A phase I/II study of thiotepa-based immunochemotherapy in relapsed/refractory primary CNS lymphoma: the TIER trial

Tracking no: ADV-2021-004779R1

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Abstract:
Relapsed or refractory primary central nervous system lymphoma (rrPCNSL) confers a poor prognosis with no accepted standard of care. Very few prospective studies have been conducted in this patient group. This multicenter, phase I/II study investigated thiotepa in combination with ifosfamide, etoposide and rituximab (TIER), for the treatment of PCNSL relapsed or refractory to high-dose methotrexate-based chemotherapy. A 3+3 design investigated the recommended phase II dose of thiotepa for a single-stage phase II cohort, assessing activity of two cycles of TIER against rrPCNSL. The primary outcome was overall response rate. The dose-finding study demonstrated 50mg/m2 of thiotepa could be safely delivered within the TIER regimen. No dose-limiting toxicities were encountered in phase I, and TIER was well-tolerated by the 27 patients treated in phase II. The most common Grade 3/4 toxicities were neutropenia (56% of patients) and thrombocytopenia (39%). An overall response was confirmed in 14 (52%) patients, meeting the pre-specified threshold for clinically relevant activity. The median progression-free survival was 3 months (95% confidence interval 2 to 6 months) and overall survival 5 months (3 to 9 months). Exploratory analyses suggest a greater benefit for thiotepa-naïve patients. Six patients successfully completed autologous stem cell transplant consolidation (ASCT), with 4 experiencing durable remissions after median follow-up of 50 months. The TIER regimen can be safely delivered and is active against rrPCNSL, and followed by ASCT can provide durable remission and long-term survival. However, for the majority of patients, prognosis remains poor and novel treatment strategies are urgently needed.

Conflict of interest: COI declared - see note

COI notes: CPF: Roche (remunerated consultant and research funding). Adienne (remunerated consultant and research funding). JS: ABBvIE and Janseen funding to attend EHA (2018) and ICML (2019) GPC: Roche (remunerated consultant) AJMF: speaker fee from Adienne; research grants from BMS, Beigene, Pharmacyclics, Hutchison Medipharma, Amgen, Genmab, ADC Therapeutics, Gilead, Novartis, and Pfizer; advisory boards from Gilead, Novartis, Juno, and PletixaPharm; inventor of patents on NGR-hTNF/RCHOP in relapsed or refractory PCNSL and SNGR-hTNF in brain tumours KC: Roche (remunerated consultant and research funding). Adienne (remunerated consultant funding All remaining authors have no conflicts of interest.

Preprint server: No;

Author contributions and disclosures: All authors made substantial contributions to the trial design, data acquisition, or data interpretation of this study. All authors were involved in drafting and revising the manuscript, and all gave approval of the final version. All authors are accountable for the accuracy and integrity of the work.

Non-author contributions and disclosures: No;
Agreement to Share Publication-Related Data and Data Sharing Statement: The TIER protocol is included as a supplement to the main manuscript

Clinical trial registration information (if any): ISRCTN registry identifier: 12857473
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Sridhar Chaganti7
Jeffery Smith8
Ian Chau9
Dominic Culligan10
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Running head:
Results of the phase I/II TIER trial for rrPCNSL

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Word counts
Abstract: 248
Main text: 3989

Number of tables and figures: 5
Number of supplementary files: 2
Number of references: 26
Trial registration: ISRCTN registry identifier: 12857473
Abstract

Relapsed or refractory primary central nervous system lymphoma (rrPCNSL) confers a poor prognosis with no accepted standard of care. Very few prospective studies have been conducted in this patient group.

This multicenter, phase I/II study investigated thiotepa in combination with ifosfamide, etoposide and rituximab (TIER), for the treatment of PCNSL relapsed or refractory to high-dose methotrexate-based chemotherapy. A 3+3 design investigated the recommended phase II dose of thiotepa for a single-stage phase II cohort, assessing activity of two cycles of TIER against rrPCNSL. The primary outcome was overall response rate.

The dose-finding study demonstrated 50mg/m$^2$ of thiotepa could be safely delivered within the TIER regimen. No dose-limiting toxicities were encountered in phase I, and TIER was well-tolerated by the 27 patients treated in phase II. The most common Grade 3/4 toxicities were neutropenia (56% of patients) and thrombocytopenia (39%). An overall response was confirmed in 14 (52%) patients, meeting the pre-specified threshold for clinically relevant activity. The median progression-free survival was 3 months (95% confidence interval 2 to 6 months) and overall survival 5 months (3 to 9 months). Exploratory analyses suggest a greater benefit for thiotepa-naive patients. Six patients successfully completed autologous stem cell transplant consolidation (ASCT), with 4 experiencing durable remissions after median follow-up of 50 months.

The TIER regimen can be safely delivered and is active against rrPCNSL, and followed by ASCT can provide durable remission and long-term survival. However, for the majority of patients, prognosis remains poor and novel treatment strategies are urgently needed.

Key points

Thiotepa at 50mg/m$^2$ was safely incorporated into TIER immunochemotherapy

Despite a clinically meaningful treatment response rate, long-term survival was only seen with autologous stem cell transplant consolidation
Introduction

Primary central nervous system lymphoma (PCNSL) is a rare and aggressive malignancy with an annual incidence of approximately 4-5 per million population. Histologically, PCNSL is diffuse large B-cell lymphoma (DLBCL) restricted to the CNS or vitreoretinal compartment, although a number of pathobiological and clinical features distinguish it from systemic DLBCL. The anatomical localization presents unique challenges, including neurocognitive disability and impaired performance status due to the tumor, the impact of the blood brain barrier on treatment delivery, and the vulnerability of surrounding brain tissue to toxicity from therapy.

Multi-agent, methotrexate-based induction regimens followed by consolidation have significantly improved outcomes for patients with PCNSL: complete response (CR) rates of 43% to 66% and 2-year survival rates of 60% to 90% are now reported. However, notwithstanding intensive first-line treatment protocols incorporating autologous stem cell transplantation (ASCT), a significant proportion of patients experience relapse, and the majority of patients with relapsed or refractory (rr) PCNSL will die from their disease.

There is currently a paucity of prospective trial data and no standard of care for patients with rrPCNSL, who have a poor prognosis; population-based data show a median survival of 3.5 months. The concept of using non-cross-resistant chemotherapy regimens for rrPCNSL is intuitive and an established approach for systemic DLBCL. Previous studies have demonstrated that, for patients with rrPCNSL who undergo ASCT consolidation, durable responses are achievable, with 5-year survival rates of over 50%.

A retrospective study of patients treated with salvage rituximab, ifosfamide and etoposide (R-IE) described encouraging rates of response in a high-risk cohort of rrPCNSL patients. The R-IE regimen was well tolerated, the overall response rate (ORR) was 41%, and 18% of patients proceeded to ASCT. We hypothesized that adding a further CNS-penetrating agent, with minimal non-hematological side-effects, to the R-IE regimen could improve outcomes without significantly increasing toxicity. Thiotepa is a highly lipophilic, polyfunctional alkylator, with a steep dose-response curve and highly efficient CNS penetration. Thiotepa is an established component of ASCT conditioning regimens for CNS lymphoma and more recently has been incorporated in multi-agent chemotherapy regimens, although the dose employed in the MATRix regimen (30 mg/m²) was empirically adopted without formal dose-finding studies.

The TIER trial is a prospective, dose-finding, multicenter, phase I/II study of thiotepa in combination with ifosfamide, etoposide and rituximab, for the treatment of rrPCNSL (EudraCT 2014-000227-24, ISRCTN 12857473). The aims of this study were: 1. To establish the recommended phase II dose (RP2D) and safety of adding thiotepa to ifosfamide, etoposide and rituximab (the TIER regimen), and 2. To investigate the activity of this regimen in the treatment of rrPCNSL after failure of methotrexate-based therapy.

Methods

Participants

Adults with relapsed or refractory PCNSL (defined as CD20-positive DLBCL confined to the CNS) were eligible for this study. Relapsed or refractory disease was defined as recurrence after CR, unconfirmed CR (CRu) or partial response (PR), or failure to achieve at least PR, after one or two prior lines of chemotherapy that included at least one regimen containing high-dose methotrexate.
≥1g/m². Although histological confirmation of relapse was recommended, patients were eligible provided initial diagnostic tissue was available and magnetic resonance imaging (MRI) was consistent with PCNSL. Further inclusion criteria were: performance status of 0–2 (or 3 if attributed to lymphoma); adequate organ function; and ability to undergo MRI scanning. Key exclusion criteria included: evidence of systemic lymphoma, HIV seropositivity, recent treatment for lymphoma prior to registration (chemotherapy within 4 weeks, whole brain radiotherapy (WBRT) within 6 months, thiotepa-based ASCT within 12 months, or previous R-IE); active infection; breastfeeding or risk of pregnancy.

The TIER study was approved by the United Kingdom (UK) Research Ethics Committee (reference 14/LO/1568) and local institutional review boards of participating sites. Patients gave informed consent to enter the trial. For patients who lacked capacity due to their lymphoma, as clinically assessed by investigators, informed consent was provided by a legal representative who was independent from the trial and could represent the patient’s presumed will, according to UK law.

Patients were recruited through the Blood Cancer UK and Cure Leukaemia charity-funded Trials Acceleration Programme (TAP). This network of UK haematology/oncology centres provides patients with access to novel treatments through early phase clinical trials, through a catchment population of >20 million people.

**Trial Design**

The phase I component of TIER followed a conventional dose-finding 3+3 trial design, to establish the RP2D of thiotepa in combination with ifosfamide (2g/m²/day, days 2 to 4), etoposide (250mg/m³, day 2) and rituximab (375mg/m³/day, days 1 and 2). The dose levels of thiotepa studied were: 20mg/m², 30mg/m² (starting dose), 40mg/m², and 50mg/m², given intravenously over 1 hour on day 5 of a 21-day cycle. The full treatment regimen, delivered as a 21-day cycle for 2 cycles, is shown in Supplementary Figure S1. Antimicrobial prophylaxis was recommended according to local guidelines; aciclovir and co-trimoxazole suggested for herpes and Pneumocystis, respectively, quinolone antibiotics during neutropenic periods. Granulocyte colony-stimulating factor (G-CSF) was mandated until neutrophil recovery, or for stem cell mobilisation. Corticosteroids were tapered down and discontinued before response assessment after cycle 2 (Supplementary Figure S1).

Protocol-defined dose-limiting toxicities (DLTs) were independently assessed after 1 cycle by the Trial Steering Committee, and comprised: a treatment delay of >14 days attributable to thiotepa; grade 4 thrombocytopenia or neutropenia causing a treatment delay of >14 days; or any clinically significant grade 3 or 4 non-haematological toxicity attributable to thiotepa.

Once the RP2D was identified, patients were enrolled to the phase II component in a single-stage study based on A’Hern’s design. A pre-specified, clinically relevant ORR of 50% or greater was chosen as a basis for further investigation, whereas an ORR of 30% or less would indicate further investigation is not warranted. In order to detect a meaningful effect with 90% power and a 20% risk of adopting treatment with an ORR of 30%, 28 patients were required in phase II. Eleven patients with a radiological response, as determined by central MRI review, would be required to meet the efficacy threshold. Patients treated at the RP2D in phase I were analysed together with those treated in phase II.

Following 2 cycles of TIER, patients were treated at the discretion of investigators, according to individual patient characteristics, patient preference and treatment history. For eligible patients responding to TIER, consolidation with thiotepa-based ASCT was recommended, but not mandated. Alternative approaches for consolidation therapy included an additional 2 cycles of thiotepa, ifosfamide and etoposide (TIE), or WBRT, reflecting the available treatment options in the UK during the conduct of the study. Similarly, re-treatment with a second ASCT was not commissioned within the UK NHS. Investigators were required to state at trial entry which consolidative strategy was planned.
Outcome measures

The primary outcome of the phase I dose-escalation was the RP2D of thiotepa within the multi-drug TIER regimen. The primary outcome of the phase II component was ORR (the proportion of patients with CR, CRu or PR) by independent central neuroradiology review, after 2 cycles of TIER treatment. Response was evaluated with gadolinium-enhanced MRI according to the International Primary CNS Lymphoma Collaborative Group (IPCG) criteria, on an intention-to-treat basis. Secondary outcomes were: CR rate after 2 cycles of TIER; overall survival (OS, time from registration to death from any cause); progression-free survival (PFS, time from registration to disease progression or death from any cause); event-free survival (EFS, time from registration to any of: death from any cause, disease progression, treatment toxicity, neurological deterioration post-treatment, trial withdrawal); rate of successful stem cell harvest; proportion of patients proceeding to ASCT; and toxicity of the TIER regimen according to the Common Terminology Criteria for Adverse Events version 4.0. Relative dose intensity (RDI) was calculated as a percentage of the unadjusted protocol-defined dose. Patients from both phases of the trial are included in the safety and consolidation outcomes. Patients were followed-up for a minimum of 2 years.

Further details on the trial methods and procedures can be found in the trial protocol (Supplementary material). Trial data were analysed by CF, AA, GM, CT and AJ. All authors had access to the primary clinical data. All trial data will be uploaded onto the EudraCT database following the end of trial declaration for publication at [https://www.clinicaltrialsregister.eu/ctr-search/search](https://www.clinicaltrialsregister.eu/ctr-search/search).

Results

Patients

Between June 2015 and April 2019, 36 patients were recruited from 13 UK Trial Acceleration Programme centers – a haematology-oncology early phase trials network encompassing a catchment population of >20 million people. Median age was 62, and 47% had an ECOG performance status 2-3 at study entry. Patient characteristics and details of previous treatments are summarized in Table 1. Notably, 11 patients had previously received thiotepa within the MATRix regimen (comprising high-dose methotrexate, cytarabine, thiotepa (30mg/m²) and rituximab) and 2 patients had undergone ASCT before trial entry, all of whom were enrolled into the phase II part of the trial. Six patients (17%) lacked the capacity to consent due to PCNSL-related cognitive impairment, whose informed consent was provided by a legal representative.

Sixty-one cycles of TIER were delivered within both phases of the trial, 45 of which were at the RP2D of thiotepa (83% of 54 planned doses in 27 patients). The Trial Management Group and Safety Committee recommended stopping enrolment after reaching a sample of 27 patients at RP2D (of 28 planned), as pre-planned interim monitoring indicated that the primary endpoint had been reached. The flow of patients through the phase I and II components of the study and their inclusion within analyses is described in Figure 1.

Treatment tolerability

Twenty-six patients received both of the planned 21-day cycles of TIER, 11 of whom experienced a delayed start to cycle 2; the median delay was 2 days (IQR 1 to 4 days, range 1 to 17 days). The commonest reason for delay was administrative or organizational; only 2 treatment cycles were delayed to allow platelet recovery to the mandated count of >80 x10⁹/L. Four patients (11%)
required dose reductions in any of the TIER regimen drugs. Across both cycles of TIER, the median RDI for thiotepa was 100% (range 73% to 100%). The median RDI for ifosfamide was 100% (range 67% to 100%), and for etoposide was 100% (range 50% to 100%).

During the phase I study, there were no DLTs among patients at the starting (30mg/m², 5 patients, of whom 3 were evaluable for DLT), first escalation (40mg/m², 4 patients, 3 evaluable), or final escalation (50mg/m², 3 patients) doses of thiotepa. Thus, the RP2D of thiotepa, in combination with ifosfamide, etoposide and rituximab, was established as 50mg/m².

Across both phases, 574 adverse events (AEs) were reported in 33 patients, of which 312 (54%) reported in 27 patients were grade 3-4 (Table 2). Hematological, neurological and electrolyte disturbance accounted for 95% of grade 3-4 AEs. There was a similar pattern of toxicity when considering AEs of all grades that affected >5% of patients (Supplementary Figure S2). Of the 22 patients with available data, performance status improved (N=1) or was maintained (N=15) after two cycles of TIER, whereas it deteriorated in 6 patients (Supplementary Figure S3).

Seventeen serious adverse events (SAEs) were experienced by 12 patients, of which 13 events in 11 patients were judged to be related to TIER. The treatment-related serious adverse reactions were infection (N=5), hematological toxicity (N=4), and neurological toxicity (N=4) (see also Supplementary Table S1). A single suspected unexpected serious adverse reaction (SUSAR), was reported (serotonin syndrome). One patient death due to pneumococcal sepsis and neurological deterioration was attributed to the trial treatment and underlying PCNSL; all other deaths were due to disease.

Response to treatment

After 2 cycles of TIER, 18 patients were evaluable for objective imaging response assessment at the RP2D. In an intention-to-treat analysis, 14/27 (52%) patients allocated to the RP2D had an objective response: CR (N=4), CRu (N=5) or PR (N=5). This exceeded the pre-specified threshold of clinical interest. The secondary outcome of CR (including CRu) was observed in 9/27 (33%) patients. The remaining 4 patients were confirmed to have progressive disease on MRI after 2 cycles of TIER. Nine patients were non-evaluable due to progressive disease (N=1), death due to PCNSL (N=4), discontinuation due to toxicity (N=2, 1 prolonged infectious episode and 1 suspected serotonin syndrome) and withdrawal from the trial (N=2), prior to the post-cycle 2 MRI timepoint. Of the 14 patients who responded to TIER, 10 subsequently developed progressive disease, of whom 8 are known to have died; 1 further patient died of unknown cause; median duration of response was 5 months (95% CI 2 to 9 months). After a median follow-up of 21 months, 22/27 (81%) patients treated at the RP2D have died: 19 due to underlying PCNSL, 3 of unknown causes. The median OS was 5 months (95% CI 3 to 9 months, Figure 2). The median PFS and EFS were 3 months (95% CI 2 to 6 months, Figure 2) and 2 months (95% CI 1 to 3 months), respectively. Patients who achieved CR or CRu had a median OS of 11 months (95% CI 6 months to not calculable) and a median PFS of 6 months (95% CI 4 to 11 months).

Consolidation

At trial registration, 34/36 (94%) enrolled patients were planned to subsequently receive some form of consolidation therapy after 2 cycles of TIER. The consolidation treatments planned at study entry, and those ultimately delivered, are summarized in Figure 3. Neither patient who previously underwent ASCT were planned for a second transplant. Overall, 17/36 (47%) patients received consolidation therapy: ASCT (N=6), WBRT (N=2), and further cycles of TIE chemotherapy only (N=9).
Of the 25 patients for whom ASCT consolidation was planned at study entry, 11 attempted stem cell mobilization after 2 cycles of TIER (1 with CR, 6 CRu and 4 PR): 5 harvests were unsuccessful, while the 6 patients who successfully collected stem cells underwent ASCT. All patients undergoing ASCT were TIER responders (3 patients each with CRu and PR), and 2 patients were treated with a bridging cycle of TIE before proceeding to ASCT. Eight patients in CR/CRu did not proceed to ASCT: 4 because of failed stem cell harvest, and 3 because of progressive disease; 1 patient in CR had previously received ASCT, and underwent WBRT as planned. ASCT was planned in 8/11 patients previously treated with MATRix, of whom 3 attempted stem cell mobilization, resulting in successful ASCT in 1.

OS was longest in 6 patients who underwent ASCT. After a median follow-up of 50 months, 2 patients have relapsed and died 14 and 27 months after trial entry. The 4 surviving patients are in sustained remission 24, 36, 50 and 52 months after commencing the trial.

Two patients received WBRT consolidation, 1 as planned (who later died due to relapse at 10 months) and 1 after failed stem cell harvest (ongoing remission at 37 months). Nine patients received TIE chemotherapy consolidation, including 1 patient as planned and 4 after a failed stem cell harvest; 6 patients died, 2 were lost to follow-up (at 4 and 12 months) and one patient is alive at 25 months.

Subgroup analyses

Pre-specified subgroup analyses explored the response rate to TIER and survival times, according to prior treatment regimen. Thiotepa-naïve patients had a superior ORR of 10/16 (63%); 11 patients had previously been treated with thiotepa as part of the MATRix protocol, achieving an ORR of 4/11 (36%). Moreover, longer median OS was seen in thiotepa-naïve patients (5 months, 95% CI 2 to 14 months), compared with those previously treated with MATRix (3 months, 95% CI 2 to 9), although the number of patients in each sub-group is small.

We also analyzed whether the duration of treatment response prior to entering the study was associated with response and survival following TIER. The ORR to TIER for patients with >12 months from the start of their previous treatment to relapse was 10/15 (67%), compared with 4/12 (33%) for patients who were refractory or relapsed within 12 months of starting their prior therapy. Consistent with this observation, the median OS for these subgroups were 6 months (95% CI 4 to 14 months) and 3 months (95% CI 2 to 7 months) respectively. No formal tests of statistical significance were performed between subgroups due to small number of cases per group.

Discussion

Improved therapies are urgently required for rrPCNSL; dismal survival outcomes clearly highlight this group of patients with unmet clinical need. Conducting prospective clinical trials in this patient group is extremely challenging; there are currently no licensed therapies for rrPCNSL, and no accepted standard of care. Although thiotepa has been widely adopted for PCNSL therapy, TIER is the first thiotepa dose-finding study of its kind, and one of the few dose-finding trials of any agent in rrPCNSL.

TIER successfully met its primary endpoints for both phase I and phase II components. Thiotepa 50mg/m² was established as a safe RP2D to be incorporated into the R-IE regimen for the treatment of rrPCNSL. No DLTs were encountered during the phase I study, and TIER continued to be well-tolerated and deliverable throughout phase II. As expected, the most frequent toxicities were hematological, infectious and neurological, which also accounted for all 13 SAEs experienced by less
than one third of the patients. This represents a manageable safety profile in a group of patients whose age, neurocognitive impairment, performance status and treatment history place them at significant risk of treatment-related toxicity.

TIER also met the pre-specified threshold for clinical activity, achieving an ORR of 52% when thiotepa was given at the RP2D. This response rate was in the context of a patient group with a poor baseline performance status (47% with performance status ≥2), with adverse risk disease (72% intermediate or high risk), who had received intensive multi-drug prior treatment (including 31% exposed to MATRix). A previously published retrospective study of R-IE salvage for PCNSL, with a cohort that featured more favorable PS and disease risk profile, achieved an ORR of 41% (95% CI 41% to 61%).

However, despite the relatively high response rates to TIER, this activity did not translate into durable PFS or OS. The 2-year OS following TIER is similar to the 25% reported previously with R-IE, highlighting a very challenging group of patients for whom enrolment in clinical studies of new treatment approaches represents the most desirable therapeutic option.

Impairment of neurocognitive function is a common feature of PCNSL, in many cases limiting patients’ capacity to consent for treatment and inherently limiting such patients’ ability to participate in trials of new therapies. Importantly, 17% of patients enrolled in the TIER study lacked independent capacity to consent but were successfully enrolled in the study by virtue of Schedule 1 provisions of the UK Medicines for Human Use (Clinical Trials) Regulations 2004. With a clearly defined consent process within a legal framework, patients could be included in their best interest and according to their presumed will. This is an important outcome of our trial, demonstrating that disease-related and potentially reversible loss of capacity should not preclude access to clinical trials of novel treatment options. Moreover, inclusive enrolment into this PCNSL trial strengthens its generalizability to the real-world setting.

The first patients were recruited to the TIER trial when the standard first-line therapy for PCNSL was high-dose methotrexate plus cytarabine, which was demonstrably superior to methotrexate alone. During the course of the TIER trial, MATRix emerged as a superior first-line treatment option, and has been widely adopted in the UK, Europe and internationally. Consequently, 41% of patients recruited to the phase II component of the TIER trial were thiotepa-exposed. Exploratory analyses suggest greater benefit of TIER among the thiotepa-naive subgroup of patients. Moreover, the rate of ASCT among previously MATRix-treated patients was relatively low: only 1 of the 8 patients where the approach was intended completed this consolidation. This could be explained by a more biologically aggressive relapse after MATRix treatment, or by a lower efficacy of TIER in thiotepa-exposed patients. While the trial met its primary endpoint overall, there is likely to be a greater benefit in settings that do not include thiotepa as part of first-line PCNSL treatment. For those refractory to or relapsing after first-line MATRix, the benefit of TIER was less convincing; such patients are likely to require novel non-chemotherapy approaches.

The manageable toxicity profile allowed TIER to be delivered with few treatment delays or dose reductions, and most patients completing treatment retained their performance status. Despite the overall poor baseline characteristics and the use of an intensive multi-drug immunochemotherapy regimen, it is encouraging that stem cell mobilization was attempted in 11 patients, resulting in successful ASCT in 6 patients. The most common reason for not proceeding to stem cell mobilization was early disease relapse, emphasizing the high risk of this cohort. Nonetheless, the frequency of unsuccessful stem cell harvest was higher than expected and compared to previous studies. This may be a reflection of the higher intensity of first-line treatment in the TIER cohort. Two and 9 additional patients remained fit enough for WBRT and TIE consolidation, respectively. Where consolidation was not delivered, this was primarily due to a lack of sustained disease control. Those
patients who went on to receive ASCT consolidation benefited from prolonged survival, and most were alive at the end of 24 months follow-up. The durable OS in these patients reflects that seen previously in patients with rrPCNSL.\textsuperscript{9,10} TIER is therefore a valid immunochemotherapy option to re-induce remission in advance of consolidation ASCT. Where necessary, interim consolidation with TIE chemotherapy may provide a bridge to ASCT, although it is clear that quickly proceeding to ASCT is crucial for long-term survival.

PCNSL relapsing after first-line immunochemotherapy represents a substantial clinical challenge. For patients experiencing a ‘late’ relapse after first-line MATRix (with a PFS of at least 2 years), re-challenge with a high-dose methotrexate-based protocol should be considered.\textsuperscript{20} Alternative non-cross-resistant regimens could also be considered, for example platinum-containing regimens with efficacy in PCNSL\textsuperscript{23,24} and secondary CNS involvement of systemic lymphoma.\textsuperscript{25} The potential role for TIER in secondary CNS lymphoma would require a dedicated study. The overall performance of investigational agents in early phase trials for rrPCNSL has been disappointing, for both conventional cytotoxics and novel agents. Targeted or immunomodulatory agents have been widely investigated in rrPCNSL, including lenalidomide, ibrutinib, tirabrutinib and temsirolimus.\textsuperscript{17,26-29} Despite promising response rates, PFS duration in these studies was also short (2.1 months with temsirolimus, 2.9 months with tirabrutinib, 4.6 months with ibrutinib, to 7.8 months with rituximab plus lenalidomide), similar to that observed in our study. Further therapeutic progress for rrPCNSL is only likely to be achieved by rationally designed protocols focused on appropriate cohorts. The group of rrPCNSL patients with greatest unmet clinical need are those who experience refractory disease or early relapse following intensive first-line protocols; for such patients, clinical studies of novel agents informed by pathobiological data represent an attractive alternative. Nevertheless, there remains a role for conventional therapy including the judicious use of thiotepa-based ASCT in selected patients with rrPCNSL.

The low incidence of PCNSL, together with the significant neurocognitive morbidity and impaired performance status associated with relapsed or refractory disease, translate into challenges for clinical trial recruitment. An important feature of the TIER trial was the concurrent collection of biological samples and advanced imaging data for correlative science. Ongoing analyses of diagnostic tissues samples, sequential blood samples and advanced MRI images from the TIER cohort will allow the opportunity for new insights into PCNSL pathobiology.

The TIER regimen is a non-cross-resistant immunochemotherapy option for sufficiently fit patients whose PCNSL has relapsed after treatment with high-dose methotrexate. In meeting its prespecified endpoint, this trial demonstrates that thiotepa can be safely incorporated into a multidrug regimen, and produce a meaningful response rate worthy of further clinical development. For example, non-myelotoxic novel agents could be combined with a TIER backbone, with the aim of improving the rate and durability of response. However, in the TIER study, durable remissions were predominantly seen in those patients undergoing ASCT consolidation, and this remains the goal of therapy in fit and ASCT-naïve patients. For transplant-ineligible patients or those previously treated with combination immunochemotherapy, relapsed or refractory disease represents a substantial clinical challenge where novel approaches are urgently needed.
Acknowledgements

TIER trial was supported by the Blood Cancer UK (reference number 13069) and Cure Leukaemia Trials Acceleration Programme (TAP). Thiotepa was provided free of charge by Adienne.

The trial has been supported by the facilities funded through Birmingham Science City Translational Medicine Clinical Research Infrastructure and Trials Platform, an Advantage West Midlands (AWM) funded project which forms part of the Science City University of Warwick and University of Birmingham Research Alliance.

ST receives research funding from the Department of Health’s NIHR Biomedical Research Centre’s funding scheme to UCLH.

GPC acknowledges support from the NIHR Oxford Biomedical Research Centre and CRUK Experimental Cancer Medicines Centre

Authorship and COI declaration

All authors made substantial contributions to the trial design, data acquisition, or data interpretation of this study. All authors were involved in drafting and revising the manuscript, and all gave approval of the final version. All authors are accountable for the accuracy and integrity of the work.

CPF: Roche (remunerated consultant and research funding). Adienne (remunerated consultant and research funding).
JS: ABBviE and Janseen funding to attend EHA (2018) and ICML (2019)
GPC: Roche (remunerated consultant)
AJMF: speaker fee from Adienne; research grants from BMS, Beigene, Pharmacyclics, Hutchison Medipharma, Amgen, Genmab, ADC Therapeutics, Gilead, Novartis, and Pfizer; advisory boards from Gilead, Novartis, Juno, and PletixaPharm; inventor of patents on NGR-hTNF/RCHOP in relapsed or refractory PCNSL and SNGR-hTNF in brain tumours
KC: Roche (remunerated consultant and research funding). Adienne (remunerated consultant funding)

All remaining authors have no conflicts of interest.
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Table 1
Baseline patient characteristics of patients recruited to the TIER trial.

|                                | Overall | Thiotepa dose level |   |   |
|--------------------------------|---------|----------------------|---|---|
|                                |         | 30 mg/m² | 40 mg/m² | 50 mg/m² |
| Number of patients             | 36      | 5         | 4         | 27       |
| Age, median (range)            | 62 (31 to 76) | 48 (40 to 74) | 68 (61 to 74) | 62 (31 to 76) |
| Sex, female (%)                | 14 (39%) | 2 (20%)   | 2 (50%)   | 11 (41%) |
| IELSG risk group (%)           |         |           |           |           |
| 0-1, low                       | 10 (28%) | 2 (40%)   | 0         | 8 (30%)  |
| 2-3, intermediate              | 15 (42%) | 1 (20%)   | 2 (50%)   | 12 (44%) |
| 4-5, high                      | 11 (31%) | 2 (40%)   | 2 (50%)   | 7 (26%)  |
| Performance status (%)         |         |           |           |           |
| 0                              | 9 (25%)  | 1 (20%)   | 1 (25%)   | 7 (26%)  |
| 1                              | 10 (28%) | 0         | 2 (50%)   | 8 (30%)  |
| 2                              | 11 (31%) | 1 (20%)   | 1 (25%)   | 9 (33%)  |
| 3                              | 6 (17%)  | 3 (60%)   | 0         | 3 (11%)  |
| CSF involvement by morphology  |         |           |           |           |
| Yes                            | 1 (3%)   | 0         | 0         | 1 (4%)   |
| No                             | 18 (50%) | 3 (60%)   | 3 (75%)   | 12 (44%) |
| Not assessed                   | 17 (47%) | 2 (40%)   | 1 (25%)   | 14 (52%) |
| Vitreoretinal involvement      |         |           |           |           |
| Yes                            | 2 (6%)   | 1 (20%)   | 1 (25%)   | 0        |
| No                             | 34 (94%) | 4 (80%)   | 3 (75%)   | 27 (100%)|
| Number of prior lines (%)      |         |           |           |           |
| 1                              | 32 (89%) | 4 (80%)   | 4 (100%)  | 24 (89%) |
| 2                              | 4 (11%)  | 1 (20%)   | 0         | 3 (11%)  |
| Previous treatments (%)        |         |           |           |           |
| MATRix                         | 11 (31%) | 0         | 0         | 11 (41%) |
| Chemotherapy without thiotepa  | 25 (69%) | 5 (100%)  | 4 (100%)  | 16 (59%) |
| Consolidation                  |          |           |           |           |
| ASCT                           | 2 (6%)   | 0         | 0         | 2 (7%)   |
| WBRT                           | 11 (31%) | 2 (40%)   | 0         | 9 (33%)  |
| Time from start of previous    | 17 (2 to 35) | 25 (22 to 31) | 12 (3 to 36) | 12 (2 to 36) |
| treatment to relapse, median    |         |           |           |           |
| months (IQR)                   |         |           |           |           |

IELSG, International Extranodal Lymphoma Study Group; MATRix, methotrexate, cytarabine, thiotepa, rituximab; ASCT, autologous stem cell transplant; WBRT, whole brain radiotherapy.
### Table 2
Toxicity profile of TIER. All grade 3 and 4 adverse events are listed, CTCAE terms are arranged into clinically related groups. Total number of patients = 36.

| Adverse event                              | Events (Patients) | Grade 3 | Grade 4 |
|--------------------------------------------|-------------------|---------|---------|
| **Hematologic**                            |                   |         |         |
| Anemia                                     | 24 (10)           |         |         |
| White blood cell decreased                 | 28 (7)            | 17 (8)  |         |
| Neutrophil count decreased                 | 39 (14)           | 36 (16) |         |
| Lymphocyte count decreased                 | 29 (8)            | 11 (6)  |         |
| Platelet count decreased                   | 40 (12)           | 28 (11) |         |
| Febrile neutropenia                        | 5 (4)             |         |         |
| Investigations, other – other cytopenia    | 1 (1)             |         |         |
| **Neurologic / Ophthalmologic**            |                   |         |         |
| Seizure                                    | 2 (2)             | 1 (1)   |         |
| Confusion                                  | 2 (2)             |         |         |
| Dysphasia                                  | 1 (1)             |         |         |
| Agitation                                  | 1 (1)             |         |         |
| Psychosis                                  | 1 (1)             |         |         |
| Encephalopathy                             | 1 (1)             |         |         |
| Headache                                   | 2 (2)             |         |         |
| Somnolence                                 | 1 (1)             |         |         |
| Fatigue                                    | 1 (1)             |         |         |
| Depression                                 | 1 (1)             |         |         |
| Muscle weakness left-sided                 | 1 (1)             |         |         |
| Syncope                                    | 1 (1)             |         |         |
| Vasovagal reaction                         | 1 (1)             |         |         |
| Ataxia                                     | 1 (1)             |         |         |
| Nervous system disorders, other – drowsiness| 1 (1)             |         |         |
| Keratitis                                  | 1 (1)             |         |         |
| Eye disorders, other – right eye vision loss| 1 (1)             |         |         |
| **Metabolic**                              |                   |         |         |
| Hypophosphatemia                           | 4 (2)             | 2 (1)   |         |
| Hypokalemia                                | 4 (1)             |         |         |
| Hypomagnesemia                             | 3 (1)             |         |         |
| Hyponatremia                               | 1 (1)             |         |         |
| Hypoaalbuminemia                           | 2 (1)             |         |         |
| Hypoglycemia                               | 1 (1)             |         |         |
| **Infective**                              |                   |         |         |
| Bronchial infection                        | 1 (1)             |         |         |
| Infections and infestations, other – lower respiratory tract infection | 1 (1) |         |         |
| Upper respiratory infection                | 1 (1)             |         |         |
| General disorders and administration site conditions, other – influenza | 1 (1) |         |         |
| Urinary tract infection                    | 1 (1)             |         |         |
| Infections and infestations, other – neutropenic sepsis | 1 (1) |         |         |
| Infections and infestations, other – other infection | 1 (1) |         |         |
| **Gastro-intestinal**                      |                   |         |         |
| Dysphagia                                  | 2 (2)             |         |         |
| Diarrhea                                   | 1 (1)             |         |         |
| Mucositis oral                             | 1 (1)             |         |         |
| **Other**                                  |                   |         |         |
| Hypertension                               | 1 (1)             |         |         |
| Urinary incontinence                       | 1 (1)             |         |         |
| Lipase increased                           | 1 (1)             |         |         |
| Alanine aminotransferase increased         | 1 (1)             |         |         |
**Figure legends**

**Figure 1**
Patient flow diagram showing TIER treatment across both phases of the trial, consolidation, and inclusion in the final analyses.

**Figure 2**
Progression-free survival (top) and overall survival (bottom) of patients treated at the recommended phase II dose.

**Figure 3**
Diagram showing the post-TIER consolidation planned at baseline, and the treatment ultimately delivered.
Figure 1

Recruited to TIER, $N = 36$

Phase I dose-escalation, $N = 12$

- 30mg/m$^2$ thiotepa, $N = 5$
  - Completed 1 cycle, $N = 2$
  - Completed 2 cycles, $N = 3$

  $N = 3$ evaluable for DLT

No DLT

- 40mg/m$^2$ thiotepa, $N = 4$
  - Completed 2 cycles, $N = 4$

  $N = 3$ evaluable for DLT

No DLT

- 50mg/m$^2$ thiotepa, $N = 3$
  - Completed 1 cycle, $N = 1$
  - Completed 2 cycles, $N = 2$

  $N = 3$ evaluable for DLT

Phase II 50mg/m$^2$ thiotepa, recommended phase II dose, $N = 24$

  - Completed cycle 1 only, $N = 6$
  - Completed cycle 2, $N = 17$
  - No treatment delivered, $N = 1$

Post-TIER trial consolidation

- 30mg/m$^2$ thiotepa cohort, $N = 5$
  - ASCT, $N = 2$

Post-TIER trial consolidation

- 40mg/m$^2$ thiotepa cohort, $N = 4$
  - ASCT, $N = 2$
  - TIE, $N = 1$

Post-TIER trial consolidation

- 50mg/m$^2$ thiotepa cohort, $N = 27$
  - ASCT, $N = 2$
  - WBRT, $N = 2$
  - TIE, $N = 8$

Included in final analysis

- Phase I dose-finding, $N = 12$
- Phase II activity outcomes, $N = 27$
- Secondary consolidation outcomes, $N = 36$
- Safety analysis, $N = 36$

DLT, dose-limiting toxicity; ASCT, autologous stem cell transplantation; TIE, thiotepa, ifosfamide and etoposide; WBRT, whole brain radiotherapy.
Progression free survival of patients treated at the recommended phase II dose

Overall survival of patients treated at the recommended phase II dose

Number at risk

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Two Kaplan-Meier survival curves showing progression free survival and overall survival of patients treated at the recommended phase II dose.

**Progression free survival**
- Time (months from registration): 0, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36
- Number at risk: 27, 12, 8, 4, 3, 2, 2, 2, 2, 1, 1, 1, 1

**Overall survival**
- Time (months from registration): 0, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36
- Number at risk: 27, 17, 11, 8, 6, 4, 3, 2, 2, 1, 1, 1, 1
ASCT, autologous stem cell transplantations; WBRT, whole brain radiotherapy, TIE, thiotepa, ifosfamide and etoposide; PBSC, peripheral blood stem cell