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Primary central nervous system lymphoma: Novel precision therapies

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ABSTRACT

Primary central nervous system lymphoma (PCNSL) is a rare and aggressive form of diffuse large B-cell lymphoma. The frontline treatment with high-dose methotrexate based immunochemotherapy is not curative for the majority of patients. Gene expression profiling and next-generation sequencing have recently provided plethora of data shedding light on pathogenic mechanisms sustain PCNSL and identifying potential vulnerable mechanisms to be explored therapeutically. Here, we review established molecular drivers of PCNSL and targeted drugs that may change the current therapeutic paradigm.

1. Introduction

Primary central nervous system lymphoma (PCNSL) is a rare but aggressive form of diffuse large B-cell lymphoma (DLBCL), which can involve brain, spinal cord, meninges and eyes.(Han and Batchelor, 2017) The incidence increases with age and median age of presentation is 65 years old. Although it has a more favorable response to chemotherapy compared to other brain tumors, PCNSL has a poor prognosis compared with other DLBCL outside the brain with 5- and 10-year survival rates of 29.9% and 22.2%, respectively.(Ostrom et al., 2015)

PCNSL is classified as a distinct subtype of DLBCL in the World Health Organization (WHO) Classification (Swerdlow, 2019) and expresses pan B-cell antigens (CD19, CD20 and CD79A)(Giannini et al., 2014). Melanoma associated antigen 1 (MUM1)/interferon regulatory factor 4 (IRF4) is virtually always positive; B cell lymphoma 6 (BCL6) is expressed in about 50% of cases; BCL2 is not constantly expressed; and CD10 is present in a minority of cases.(Giannini et al., 2014) Consequently, the majority of PCNSL resembles the activated B cell (ABC) immunophenotype.(Camilleri-Broët et al., 2006)

Genomic profiling studies have provided insights into the pathogenesis of this disease. Whole-exome sequencing studies confirmed enrichment of proteins coding mutations that induce NF-kB activation, the majority of which are identified in the ABC subtype. Differently from secondary CNS (SCNSL) DLBCL (Kersten et al., 2014), mutations in the adaptor protein myeloid differentiation primary response 88 (*MYD88*) and in the B-cell antigen receptor-associated protein cluster of differentiation 79B (*CD79B*) are detected in about 55% and 40% of cases, respectively.(Knittel et al., 2016) Importantly, the two lesions often co-occur in PCNSL (Chapuy et al., 2016; Lionakis et al., 2017), suggesting a possible oncogenic cooperation in activating *NF-kB*. Notably, the mutational frequency for these genes is considerably higher in PCNSL compared to ABC DLBCL outside the brain (Braggio et al., 2015), although it is comparable to two highly overlapping ABC DLBCL subgroups, termed Cluster 5 and MCD, recently described in two separate studies (Chapuy et al., 2018; Schmitz et al., 2018). In addition, *MYD88 L265P* mutation has been detected in cerebrospinal fluid (CSF)

Abbreviations: PCNSL, primary central nervous system lymphoma; DLBCL, diffuse large B cell lymphoma; WHO, World Health Organization; MUM1, melanoma associated antigen 1; IRF4, interferon regulatory factor 4; BCL6, B cell lymphoma 6; ABC, activated B cell; SCNSL, secondary CNS; MYD88, myeloid differentiation primary response 88; CD79B, cluster of differentiation 79B; CSF, cerebrospinal fluid; IL-4, interleukin-4; HD-MTX, high-dose methotrexate; HD-ara-C, high dose cytarabine; HDC/ASCT, high-dose chemotherapy consolidation followed by autologous stem cell transplantation; R/R, relapsed/refractory; CR, complete responses; PFS, progression free survival; OS, overall survival; TEDDi-R, temozolomide, etoposide, liposomal doxorubicin, dexamethasone, rituximab plus ibrutinib; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PR, partial response; PTL, primary testicular lymphoma; IMiD, immunomodulatory drug; AE, adverse event; IV, intravenous; WBRT, whole brain radiation therapy; MVBP, HD-MTX, teniposide, carmustine, and prednisone; CAR, chimeric antigen receptor

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and as such is the only molecular marker feasible for minimally invasive liquid biopsy analysis. (Hiemcke-Jiwa et al., 2018) Aberrations of other proteins that reinforce or activate the NF-kB pathway, such as *CARD11* (Montesinos-Rongen et al., 2010) and *TNFAIP3* (Chapuy et al., 2016), have been identified in PCNSL, however they are less frequent.

Gene expression profiling has showed also upregulated *MYC* expression in PCNSL, and increased *MYC* protein was confirmed in CALGB 50202 study.(Rubenstein et al., 2013a) Furthermore, upregulation of microRNAs associated with *MYC* (miR-17-5p, miR-20a, miR-9) has been demonstrated.(Fischer et al., 2011) *PIM1*, which cooperates with *MYC*, is frequently mutated in PCNSL as well.(Grommes et al., 2017a)

The JAK/STAT pathway seems also to be involved as activated signaling pathway in PCNSL: interleukin-4 (IL-4) and IL-10, two activators of this pathway, are upregulated in PCNSL. (Rubenstein et al., 2013c, 2006) In particular, changes in CSF concentration of IL-10 correlates with prognosis after standard first line therapy.(Rubenstein et al., 2013c)

Despite these advances in understanding the pathophysiologic processes in PCSNL, the standard first line treatment has not been established. High-dose methotrexate (HD-MTX) plays a crucial role in PCNSL and is considered the backbone of multimodal therapy, which can include other chemotherapeutic agents. (Citterio et al., 2017; Han and Batchelor, 2017) In particular, combination of high dose cytarabine (HD-ara-C) to HD-MTX demonstrated significantly improved response (CRR = 46% vs 18%; p = 0.006) and survival rate (3-year OS: 46% vs 32%; p = 0.07) compare to single agent therapy (Ferreri et al., 2009), becoming the current preferred frontline approach. Surgical resection has not been associated with survival benefit (Reni et al., 1997), therefore it should be reserved for neurologic deterioration due to brain herniation or ventricle dilation. Consolidation radiotherapy has also been used for decades, but its role has been diminishing lately due to the frequent neurotoxicities.(Benković et al., 2009; Correa et al., 2004) Alternatively, high-dose chemotherapy consolidation followed by autologous stem cell transplantation (HDC/ASCT) has proven to induce high remission rate and excellent long-term outcomes in eligible patients (Ferreri et al., 2017). However, only young patients, without relevant comorbidity and preserved neurocognitive functions are referred to HDC/ASCT. Given the needs of more effective treatment for PCNSL, the number of therapeutic tools has been progressively increasing. Here, we describe the more recent tailored strategies to overcome hurdles of heterogenous PCNSL biology (Table 1).

1.1. Ibrutinib

Given the high frequency of mutations in the BCR and MYD88 pathways, the BTK inhibitor ibrutinib appears as a rational novel therapeutic option in PCNSL. In a dose-escalation phase 1 trial, 20 patients with relapsed/refractory (R/R) CNS lymphoma (13 with PCNSL and 7 SCNSL) were treated with single agent ibrutinib. (Grommes et al., 2017b) Clinical response occurred in 10 of 13 (77%) patients with PCNSL, including five complete responses (CR). Median progression free survival (PFS) and overall survival (OS) were 4.6 and 15 months, respectively. Ibrutinib was well tolerated at the 560 mg and 840 mg dose levels, with the exception of one pulmonary aspergillosis. (Grommes et al., 2017b) The treatment outcome obtained with ibrutinib in PCNSL is superior compared to DLBCL outside the CNS, in which PFS and OS were 1.6 months and 6.4 months, respectively, (Wilson et al., 2015) suggesting a divergent molecular pathogenesis. In this phase 1 trial a correlation was observed between resistance to ibrutinib and mutation in the BCR pathway such as *CARD11* and *TNFAIP3*. Among the 10 patients with available molecular information, complete resistance to ibrutinib was associated with the presence of a mutant *CARD11*, wild type *MYD88*, *CD79B* and *TNFAIP3*.(Grommes et al., 2017b) The interim analysis of the French Lysa phase 2 trial (NCT02542514) evaluating the efficacy of ibrutinib at 560 mg in 18 R/R PCNSL (n = 11) or primary vitreo-retinal lymphoma (n = 7) demonstrated a disease control rate of 83%, including 56% objective response rate.(Choquet et al., 2016) Given the promising results obtained as single agent, ibrutinib was tested as part of a novel polychemotherapy regimen in order to increase its efficacy. Because of the synergy between ibrutinib and DNA-damaging agents, a recent phase 1b study investigated the DA-TEDDi-R regimen (temozolomide, etoposide, liposomal doxorubicin, dexamethasone, rituximab in combination with ibrutinib) which included 2-week window of ibrutinib monotherapy in 18 PCNSL, 5 of whom were newly diagnosed. Patients were treated at ibrutinib dose levels of 560 mg, 700 mg and 840 mg. (Lionakis et al., 2017) Ninety-four percent showed tumor reduction with ibrutinib alone, and ultimately 86% achieved CR with DA-TEDDi-R.(Lionakis et al., 2017) Among 11 responders, remission duration exceeded 6 months in 6 of them. Increased aspergillosis was observed as main adverse effect (39% of patients). The increased susceptibility to fungal infection needs to be further investigated. Probably multiple mechanisms are involved. BTK plays a crucial role in neutrophil differentiation and function.(Fiedler et al., 2011) Mice lacking of BTK gene had a higher mortality rate when exposed to Aspergillus compared to the wild type BTK, suggesting its important function in the immunoresponse against Aspergillus.(Lionakis et al., 2017) However, the X-linked agammaglobulinemia has not an increased risk for Aspergillus infections.(Ochs and Smith, 1996) Probably off-target effects outside BTK inhibitions should be considered. It is also possible that glucocorticoids and/or immunosuppressive mechanisms intrinsic of CNS lymphoma may contribute to risk of aspergillosis. Ninety-four percent developed grade 4 neutropenia and 28% died of treatment-related toxicities.(Lionakis et al., 2017) Nevertheless, the average treatment-related deaths with conventional high-dose chemotherapy strategies in CNS lymphoma is around 10%.(Grommes and Younes, 2017) Overall, the DA-TEDDi-R showed to induce a higher response rate and durable remissions. Further development of this regimen needs to focus on reducing incidence of aspergillosis for example with voriconazole prophylaxis.

Table 1
Clinical trials of novel therapies in PCNSL.

Reference	Regimen	Patients	Median PFS (months)	Median OS (months)
Grommes et al., 2017a, b	Ibutinib	20	4.6	15
Lionakis et al., 2017	DA-TEDDi-R	18	15.3	Not reached
Nayak et al., 2017	Nivolumab	5	15	–
Molaie et al., 2018	Lenalidomide	3	15	–
Rubenstein et al., 2018	Lenalidomide plus rituximab	14	11.3	–
Rubenstein et al., 2018	MTX + Rituximab or RT followed by lenalidomide maintenance	10	40	45
Vu et al., 2019	MTX + Rituximab or MTX + Rituximab + temozolimide followed by lenalidomide maintenance	13	Not reached	Not reached
Ghesquieres et al., 2019	Lenalidomide plus rituximab	50	7.8	17.7

1.2. Nivolumab

Immune checkpoints regulate proliferation and activation of T-cells, and are activated to maintain self-tolerance and prevent autoimmunity. (Pardoll, 2012) One of the most critical checkpoint pathways is mediated by the programmed cell death protein 1 (PD-1) and its ligand, programmed death ligand 1 (PD-L1). PD-1 is highly expressed by activated T cells, B cells, dendritic cells, and natural killer cells, whereas PD-L1 is expressed on several types of tumor cells as a means to escape immune-surveillance.(Batlevi et al., 2016) The recent discovery of the frequent 9p24.1/PD-L1/PD-L2 copy number alterations and consequent increased expression of PD-L1 in PCNSL and primary testicular lymphoma (PTL)(Chapuy et al., 2016) provided the rationale to evaluate the efficacy of nivolumab, a human IgG4 antibody that targets PD-1 and blocks its interactions with PD-L1, in patients with relapsed PCNSL and SCNSL from PTL. One retrospective case series reported five patients with R/R PCNSL who were treated with nivolumab 3 mg/kg intravenous (IV) every 2 weeks.(Nayak et al., 2017) Four patients achieved a CR and one partial response (PR). Treatment was well tolerated except for worsening of kidney function in one patient which led to drug discontinuation. However, these positive results must be interpreted with caution since two patients received whole-brain or focal irradiation immediately prior to nivolumab. In addition, only one of five patients received dexamethasone as associated treatment, which represents a rare situation in relapsed PCNSL patients.(Nayak et al., 2017) Nevertheless, these promising data prompted the ongoing phase 2 study of nivolumab in R/R PCNSL and PTL (NCT02857426). Another ongoing phase 2 study investigates pembrolizumab, a humanized IgG4 isotype antibody against PD-1, in 21 R/R PCNSL (NCT02779101), but no results have been reported so far. **(**Table 2**)**

1.3. Lenalidomide

Lenalidomide is an immunomodulatory drug (IMiD) with direct and indirect antineoplastic activity mediated through distinct immunomodulatory properties.(Thieblemont et al., 2012; Yang et al., 2012) Lenalidomide also has cell-autonomous cytotoxicity effects that are relevant to PCNSL, including inhibition of IRF4 and MYC pro-survival signals.(Krönke et al., 2014; Lopez-Girona et al., 2012; Lu et al., 2014) Furthermore, it enhances antibody-dependent cell-mediated cytotoxicity.(Wu et al., 2008) The phase 2 NHL-002 and NHL-003 trials confirmed the efficacy of lenalidomide monotherapy in R/R DLBCL. The overall response rate (ORR) was 35%, with CR of 7–12% after lenalidomide at 25 mg. Responses were durable with a median response duration of 4.6 months. Treatment was well tolerated. Grade 3/4 toxicity was mainly hematological and reversible with dose reduction.(Habermann et al., 2009; Wiernik et al., 2008) Lenalidomide showed to be more effective in non-GCB DLBCL compared to GCB DLBCL, with ORR of 53–65% and 3–9%, respectively. (Hernandez-Ilizaliturri et al., 2011; Mondello et al., 2016) It is likely that the advantage of lenalidomide in the setting of non-GCB DLBCL depends on its inhibitory activity on NF-kB, which is aberrant in this subtype.(Zhang et al., 2013) Lenalidomide monotherapy has showed to have activity also in R/R PCNSL.(Houillier et al., 2014; Molaie et al., 2018)

Based on the preclinical data showing synergy between lenalidomide and rituximab(Hernandez-Ilizaliturri et al., 2005), a phase 1 study investigated the antitumor activity of this drugs combination in 14 patients with R/R PCNSL (five with intraocular involvement, seven with CSF/leptomeningeal disease, and ten with brain parenchyma involvement).(Rubenstein et al., 2018) In the study, lenalidomide was examined at 10, 20, and 30 mg in combination with intraventricular rituximab. Nine out of 14 patients achieved PR and six maintained response for more than 9 months. In particular, two of three patients receiving 10 mg lenalidomide dose achieved PR, while at a dose of 20 mg of lenalidomide 100% of patients showed a response (2 CR and 4 PR). In four cases response was persistent up to 20 months. Overall, toxicity was manageable, with bacterial infections and neutropenia as the principal toxicities. The CSF/plasma partition coefficient of lenalidomide was > 20% at 15 and 20 mg dose levels, supporting the 15 mg dose level as the recommended dose for phase 2 trial.(Rubenstein et al., 2018) As an alternative to whole brain irradiation, low dose lenalidomide maintenance (5–10 mg) was administrated after confirmed CR to eight patients with R/R PCNSL and 2 patients with SCNSL with a median age of 70 years (range, 45–81). Lenalidomide was found to potentiate the effects of salvage therapy, including resection, Gamma Knife, and/or methotrexate/rituximab. At median follow-up of 18 months, this cohort demonstrated a durable PFS with 5 patients maintaining durable responses for 2 or more years. Nine patients achieved a CR and one patient experienced stable disease. Forty percent of patients remained PFS for longer than 50 months. The 5-year overall survival was 100% in patients receiving monotherapy lenalidomide as maintenance therapy with a median OS of 45 months. There was minimal toxicity in this elderly population with one case of non-invasive basal cell carcinoma reported. Of three patients receiving lenalidomide at 10 mg plus rituximab from 4 to 92 weeks, one grade 3/4 adverse event (AE) of fatigue was observed. In six patients receiving 20 mg lenalidomide from 4 to 92 weeks, grade 3/4 AEs of fatigue and neutropenia occurred in one patient each and two patients had infections. No grade 3/4 AEs were reported for four patients.(Rubenstein et al., 2018) Based on lenalidomide maintenance data in this phase 1 trial, a phase 2 trial investigating maintenance therapy with low-dose lenalidomide following standard MTX/Rituximab-based induction in patients with PCNSL over 70 year-old is ongoing. Results from the interim analysis confirmed a significant improvement in PFS and OS.(Vu et al., 2019) The phase 2 REVLRI trial studied the effect of eight 28-day cycles of R2 (rituximab 375/m2 IV, D1 lenalidomide 20 mg/day, D1-21

Table 2
Ongoing clinical trials in patients with PCNSL.

Study type	Clinical trial registration no.	Patient population	Trial arms
Phase 2	NCT02857426	R/R PCNSL or R/R PTL	Nivolumab
Phase 2	NCT02779101	R/R PCNSL	Pembrolizumab
Phase 2	NCT03495960	Newly diagnosed PCNSL > 70 yrs	Lenalidomide maintenance following MTX/Rituximab-based induction
Phase 1	NCT03703167	R/R PCNSL or SCNSL	R2 plus ibrutinib
Phase 1/2	NCT03558750	R/R non-GCB DLBCL or PCNSL	R2 plus nivolumab
Phase 2	NCT03003520	Newly diagnosed high-risk DLBCL	Durvalumab consolidation following R-CHOP/R2CHOP induction
Phase 1	NCT01722305	R/R PCNSL or newly diagnosed or R/R Intraocular lymphoma	Pomalidomide plus dexamethasone
Phase 2	NCT02669511	R/R PCNSL	PQR309
Phase 1	NCT02631044	R/R B-cell NHL	JCAR017

Abbreviations: R/R, relapsed/refractory; PCNSL, primary central nervous system lymphoma; PTL, primary testicular lymphoma; MTX, methotrexate; SCNL, secondary central nervous system lymphoma; R2, rituximab and lenalidomide; non-GCB, non-germinal center B cell; DLBCL, diffuse large B cell lymphoma; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; NHL, non Hodgkin lymphoma.

for cycle 1; and 25 mg/day cycles of lenalidomide alone for the subsequent cycles) in R/R PCNSL. In addition, responding patients received maintenance with lenalidomide 10 mg/day, D1-21. The ORR was 35.6% (CR 29% and PR 7%). At the median follow-up of 19.2 months, the median PFS and OS were 7.8 months and 17.7 months, respectively. These promising results support the assessment of efficacy of R2 combined with MTX-based chemotherapy as first-line treatment for PCNSL. (Ghesquieres et al., 2019) In addition, the R2 combination is currently investigated in association with ibrutinib (NCT03703167), nivolumab (NCT03558750) and durvalumab (NCT03003520), a PD-L1 inhibitor. Investigation of a related, second generation IMiD, pomalidomide, in combination with dexamethasone, in relapsed CNS lymphoma, is also in progress (NCT01722305).

1.4. Temsirolimus

The PI3K/AKT/mTOR pathway is an important pro-survival pathway often aberrantly activated in different types of cancer including lymphomas.(Altman and Platanias, 2008; Courtney et al., 2010) Temsirolimus, an inhibitor of mTOR, has demonstrated activity in DLBCL, achieving an ORR of 20–30%.(Smith et al., 2010) A recent phase 2 trial showed a promising efficacy of temsirolimus also in PCNSL, with an ORR of 54% and median PFS and OS of 2.1 and 3.7 months, respectively. Nevertheless, treatment associated toxicity was substantial with a treatment related mortality of 13.5%, mainly due to pneumonia.(Korfel et al., 2016) Currently, a phase 2 trial using the brain penetrant pan PI3K/mTOR inhibitor bimiralisib (PQR309) in patients with relapsed PCNSL is ongoing (NCT02669511).

1.5. Rituximab

Despite the survival advantages obtained in DLBCL (Coiffier et al., 2002), the role of Rituximab, a monoclonal antibody direct against CD20, in combination with chemotherapy, remains unclear in PCNSL. Its CNS penetration is very low with IV administration, achieving 0.1%–4.4% of serum levels.(Shah et al., 2007) Single-arm trials have demonstrated its efficacy at doses of 375–500 mg/m^2 IV as induction (Fritsch et al., 2011; Holdhoff et al., 2014; Morris et al., 2013; Shah et al., 2007; Wieduwilt et al., 2012) or salvage chemotherapy (Batchelor et al., 2011). The phase 2 IELSG 32 trial randomized PCNSL patients to receive frontline therapy with HD-MTX and HD-ara-C with or without thiotepa and with or without rituximab followed by whole brain radiation therapy (WBRT) (45 Gy) or HDC/ASCT as consolidation. The addition of rituximab to HD-MTX/HD-ara-C resulted in improved ORR (73% vs 53%) and median PFS (20 months vs 6 months).(Ferreri et al., 2016) However, the phase 3 HOVON/ALLG trial which randomized newly diagnosed PCNSL to receive HD-MTX, teniposide, carmustine, and prednisone (MVBP) with or without rituximab followed by HD-ara-C and WBRT consolidation, did not confirm the encouraging results previously observed (event free survival at 1 year was 49% in MBVP and 52% in the R-MBVP group; p = 0.99).(Bromberg et al., 2019) Despite the negative results of this study, rituximab has been routinely incorporated as a component of standard treatment in PCNSL.

Given the limited penetration of the blood-brain barrier (BBB) by most therapeutics, a potential therapeutic strategy is the direct intraventricular administration in order to achieve the optimal concentration within the brain tumor.(Kadoch et al., 2014) A phase 1 study showed the safety and efficacy of intraventricular rituximab either as monotherapy or in combination with MTX. In particular, the combination therapy achieved 75% complete cytologic response in R/R leptomeningeal disease.(Rubenstein et al., 2013b) However, all the patients of this phase 1 study developed resistance. The mechanism behind this is under investigation. It might probably be associated with the significantly shortened half-life of the intraventricular compared to the systemic rituximab (Rubenstein et al., 2007), or alternatively with other immunogenic effects.

Currently, there are ongoing several trials evaluating the effectiveness of other CD20 antibodies such as obinutuzumab in PCNSL (NCT02498951).

1.6. Chimeric antigen receptor T-Cell therapy

Chimeric antigen receptor (CAR) T-cell therapies utilize the patient's own T cells that have been genetically engineered to bind to a specific antigen on target cancer cells, such as CD19 protein which is expressed on most B-cell leukemias and lymphomas. CAR T-cell therapy has shown encouraging results in R/R DLBCL, with more than 50% of CR rates (Kochenderfer et al., 2015; Turtle et al., 2016), however all available CAR T-cell trials have excluded patients with CNS involvement. Recently, a report showing the efficacy of CAR T-cell therapy in the CNS has been published.(Abramson et al., 2017) A 68-year-old woman with DLBCL and cerebral involvement that had not responded neither to conventional chemotherapies nor to a stem-cell transplant was enrolled in the TRANSCEND-NHL-001 phase 1 trial (NCT02631044). One month after the study treatment, which consisted of fludarabine and cyclophosphamide followed by intravenous infusion of the CD19-directed CAR T-cell product JCAR017, the restaging imaging (PET/CT and brain MRI) showed a complete regression of the brain lesion. Only two months after, the patient suffered a histologically confirmed subcutaneous relapse. After the surgical biopsy, the CAR T-cells spontaneously re-expanded and the tumor again went into complete remission.(Abramson et al., 2017) The mechanism behind the spontaneous re-expansion of CAR T-cells after biopsy in this patient remains unclear. Since the area of recurrence was previously irradiated, perhaps there was poor vascularity and diminished exposure of the CAR T-cells to the tumor cells, but the surgical incision allowed re-exposure of persistent circulating CAR T-cells to the tumor cell antigen, leading to re-expansion. The patient eventually relapsed and died more than a year after CAR T-cell therapy, but the brain tumor never recurred. No neurotoxicity, graft versus host disease or cytokine release syndrome were observed.(Abramson et al., 2017) This result has implications not only for secondary DLBCL as in this case but also for PCNSL. For the first time CAR T-cell therapy has demonstrated the ability to cross the BBB and induce responses in the CNS. Other studies have identified CAR T cells in the CSF (Grupp et al., 2013; Kochenderfer et al., 2015), confirming the ability of these cells to cross the BBB. Furthermore, the spontaneous CAR-T cells re-expansion after biopsy highlights this therapy as a 'living drug' that can re-expand and proliferate in response to biologic stimuli. Based on this case, the ongoing TRANSCEND-NHL-001 has been amended to allow enrollment of secondary CNS DLBCL. Furthermore, clinical trials specifically for R/R PCNSL are warranted.

2. Conclusions and future directions

Significant progress has been achieved in the treatment of PCNSL over the last decades, however relapse is common and prognosis is dismal. While the optimal treatment approach has yet to be established, high-dose MTX-based chemotherapy is currently considered as the standard induction therapy for newly diagnosed PCNSL. The main goal is to optimize the frontline treatment of PCNSL in order to reduce the number of refractory patients, to prolong remission, and to improve outcomes. Recent insight into the PCNSL biology has provided rationale for designing treatments that incorporate target agents. In particular ibrutinib and lenalidomide have demonstrated the most promise in PCNSL. However, it is unlikely that a novel agent could be curative as monotherapy, but its rational combination with polychemotherapy regimen might paint a brighter therapeutic prospective.

Authors' contribution

PM conceived the structure of the review, revised literature, wrote the manuscript and made tables; FB and MM revised the manuscript. All

authors read and approved the final manuscript.

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