutinib during the first cycle with a dose ranging from 560 to 840 mg (n = 6, 560 mg; n = 4, 700 mg; n = 8, 840 mg). In those 18 patients starting on single-agent ibrutinib, 16 (89%) achieved ≥50% in regression of the lymphoma before starting the first cycle of DA-TEDDI-R. Comprehensive pharmacokinetic analyses revealed an ibrutinib CSF/plasma ratio of 28.7% (corrected for protein binding), which is a meaningful concentration of ibrutinib in the CNS. PFS was not reported for the entire cohort, but considering all 13 patients with r/r disease, median PFS was 15.3 months, while median OS was not reached with 51.3% of patients being alive. Regarding those 5 patients with newly diagnosed disease, 2 have died <6 months after starting DA-TEDDI-R and 1 progressed after 6 months. Overall, 8 of 18 patients (44%) patients died (3 from disease progression and 5 during treatment). Of the 5 deaths during treatment, at least 3 (2 from Aspergillus infection and 1 from neutropenic sepsis) were reported being treatment related, which accounts for a treatment-related mortality of 17% with the DA-TEDDI-R regimen. The investigators suggested that the increased number of aspergillosis cases may be caused by a direct impact of ibrutinib on fungal immune surveillance, which they backed with results from a murine model, but only 27% of BTK-/− mice died of aspergillosis; therefore, this important safety finding may also be explained by other factors.

The risk for severe fungal infections in PCNSL patients treated with ibrutinib should not be underestimated.

Chamoun and colleagues reported on a retrospective series of 13 patients with r/r PCNSL and 1 patient with testicular lymphoma.29 Three patients achieved CR and 4 PR (overall response rate, 50%) within the first 3 months of treatment. However, 11 patients received ibrutinib for only ≤5 months due to progression. Only 3 patients were still on ibrutinib at the time of publication.

**Comment on BTK inhibition**

BTK inhibition in PCNSL is supported by insights into its biology, especially regarding BCR signaling dependency. Clinical evidence for ibrutinib in PCNSL is currently limited to noncomparative studies, but meaningful chances for lymphoma regression in at least 50% of patients can be expected in r/r PCNSL. Interestingly, with all the limitations of interstudy comparisons, the observed response rate in r/r PCNSL patients receiving ibrutinib was higher (77%) than the response rate in patients with r/r DLBCL outside the CNS (37%, 14/38 ABC subtype).24 This observation is not clearly understood but suggests that not only genetic factors but also the lymphoma microenvironment may play a substantial role regarding lymphoma responsiveness to BTK inhibition. On the other hand,
remissions do not seem durable with a median PFS of ~5 months, and infections with Aspergillus is an important safety signal of ibrutinib in PCNSL requiring further investigation. The DA-TEDDI-R protocol (an experimental chemotherapy protocol combined with ibrutinib) was associated with a relatively high treatment-associated mortality of 17% (in a relatively young cohort [median age, 66 years] in which most patients had good performance status [72% with performance status of 1]). Because it is unclear which component of DA-TEDDI-R has driven this high mortality rate, future studies on combination protocols with ibrutinib should preferably be based on chemotherapy protocols with established efficacy and safety profiles.

Grommes et al are currently running a study investigating the combination of ibrutinib and HD-MTX. Preliminary safety data of 6 patients revealing the feasibility of this combination were recently presented (NCT02315326). Apart from the studies summarized above, there is another ongoing study investigating ibrutinib maintenance treatment in elderly patients with de novo PCNSL after achieving first remission (NCT02623010).

**mTOR and PI3K inhibition**

The mammalian target of rapamycin (mTOR) is a serine-threonine protein kinase that belongs to the phosphoinositide 3-kinase (PI3K)–related kinase family. The PI3K/AKT/mTOR pathway adjusts protein synthesis to regulate cell growth and proliferation by integrating signals arising from growth factors, hormones, nutrients, and energy metabolism. Preclinical data have suggested activity in lymphoma cells, which has subsequently been shown in a randomized trial in patients with relapsed mantle cell lymphoma as well as smaller single-arm studies.

Korfel and colleagues initiated a multicenter phase 2 trial investigating efficacy and safety of temsirolimus 37 in patients with r/r PCNSL. 37 patients (median age 70 years) were treated with weekly temsirolimus (6 patients with 25 mg and 29 patients with 75 mg). A CR was observed in 8 patients (including 3 with unconfirmed CR), and 12 patients achieved a PR (overall response 54%). Median PFS was 2.1 months, and median OS was 3.7 months. The most frequent toxicities were hyperglycemia, bone marrow suppression, infections (mostly pneumonias), and fatigue. Five patients died due to treatment-associated complications, accounting for a treatment-related mortality of 13%.

Grommes et al reported on a phase 2 trial enrolling patients with r/r PCNSL to receive single-agent buparlisib, a pan-PI3K inhibitor. Results of 4 patients were presented at the 2016 annual meeting of the European Society for Medical Oncology and revealed that buparlisib levels in the CNS were clearly below the 50% inhibitory concentration observed to induce cell death in lymphoma cells in vitro; furthermore, only 1 patient showed a PR but later developed psychiatric symptoms and was taken off study within 8 weeks after study start.

**Comment on mTOR and PI3K inhibition**

Only 1 prospective study investigated mTOR inhibition in r/r PCNSL using temsirolimus. Although a remission was observed in almost half of all patients, the median PFS was only 2.1 months, and treatment-associated toxicity was substantial. We could not identify any ongoing study further investigating mTOR inhibition with temsirolimus; however, the pan PI3K/mTOR inhibitor POQ309 is currently tested in an international single-arm study (NCT02669511), though no results have been reported yet.

**Immunomodulating agents**

Lenalidomide is an immunomodulatory agent interfering with growth and survival of aggressive lymphoma via multiple mechanisms of action, including alteration of the lymphoma cell microenvironment and stimulation of effector cells such as cytotoxic T and natural killer cells. Furthermore, activity of immunomodulatory drugs seems to be mediated by cereblon, a component of a ubiquitin-ligase complex, especially in ABC-subtype systemic DLBCL. Single-arm studies have shown clinical activity in r/r systemic non-Hodgkin lymphoma as single agent and in combination with R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone) for newly diagnosed DLBCL. Lenalidomide as maintenance treatment has been shown to improve PFS (but not OS) in elderly patients with newly diagnosed DLBCL who achieved at least a PR after completing R-CHOP induction.

The French LOC network conducted a multicenter single-arm study (REVRI study) investigating lenalidomide plus rituximab in 50 patients [45 evaluable] (recruited between September 2013 and September 2015) with r/r PCNSL (including intracranial lymphoma). Patients were treated with 8 28-day cycles of lenalidomide (20-25 mg daily on days 1-21) and rituximab (375 mg/m²) as induction; patients achieving at least a PR continued on maintenance treatment with lenalidomide (10 mg on days 1-21) for another 12 28-day cycles. Median age was 69 years (range, 46-86 years), with a large proportion (49%) of patients showing a reduced clinical performance status (Eastern Cooperative Oncology Group 2 to 4). The best response rate achieved was 67% (18 CRs and 12 PRs of 45 evaluable patients); however, after completion of induction treatment, the response rate decreased to 36%. After a median follow-up of 19 months, median PFS was 8.1 and median OS was 19.2 months.

Rubenstein and colleagues reported on a phase 1 study investigating lenalidomide (10, 20 or 30 mg) in 13 patients with refractory CNS DLBCL (8 PCNSL, 5 secondary CNS lymphomas; median age 63, range 46-78). Eight of 13 patients achieved a response (5 CRs). Four CRs were maintained >9 months and >1.8 years. In the same abstract, the investigators also reported on 12 patients with recurrent CNS of DLBCL (10 PCNSLs and 2 secondary CNS lymphomas) who received lenalidomide (5-10 mg) and rituximab as maintenance treatment after completion of salvage treatment. After a median follow-up of 18 months, 5 patients maintained remission over 2 years. In another abstract, Rubenstein and colleagues report on an interim analysis of a single study enrolling elderly patients (>70 years) to be treated with low-dose lenalidomide maintenance (5-10 mg/d) in combination with rituximab after achieving first partial or CR after HD-MTX–based induction treatment. Nine patients were included (median age, 76 years), and after a median follow-up of 18 months, the median time on lenalidomide maintenance was 9 months. Overall, treatment was well tolerated, suggesting that low-dose lenalidomide may be an interesting option for...
reducing risk of relapse; however, patient numbers are still very small, and comparative studies are needed to investigate the actual impact of maintenance lenalidomide.

Tun et al reported on a phase 1 dose-escalation study investigating pomalidomide in 25 patients with r/r PCNSL and ocular lymphoma. The maximum tolerated dosage was 5 mg for 21 days, repeated every 28 days (20 mg weekly dexamethasone for the first 2 cycles). Nine of 21 evaluable patients (43%) showed a response, including 6 patients who remain on treatment. Response rates were similar among patients treated at the maximum tolerated dose level of 5 mg (5 out of 12 patients). Full publication of this study is needed for comprehensive appraisal.

Houllier et al reported on a small retrospective series of 6 patients with r/r PCNSL. Of the 2 patients who achieved a CR, one was in ongoing remission 24 months later. One patient achieved a PR, and the remaining patients showed progressive disease.

Comment on immunomodulating agents
Combination of lenalidomide with rituximab is associated with a response rate of ~70% in r/r PCNSL; however, durable remissions are limited, resulting in a median PFS of 8 months. OS in the only prospective multicenter study was ~19 months, which is relatively long given the unfavorable prognostic factors of the study population and short PFS, but details on poststudy management have yet not been reported. Full journal publications need to be awaited to comprehensively assess efficacy and safety outcomes of lenalidomide and rituximab. There is one registered study planning to investigate the combination of lenalidomide with durvalumab (NCT03212807, not yet recruiting).

Checkpoint inhibition with PD-1 antibodies
There is currently no clinical evidence for PD-1 or PD-L1 inhibition from prospective studies in r/r or newly diagnosed PCNSL. One retrospective case series reported 5 patients with r/r PCNSL who were treated with single-agent nivolumab. Four patients achieved a CR, and 1 patient achieved a PR. However, it needs to be mentioned that 1 patient received whole-brain radiotherapy and another patient received focal radiotherapy immediately prior to the initiation of nivolumab. Only 1 out of 5 patients received steroids (dexamethasone at 2 mg oral daily) when commencing treatment with nivolumab, which is a situation very seldom seen in patients with relapsed symptomatic disease.

Comment on checkpoint inhibition
In summary, frequently observed 9p24.1/PD-L1/PD-L2 copynumber alterations and translocations suggest genetic bases of immune evasion in PCNSL. In systemic Hodgkin lymphoma, there is evidence supporting that 9p24.1 copy gain and increased PD-L1 expression on Reed-Sternberg cells are associated with favorable outcome in patients treated with nivolumab. Whether this principle also applies to PCNSL is unknown. Results from an ongoing international study (N = 65) investigating nivolumab in r/r PCNSL and testicular lymphoma (NCT02857426) are eagerly awaited. Another ongoing phase 2 study investigates pembrolizumab (NCT02779101) in patients with r/r PCNSL (target sample size, N = 21), but no results have been reported so far.

Perspectives
Similar to systemic DLBCL, it is unlikely that a novel agent used as monotherapy is of curative potential for patients with PCNSL. Ibrutinib and lenalidomide are the only novel agents that have shown meaningful clinical activity. Recent insights into PCNSL biology and its mutational landscape provide new hypotheses for potential predictive markers. However, until now, robust predictive biomarkers for the treatment of PCNSL with novel agents are still lacking; though exciting, we are still in an explorative era regarding novel agents in PCNSL, a situation that is, again, very similar to systemic DLBCL. Current treatment strategies with novel agents are far from being considered precision medicine for PCNSL.

Current perspectives
Considering the yet-available clinical evidence, how could the draft of a potential trial using novel agents challenge current concepts? We think that it would be interesting to test the combination of a BTK inhibitor, an immunomodulatory drug (eg, lenalidomide), and a CD20-directed antibody vs chemotherapy in a randomized trial aiming to reduce toxicity by preserving or even enhancing remission rates during induction treatment. After completion of induction, patients could be randomized to either the above-mentioned combination (eg, for 12 months) or consolidation/maintenance chemotherapy. By this, we could investigate the potency of such chemotherapy-free combinations for induction treatment as well as its potential to maintain long-term remission or even cure. Elderly PCNSL patients often cannot tolerate aggressive induction or consolidation chemotherapy; these patients are usually treated with oral chemotherapy after achieving good remission. Therefore, such a trial would be interesting for this vulnerable population with great medical need. Clinical evidence for checkpoint inhibition is still limited; however, anti–PD-1 treatment may find its role in the framework of combination treatments, including maintenance, but we speculate that it is very unlikely to be used as a single agent inducing remissions. Although available evidence for mTOR or PI3K inhibition is not convincing, preclinical studies have shown a synergistic antilymphoma effect of BTK inhibition in combination with PI3K or mTOR inhibition, especially in CD79B mutant cells. This effect is likely explained by the observed upregulation of genes associated with mTOR and additional increased staining with PI3K/mTOR activation markers. Given that CD79B is mutated in a great majority of PCNSL patients, and given the availability of PI3K, mTOR, and BTK inhibitors, these findings provide a very interesting rationale to setup an appropriate trial. Another interesting agent for PCNSL is the BCL2 inhibitor venetoclax, which is supported by the fact that gains of 18q21 (which includes the BCL2 locus) are one of the most frequent genetic imbalances in PCNSL. Recent studies have investigated mechanisms of interaction between the unique CNS microenvironment and PCNSL cells. A deeper understanding of these cross-talks may reveal further strategies for CNS lymphoma treatment.

Apart from thinking about new combinations and treatment sequences, selection of the study population should also receive more attention. All studies reported so far investigating...
further-line treatments have included patients with r/r disease. This is still a heterogeneous patient population, and more investigations on relapse patterns and associated biomarkers should be conducted to further refine subgroups (eg, refractory and early relapse [eg, 6 months after last treatment]) to be selected for dedicated studies. Patients eligible for HCT-ASCT still have a reasonable chance (up to 50%) for long-term remissions, and approaches including novel agents still have to show that they are able to improve that benchmark. Another approach worth mentioning is chimeric antigen receptor T-cell therapy, which has recently shown impressive results in r/r CD19-positive lymphoma. Although patients with r/r PCNSL were not included in these studies, we speculate that it is very likely that they could also benefit and dedicated studies should be designed.

Further perspectives
Improving outcomes in patients with fatal malignant diseases requires much more than just novel agents or single biomarkers. In the era of high-throughput biotechnologies, we face huge amounts of complex data requiring dedicated computational approaches and rigorous clinical studies to investigate the additional clinical benefit (or malefit). Within that framework, what perspectives do we have for PCNSL, and what are some meaningful next steps for PCNSL research that will accelerate the identification of successful treatment concepts that can provide precision medicine to PCNSL patients?

First, we think that there is still a great need for more comprehensive biosampling in PCNSL patients; that is, we need systematic collection of lymphoma tissue, CSF, and peripheral blood to identify and validate robust predictive biomarkers, not only between patients but also within patients (intrapatient validity). Exemplary approaches have been realized (eg, for metastatic lung cancer). Second, we should challenge the current drug development process where treatment is based on a single predictive marker and treatment is given until toxicity or progression. Acknowledging the complexity of biology, future approaches should aim at identifying patterns and dynamics of several biomarkers (including imaging), not only at diagnosis but also over time; this certainly requires dedicated logistics, funding, and substantial input from bioinformatic modeling to predict drugs or combinations most likely leading to lymphoma regression. Third, prediction algorithms arising from this approach should be backed by in vitro drug (drug combination) sensitivity testing, as previously shown for systemic lymphoma, and then be tested in a randomized fashion. In such a trial, it is not a certain drug or drug combination being investigated but whether the prediction algorithm leads to better treatment selection and ultimately to a better clinical outcome compared with current approaches.

Conclusions
We speculate that there is still room to improve the outcomes of PCNSL patients by optimizing current chemotherapy protocols, especially in the first-line setting. An outstanding example of this potential is advanced classical Hodgkin lymphoma, where the great majority of patients can be cured thanks to systematic series of randomized trials over time. However, patients with r/r PCNSL and those not tolerating aggressive chemotherapy urgently require new approaches to improve their still-dismal prognosis. Besides the current way of drug development, it requires new ways to tap the full potential of precision medicine. Overall, it requires international collaborative efforts to reach these goals.

Authorship
Contribution: G.I. drafted and wrote the paper; E.S. analyzed the literature and wrote the paper; and B.K. conducted the systematic literature search and wrote the paper.

Conflict-of-interest disclosure: G.I. received support from BMS (travel sponsoring), Abbie (research grant), and Roche (research grant). The remaining authors declare no competing financial interests.

Correspondence: Gerald Illerhaus, Department of Hematology/Oncology and Palliative Care, Klinikum Stuttgart, Stuttgart, Germany; e-mail: g.illerhaus@klinikum-stuttgart.de.

Footnote

REFERENCES
10. Kasenda B, Schorb E, Fritschi K, Finke J, Illerhaus G. Prognosis after high-dose chemotherapy followed by autologous stem-cell transplantation as first-line treatment in


