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Original Research

# Impact of rituximab on treatment outcomes of patients with angioimmunoblastic T-cell lymphoma; a population-based analysis



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**KEYWORDS**

Angioimmunoblastic  
T-cell lymphoma;  
Treatment;  
Rituximab;  
Outcome;  
Peripheral T-cell  
lymphoma

**Abstract**

**Background:** Patients with angioimmunoblastic T-cell lymphoma (AITL) are treated with cyclophosphamide, doxorubicin, vincristine and prednisone with or without etoposide (CHO(E)P). In the majority of cases, Epstein–Barr virus (EBV)-positive B-cells are present in the tumour. There is paucity of research examining the effect of rituximab when added to CHO(E)P. In this nationwide, population-based study, we analysed the impact of rituximab on overall response rate (ORR), progression-free survival (PFS) and overall survival (OS) of patients with AITL.

**Methods:** Patients with AITL diagnosed between 2014 and 2020 treated with  $\geq$ one cycle of CHO(E)P with or without rituximab were identified in the Netherlands Cancer Registry. Survival follow-up was up to 1st February 2022. Baseline characteristics, best response during first-line treatment and survival were collected. PFS was defined as the time from diagnosis to relapse or to all-cause-death. OS was defined as the time from diagnosis to all-cause-death. Multivariable analysis for the risk of mortality was performed using Cox regression.

**Findings:** Out of 335 patients, 146 patients (44%) received R–CHO(E)P. Rituximab was more frequently used in patients with a B-cell infiltrate (71% versus 89%,  $p < 0.01$ ). The proportion of patients who received autologous stem cell transplantation (ASCT) was similar between CHO(E)P and R–CHO(E)P (27% versus 30%, respectively). The ORR and 2-year PFS for patients who received CHO(E)P and R–CHO(E)P were 71% and 78% ( $p = 0.01$ ), and 40% and 45% ( $p = 0.12$ ), respectively. The 5-year OS was 47% and 40% ( $p = 0.99$ ), respectively. In multivariable analysis, IPI-score 3–5, no B-cell infiltrate and no ASCT were independent prognostic factors for risk of mortality, whereas the use of rituximab was not.

**Interpretation:** Although the addition of rituximab to CHO(E)P improved ORR for patients with AITL, the PFS and OS did not improve.

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**1. Introduction**

Angioimmunoblastic T-cell lymphoma (AITL) is an aggressive, mature T-cell lymphoproliferative neoplasm that is classified as one of the peripheral T-cell lymphomas (PTCL) [1]. AITL is one of its most prevalent subtypes in Europe and North America, accounting for 13–36% of PTCL diagnoses [2–5].

AITL primarily presents itself as generalised nodal disease with also frequent involvement of the skin, spleen, liver and bone marrow. The disease is often accompanied by paraneoplastic phenomena due to immune dysregulation, including pruritic skin rash, pleural effusion, ascites and arthritis. Anti-smooth muscle antibodies, rheumatoid factor, circulating immune complexes and cold agglutinins with haemolytic anaemia can be observed [6–9].

AITL originates from T-follicular helper cells ( $T_{FH}$ ) [10,11].  $T_{FH}$  are a subset of  $CD4^+$  T-cells that are formed from naïve T-cells under the influence of antigen recognition. In healthy individuals,  $T_{FH}$  are involved in germinal centre formation and support B-cells in the development of high affinity antibodies [10,12–14]. In the majority of patients (66–91%), Epstein–Barr virus (EBV)-positive, CD20-positive B-cells are present in the tumour infiltrate while the neoplastic T-cells are EBV negative [5,8,9,15–19]. The exact role that EBV plays in the course of AITL is still unknown. The EBV-positive CD20-positive B-cell infiltrate is likely to be a manifestation of the immunocompromised state of the patient

rather than being a dominant driver of lymphomagenesis of AITL [12]. Clonal B-cell expansion can result in B-cell lymphomas [1].

Patients are treated with either cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or with the same regimen with additional etoposide (CHOEP). CHOEP is favoured in some countries for the treatment of PTCL, but the evidence supporting this treatment strategy in AITL is controversial [2,20,21]. Recently, in a large population-based analysis, there was no effect of etoposide on the outcome in patients with AITL below 65-years of age [22]. Complete remission (CR) is achieved in 70% of patients, however, relapses frequently occur [23]. The prognosis of patients with AITL is poor, with a median 5-year overall survival (OS) of 32–36% [2–4,23]. Patients who progress or relapse have a dismal outcome with a 3-year OS of less than 10% [24]. In younger patients, consolidation with high-dose chemotherapy and autologous stem cell transplantation (ASCT) is often performed in chemo-sensitive disease. However, the impact of ASCT remains a matter of debate [20,25].

It has been postulated that targeting CD20-positive B-cell infiltrates in AITL with the anti-CD20 monoclonal antibody rituximab (R) might improve outcome. However, this hypothesis has only been studied in non-randomised, small series—the largest study containing 25 patients [13,26,27]. While these studies do not show a clear clinical advantage, rituximab is regularly used in daily practice given its biological rationale.

### 1.1. Objective

This nationwide, population-based study analysed the impact of rituximab on best response, progression-free survival (PFS) and OS of patients with AITL treated with CHO(E)P.

## 2. Material and methods

### 2.1. Registry and study population

The nationwide population-based Netherlands Cancer Registry (NCR) is maintained and hosted by the Netherlands Comprehensive Cancer Organisation (IKNL) and has nationwide coverage of at least 95% of all malignancies since 1989. The NCR relies on comprehensive case notification through the Nationwide Histopathology and Cytopathology Data Network and the Nationwide Registry of Hospital Discharges (i.e. inpatient and outpatient discharges). Information on dates of birth and diagnosis, sex, topography and morphology, hospital type of diagnosis and first-line therapy is routinely recorded by trained registrars of the NCR through retrospective medical records review. Information on the last known vital status for all patients (i.e. alive, dead or emigration) is obtained through annual linkage with the Nationwide Population Registries Network that holds vital statistics on all residents of the Netherlands. Since 1st January 2014, detailed information on diagnostic and treatment characteristics for all haematological malignancies diagnosed in the Netherlands is recorded in the NCR.

Patients with AITL were identified from the NCR, using the International Coding system of Disease–Oncology (ICD-O) of the World Health Organization (WHO) morphology code 9705/3. The status of EBV+ B-cell infiltrates was retrieved by NCR clerks based on the information in the pathology reports. All patients diagnosed with AITL between 2014 and 2020 who received at least one cycle of CHO(E)P either with or without rituximab were included. Patients who were treated differently, not treated at all or patients who were diagnosed through autopsy were excluded from all analyses. The registry clerks went through the digital pathology reports of the included patients, thereby depending on key words or terms regarding (EBV+) B-cell infiltrate, used by the pathologists. Terms like ‘B-cell infiltrates and/or EBV present/observed/positive/+’ were registered as ‘positive’ in the NCR, whereas terms like ‘B-cell infiltrates and/or EBV absent/negative/-’ were registered as ‘negative’. If no information on B-cell infiltrate or EBV could be retrieved, registry clerks registered ‘unknown’. Registry clerks were blinded for treatment regimen as well as for outcome. Survival follow-up was available through 1st February 2022.

According to the Central Committee on Research involving Human Subjects (CCMO), this type of

observational study does not require approval from an ethics committee in the Netherlands. The Privacy Review Board of the NCR approved the use of anonymous data for this study.

### 2.2. End-points

The primary end-point was OS, which was defined as the time between AITL-diagnosis and all-cause-death. Patients alive were censored on February 1st, 2022. The secondary end-points were PFS and best response, i.e. CR, partial response (PR) or stable/progressive disease (SD/PD), to first-line treatment, as such routinely collected by trained registrars of the NCR through retrospective medical record review. Best response was determined by physician assessment, using the Lugano classification as of 2014 onward. PFS was defined as the time between AITL-diagnosis and tumour progression or all-cause-death, whichever occurred first.

### 2.3. Statistical analyses

Descriptive statistics were used to present patient and treatment characteristics between patients who received R–CHO(E)P and patients who received CHO(E)P. The Pearson chi-square test was used to compare categorical covariables, and the Kruskal–Wallis test was used to compare non-normally distributed continuous covariables between the two treatment groups. A *p*-value below 0.05 was considered statistically significant.

The Kaplan–Meier method served to estimate OS, and the log-rank test to examine differences in survival distributions. OS was calculated for the two treatment groups. Then, the impact of age, sex, Ann Arbor stage, LDH, extranodal localisation, WHO Performance score, IPI-score, EBV status, type of chemotherapy and ASCT as a time-varying covariate on risk of mortality was evaluated using univariable and multivariable Cox proportional hazard regression analysis.

The results from the Cox regression analyses produce hazard ratios (HRs) with associated 95% confidence intervals (CIs). The proportional hazard assumption was tested based on the Schoenfeld residuals. All covariables, presented as patient and clinicopathological factors in [Table 1](#), were introduced in the multivariable regression model simultaneously, thereby using a backward selection method to exclude covariables with a *p*-value below 0.05. All analyses were performed using STATA/SE 17.1 (StataCorp LP, College Station, Texas, USA).

## 3. Results

### 3.1. Patient characteristics

Between 2014 and 2020, 462 patients were newly diagnosed with AITL in the Netherlands; 87 (19%) patients did not receive first-line therapy, whereas 375 (81%)

Table 1  
Characteristics of patients treated with R-CHO(E)P vs. CHO(E)P.

	R-CHO(E)P		CHO(E)P		p-value
	No.	%	No.	%	
<b>Number of patients (% row)</b>	146	44	189	56	
<b>Female sex</b>	52	36	79	42	0.25
<b>Age at diagnosis</b>					
Median age at diagnosis (years, range)	69 (27–85)		67 (28–88)		0.57
18-60	42	29	62	33	0.43
>60	104	71	127	67	
<b>Clinicopathological factors</b>					
<b>Ann Arbor stage</b>					0.33
1-2	7	5	13	7	
3-4	136	93	175	93	
Unknown	3	2	1	0	
<b>Elevated LDH</b>	88	60	104	55	0.56
<b>WHO Performance score</b>					0.87
0-1	62	42	76	40	
2-4	18	12	22	12	
Unknown	66	45	91	48	
<b>&gt; 1 Extranodal localisation (yes)</b>	20	14	28	15	0.32
<b>IPI-score</b>					0.61
0-2	67	46	92	49	
3-5	79	54	97	51	
<b>EBV status</b>					<0.01
B-cell infiltrate+, EBV+	110	75	99	52	
B-cell infiltrate+, EBV-	21	14	44	19	
No B-cell infiltrate	14	10	38	20	
Unknown	1	1	8	4	
<b>First-line treatment</b>					
<b>Type of chemotherapy</b>					0.95
CHOP	94	64	121	64	
CHOEP	52	36	68	36	
<b>Number of CHO(E)P cycles</b>					0.36
<6	35	24	58	31	
≥6	110	75	129	68	
Unknown	1	1	2	1	
<b>Stem cell transplantation</b>					0.36
No	102	70	137	72	
Autologous	44	30	50	27	
Allogenic	0	0	2	1	

patients did. The group that received first-line treatment (n = 375) was treated with CHO(E)P (n = 189, 50%) or R-CHO(E)P (n = 146, 39%); 40 (11%) were treated with other types of chemotherapy. For the current study, 335

patients treated with CHO(E)P with (n = 146, 44%) or without (n = 189, 56%) rituximab were included for analyses and their clinical factors are presented in Table 1. In the CHO(E)P group, B-cell infiltrates were less frequently

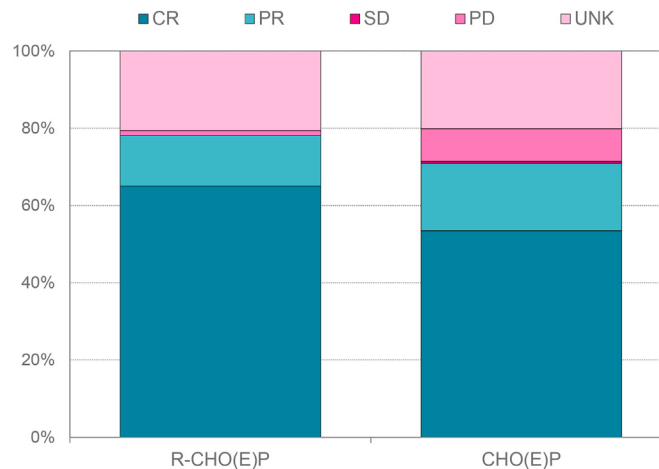


Fig. 1. Response to treatment according to regimen; R-CHO(E)P versus CHO(E)P.

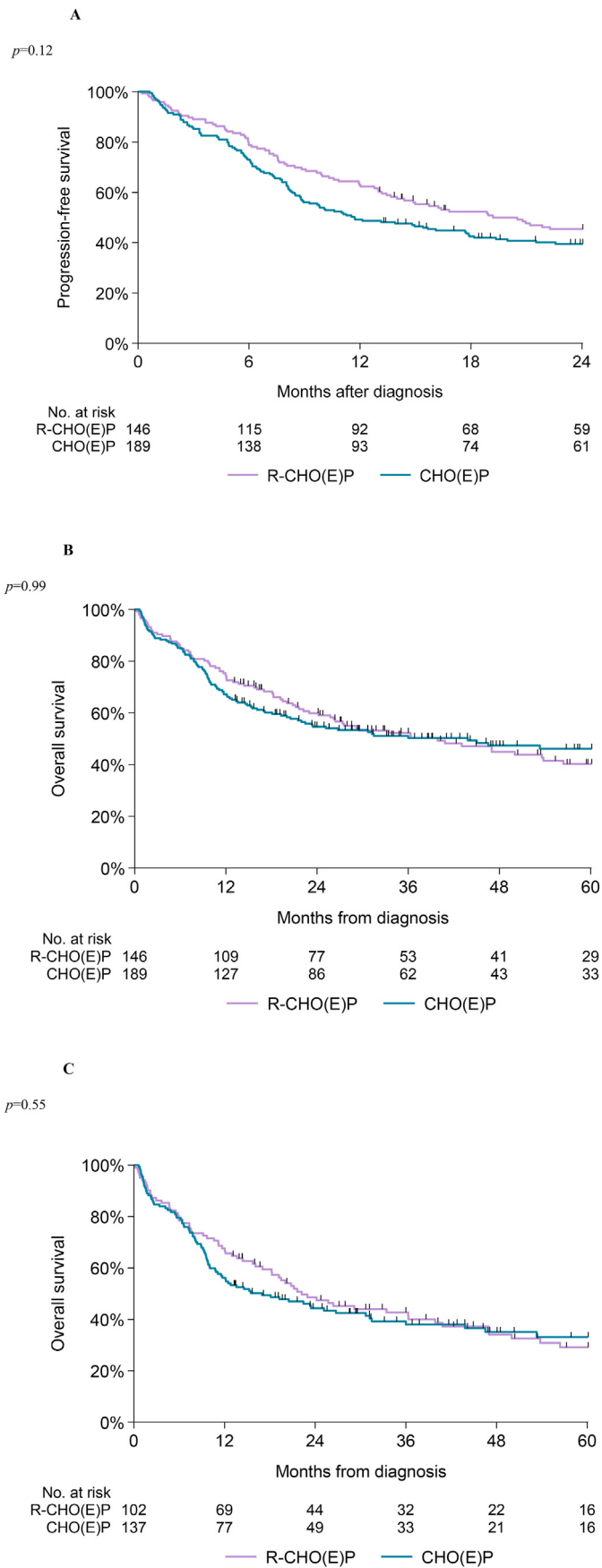


Fig. 2. A. Progression-free survival for patients treated with R-CHO(E)P versus CHO(E)P B. Overall survival for patients treated with R-CHO(E)P versus CHO(E)P. C. Overall survival for patients not proceeding to ASCT, according to R-CHO(E)P and CHO(E)P.

observed than in the R-CHO(E)P group (71% and 89%, respectively;  $p < 0.01$ ). In 69% and 84%, respectively, the B-cell infiltrates were EBV+. There were no significant differences in the remaining patient factors such as age and sex or clinical factors related to Ann Arbor stage and IPI-score (Table 1).

### 3.2. First-line therapy

Rituximab was given in 44% ( $n = 146$ ) of patients treated with CHO(E)P (Table 1). Between 2014 and 2020, the addition of rituximab to CHO(E)P increased from 36% in 2014 to 53% in 2016, thereafter decreased to 47% in 2020 (Supplementary Fig. 1). CHOP was preferred over CHOEP in both treatment groups (64% in both) (Table 1).

### 3.3. Outcome

The best overall response rates (ORR; CR + PR) for patients who received CHO(E)P and R-CHO(E)P were 71% and 78%, respectively ( $p = 0.01$ ) (Fig. 1). CR was more frequently observed in patients treated with R-CHO(E)P (65% versus 53%, respectively,  $p = 0.02$ ). There was no significant difference in patients proceeding to ASCT between patients receiving CHO(E)P and R-CHO(E)P (27% versus 30%,  $p = 0.36$ ). The 2-year PFS for all patients was 42% and was not statistically different between patients treated with CHO(E)P and R-CHO(E)P (40% and 45%,  $p = 0.12$ ; Fig. 2A). The 5-year OS for the entire cohort was 43% and was not statistically different between patients treated with CHO(E)P and R-CHO(E)P (46% and 40%,  $p = 0.99$ ;

Fig. 2B). For patients not proceeding to ASCT, we observed no significant difference in outcome between patients treated either with or without rituximab (5-year OS 29% and 33%,  $p = 0.55$ ) (Fig. 2C). HRs and corresponding 95% CIs of univariable and multivariable analyses for OS is presented in Fig. 3. The risk of mortality was similar for patients treated with CHO(E)P and R-CHO(E)P (HR, 1.04; 95%CI, 0.77–1.39;  $p = 0.81$ ). In multivariable analysis, IPI-score 3–5 (HR 1.59,  $p < 0.01$ ), the absence of a B-cell infiltrate (HR 2.32,  $p < 0.01$ ) and no ASCT (HR 3.00,  $p < 0.01$ ) were independent prognostic factors for the risk of mortality, whereas rituximab treatment was not (Fig. 3). HRs and corresponding 95% CIs for the risk of relapse are presented in Supplementary Fig. 2.

## 4. Discussion

The hypothesis that targeting CD20-positive B-cell infiltrates in AITL with rituximab might improve outcome has been studied only in small non-randomised studies. While these studies showed no clear advantage, rituximab has been widely used in the Netherlands in the first-line treatment of AITL between 2014 and 2020. Rituximab was even used in patients without clear evidence of an (EBV+) B-cell infiltrate (10%). This finding in itself is remarkable. This might have occurred due to rare occurrence and lack of clinical trials in PTCL. For clinicians, conjecture may play a role in the treatment choice—since outcomes are poor—even more so because rituximab is generally well tolerated.

In this largest population-based cohort study to date assessing the impact of rituximab on the treatment of

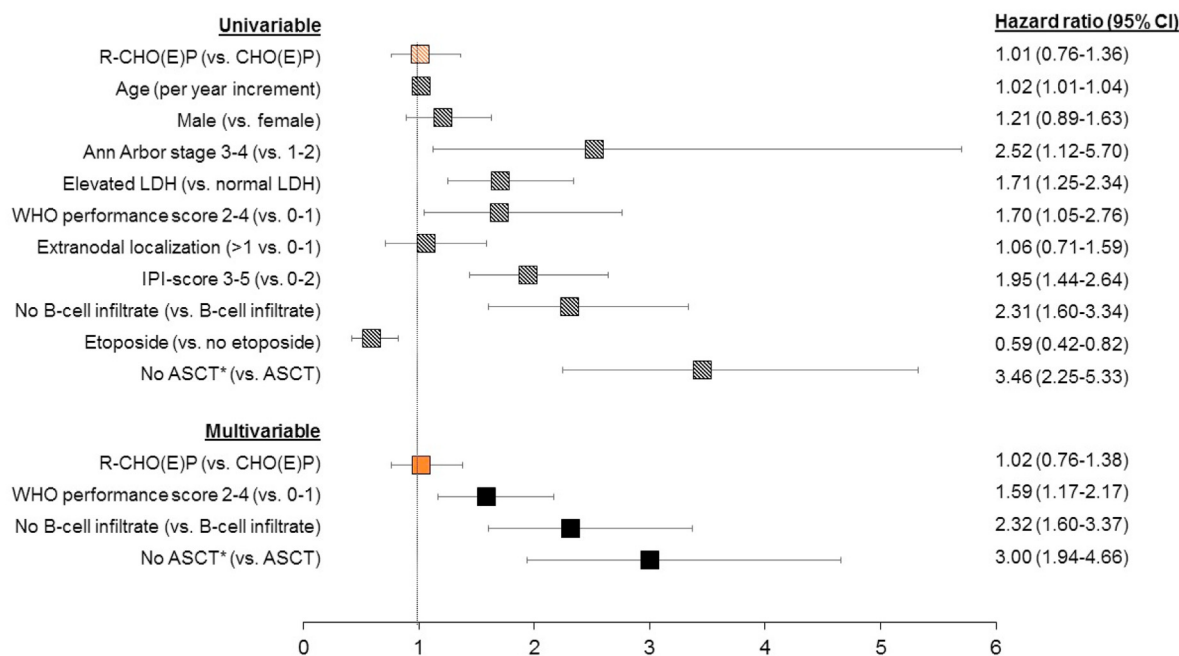


Fig. 3. Forest plot of univariable and multivariable analysis for the risk of mortality.

Table 2  
Agents of interest in future research in AITL.

Regimen	Study population	Design	Outcome	Future plans
Brentuximab-CHP [31]	PTCL (n = 452) AITL n = 54	Randomised phase III study of the CD30 monoclonal antibody brentuximab + CHP (A-CHP) versus CHOP in first-line patients	A-CHP: ORR 83% (PTCL) CHOP: ORR 72% (PTCL) HR 0.87 for OS (CI 0.29–2.58) favouring A + CHP in AITL	
Nivolumab [32]	PTCL (n = 12) AITL n = 6	Phase II study of the PD-1 inhibitor nivolumab in relapsed/refractory patients	Halted due to hyperprogression in 4 patients	A randomised study of gemcitabine, oxaliplatin versus nivolumab, gemcitabine, oxaliplatin (the NIVEAU study for patients with relapsed/refractory aggressive lymphoma, not eligible for high-dose chemotherapy ( <a href="https://clinicaltrials.gov/ct2/show/study/NCT03366272">ClinicalTrials.gov Identifier:NCT03366272</a> )).
Romidepsin + CHOP [33]	PTCL (n = 421) AITL n = 195	Randomised phase III study of the HDAC inhibitor romidepsin + CHOP (Ro-CHOP) versus CHOP in first-line patients	Ro-CHOP: ORR 83% (PTCL) CHOP: ORR 72% (PTCL) Ro-CHOP: OS 51,8 months (PTCL) CHOP: OS 42,9 months (PTCL) ( $P = 0.477$ ) HR 0.69 (0.48–1.00)AITL: PFS 19,5 months (Ro-CHOP) versus 10.6 months (CHOP); HR 0.69 (CI 0.48–1.00); $P = 0.046$	
Azacitidine [34]	PTCL (n = 21) PTCL-TFH n = 17; AITL n = 16	Phase II study of CHOP + hypomethylating agent azacitidine in first-line patients	ORR 76,5%; CR 76,5% Estimated 1-yr OS for all patients was 74.4% (95%CI of 48.8%–100.0%), with 1-yr OS for PTCL-TFH at 88.9% (95%CI of 68.4%–100.0%)	A randomised phase II study comparing CHO(E)P with CHO(E)P + oral azacitidine and CHO(E)P + duvelisib is for CD30 negative PTCL (including AITL) is being performed at the moment ( <a href="https://clinicaltrials.gov/ct2/show/study/NCT04803201">ClinicalTrials.gov Identifier: NCT04803201</a> ).
Duvelisib [35]	PTCL (n = 16) AITL n = 3	Phase I study of the PI3K inhibitor duvelisib in relapsed/refractory patients	AITL: one CR, one PR and one response rate n/a	A randomised phase II study comparing CHO(E)P with CHO(E)P + oral azacitidine and CHO(E)P + duvelisib is for CD30 negative PTCL (including AITL) is being performed at the moment ( <a href="https://clinicaltrials.gov/ct2/show/study/NCT04803201">ClinicalTrials.gov Identifier: NCT04803201</a> ).
Enasidenib	PTCL n = 21	A phase 1/2, dose-escalation study of the IDH-2 inhibitor enasidenib in relapsed/refractory patients	n/a	( <a href="https://clinicaltrials.gov/ct2/show/study/NCT02273739">ClinicalTrials.gov Identifier: NCT02273739</a> ).
Ruxolitinib [34]	PTCL (n = 45) AITL (n = 9)	A phase 2 study of the JAK1/2 inhibitor ruxolitinib in relapsed/refractory patients	ORR 33%	
Cerdulatinib [39]	PTCL (n = 60) and CTCL AITL n = 22	A phase 2 study of the dual SYK/JAK inhibitor cerdulatinib in relapsed/refractory patients	PTCL: ORR 35% AITL: ORR 55% (41% CR)	
Cyclosporine [40]	AITL (n = 26)	Literature review of case series and case reports of the calcineurin inhibitor cyclosporine in relapsed/refractory patients	ORR 86%	A phase II trial studying cyclosporine in relapsed/refractory AITL has been terminated due to slow accrual ( <a href="https://clinicaltrials.gov/ct2/show/study/NCT00070291">ClinicalTrials.gov Identifier: NCT00070291</a> )

**Abbreviations:** CI: confidence interval; CR: complete response; HR: hazard ratio; ORR: overall response rate; OS: overall survival; PFS: progression-free survival.



AITL, the CR rates were higher in the rituximab group. However, this neither translated into an increased percentage of patients going into ASCT consolidation nor did it translate into a statistically significant difference in 2-year PFS or 5-year OS. Therefore, if rituximab would be of added value in the treatment of AITL, its effect is only short-lived. While rituximab is generally considered to have a tolerable safety profile, there is an increased risk of contracting infections. Especially during the COVID pandemic, a lack of response to SARS-CoV-2 RNA vaccines has been observed in patients receiving rituximab [28].

Although not available for every case, the absence of a B-cell infiltrate was associated with an inferior outcome, whereas hitherto the presence or absence of an EBV + B-cell infiltrate in the tumour was not associated with survival outcomes in all, but one study. This effect might have been revealed due to our larger sample size [9,13,18,29]. In patients with AITL, a high EBV viral load in plasma or serum may be found. Patients with a detectable EBV viral load in peripheral blood seem to have an inferior prognosis [13,30]. Although it seems plausible to administer rituximab in patients with elevated EBV plasma loads, there is no evidence to support this practice in AITL.

The 5-year OS in the current study is significantly higher than other past cohorts of patients with AITL [2–4,23]. This is likely due to the fact that patients in the current study received at least one cycle of CHO(E)P. Patients that were treated otherwise or were not treated at all were excluded. The prognosis of AITL remains poor. In our cohort, 57% of patients did not manage to finish their treatment with six cycles of (immuno-) chemotherapy (data not shown), likely due to lack of response, toxicity, infections or poor performance status. Therefore, more effective first-line treatments for AITL are urgently needed.

There are several agents that offer perspective for further research. For an overview, see Table 2. Despite 63–75% of AITL cases express CD30 at the cell surface, patients with AITL do not seem to benefit from the anti-CD30 antibody drug conjugate brentuximab vedotin combined with CHP [31]. While PD1 is expressed on the majority of neoplastic T<sub>FH</sub> in AITL, a phase II clinical trial with nivolumab was terminated prematurely due to several patients showing hyper-progressive disease [32]. Epigenetic regulators such as *TET2*, *DNMT3A* and *IDH2* are frequently mutated in AITL. Targeting these epigenetic regulators could bear potential. In a subgroup analysis of a phase III trial, romidepsin had a marginal benefit when added to CHOP in AITL patients [33]. Azacitidine showed promising results when added to CHOP [34]. Several targeted strategies have been studied in relapsed PTCL. Inhibition of phosphatidylinositol 3-kinase (PI3K) can lead to antitumour effects in lymphoma by blocking mitogenic and survival signalling

within the tumour, its microenvironment and to activate immune responses [19,35,36]. Duvelisib showed promising results in a phase I trial in patients with relapsed/refractory PTCL [35]. The JAK/STAT pathway is known to be activated in PTCL [36]. However, few patients with AITL seem to have a JAK2 or STAT3 mutation so it is unclear how relevant these findings are for patients with AITL [37,38]. Cerdulatinib is an oral dual SYK/JAK inhibitor that has demonstrated responses in relapsed/refractory PTCL, especially AITL with an ORR of 55% of which 41% achieved CR [39]. Cyclosporine has been used in relapsed/refractory AITL in order to suppress the hyperactive state of the immune system. In a literature review, an excellent ORR of 86% has been found. However, no data on its use in first-line treatment are available and its report is prone to publication bias [40].

Our study has several limitations. The pathological diagnosis of AITL (and PTCL in general) is difficult [3]. Due to the design of our study, a central pathology review has not been possible so there is potential misclassification. However, an underestimation of AITL cases is most likely and therefore has limited impact on the primary outcome measure. Moreover, there are no guidelines on when the pathologist should regard a specimen as having an (EBV+) B-cell infiltrate. Furthermore, the reasoning of the treating physician why rituximab was either added to or withheld from the treatment regimen is unknown. Finally, the number of patients analysed in our study is not sufficiently powered to fully exclude small differences (HR 0.74). Despite these limitations, cancer registries remain the standard for population-based analysis of treatment outcomes in real world populations.

## 5. Conclusion

In this large group of patients with AITL, the addition of rituximab to CHO(E)P did not improve ORR, PFS or OS. To our knowledge, this study reports the largest nationwide and population-based cohort published on this subject thus far. Although widely used, our data do not support the routine use of rituximab in the first-line treatment of AITL.

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## Authorship

MN and MB designed the study. MB collected the data. MB, MN and FM analysed the data. FM, MB and MN wrote the paper. All authors revised the manuscript and accepted its final version.

## Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2022.09.008>.

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