The Oncologist®

Clinical Trial Results

Pemetrexed in Recurrent or Progressive Central Nervous System Lymphoma: A Phase I Multicenter Clinical Trial

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT00916630
- **Sponsor**: Eli Lilly & Co.
- **Principal Investigator**: Jorg Dietrich
- **IRB Approved**: Yes

Lessons Learned

- The findings from this study using monotherapy with pemetrexed in a pretreated patient population are, overall, encouraging.
- Unlike high-dose methotrexate, which requires several days of inpatient hospitalization, pemetrexed is relatively easy to administer in the outpatient setting and remains a viable treatment option in this patient population.
- The maximum tolerated dose of pemetrexed administered (900 mg/m^2 every 2 weeks) was generally well tolerated and showed activity in patients with relapsed or refractory CNSL.

Abstract

Background. There is currently no standard salvage treatment for patients with relapsed/refractory central nervous system (CNS) lymphoma (CNSL). We report the results of a phase I study of pemetrexed, an antifolate drug with broader activity than methotrexate (MTX). We provide the safety, tolerability, and maximum tolerated dose (MTD) of pemetrexed in patients with recurrent CNSL.

Methods. Through October 2015, 17 patients with relapsed/refractory CNSL received pemetrexed every 2 weeks with the first cohort receiving 600 mg/m^2 and dose escalation in increments of 300 mg/m^2 to a maximum of 1,200 mg/m^2. Three patients were to enroll at each dose level with expansion to six patients in the event of dose-limiting toxicity. Patients with both primary CNS lymphoma (PCNSL) and secondary CNS lymphoma (SCNSL) could be enrolled.

Results. Seventeen patients were evaluable with a median age of 63.7 years. Main adverse events included fatigue (82.4%), anemia (82.4%), and neutropenia (70.6%). The MTD was established at 900 mg/m^2. Dose-limiting toxicities were recorded in one patient in the 600 mg/m^2 cohort and in two patients in the 1,200 mg/m^2 cohort. Fourteen patients were evaluable for response assessment; 21.4% achieved a complete response, 35.7% had a partial response, 14.3% had stable disease, and 28.6% had progressive disease. The median progression-free survival was 4.2 months. The median overall survival was 44.5 months.

In the original study protocol, the plan was to add an expansion cohort of six patients at MTD level. However, the first phase of the study was characterized by slow recruitment. Therefore, after achieving the primary objective of the study and establishing the MTD, the investigators decided to amend the protocol and to close the study.

Conclusion. Pemetrexed administered at 900 mg/m^2 every 2 weeks exhibits single-agent activity in patients with recurrent CNSL; it is well tolerated, and side effects are manageable. ***The Oncologist*** 2020;25:747–e1273

Discussion

The MTD of 900 mg/m^2 every 2 weeks was identified. Treatment was generally well tolerated with encouraging activity of pemetrexed. Pemetrexed responses were promising, with overall response rate (ORR) of 57.1%, disease control rate (DCR) of 71.4%, median progression-free survival (PFS) of 4.2 months, and median overall survival (OS) of 44.5 months.

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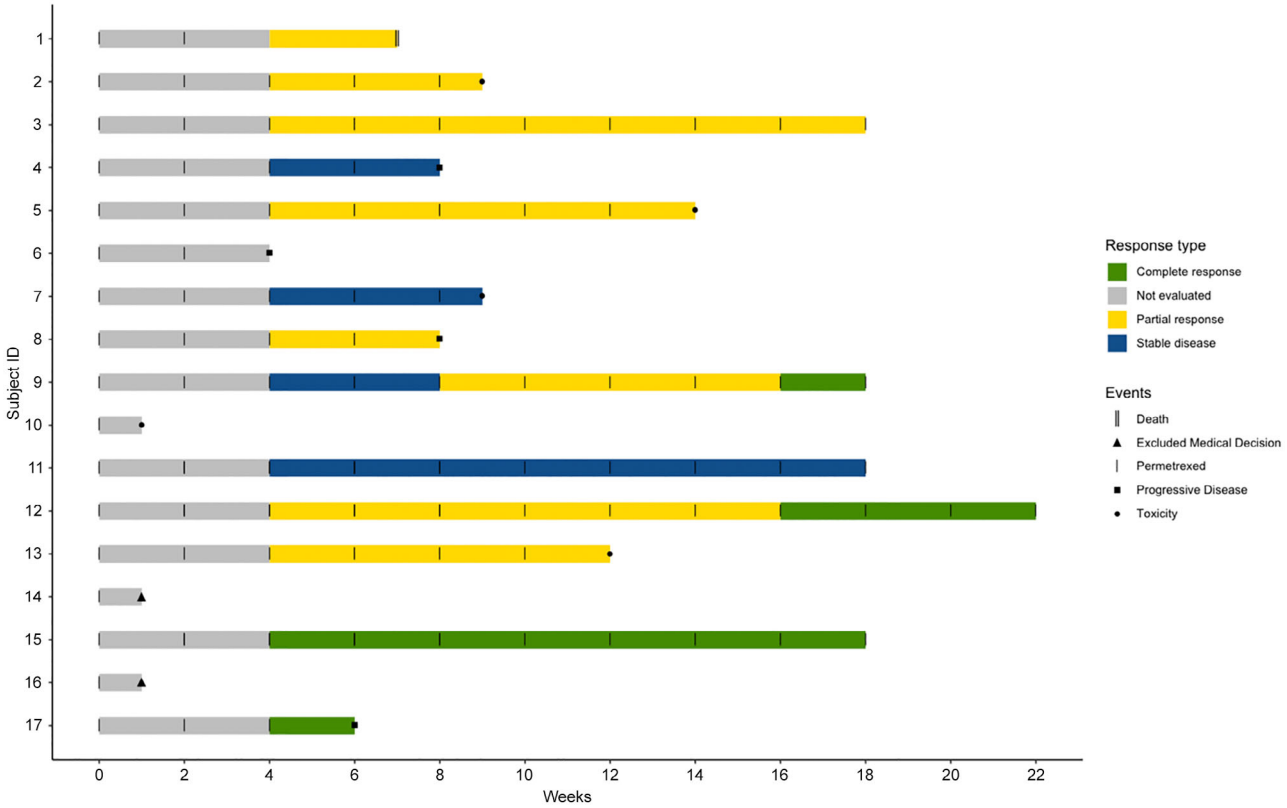

Figure 1. Swimmer plot representing the durations and responses of treatment (pemetrexed) in patients with CNSL. Response rate was evaluated by magnetic resonance imaging of the brain every two cycles (4 weeks).

All patients received at least one line of treatment including methotrexate prior to enrollment in this study. Figure 1 shows a swimmer plot of the durations and responses of treatment.

Zhang et al. [1] reported outcomes and toxicities for 30 patients with CNSL (18 PCNSL and 12 SCNSL) with pemetrexed. The median number of prior CNS relapses was 1.5, and most patients (86.7%) had received prior MTX, suggesting that pemetrexed may not exhibit cross-resistance with MTX; 73.3% of their patients received pemetrexed at 900 mg/m^2 every 3 weeks as their initial dose. The ORR was 62%, and the DCR was 68.9%. The median PFS was 4.1 months (5.8 months in the PCNSL subgroup). The median OS was not reached, but at 22.6 months, the OS rate was 54%. There was no significant difference in PFS or OS between patients who received pemetrexed at 900 mg/m^2 (22 patients) and those who received lower initial doses of pemetrexed (8 patients). The most common grade > 3 adverse events included leukopenia and fatigue, consistent with the findings from our study.

Although pemetrexed showed efficacy and disease control in the majority of our patients, we were only able to evaluate response is a cohort of 14 patients, limiting the conclusions of our findings. None of our patients had a diagnosis of active ocular or leptomeningeal disease, thereby limiting the conclusion of whether pemetrexed has activity in this context. The efficacy of pemetrexed in recurrent CNS lymphoma warrants further evaluation in future studies, potentially in combination with other agents with known activity in this disease population.

As secondary objectives, analysis of pharmacokinetics and pharmacodynamics was initially included in the protocol. Unfortunately, the lack of a sufficient number of cerebrospinal fluid and serum samples rendered such analyses inconclusive. Finally, although we observed a median OS of 44.5 months in our study, most patients received several additional lines of treatment after pemetrexed, which contributed to their extended survival.

Trial Information	
Disease	Brain cancer – primary
Disease	Lymphoma – non-Hodgkins
Stage of Disease/Treatment	Primary
Prior Therapy	Two prior regimens
Type of Study — 1	Phase I, 3 + 3
Primary Endpoints	Maximum tolerated dose, tolerability, safety

Secondary Endpoints	Progression-free survival, overall survival, overall response to treatment

Additional Details of Endpoints or Study Design

We conducted a multicenter, open-label, single-agent phase I study of pemetrexed. Patients were enrolled using a 3 + 3 dose-escalating design. The MTD was defined as the dose level below which dose-limiting toxicity (DLT) was encountered in one-third of the patients. DLT was defined as any grade 4 toxicity (except grade 4 febrile neutropenia lasting less than 5 days) and any grade 3 nonhematologic, non-neurologic toxicity (except grade 3 hepatic transaminase elevations and grade 3 fatigue or generalized weakness) within the first two cycles (28 days) of therapy or the 14-day observation period between each dose level cohort. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 was used to grade all the toxicities.

Pemetrexed was administered as an intravenous infusion over 10–20 minutes every 2 weeks. Three patients per dose-level cohort were treated and evaluated for toxicity over a period of 28 days (two cycles of pemetrexed per dose). After the third patient in each dose-level cohort completed the second administration of pemetrexed, there was a 14-day observation period. If no DLT was observed in any of the three patients in the cohort, escalation to the next dose-level cohort was performed. A starting dose at 600 mg/m^2 was chosen. The dose was escalated in increments of 300 mg/m^2 to a maximum of 1,200 mg/m^2 of pemetrexed. If a drug-related DLT occurred at any dose-level cohort, an additional three patients were added to a total accrual of six patients at this dose-level cohort.

Patients received dexamethasone (4 mg of oral or equivalent) twice daily, on the day before, the day of, and the day after each dose of pemetrexed, for prophylaxis of skin-related adverse effects and rashes. To reduce potential side effects of pemetrexed, patients were also instructed to take folic acid 800 μg daily, starting 7 days before the first dose of pemetrexed and continuing for 3 weeks after the last dose. Vitamin B12 1,000 μg supplementation, as an intramuscular injection, was also administrated, starting 7–14 days prior to the first dose of pemetrexed, and was repeated every 9 weeks until 3 weeks after the last dose. Because of grade 4 neutropenia toxicity observed in the first treatment cohort, all patients were subsequently treated with granulocyte colony-stimulating factor. Patients remained on treatment until complete response or cycle 8. Patients with complete response received up to two additional consolidation cycles.

In the original study protocol, the plan was to add an expansion cohort of six patients at MTD level. However, the first phase of the study was characterized by slow recruitment. Therefore, after achieving the primary objective of the study and establishing the MTD, the investigators decided to amend the protocol and to close the study.

Investigator's Analysis	Correlative endpoints met but not powered to assess activity

Drug Information

Generic/Working Name	Pemetrexed
Trade Name	Alimta
Company Name	Eli Lilly & Co.
Dose	600 milligrams (mg) per squared meter (m^2)
Route	IV
Schedule of Administration	Pemetrexed was administered as an intravenous infusion over 10–20 minutes every 2 weeks.

Dose Escalation Table

Dose level	Dose of drug: Pemetrexed	Number enrolled	Number evaluable for toxicity
600	600 mg/m^2	6	6
900	900 mg/m^2	4	3
1,200	1,200 mg/m^2	7	6

Patient Characteristics

Number of Patients, Male	9
Number of Patients, Female	8
Age	Median (range): 63.7 years (range 47–77 years)
Number of Prior Systemic Therapies	Median (range): 1.6 (range 1–3)

Performance Status: ECOG	0 — 0 1 —0 2 —0 3 —0 Unknown — 17

Other

Through October 2015, 18 patients with CNSL were enrolled from three centers in Boston: Massachusetts General Hospital (*n* = 9), Dana-Farber Cancer Institute (*n* = 7), and Beth Israel Deaconess Medical Center (*n* = 2). Seventeen patients received treatment (one patient withdrew consent before receiving treatment). Basic demographics and patient characteristics are presented in Table 1. The sex ratio was 1:1.1 with a median age of 63.7 (range 47–77 years). Performance status was assessed by Karnofsky performance status. Initial diagnosis of CNSL was established by brain biopsy in all patients. All 17 patients were considered in the intention-to-treat (ITT) analysis. Among these, 14 of 17 patients had at least one magnetic resonance imaging (MRI) and were evaluable for response assessment. The remaining 3 of 17 patients prematurely stopped the study before the first MRI was obtained (before the second cycle) because of medical decision by the treating provider (*n* = 2) or toxicity (*n* = 1). From the evaluable patients, the median number of treatment cycles was 6.4 $\pm$ 3.4.

Cancer Types or Histologic Subtypes	PCNSL, 14; SCNSL, 3

Primary Assessment Method	
Number of Patients Screened	18
Number of Patients Enrolled	17
Number of Patients Evaluable for Toxicity	17
Number of Patients Evaluated for Efficacy	14
Evaluation Method	Other (toxicity: CTCAE version 3; efficacy: MacDonald criteria)
Response Assessment CR	*n* = 3 (21.4%)
Response Assessment PR	*n* = 5 (35.7%)
Response Assessment SD	*n* = 2 (14.3%)
Response Assessment PD	*n* = 4 (28.6%)
Response Assessment OTHER	*n* = 0 (0%)
(Median) Duration Assessments PFS	4.2 months
(Median) Duration Assessments OS	44.5 months
Outcome Notes	Treatment response was assessed by MRI of the brain every 4 weeks. Patients remained on treatment until complete response was achieved, or after completion of a maximum of eight cycles. Response assessment was defined using modified MacDonald criteria on brain MRI, as follows: • Complete response (CR): absence of gadolinium enhancing tumor on MRI or clearance/absence of malignant cells in cerebrospinal fluid. • Partial response (PR): 50% or more decrease in gadolinium enhancing tumor on MRI on cross-sectional dimensions but not qualifying for complete response. • Stable disease (SD): does not qualify for complete response, partial response, or progression. • Progressive disease (PD): 25% or more increase in gadolinium enhancing tumor on MRI on cross-sectional dimensions lesion. The response was assessed at the end of the treatment for each patient. Among all 17 patients, 14 patients were evaluable for response assessment: 3 patients achieved a CR, 5 patients had a PR, 2 patients had SD, and 4 patients had PD (Table 1, Fig. 1). CR was seen after two and eight cycles of pemetrexed in two patients at 1,200 mg/m^2 and after eight cycles in one patient at 900 mg/m^2. An additional

patient achieved CR as the best response after two cycles at a dose level of 1,200 mg/m^2; however, this patient ultimately progressed after two more cycles.

The ORR including CR + PR was 57.1%, and the DCR including PR + CR + SD was 71.4%. The 6-month PFS and 12-month PFS were 35.7% (95% confidence interval [CI], 18%–72%) and 21.4% (95% CI, 8%–58%), respectively, with a median PFS of 4.2 months (95% CI, 2 months, not reached [NR]). The median OS was 44.5 months (95% CI, 19 months, NR). The estimated 1-year, 2-year, and 5-year survival rates were 78.6%, 64.3%, and 35.7%, respectively. In the ITT analysis (17 patients), the DCR and ORR were 58.8% and 47.1%, respectively, with a median OS at 30 months (95% CI, 17 months, NR; Figs. 2, 3). Reason for study discontinuation was completion of treatment in five patients, PD in four patients, toxicity in five patients, medical decision in two patients, death for one patient, and withdrawal of consent for one patient.

Adverse Events

All Cycles

Name	NC/NA, %	Grade 1, %	Grade 2, %	Grade 3, %	Grade 4, %	Grade 5, %	All grades, %
Anemia	17	47	24	12	0	0	83
Fatigue	18	41	35	6	0	0	82
Neutropenia	28	18	24	18	12	0	72
Alanine aminotransferase increased	29	47	12	12	0	0	71
Hypophosphatemia	41	6	41	6	6	0	59
Thrombocytopenia	47	47	6	0	0	0	53
Hyperglycemia	46	24	24	6	0	0	54
Aspartate aminotransferase increased	47	41	6	6	0	0	53
Generalized muscle weakness	58	24	18	0	0	0	42
Leukopenia	58	18	6	18	0	0	42
Lymphopenia	53	0	29	6	12	0	47
Anxiety	65	29	6	0	0	0	35
Nausea	70	24	6	0	0	0	30
Constipation	76	24	0	0	0	0	24
Depression	76	24	0	0	0	0	24
Peripheral sensory neuropathy	76	18	6	0	0	0	24
Creatinine increased	76	12	12	0	0	0	24
Low serum bicarbonate	82	18	0	0	0	0	18
Headache	82	18	0	0	0	0	18
Hyponatremia	82	18	0	0	0	0	18
Insomnia	82	18	0	0	0	0	18
Proteinuria	82	18	0	0	0	0	18
Seizure	82	18	0	0	0	0	18

Adverse Events Legend
All 17 patients were evaluable for safety and tolerability.
Abbreviation: NC/NA, no change from baseline/no adverse event.

Dose-Limiting Toxicities

Dose level	Number enrolled	Number evaluable for toxicity	Number with a dose-limiting toxicity	Dose-limiting toxicity information
600	6	6	1	Neutropenia grade 4
900	4	3	0	
1,200	7	6	2	Lymphopenia grade 4

DLT Table Legend

Patients were started at a pemetrexed dose of 600 mg/m^2, and dose escalations were done up to 1,200 mg/m^2. Pemetrexed at a dose of 600 mg/m^2 was administered to six patients, 900 mg/m^2 to four patients, and 1,200 mg/m^2 to seven patients. Two patients were not evaluable for DLTs (one in the cohort at 900 mg/m^2 and one in the cohort at 1,200 mg/m^2). DLTs were recorded in one patient in the 600 mg/m^2 cohort (neutropenia grade 4) and in two patients in the 1,200 mg/m^2 cohort (lymphopenia grade 4).

The dose of pemetrexed was reduced in three patients: one dose reduction (n = 2, in one patient because of elevated transaminase at the 900 mg/m^2 dose level and in one patient because of neutropenia at the 600 mg/m^2 dose level) and two dose reductions (n = 1, secondary to neutropenia at the 600 mg/m^2 dose level). The most common treatment-related adverse events (AEs) of any grade encountered in all treatment cycles were fatigue (82.4%), anemia (82.4%), and neutropenia (70.6%). At the 1,200 mg/m^2 dose level, hematologic AEs of neutropenia, lymphopenia, and fatigue were the most commonly encountered treatment-related AEs of grade >3 or higher.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Correlative endpoints met but not powered to assess activity

We here report the safety and tolerability data from a multi-institutional phase I study using pemetrexed as monotherapy in recurrent/progressive central nervous system lymphoma (CNSL; NCT00916630). This is the first study to establish the maximum tolerated dose (MTD) of pemetrexed in patients with recurrent CNSL. The MTD of 900 mg/m^2 *every 2 weeks* was identified. Treatment was generally well tolerated with encouraging activity of pemetrexed. Additionally, responses were promising, with overall response rate (ORR) of 57.1%, disease control rate (DCR) of 71.4%, median progression-free survival (PFS) of 4.2 months, and median overall survival (OS) of 44.5 months. All patients received at least one line of treatment including methotrexate (MTX) prior to enrollment in this study. These results are comparable to the findings from a previous phase II study by Raizer et al. [2], assessing the efficacy of pemetrexed in patients with relapsed/refractory primary CNSL (PCNSL). They reported outcomes from 11 patients, treated with 900 mg/m^2 of pemetrexed *every 3 weeks*. All patients in this study had previously received high-dose MTX. The ORR was 55%, and the DCR was 91%, with a median PFS of 5.7 months, 6-month PFS of 45%, and 12-month OS of 45%.

In a retrospective study, Zhang et al. [1] reported outcomes and toxicities for 30 patients with CNSL (18 PCNSL and 12 secondary CNSL) with pemetrexed. The median number of prior central nervous system (CNS) relapses was 1.5, and most patients (86.7%) had received prior MTX, suggesting that pemetrexed may not exhibit cross-resistance with MTX. Of patients in this study, 73.3% received pemetrexed at 900 mg/m^2 *every 3 weeks* as their initial dose. The ORR was 62%, and the DCR was 68.9%. The median PFS was 4.1 months (5.8 months in the PCNSL subgroup). The median OS was not reached, but at 22.6 months, the OS rate was 54%. There was no significant difference in PFS or OS between patients who received pemetrexed at 900 mg/m^2 (22 patients) and those who received lower initial doses of pemetrexed (8 patients). The most common grade > 3 adverse events included leukopenia and fatigue, consistent with the findings from our study.

Han et al. [3] reviewed the efficacy of pemetrexed (dose level of 600 mg/m^2 *every 3 weeks*) in elderly patients with PCNSL. They reported a median PFS of 9 months and median OS of 19.5 months in this population. The ORR and the DCR were 83.3%. This study demonstrated that pemetrexed was active and well tolerated and resulted in less toxicity compared with other chemotherapy regimens used in elderly patients.

Zhao et al. [4] studied the association of pemetrexed plus rituximab as second-line treatment for PCNSL in 27 patients. All patients had previously received MTX. Rituximab at a dose of 375 mg/m^2 was administered on day 0, and pemetrexed 500 mg/m^2 was administered every 3 weeks. The response rate was 62.9% and the disease control rate was 92.5% The median PFS was 6.9 months, and the median OS was 11.2 months. These findings were superior to the data from our study in terms of median PFS, ORR, and DCR despite a lower dose of pemetrexed at 500 mg/m^2 every 3 weeks. It therefore is possible that the combination with rituximab may have conferred improved outcomes.

A few studies have investigated the distribution of pemetrexed into the brain. In the study by Dai et al., the distributional clearance into the CNS was approximately 10% of the clearance outside the brain in both the compartmental and noncompartmental analyses [5]. Stapleton et al. demonstrated that the cerebrospinal fluid distribution of pemetrexed in non-human primates was less than 2% [6]. Despite limited CNS penetration, pemetrexed demonstrated activity in patients with non-small cell lung carcinoma with brain metastasis [7] and in patients with CNSL.

Prior studies in solid cancer have raised potential concerns of pemetrexed-associated renal toxicity [8–10]. However, these findings may have been confounded by using pemetrexed in conjunction with other potentially nephrotoxic chemotherapy regimen. Of note, renal toxicity was not a concerning adverse effect in our study.

MTX remains the most active agent in newly diagnosed CNSL, but the optimal management of recurrent CNSL has not

been established. Several studies evaluated second-line salvage therapies, including rechallenge with high-dose MTX [11], temozolomide with or without rituximab [12–15], rituximab [16], rituximab-ifosfamide-etoposide [17], topotecan [18, 19], lenalidomide [20], ibrutinib [21], Temozolomide, Etoposide, Doxil, Dexamethasone, Ibrutinib and Rituximab (TEDDI-R) [22], and whole brain radiotherapy [23] with varying response rates (ranging from 14% to 85%) and survival (ranging from 4 to 61 months). A median PFS of 2–5 months has been achieved with most regimens.

Although pemetrexed showed efficacy and disease control in the majority of our patients, we were only able to evaluate response is a cohort of 14 patients, limiting the conclusions of our findings. None of our patients had a diagnosis of active ocular or leptomeningeal disease, thereby limiting the conclusion of whether pemetrexed has activity in this context. The efficacy of pemetrexed in recurrent CNS lymphoma warrants further evaluation in future studies, potentially in combination with other agents with known activity in this disease population.

As secondary objectives, analysis of pharmacokinetics and pharmacodynamics was initially included in the protocol. Unfortunately, the lack of a sufficient number of cerebrospinal fluid and serum samples rendered such analyses inconclusive. Finally, although we observed a median OS of 44.5 months in our study, most patients received several additional lines of treatment after pemetrexed, which contributed to their extended survival.

The 2-week schedule was based on a phase I study of pemetrexed and gemcitabine in patients with advanced solid tumors [24]. Toxicity data in our study were comparable to the findings from a previous phase II study by Raizer et al. [2] using a 3-week schedule. PFS and OS were slightly higher with a 3-week schedule with the limitation of a small number of subjects in both studies (fewer than 20 patients). Because response assessment was not the primary objective of the current study, it presently cannot be determined based on all available data whether a 2-week or 3-week regimen is associated with improved outcome.

In this context, the findings from our study using monotherapy with pemetrexed in a pretreated patient population, including some patients with prior bone marrow transplantation, are overall encouraging. Unlike high-dose methotrexate, which requires several days of inpatient hospitalization, pemetrexed is relatively easy to administer in the outpatient setting and remains a viable treatment option in this patient population. Assessment of potential combination regimens with other active agents should be considered in this challenging disease. In summary, a maximum tolerated dose of pemetrexed administered at 900 mg/m^2 every 2 weeks was generally well tolerated and showed activity in patients with relapsed or refractory CNSL.

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Figures and Table

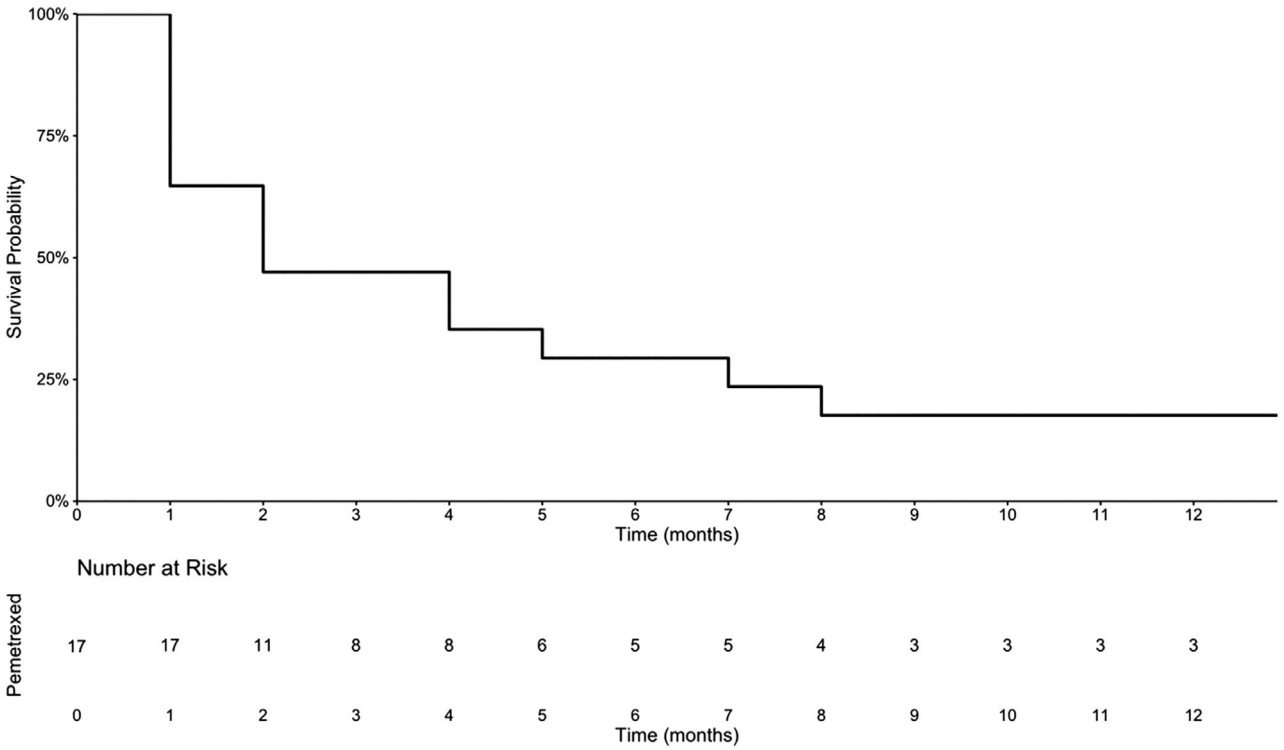

Figure 2. Progression-free survival in all 17 patients with CSNL (intention-to-treat analysis).

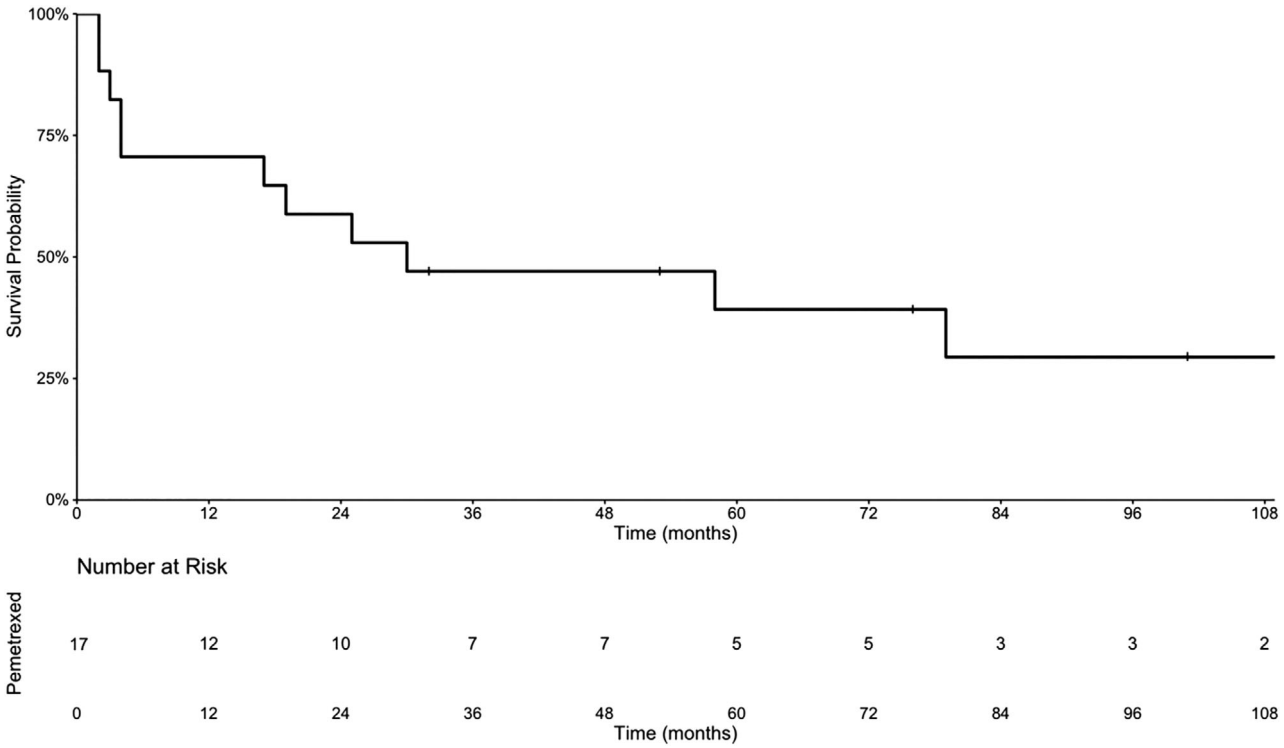

Figure 3. Overall survival in all 17 patients with CSNL (intention-to-treat analysis).

Table 1. Patient demographics, clinical characteristics, and treatment data

Age, (years)	Gender	KPS	Disease status	Focality	Tumor localization	Prior treatment	Disease status prior to pemetrexed	Time between last treatment and start of pemetrexed, (months)	Dose	Cycle number	Response
76	F	60	PCNSL	Multi	Frontal lobe, thalamus/basal ganglia	HD-MTX	Relapse	1	600	2	PR
77	M	60	PCNSL	Uni	Occipital lobe	HD-MTX	Relapse	1	600	5	PR
66	M	90	PCNSL	Uni	Midbrain/pons	(a) HD-MTX, (b) MTX-thiotepa	Relapse	38	600	10	PR
68	F	80	PCNSL	Uni	Temporal lobe	MTX-TMZ-R then HD-MTX	Relapse	1	600	4	PD
64	M	80	PCNSL	Uni	Thalamus/basal ganglia	HD-MTX	Intolerant to MTX	1	600	7	PR
53	F	90	PCNSL	Uni	Parietal lobe	MTX-TMZ-R then HD-MTX	Relapse	1	600	2	PD
71	M	80	SCNSL	Uni	Corpus callosum	(a) HD-MTX, (b) R-CHOP, (c) radiation	Relapse	2	900	5	SD
67	M	70	SCNSL	Uni	Fronto-parieto-temporal	(a) R-CHOP, (b) HD-MTX	Relapse	1	900	4	PD
54	F	100	PCNSL	Uni	Frontal lobe	MTX-TMZ-R, then cytarabine/ etoposide	Relapse	19	900	10	CR
49	M	90	PCNSL	Multi	Frontal lobe	(a) R-EPOCH avastin + MTXi, (b) MTX-TMZ-R, R-Ara-C, and radiation	Relapse	1	1,200	1	—
72	F	100	PCNSL	Multi	Frontal/ temporal lobe	MTX-TMZ	Relapse	4	1,200	10	SD
66	F	100	PCNSL	Uni	Temporal lobe	(a) HD-MTX, (b) HD-MTX-R and radiation, (c) HD-MTX	Relapse	1	1,200	12	CR
51	M	90	PCNSL	Uni	Corpus callosum	MTX-TMZ-R then ASCT	Relapse	44	1,200	6	PR
61	M	80	SCNSL	Uni	Parietal lobe	(a) R-CVP, (b) R-CHOP, (c) HD-MTX	Refractory	1	1,200	1	—
47	M	60	PCNSL	Multi	Cerebellum	HD-MTX-TMZ-R then ASCT	Relapse	30	1,200	10	CR
68	F	*	PCNSL	Multi	Parieto-occipital lobe	(a) HD-MTX, (b) ioMTX, (c) ioMTX	Relapse	24	900	1	—
73	F	90	PCNSL	Multi	Parietal lobe, periventricular, mid brain	MTX-TMZ-R, Ara-C	Relapse	11	1,200	3	PD

Abbreviations: *, not evaluable; CR, complete response; F, female; HD-MTX, high-dose methotrexate; HD-MTX-R, high-dose methotrexate rituximab; ioMTX, intraocular methotrexate; KPS, Karnofsky performance status; M, male; MTXi, methotrexate intrathecal; MTX-TMZ-R, methotrexate temozolomide rituximab; OS, overall survival; PCSNL, primary central system nervous lymphoma; PD, progressive disease; PFS, progression-free survival; PR, partial response; R-Ara-C, rituximab cytarabine; R-CHOP, rituximab cyclophosphamide hydroxydaunomycin oncovin prednisone; R-CVP, rituximab cyclophosphamide vincristine prednisone; R-EPOCH, rituximab etoposide prednisone oncovin cyclophosphamide hydroxydaunomycin; SCNL, secondary central system nervous lymphoma; SD, stable disease.