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ORIGINAL REPORT

Phase II Trial of Temsirolimus for Relapsed/Refractory Primary CNS Lymphoma

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ABSTRACT

Purpose
In this phase II study (NCT00942747), temsirolimus was tested in patients with relapsed or refractory primary CNS lymphoma (PCNSL).

Patients and Methods
Immunocompetent adults with histologically confirmed PCNSL after experiencing high-dose methotrexate-based chemotherapy failure who were not eligible for or had experienced high-dose chemotherapy with autologous stem-cell transplant failure were included. The first cohort (n = 6) received 25 mg temsirolimus intravenously once per week. All consecutive patients received 75 mg intravenously once per week.

Results
Thirty-seven eligible patients (median age, 70 years) were included whose median time since their last treatment was 3.9 months (range, 0.1 to 14.6 months). Complete response was seen in five patients (13.5%), complete response unconfirmed in three (8%), and partial response in 12 (32.4%) for an overall response rate of 54%. Median progression-free survival was 2.1 months (95% CI, 1.1 to 3.0 months). The most frequent Common Toxicity Criteria ≥ 3° adverse event was hyperglycemia in 11 (29.7%) patients, thrombocytopenia in eight (21.6%), infection in seven (19%), anemia in four (10.8%), and rash in three (8.1%). Fourteen blood/CSF pairs were collected in nine patients (10 pairs in five patients in the 25-mg cohort and four pairs in four patients in the 75-mg cohort). The mean maximum blood concentration was 292 ng/mL for temsirolimus and 37.2 ng/mL for its metabolite sirolimus in the 25-mg cohort and 484 ng/mL and 91.1 ng/mL, respectively, in the 75-mg cohort. Temsirolimus CSF concentration was 2 ng/mL in one patient in the 75-mg cohort; in all others, no drug was found in their CSF.

Conclusion
Single-agent temsirolimus at a weekly dose of 75 mg was found to be active in relapsed/refractory patients with PCNSL; however, responses were usually short lived.

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INTRODUCTION

Approximately one-quarter of patients with primary CNS lymphoma (PCNSL) do not respond to first-line therapy and more than one half relapse.[1] The prognosis of patients with refractory/relapsed PCNSL is poor, and therapeutic options remain limited. Whole-brain radiotherapy (WBRT) is probably the most effective salvage treatment with response rates of 60% to 79% and median overall survival (OS) of 10.9 to 16 months after retreatment.[2,3] However, WBRT exposes patients to a higher risk of late neurotoxicity than chemotherapy.[4,5] Thus, salvage chemotherapy is frequently preferred, particularly in patients with good performance status and who responsed well to previous chemotherapy.

Single-agent chemotherapy/immunotherapy with topotecan,[6,7] rituximab,[8] temozolomide with or without rituximab,[9-11] ifosfamide- and/or etoposide-based polychemotherapy,[12-14] and yttrium-90 (^{90}Y)–labeled ibritumomab tiuxetan[15] have been evaluated as salvage treatment in several small and frequently retrospective analyses. A wide range of response rates from 14% to 53% have been observed with, not surprisingly, a much lower response rate when more stringent response criteria were used, such as response confirmation.[11] The median progression-free survival (PFS) was uniformly short (2 to 5 months). Rechallenge with

high-dose methotrexate (HDMTX) is an option for patients who experienced long-term remission after primary HDMTX therapy.[16]

High-dose chemotherapy with an autologous stem-cell transplant (HD-ASCT) might be considered for younger patients who can tolerat intensive therapy. In a retrospective trial, 79 patients with a median age of 52 years who experienced HDMTX-based therapy failure (including, however, 11 patients with partial remission [PR]) received high-dose cytarabine-based salvage treatment followed by high-dose chemotherapy with thiotepa, busulfan, cyclophosphamide, and ASCT. The 5-year probability of disease-free survival was 49.5%, but six patients who received HD-ASCT died. Seven patients died from severe CNS toxicity.[17]

Mammalian target of rapamycin (mTOR) is a ubiquitously expressed serine-threonine protein kinase that belongs to the phosphoinositide 3-kinase (PI3K)—related kinase family. The PI3K/AKT/mTOR pathway is a critical switch constituting the core of a highly conserved evolutionary pathway that adjusts protein synthesis to regulate cell growth and proliferation by integrating signals arising from growth factors, hormones, nutrients, and energy metabolism.[18] There is preclinical and clinical evidence that the mTOR pathway is important in the tumor biology of aggressive lymphoma. In a randomized phase III trial[19] of patients with relapsed/refractory mantle cell lymphoma, the response rate to temisirolimus 175 mg every 3 weeks followed by 75 mg weekly was 22% and significantly higher when compared with investigator's choice; the median PFS was 4.8 months. In a trial of patients with different aggressive non-Hodgkin lymphomas, the response rate with diffuse large B-cell lymphoma (DLBCL) to everolimus was 30%.[20] In another trial,[21] the response rate to temsirolimus in the refractory DLBCL subpopulation was 28.1% (complete response [CR] rate, 12.5%) with a median PFS of 2.6 months and OS of 7.2 months.

In a study on relapsed malignant glioma, high concentrations of temsirolimus were found in brain tumor specimens with a brain/blood ratio of 1.43 for temsirolimus and 0.84 for its metabolite sirolimus.[22]

Based on its activity and relatively good tolerability in patients with refractory/relapsed aggressive lymphoma, and its ability to penetrate the brain tumor tissue, we decided to evaluate temsirolimus in patients with refractory/relapsed PCNSL.

PATIENTS AND METHODS

Inclusion Criteria

Eligibility criteria included patients older than 18 years with PCNSL proven histologically or cytologically (in the CSF) and with evidence of a relapse or progression (on magnetic resonance imaging or in the CSF) after HDMTX-based primary chemotherapy; the time interval since the patient's last chemotherapy had to be $\geq$ 3 weeks and their Eastern Cooperative Oncology Group performance score $\leq$ 2. Criteria also included adequate renal function (glomerular filtration rate $>$ 30 mL/min), neutrophils $>$ 1,500/μL, thrombocytes $>$ 80,000/μL, bilirubin $<$ 1.5-fold the upper limit of normal, transaminases $<$ 3$\times$ the upper limit of normal, and the patient's signed informed consent. Exclusion criteria were secondary CNS lymphoma, eligibility for more intensive treatment such as HD-ASCT, uncontrolled infection, HIV positivity, serious comorbidity, other active malignant disease, concomitant treatment with potent CYP3A4/5 inductors or inhibitors, and pregnancy/breastfeeding. The protocol was approved by the responsible ethics committees. Study conduct followed International Conference on Harmonization Guidelines for Good Clinical Practice, including written informed consent and data monitoring. Baseline assessments included physical and neurologic examination, cranial magnetic resonance imaging (spinal on clinical suspicion only), and ophthalmologic and CSF examination.

Study Design and Treatment

This was a phase II, nonrandomized, open-label study with a two-stage design using single-agent temsirolimus in patients with relapsed or refractory PCNSL. In the first stage, patients were treated with temsirolimus 25 mg intravenously once per week with clemastine premedication. In case of Common Toxicity Criteria grades 3 to 4 toxicity, three additional patients were to be treated with the same dose. If no Common Toxicity Criteria grades 3 to 4 toxicity were observed, all following patients were treated with 75 mg once per week. Treatment was administered until progressive disease (PD), unacceptable toxicity, death, or the patient's or investigator's decision to terminate participation, for a maximum of 12 months. Five dose reductions for toxicity were permitted (to 60, 40, 30, 20, 15 mg), after which treatment was discontinued. Interruption of temsirolimus for longer than 3 weeks also resulted in discontinuation.

Evaluation During Treatment

Safety assessments included physical examinations, adverse event monitoring, and laboratory parameter changes before each infusion. Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Response assessment was performed after 4 weeks and every 8 weeks thereafter. Additionally, response assessment was recommended at each time point when progression was suspected. After discontinuing therapy, patients completed an end-of-treatment visit 30 days after their last temsirolimus dose. In patients with PR or CR, remission status was evaluated every 3 months. Survival data were collected every 3 months for up to 2 years from start of study treatment or until study closure.

Serum and CSF samples for pharmacokinetic analysis were obtained immediately after the first, fourth, and twelfth infusion. The samples were immediately frozen at -80°C and stored until measurement.

Drug concentration was measured using high-performance liquid chromatography with mass spectrometric detection; the lower limit of detection was 1 ng/mL.

End Points and Statistical Analysis

The primary end point was overall response rate (ORR), which included CR, CR unconfirmed (uCR), and PR. Secondary end points included penetration of temsirolimus into the CSF, toxicity, PFS, and OS. Response was defined according to the criteria of the International Primary CNS Lymphoma Cooperative Group.[23] PFS was calculated from the time of enrollment in the study until progression, relapse, or death. OS was calculated from the time of enrollment in the study until death.

Because no data on temsirolimus in PCNSL were available and inclusion of mostly elderly patients unfit for heavy pretreatment was intended, a Simon optimum design[24] was used for patients' number calculation (to minimize the risk that too many patients were treated with ineffective therapy) with an unacceptable ORR of 0.05 (p_0 in the terminology of Simon) and a favorable ORR of 0.20 (p_1 in the terminology of Simon), and error probabilities of $\alpha = \beta = 0.10$. Based on these hypotheses, 12 patients were needed for stage 1 and further accrual was stopped if less than one patient responded. The second stage of the trial was planned to enroll 25 additional patients. After termination of this study stage, the therapy was considered ineffective if fewer than four patients responded.

Results are expressed as percentages or medians and ranges. PFS and OS were calculated using the Kaplan-Meier method. For the ORR, the median PFS and the median OS, two-sided 95% confidence limits are given. The CIs of median PFS and OS were estimated as described by Collett et al.[25] For the ORR, PFS, and OS, two-sided 95% confidence limits

are given. Analysis was done using SPSS software, version 22 (SPSS, Chicago, IL) and R (2.9.2).

RESULTS

Patient Characteristics

Between September 2009 and November 2014, 37 patients were enrolled at four German centers (Table 1). With the exception of one patient with T-cell lymphoma, all patients had DLBCL. The vast majority of patients had intermediate- or high-risk disease according to the Memorial Sloan Kettering Cancer Center score.[26] Patients had received a median of one prior therapy (range, one to five therapies) comprising HDMTX in all patients and high-dose cytarabine in 11 (30%). Two patients (5%) were pretreated with WBRT, three patients (8%) with HD-ASCT, and four patients (11%) with both. The median time since last pretreatment was 3.9 months.

Therapy and Efficacy

Among the first three patients who were given 25 mg temsirolimus, two had grade 3 toxicity (one patient had diarrhea, thrombocytopenia, and leukopenia with pneumonia; one patient had pneumonia). Thus, an additional three patients were treated with the same dose. In these patients, no grade 3 to 4 toxicity was observed, and there was a PR in one patient. Thus, per protocol, the study was continued with 75 mg temsirolimus once per week.

A total of 296 infusions were given: 42 at the 25-mg dose level and 254 at the 75-mg dose level. The median number of infusions per patient was six (range, one to 28 infusions). Dose reduction was performed three times at the 25-mg dose level and 50 times at the 75-mg dose level. Infusions were delayed > 1 day in 47 cases.

Five patients (13.5%) achieved CR, three (8%) uCR, and 12 (32.4%) PR for an ORR of 54% (95% CI, 37% to 71%) The details on all responders are given in Table 2 and an example of response is shown in Figure 1. Seven patients (18.9%) had stable disease (SD), five (13.5%) had PD, and five (13.5%) had no response evaluation. Of the six patients pretreated with WBRT, only one responded with a CR (three had SD, one had PD, and one had no response evaluation). Of the seven patients pretreated with HD-ASCT, two responded with CR and one with uCR (two had SD, one had PD, and one had no response evaluation). One of the responding patients was taking steroids at the time of response evaluation. Seven patients had not been taking steroids for 1 week, three for 2 weeks, two for 3 weeks, and seven for > 3 months. The median time to response was 3.5 weeks.

The median PFS was 2.1 months (95% CI, 1.1 to 3.0 months) with 1-year PFS of 5.4% (95% CI, 0% to 11.2%; Fig 2A). The median OS was 3.7 months (95% CI, 1.5 to 5.8 months) with 1-year OS of 19% (95% CI, 6.1% to 31.7%) and 2-year OS of 16.2% (95% CI, 4.1% to 28.4%; Fig 2B). Seven patients received further treatment after study termination. Two patients received topotecan. Two patients received topotecan plus intrathecal chemotherapy. Two patients were treated with WBRT and one patient was treated with rituximab plus chemotherapy intrathecally followed by fludarabine plus cyclophosphamide plus busulfan plus thiothepa and an allogenic stem-cell transplant.

Table 1. Demographic and Patient Characteristics

Characteristic	Patients*	%
Age, years, median (range)	70 (22-83)	
Female/male	19/18	51/49
ECOG performance status, median (range)	2 (0-2)	
MSKCC score		
1	2	5
2	29	78
3	6	16
Pretreatment		
High-dose methotrexate	37	100
Monotherapy	5	13.5
Combination†	32	86.5
Rituximab	21	57
High-dose cytarabine	11	30
High-dose chemotherapy followed by ASCT	7	19
Whole-brain radiotherapy	6	16
Topotecan	6	16
Temozolomide	2	5
R-CHOP	1	3
Cytarabine, methotrexate, dexamethasone i.th.	1	3
No. of previous treatment regimens		
1-2	29	78
3-5	8	22
Median time since last pretreatment, months	3.9	
Lymphoma localization		
Parenchymal only	30	81
Meningeal only	4	11
Combined	3	8

Abbreviations: ASCT, autologous stem-cell transplantation; ECOG, Eastern Cooperative Oncology Group; i.th., intrathecally; MSKCC, Memorial Sloan Kettering Cancer Center; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.
*Values are expressed as No. of patients unless otherwise stated.
†Mostly combined with ifosfamide.

Safety

Toxicity is summarized in Table 3. The most frequent toxicities were hyperglycemia, bone marrow suppression, infections (mostly pneumonias), and fatigue. There were a total of 28 severe adverse events in 21 patients: 14 infectious episodes, four hospital admissions because of clinical worsening due to PD, two cases of deep venous thrombosis, two cases of hyperglycemia, and one case each of seizures, grade 4 thrombocytopenia, drug fever, hyponatremia, renal insufficiency, and atrial fibrillation. A total of 10 patients—one with CR, three with PR, two with SD, one with PD, and three with unknown remission status—died within 4 weeks after administration of last study therapy: five due to toxicity (pneumonia in two patients and GI infection with sepsis, sepsis without focus, and cerebral bleeding in one patient each) and five due to tumor progression.

CSF Penetration of Temsirolimus and Sirolimus

Fourteen blood/CSF pairs were collected in nine patients: 10 pairs in five patients in the 25-mg cohort and four pairs in four patients in the 75-mg cohort. The mean maximum blood concentration was 292 ng/mL for temsirolimus and 37.2 ng/mL for sirolimus in the 25 mg cohort and 484 ng/mL for temsirolimus and 91.1 ng/mL for sirolimus in the 75-mg cohort. In one patient in the 75-mg cohort, a marginal temsirolimus CSF concentration of

Table 2. Responders' Characteristics

Patient Age (Years)	No. of Pretreatments	Pretreatment Regimens	Steroid-Free Interval Before First Response Assessment	Successive Assessments	Response, Reason for Termination of Study	PFS (months)	OS (months)
69	1	HDMTX+ifosfamide	No steroids	1 2	PR PD	2.7	3.6
75	1	HDMTX	No steroids	1 2 3 4 5 6	PR uCR CR CR CR PD	8.1	> 59.2
81	1	HDMTX	1 week	1 2 3 4	PR PR PR PD	5.2	7.1
68	1	HDMTX+rituximab	3 weeks	1 2 3 4	PR PR PR PD	3.1	> 56.1
61	2	1. HDMTX+rituximab, HDAraC+HD-ASCT+ 2. AraC+MTX+ prednisolone icv	1 week	1 2	uCR PD	2.6	18.6
67	2	1. HDMTX+ifosfamide 2. TT+HDAraC	Continuous steroids	1	PR, thrombocytopenia	1.3	1.4
69	4	1. HDMTX 2. HDMTX + ifosfamide 3. topotecan 4. HDAraC	No steroids	1 2	PR PD	2.0	2.0
68	1	HDMTX+ifosfamide+ rituximab	No steroids	1 2 3	PR uCR PD	3.8	> 52.5
78	1	HDMTX+ifosfamide	2 weeks	1 2	PR PD	2.1	10.0
72	1	HDMTX+rituximab	1 week	1 2 3	PR 2. PR CR, patient's decision	15.8	> 45.3
77	1	HDMTX+ifosfamide	No steroids	1 2 3	CR CR PD	3.1	4.7
43	1	HDMTX+ifosfamide, HDAraC+HD-ASCT	1 week	1 2 3	1. PR 2. PR CR, patient's decision	44.4+	> 44.4
72	2	1. HDMTX+ifosfamide 2. ifosfamide	2 weeks	1 2	1. PR 2. PD	2.8	8.5
81	2	1. HDMTX+ifosfamide 2. topotecan	No steroids	1	PR, late neurotoxicity	2.0	2.0
73	1	HDMTX+ifosfamide+ rituximab	No steroids	1 2 3	PR PR PD	4.1	5.3
63	2	1. HDMTX+ifosfamide+ rituximab 2. HDAraC+TT	2 weeks	1	PR, late neurotoxicity	2.9	2.9
77	1	HDMTX+ifosfamide+ HDAraC+rituximab	1 week	1	uCR, pneumonia	1.4	1.4
83	2	1. HDMTX+ifosfamide+ HDAraC+rituximab 2. temozolomide	1 week	1 2	PR PD	3.4	3.4
72	1	HDMTX+ifosfamide+ cyclophosphamide+ HDAraC	3 weeks	1 2 3 4	PR PR PR PD	7.9	10.9
22	3	1. HDMTX+ifosfamide+ HDAraC+rituximab 2. temozolomide	1 week	1 2 3	CR CR PD	6.3	> 20.5

Abbreviations: AraC, cytarabine; CR, complete remission; HDAraC, high-dose cytarabine; HD-ASCT, high-dose chemotherapy followed by autologous stem-cell transplant; HDMTX, high-dose methotrexate; icv, intraventricular; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial remission; TT, thiotepa; uCR, unconfirmed remission; WBRT, whole-brain radiotherapy.

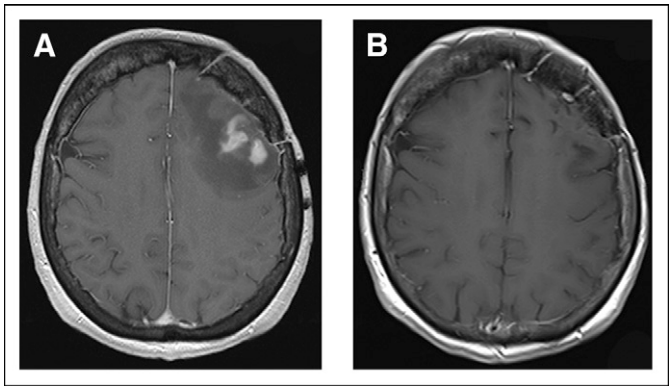

Fig 1. Complete response to temsirolimus in a 67-year-old patient. (A) Relapse after high-dose methotrexate and ifosfamide. (B) After eight infusions of temsirolimus 75 mg/m^2 intravenously once per week.

2 ng/mL was found; in all others, no drug was detected in the CSF (Appendix Table A1, online only).

DISCUSSION

This is the first completed prospective trial of a targeted agent in PCNSL. Conducting prospective studies of patients with refractory/relapsed PCNSL is particularly difficult due to the frequently aggressive course of this disease with rapid deterioration of patients' performance status, often preventing physicians from enrolling them in prospective trials and sometimes from providing any treatment at all.

Response rate in the present trial is in the upper range of responses in other studies on refractory/relapsed PCNSL,[6-15] which is remarkable considering the accumulation of negative prognostic factors such as relatively old age, poor Memorial Sloan Kettering Cancer Center score, heavy pretreatment (including HD-ASCT and WBRT), and short interval since last pretreatment. Comparison of studies on refractory/relapsed PCNSL is, however, difficult due to use of different response criteria, wide spectrum of patients' ages, heterogeneous pretreatment, and a frequent lack of detailed information on the potentially confounding use of steroids. Unfortunately, the relatively high response rate in the current study did not translate into a longer PFS, which was comparable with other studies. A possible explanation could be that the effects of targeted agents in PCNSL, which are currently almost unknown, are different from those seen with classical chemotherapy. The short life span of the responses indicates that temsirolimus is active in PCNSL, but its activity is often transient, probably due to development of tumor cell resistance. Thus, incorporation of temsirolimus into earlier treatment lines or combining it with other cytostatic drugs or rituximab (as is being done for systemic DLBCL in an ongoing study [NCT01653067[27]] and has been done in other lymphomas[28,29]) seems worth consideration. Given the toxicity observed in this study, this should be done in younger patients who are fitter for treatment and using primary antibiotic prophylaxis. Interestingly, a synergism between temsirolimus and MTX has been demonstrated in vitro in cell lines of acute lymphoblastic leukemia and in vivo in a mouse model,[30] suggesting the evaluation of this combination in patients with untreated PCNSL or in patients relapsing after long remission duration to first HDMTX treatment.

Because of the relatively low response rate of relapsed/refractory systemic DLBCL of 20% to 30% and the lack of registration for malignant lymphoma in many countries including the United States, mTOR inhibitors have not been incorporated into the treatment of these patients. The response rate of 54% in the present trial was higher compared with studies on systemic DLBCL. Given that PCNSL biology is not fully understood, we can only speculate about

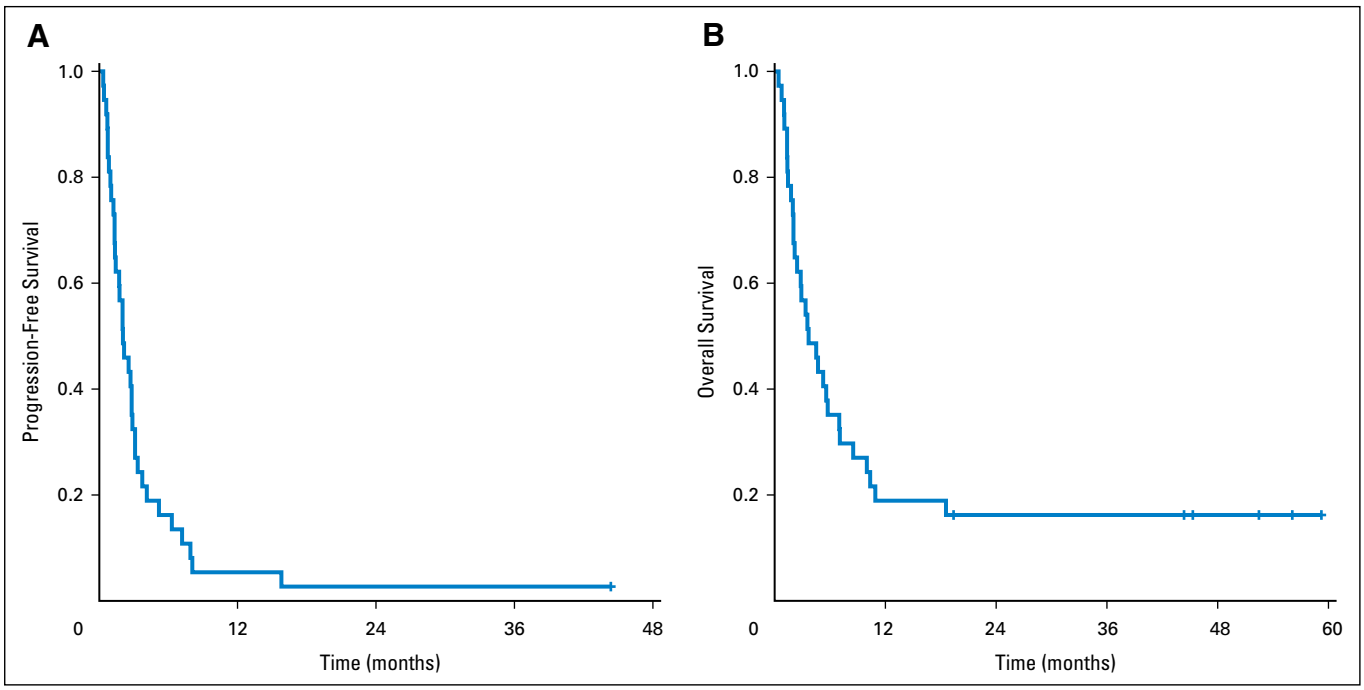

Fig 2. (A) Progression-free survival in all patients (N = 37). (B) Overall survival in all patients (N = 37).

Table 3. Maximal Toxicity Per Patient

Toxicity	All Grades Patient No. (%)	Grade 1-2 Patient No. (%)	Grade 3-4 Patient No. (%)
Hematologic			
Thrombocytopenia	23 (62.2)	15 (40.5)	8 (21.6)
Anemia	22 (59.5)	18 (48.6)	4 (10.8)
Leukopenia	22 (59.4)	20 (54)	2 (5.4)
Nonhematologic			
Hyperglycemia	31 (83.8)	20 (52.6)	11* (29.7)
Transaminases elevation	16 (43.2)	15 (40.5)	1 (2.7)
Fatigue	16 (43.2)	14 (37.8)	2 (5.4)
Skin toxicity	13 (35)	10 (27)	3 (8.1)
Infection	12 (32.4)	5 (13.5)	7 (18.9)
Creatinine elevation	11 (29.7)	10 (27)	1 (2.7)
Stomatitis	10 (27)	10 (27)	1 (2.7)
Nausea	5 (13.5)	5 (13.5)	2 (5.4)
Vomiting	2 (5.4)	2 (5.4)	1 (2.7)
Diarrhea	2 (5.4)	1 (2.7)	1 (2.7)

*Six patients were taking steroids.

the reason for its higher sensitivity to mTOR inhibitors compared with systemic DLBCL. Based on gene expression patterns, PCNSL mostly corresponds to the activated B-cell (ABC) subtype of DLBCL.[31] Unfortunately, the available efficacy data of temsirolimus in DLBCL did not differentiate between ABC and non-ABC subtype. However, ibrutinib, an upstream inhibitor of the B-cell receptor pathway, has shown striking efficacy, especially in the ABC subtype.[32]

Toxicity observed in this trial was considerable, with 13.5% treatment-associated mortality. This underscores the compromised condition of patients with relapsed/recurrent PCNSL who are not eligible for HD-ASCT or who have experienced treatment failure. Infections, mostly pneumonias, were among the most frequent toxicities and were also observed with 25 mg temsirolimus and without leukopenia. It cannot be excluded that some of the patients classified as having pneumonia in fact had pneumonitis, a well-known adverse effect of mTOR inhibitors, which can also present with fever, cough, shortness of breath, and pulmonary infiltrates on chest x-ray. The treatment of these patients in our study targeted both conditions and included both antibiotics and steroids. The frequency of severe infections of 18.9% was higher than the 9% in the study by Hess et al.[19] This could be due to the frequent pretreatment with steroids and poorer performance status of our patients, with only 40.5% of patients with Eastern Cooperative Oncology Group grades 0 to 1 compared with 91% in the study by Hess et al. Severe hematotoxicity was less frequent in the current study compared with patients with mantle cell lymphoma treated with 75 mg temsirolimus once per week (grades 3 to 4 thrombocytopenia 22% *v* 59% in the study by Hess et al, grades 3 to 4 anemia 11% *v* 20%). This might have been due to a relatively high proportion of patients (44%) with bone marrow infiltration and higher temsirolimus dose in the induction phase in the study by Hess et al. Although we did not check for bone marrow involvement in our patients, we can exclude it in the vast majority of them based on the known relapse/progression pattern of PCNSL, which almost exclusively involves the CNS.

There is an obvious discrepancy between temsirolimus activity and lack of detectable concentration of the drug and its main metabolite in the CSF. One explanation could be that CSF and brain parenchyma represent different compartments, and CSF levels do not necessarily reflect brain parenchyma concentrations. Moreover, there is a breakdown of the normal blood-brain barrier within the tumor bulk, allowing penetration of drugs which do not cross the intact blood-brain barrier. High drug concentrations in the tumor tissue and the adjacent brain, with no or barely measurable CSF concentrations, have been reported for several cytostatic agents such as platinum and epidophylotoxins.[33] However, the limited data available suggest that drug concentrations in the brain tissue usually drop with increasing distance from the tumor, to levels that are frequently too low to eradicate infiltrating tumor cells.

Frequent administration of steroids before response assessment has to be considered a confounding factor for response evaluation due to their lymphotoxic effect, which may persist for several weeks after discontinuation. Only in seven of 20 responders not taking steroids for at least 3 months before first response assessment could the therapeutic effect be attributed solely to temsirolimus. Another limitation was the preferential inclusion of elderly patients whose initial treatment is frequently not according to the current standards used in younger patients. Generalization of our results to unselected patients with PCNSL should thus be viewed with caution.

In summary, temsirolimus proved active in relapsed/refractory PCNSL. Although most responses were short lived, some patients achieved long-term control. Thus, further evaluation in combination with other drugs seems reasonable. However, one has to be aware of the risk of hematotoxicity and infections necessitating primary antibiotic prophylaxis. Definition of biomarkers allowing identification of potential responders and those who are at particular risk for toxicity would be highly desirable.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Agnieszka Korfel, Eckhard Thiel, Peter Martus, Philipp Kiewe
Provision of study materials or patients: Agnieszka Korfel, Uwe Schlegel, Ulrich Herrlinger, Martin Dreyling, Christian Schmidt, Luisa von Baumgarten, Antonio Pezzutto, Eckhard Thiel, Philipp Kiewe
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Manuscript writing: All authors
Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Phase II Trial of Temsirolimus for Relapsed/Refractory Primary CNS Lymphoma

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Appendix

Table A1. Concentrations of Temsirolimus and Sirolimus in Blood and CSF of Individual Patients

Patient	Temsirolimus Dose (mg)	Infusion No.	Temsirolimus (ng/mL)		Sirolimus (ng/mL)	
			Blood	CSF	Blood	CSF
0101	25	1	399	< 1	13.1	< 1
		2	675	< 1	19.0	< 1
		4	258	< 1	18.4	< 1
0102	25	1	181	< 1	105	< 1
0103	25	1	315	< 1	28.9	< 1
		4	130	< 1	78.8	< 1
0104	25	1	217	< 1	13.2	< 1
		3	203	< 1	15.7	< 1
		6	256	< 1	18.4	< 1
0105	25	1	287	< 1	61.7	< 1
0107	75	1	565	< 1	97.6	< 1
0110	75	1	813	< 1	79.4	< 1
0111	75	1	237	2	65.4	< 1
0112	75	1	322	< 1	122	< 1