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ACT-2 Study Investigators; Wulf, Gerald G.; Altmann, Bettina; Ziepert, Marita; D'Amore, Francesco; Held, Gerhard; Greil, Richard; Tournilhac, Olivier; Relander, Thomas; Viardot, Andreas

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ARTICLE

Lymphoma

Alemtuzumab plus CHOP versus CHOP in elderly patients with peripheral T-cell lymphoma: the DSHNHL2006-1B/ACT-2 trial

Gerald G. Wulf[1] · Bettina Altmann[2] · Marita Ziepert[2] · Francesco D'Amore[3] · Gerhard Held[4] · Richard Greil[5,6] · Olivier Tournilhac[7] · Thomas Relander[8] · Andreas Viardot[9] · Martin Wilhelm[10] · Christian Wilhelm[11] · Antonio Pezzutto[12] · Josee M. Zijlstra[13] · Eric Van Den Neste[14] · Pieternella J. Lugtenburg[15] · Jeanette K. Doorduijn[15] · Michel van Gelder[16] · Gustaaf W. van Imhoff[17] · Florian Zettl[18] · Friederike Braulke[1] · Maike Nickelsen[19] · Bertram Glass[20] · Andreas Rosenwald[21] · Philippe Gaulard[22] · Markus Loeffler[2] · Michael Pfreundschuh[23] · Norbert Schmitz[24] · Lorenz Trümper[1] · for the ACT-2 study investigators

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Abstract

PTCL patients exhibit poor survival with existing treatments. We investigated the efficacy of CHOP combined with alemtuzumab in 116 PTCL patients age 61–80 in an open-label, randomized phase 3 trial. Alemtuzumab was given on day 1, to a total of 360 mg in 21 patients, or 120 mg in 37. Hematotoxicity was increased with A-CHOP resulting in more grade ≥3 infections (40% versus 21%) and 4 versus 1 death due to infections, respectively. CR/CRu rate was 60% for A-CHOP and 43% for CHOP, and OR rate was 72% and 66%, respectively. Three-year-EFS, PFS and OS were 27% [15%–39%], 28% [15%–40%], and 37% ([23%–50%] for A-CHOP, and 24% [12%–35%], 29% [17%–41%], and 56% [44%–69%] for CHOP, respectively, showing no significant differences. Multivariate analyses, adjusted for strata and sex confirmed these results (hazard ratio HR_{EFS}: 0.7 ([95% CI: 0.5–1.1]; $p = 0.094$), HR_{PFS}: 0.8 ([95% CI: 0.5–1.2]; $p = 0.271$), HR_{OS}: 1.4 ([95% CI: 0.9–2.4]; $p = 0.154$). The IPI score was validated, and male sex (HR_{EFS} 2.5) and bulky disease (HR_{EFS} 2.2) were significant risk factors for EFS, PFS, and OS. Alemtuzumab added to CHOP increased response rates, but did not improve survival due to treatment-related toxicity.

These authors contributed equally: Gerald G. Wulf, Bettina Altmann

Deceased: Michael Pfreundschuh

This study was presented by L. Trümper et al. J Clin Oncol 34, 2016 (suppl; abstr 7500) Alemtuzumab added to CHOP for treatment of peripheral T-cell lymphoma (pTNHL) of the elderly: Final results of 116 patients treated in the international ACT-2 phase III trial. Altmann B, Wulf G, Truemper L, et al., Blood 132, 2018 (abstract, 1622-1622) Alemtuzumab Added to CHOP for Treatment of Peripheral T-Cell Lymphoma (PTCL) in Previously Untreated Young and Elderly Patients: Pooled Analysis of the International ACT-1/2 Phase III Trials.

Members of the ACT-2 study investigators are listed in Supplementary information.

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✉ Gerald G. Wulf
gerald.wulf@med.uni-goettingen.de

Extended author information available on the last page of the article

Introduction

Peripheral T-cell lymphoma (PTCL) is a rare and heterogeneous group of lymphomas comprising 29 distinct histological entities according to the revised 2016 World Health Organization classification [1, 2]. Anthracycline-based chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOEP (CHOP plus etoposide) remain first-line therapy in the most frequent entities PTCL-NOS, AITL, and ALK-negative anaplastic large cell lymphomas (ALCL), inducing cure in no more than 20–50% of patients [3–5]. Therefore, the search for better treatment options continues to represent an urgent medical need. Alternative chemotherapy [6, 7], high-dose chemotherapy [8–11], or approaches adding novel agents such as the antimetabolite pralatrexate, the histone deacetylases (HDAC) inhibitors romidepsin or belinostat [12, 13], or combinations thereof [14] have all been met with limited success. Humoral immunotherapy is another attractive option as antibodies

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represent targeted drugs with mostly non-overlapping toxicity to chemotherapy. Most prominent, anti-B-cell directed therapy with the anti-CD20 antibody rituximab has led to major improvements in survival for patients with B-cell lymphomas [15]. The CD52 antigen is a glycosylphosphatidylinositol-linked protein expressed at high density on the cell surface of normal and malignant lymphocytes, including most T-cell lymphoma subtypes except ALCL [9, 16–19]. Alemtuzumab (CAMPATH-1H) was obtained by inserting the hypervariable regions of the parental rat IgM anti-CD52 monoclonal antibody into the human IgG1 immunoglobulin (*IgG1*) gene sequence [20–22]. Alemtuzumab has been used extensively to ameliorate graft-versus-host disease after allogeneic stem cell transplantation [23], but it has also been licensed for the treatment of advanced stage chronic lymphocytic leukemia [24], and showed significant efficacy against T-PLL [25] and other T-cell lymphomas [26]. Consequently, alemtuzumab combined with CHOP (A-CHOP) was investigated in three non-randomized phase 2 trials, documenting feasibility of this approach and suggesting clinical benefit [27–29]. The German High-Grade Lymphoma Study Group (DSHNHL), now part of the German Lymphoma Alliance (GLA) embarked on a prospective, randomized phase 3 study (DSHNHL2006-1B/ACT2) comparing A-CHOP to CHOP alone in patients with newly diagnosed PTCL. The ACT-2 trial enrolled patients between 61 and 80 years of age, while the simultaneously active ACT-1 trial [30] and the AATT trial [31] incorporating autologous and allogeneic transplantation in first-line treatment of T-cell lymphoma accrued younger patients with PTCL.

Patients and methods

Study design and primary endpoint

This prospective, randomized, two-arm, open-label, phase 3 trial was a European collaboration by the Austrian Group of Medical Tumor Therapy, DSHNHL/GLA, LYSA (Lymphoma Study Association), HOVON (Haemato Oncology Foundation for Adults in the Netherlands), and Nordic Lymphoma Group study groups, enrolling patients from 52 study sites in Austria, Belgium, Denmark, France, Germany, Sweden, and The Netherlands [details on study investigators, and sites are included in the Appendix]. The protocol was approved by institutional review boards and/or ethics committees at all sites, and the study was conducted in compliance with all applicable regulatory requirements including International Conference on Harmonization Guidelines for Good Clinical Practice and in accordance with the Declaration of Helsinki. All patients gave written informed consent.

The study was designed to determine whether alemtuzumab given in addition to CHOP improved the event-free survival (EFS) of patients aged 61–80 years with newly diagnosed PTCL when compared with CHOP chemotherapy alone.

The protocol was amended twice. The first amendment dated 26 January 2009 introduced mandatory EBV monitoring, at a time when an increased risk for EBV reactivation had been observed in the HOVON-60 trial [28]. After the data safety monitoring committee (DSMC) had reviewed the clinical course of the first 30 patients, the protocol steering committee and the DSMC agreed to reduce the cumulative alemtuzumab dose from 360 mg (60 mg given with each chemotherapy course) to 120 mg (30 mg with the first four cycles only), implemented by the second amendment effective 02 June 2010. At the same time, with data accumulating that ALCL lacked CD52 expression [9, 16–19], ALCL, ALK-negative patients became no longer eligible, and the recruitment period was extended from 4 to 6 years. Recruitment and outcomes were discussed by the steering committee and the DSMC at the planned interim analysis on 13 June 2013. The DSMC recommended enrollment through the full accrual period planned, permitting an exploratory meta-analysis together with the ACT-1 trial testing the adjunct of alemtuzumab to CHOP in PTCL younger patients [30, 32]. Through the full recruitment period 116 patients were included, representing 42% of the 274 patients of the originally planned sample size. Based on a sample size of 116 patients the power for detecting the planned EFS difference of 15% was 48%. The data cut-off for the final analysis presented here was 31 March 2016 (end of study).

Patients

Eligible patients were 61–80 years of age, had PTCL, including PTCL-NOS, angioimmunoblastic lymphoma of T-cell type (AILT), follicular, or perifollicular variant of T-cell lymphoma, intestinal T/NK-cell lymphoma (±enteropathy), ALCL, ALK-negative before amendment 2, or extranodal natural killer [NK]/T-cell lymphoma nasal type) without prior systemic therapy. For patients with ENKT lymphoma-specific protocol recommendations for the planning of radiotherapy were provided. Patients at all stages of disease qualified for inclusion, except patients with disease stage I N, IPI 0 (except age >60) and without bulk.

Randomization and treatment

In this prospective, open-label, centrally randomized (1:1) trial patient enrollment was stratified by center, IPI factors, bulky disease (≥7.5 cm), histology (extranodal natural killer

[NK]/T-cell lymphoma nasal type yes/no) and age ≤70 versus >70 years. Prephase treatment with 1.4 mg/m² (maximum: 2 mg) vincristine at day 1, and 100 mg prednisolone days 1–5 was mandatory. In arm A, patients were to receive six courses of CHOP-14 (750 mg/m² cyclophosphamide, 50 mg/m² doxorubicin, 1.4 mg/m² (maximum: 2 mg) vincristine at day 1, and 100 mg prednisolone days 1–5 at 14 day intervals with G-CSF support). Patients in arm B were to receive CHOP-14 with the addition of 60 mg alemtuzumab SC given at day 1 of each chemotherapy cycle, totaling 360 mg. As of 02 June 2010, the alemtuzumab dose was reduced to 30 mg in cycles 1–4 of the chemotherapy, totalling 120 mg. Mandatory antiinfective measures comprised prophylactic aciclovir or valganciclovir through month 3 after completion of chemotherapy, cotrimoxazole through month 2 after completion of chemotherapy, and ciprofloxacin each time leukocytes dropped below 1000/µl. CMV monitoring by PCR or pp65 by PCR was recommended as well as EBV monitoring by PCR at intervals according to local standards following amendment 1. For cases of CMV reactivation recommendations for ganciclovir treatment and pausing alemtuzumab were provided.

Assessments

Reference pathology was required, following predefined algorithms of expert review in the respective study groups. The extent of disease was evaluated according to International Working Group criteria. Response to therapy was assessed at week three to six after day 1 of the last treatment course, using computer tomography (CT) scans. Partial response by imaging studies initiating salvage treatment (PR treated) was considered as treatment failure. Patients were followed for disease activity and survival every 3 months for 2 years, and thereafter every 6 months until the end of the study. Investigators recorded all observed or volunteered adverse events (AEs), severity of the events, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v.3.0, and the investigator's opinion of the relationship to the study treatment.

Study populations and statistical analysis

The aim of the trial was to detect an improvement of EFS at 3 years from 20% for CHOP alone patients to 35% for A-CHOP patients. This was the primary endpoint of the study. The planned sample size was 274 patients including a 5% loss in order to detect this difference at a power of 80% and an α-error of 5%, two sided (hazard ratio HR = 0.652). Secondary endpoints included complete remission rate, overall response rate (ORR), rate of primary progression, relapse rate, rate of treatment-related deaths, overall survival (OS), progression-free survival (PFS), as well as safety and tolerability. EFS was calculated as time from randomization to disease progression, start of salvage treatment, start of any additional, unplanned treatment, stable disease response, response unknown, relapse, or death from any cause. PFS was defined as time from randomization to progression, relapse, or death from any cause [33, 34]. OS was defined as time from randomization to death from any cause. Patients with no reported event at the time of analysis were censored at the most recent assessment date. Kaplan–Meier curves were drawn and log-rank tests were calculated for EFS, PFS, and OS. Three and five year rates of EFS, PFS, and OS with 95% confidence intervals (CI) were determined. A Cox multivariate regression model was used to test whether therapeutic effects emerging from univariate analyses remained stable after adjustment for IPI factors (lactate dehydrogenase (LDH) > normal, Eastern Cooperative Oncology Group performance score (ECOG PS) > 1, stages III/IV, and extralymphatic involvement > 1) and, in a further analysis, for IPI factors, age > 70 years, bulky disease, and sex. Estimates are given as hazard ratios with 95% CI and corresponding p values. Subgroup analyses according to IPI, alemtuzumab dose, and sex were done as planned in the statistical analysis plan to investigate whether the treatment effects were homogeneous. Baseline characteristics were reported as percentages except for age, which was reported as the median. Patient characteristics, response rates and selected rates of AEs were analyzed by use of χ^2 test and, if necessary, by Fisher´s exact test. Differences between groups were classified as significant for p values less than or equal to 0.050. Statistical analyses were done with IBM SPSS 24 software. Following the intention-to treat (ITT) principle the full-analysis-set (FAS) population, defined as all randomized patients receiving study treatment, was used for analysis of EFS, PFS, and OS. Additional explorative analysis were performed for the per protocol sets PPS1 and PPS2. Patients meeting inclusion criteria and actual alemtuzumab treatment (if randomized to A-CHOP) were included in PPS1. In PPS2 patients from PPS1 with confirmed reference pathology were considered.

Results

Between 12 October 2007 and 30 September 2013, 116 patients were enrolled in the study and randomized (ITT population) to receive A-CHOP or CHOP (58 patients in both arms, Fig. 1). Twenty-one patients in the A-CHOP arm were planned to receive a cumulative alemtuzumab dose of 360 mg before amendment 2, 37 patients were planned to receive a cumulative alemtuzumab dose of 120 mg thereafter. Reference pathology was obtained for 108 patients

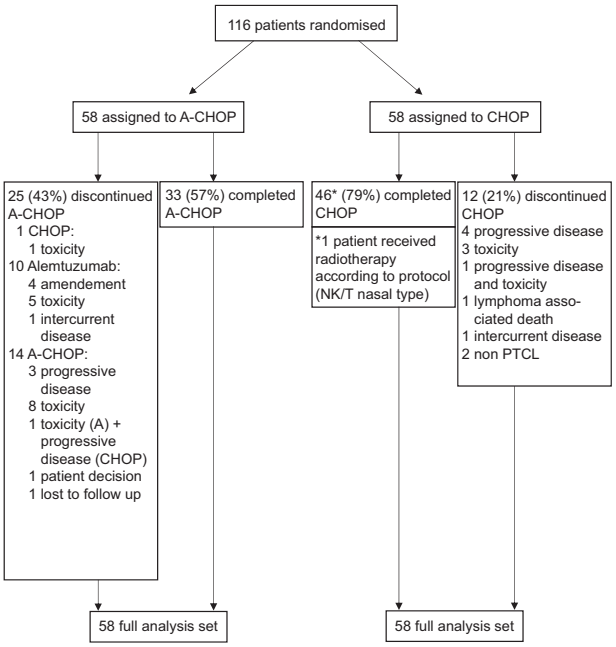

Fig. 1 CONSORT diagram of the DSHNHL2006-1B/ACT-2 trial. The reasons for individual treatment discontinuations are listed according to treatment arms.

(93%). T-cell entities were similarly distributed between the two treatment arms. Reference pathology confirmed the diagnosis of PTCL in 106 cases. One case of Hodgkin lymphoma and one case of lymphoepithelial carcinoma were diagnosed in the standard arm of the trial (Table 1). Baseline demographic and disease characteristics were not significantly different, but generally balanced across treatment arms with a slight trend to more male patients in the A-CHOP arm (Table 1). The median age in both treatment arms was 69 years, 83% of enrolled patients had Ann Arbor Stage III or IV disease at study entry, 56% of patients exhibited an IPI >3.

Protocol adherence

Overall, protocol adherence was high, and parameters for protocol adherence did not differ between treatment arms. The median duration of chemotherapy (day 1 of the first through day 1 of the last course of chemotherapy) was 72 and 74 days (per protocol: 70 days) for the experimental and the standard arm, respectively (Fig. 2). Early termination of chemotherapy occurred in 15 of 58 and in 12 of 58 patients in the investigational and the standard treatment arm, respectively (Fig. 1). There were no relevant deviations from absolute or relative drug doses of CHOP according to protocol, as well as no significant differences between treatment arms (Fig. 2). One patient assigned to the A-CHOP arm did not receive any alemtuzumab due to logistic problems and early disease progression. The median alemtuzumab dose actually administered matched the dose per protocol (median: 120 mg absolute, 1.0 relative, $n = 37$) after amendment 2, patients planned to receive the higher alemtuzumab dose prior to amendment frequently received less alemtuzumab than stipulated per protocol (median: 270 mg, 0.75 relative, $n = 21$) (Fig. 2). The main reasons for alemtuzumab dose reductions were toxicity ($n = 14$) and dose reduction due to amendment ($n = 4$), associated with early termination of alemtuzumab therapy (Fig. 1).

Table 1 Baseline patients' demographic and disease characteristics.

	Patients treated with A-CHOP $n = 58$	Patients treated with CHOP $n = 58$
Male	38 (66%)	29 (50%)
Female	20 (34%)	29 (50%)
Age, median (range)	69 (60[a],80)	69 (61,80)
LDH > N	27 (47%)	29 (50%)
ECOG > 1	12 (21%)	11 (19%)
Stage III/IV	48 (83%)	48 (83%)
E > 1	12 (21%)	13 (22%)
IPI 1	7 (12%)	8 (14%)
IPI 2	21 (36%)	15 (26%)
IPI 3	15 (26%)	22 (38%)
IPI 4, 5	15 (26%)	13 (22%)
E-involvement	29 (50%)	34 (59%)
Bulky disease	5 (9%)	6 (10%)
B-symptoms	31 (53%)	38 (66%)
Bone marrow involved	12 (21%)	8 (14%)
Histology		
Not reviewed	5 (9%)	3 (5%)
Reviewed	53 (91%)	55 (95%)
Peripheral T-cell lymphoma, unspecified (PTCL-NOS)	20 (38%)	13 (24%)
T-cell lymphoma of the AIL type	24 (45%)	25 (45%)
Anaplastic large cell lymphoma ALK-neg	3 (6%)	4 (7%)
Perifollicular variant	1 (2%)	2 (4%)
Follicular variant	1 (2%)	1 (2%)
Extranodal NK/T-cell lymphoma, nasal type	0 (0%)	1 (2%)
Intestinal T/NK-cell lymphoma (±enteropathy)	2 (4%)	3 (5%)
T-cell lymphoma, specification of subtype listed above not yet possible	1 (2%)	3 (5%)
Other T-cell	1[b] (2%)	1[c] (2%)
No T-cell	0 (0%)	2 (4%)

[a]One patient with violation of inclusion criterium.

[b]Gamma/delta T-cell lymphoma, unclassifiable.

[c]PTCL, unclassifiable.

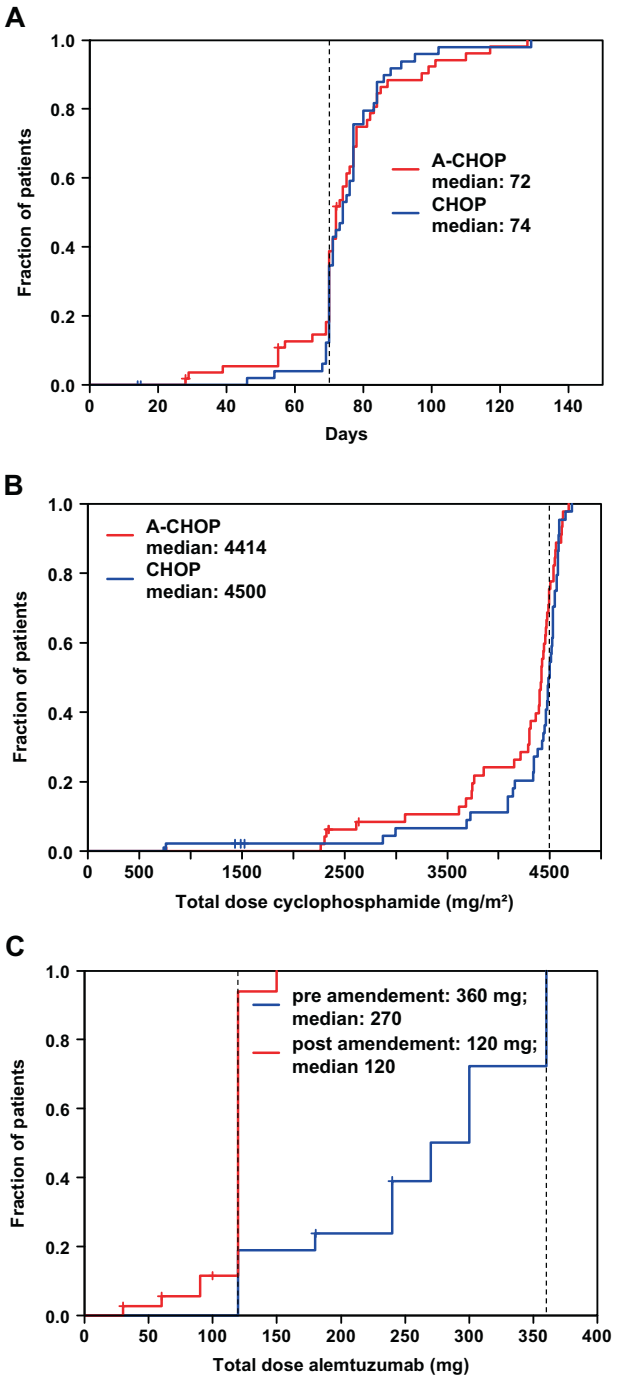

Fig. 2 Protocol adherence. a Duration of chemotherapy according to treatment arm (day 1 of the first through day 1 of the last course of chemotherapy). Only patients with at least two courses of treatment were included. Early terminations of therapy due to progressive disease were censored. The dashed line depicts the planned duration of 70 days for courses 1 through 6. **b** Cumulative dose of cyclophosphamide (mg/m²). Dosing of patients with early termination of chemotherapy due to insufficient response was censored. The dashed line depicts the planned total dose of 3500 mg/m². **c** Cumulative dose of alemtuzumab applied to patients in the A-CHOP arm. The planned alemtuzumab dose was 360 mg (6 × 60 mg) preamendment and 120 mg (4 × 30 mg) post-amendment, respectively. Doses for patients with early termination of alemtuzumab due to insufficient response were censored. Two patients received a cumulative dose of 150 mg alemtuzumab erroneously.

Table 2 Non-hematological adverse events grades 3–5 and hematotoxicity grades 3–4 according to A-CHOP versus CHOP.

	Patients treated with A-CHOP $n = 58$	Patients treated with CHOP $n = 58$
Non-hematological adverse events grade 3–5		
Nausea	2/58 (3%)	3/58 (5%)
Vomiting	1/58 (2%)	2/58 (3%)
Diarrhea	5/58 (9%)	2/58 (3%)
Constipation	2/58 (3%)	0/58 (0%)
Mucositis/stomatitis	3/58 (5%)	0/57 (0%)
Cardiac arrhythmia	1/58 (2%)	0/57 (0%)
Cardiac general	4/58 (7%)	1/58 (2%)
Hemorrhage/bleeding	1/58 (2%)	1/58 (2%)
Renal/genitourinary	3/58 (5%)	5/58 (9%)
Neuropathy sensory	5/58 (9%)	4/58 (7%)
Mood alteration	1/58 (2%)	0/58 (0%)
Allergic reaction/ hypersensitivity	1/58 (2%)	0/58 (0%)
Infections	23/58 (40%)	12/58 (21%)
Hematological adverse events		
Leukocytopenia grade 4[a]	35/50 (70%)	22/41 (54%)
Thrombocytopenia grade 3, 4[a]	8/42 (19%)	4/30 (13%)
Anemia grade 3, 4	17/58 (29%)	11/57 (19%)

The number of patients with infections grade 3–5 was significantly higher in the A-CHOP treatment arm ($p = 0.026$). For details on infections see Supplementary Fig. 2.

[a]Some patients without documentation of blood values within the nadir.

Safety

Non-hematological AEs CTC grades 3–5 except infections were similar between treatment arms. Hematotoxicity grade 3/4 was more frequent in patients in the A-CHOP arm (leukocytopenia grade 4: 70 versus 54%, thrombocytopenia grade 3/4: 19 versus 13%). In particular, alemtuzumab treatment lead to significant peripheral blood lymphocyte depletion already after three courses of treatment (Supplementary Fig. 1) associated with more grade ≥3 infections (40 versus 21%, $p = 0.026$) (Table 2). This difference was mainly due to an increase in CMV infections, observed as CMV reactivation/infection alone or in combination with bacterial or fungal infections in the experimental treatment arm (Supplementary Table 1). All five treatment-related deaths were caused by infections, four occurring in patients treated with alemtuzumab. The causes of death during therapy in two cases were hepatic failure due to systemic adenoviral infection and stenotrophomonas maltophilia pneumonia. Both lethal events occurred late during treatment, i.e., after course 5 of A-CHOP. The remaining three

Table 3 Treatment response according to treatment arms.

	Patients treated with A-CHOP $n = 58$	Patients treated with CHOP $n = 58$
Response		
OR	42 (72%)	38 (66%)
CR, CRu	35 (60%)	25 (43%)
PR	7 (12%)	13 (22%)
SD, unknown[a]	3 (5%)	3 (5%)
PD	11 (19%)	17 (29%)
Treatment related death	2 (3%)	0 (0%)
Response rates with [95% CI]		
CR, CRu	35/58 (60%) [47%; 73%]	25/58 (43%) [30%; 57%]
OR	42/58 (72%) [59%; 83%]	38/58 (66%) [52%; 78%]
Relapse after CR, CRu	15/35 (43%) (26%; 61%)	12/25 (48%) [28%; 69%]
EFS, PFS, OS rates with [95%] CI		
EFS		
3-year	27% [15%; 39%]	24% [12%; 35%]
5-year	21% [9%; 33%]	10% [0%; 20%]
PFS		
3-year	28% [15%; 40%]	29% [17%; 41%]
5-year	22% [10%; 34%]	13% [1%; 24%]
OS		
3-year	37% [23%; 50%]	56% [44%; 69%]
5-year	25% [12%; 38%]	39% [23%; 56%]

CI confidence interval, *OR* overall response, *CR* complete response, *CRu* unconfirmed complete remission, *PR* partial response, *PD* progressive disease, *SD* stable disease, *EFS* event-free survival, *PFS* progression-free survival, *OS* overall survival.

[a]SD, unknown: A-CHOP: 1, 2 patients; CHOP: 1, 2 patients.

cases of treatment-related deaths occurred during early follow up. Two deaths occurred within the first 3 months of follow-up, comprising one death due to combined candida pneumonia and stenotrophomonas septicemia in a patient of the A-CHOP arm, and one death due to CMV infection associated with haemophagocytic syndrome in a patient treated with CHOP. The third patient, treated with A-CHOP, died at 6 months of follow-up due to CMV septicemia/encephalitis. Three out of the four patients who died due infectious complications after A-CHOP treatment had received 300, 300, and 360 mg alemtuzumab, respectively, while one patient who died due to infection had 100 mg alemtuzumab. Severe unexpected adverse reactions (SUSARs) were not observed.

The cumulative incidence of secondary neoplasms during follow-up was comparable between treatment arms, i.e., eight in the experimental arm versus six in the standard arm (Supplementary Table 2). As for the cancer types, there were no versus three cases of myeloid neoplasia, but four versus no case of aggressive B-cell lymphoma in the experimental versus the standard arm, respectively (Supplementary Table 2). Concurrent EBV reactivation was documented in two of the four aggressive B-cell lymphoma cases, with EBER-positive lymphoma cells compatible with an immune-suppression associated B-cell lymphoma in one case. In six cases carcinoma occurred, one case each of skin and colon cancer in the control group, and one case each of skin, colon, lung, and breast cancer in the experimental arm.

Treatment outcome

Complete remissions were achieved in 60% [47%–73%] of A-CHOP as opposed to 43% [30%–57%] of CHOP patients ($p = 0.063$). ORR were 72% [95% CI: 59%–83%] for patients included in the experimental treatment arm, and 66% [95% CI: 52%–78%] for patients in the standard treatment arm ($p = 0.422$) (Table 3).

Median time of observation from the day of randomization was 54 months for the primary endpoint EFS. EFS at 3 year for A-CHOP 27% [15%–39%] versus CHOP 24% [12%–35%]; $p = 0.248$), as well as PFS (28% [15%–40%] versus 29% [17%–41%]; $p = 0.537$) and OS (37% [23%–50%] versus 56% [44%–69%]; $p = 0.079$) showed no significant differences (Fig. 3, Table 3). The Kaplan–Meier estimates suggest a trend toward worse OS for patients in the experimental arm. These results were confirmed in a multivariate Cox regression model with adjustment for IPI factors (hazard ratio HR_{EFS}: 0.8 ([95% CI: 0.5–1.2]; $p =$

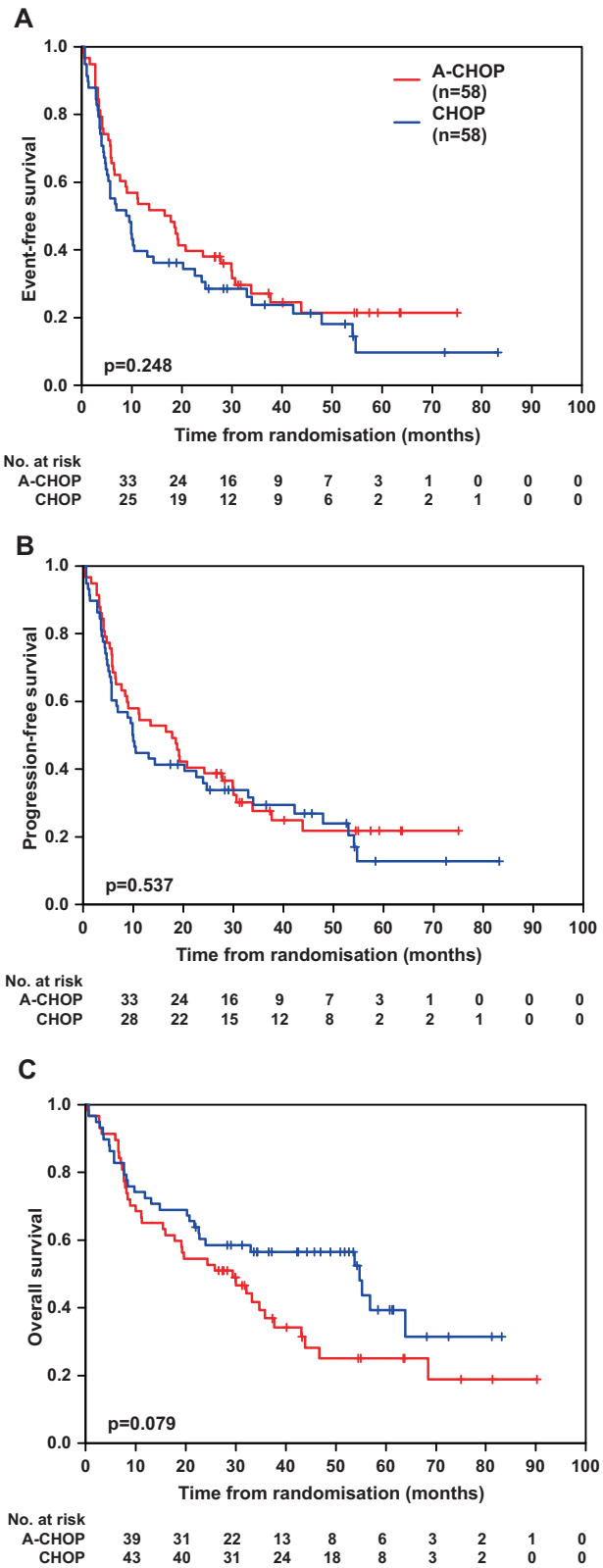

Fig. 3 Survival according to treatment arms. Event-free survival (**a**), progression-free (**b**) and overall survival (**c**) according to treatment arms.

0.293), HR_{PFS}: 0.9 ([95% CI: 0.6–1.4]; $p = 0.620$), HR_{OS}: 1.6 ([95% CI: 1.0–2.7]; $p = 0.044$) and in multivariate analyses, adjusted for IPI factors, age >70 years, bulky disease, and sex (hazard ratio HR_{EFS}: 0.7 ([95% CI: 0.5–1.1]; $p = 0.094$), HR_{PFS}: 0.8 ([95% CI: 0.5–1.2]; $p = 0.271$), HR_{OS}: 1.4 ([95% CI: 0.9–2.4]; $p = 0.154$) (Table 4). Male sex (HR $_{EFS}$: 2.5, $p < 0.001$) and bulky disease (HR_{EFS}: 2.2, $p = 0.019$) were additional prominent and significant risk factors for EFS, PFS, and OS (Table 4). Among patients treated with alemtuzumab, we found no differences in EFS, PFS, and OS estimates according to the intended cumulative alemtuzumab dose, i.e., 360 mg in 21 patients compared with 120 mg in 37 patients (Supplementary Fig. 2). Given the lack of CD52 expression in ALCL versus the strong expression in PTCL-NOS and AITL, we performed subgroup analyses for these entities, revealing no differences between treatment arms upon exclusion of ALCLs or limiting the analysis to PTCL-NOS and AITL, as shown for the primary endpoint EFS (Supplementary Fig. 3). Overall, 39 (67%) patients in the experimental treatment arm and 30 (52%) patients in the standard treatment arm died. Causes of death were lymphoma related in 25/39 (64%) cases versus 22/30 (73%) cases in the experimental and in the standard arm, respectively (Table 5). The outcome results within PPS1 and PPS2 were comparable with that of FAS.

Planned additional analyses

Importantly, the IPI was prognostic on patient outcome, confirming previous results [3], and the IPI factors significantly separated EFS, PFS, and OS for the whole study cohort (Fig. 4a–c). However, there were no significant differences in survival between patients treated with A-CHOP or CHOP upon separation into the IPI groups 1–2 and 3–5 (Fig. 4d–f). In addition, we found that male sex was associated with significantly inferior EFS, PFS, and OS (Supplementary Fig. 4).

Discussion

This randomized phase 3 study for the first time provides prospective long-term results on survival and other endpoints of interest after standard treatment with CHOP in patients with PTCL beyond 60 years who represent the majority of PTCL patients, generally less eligible for more intense therapies like autologous and allogeneic transplantation. Moreover, it verifies data from retrospective analyses suggesting a significant impact of the IPI on survival also for patients with PTCL.

Table 4 Multivariate analysis of event-free, progression-free, and overall survival adjusted for IPI factors or for strata and sex, respectively.

	EFS HR (95% CI)	*p*	PFS HR (95% CI)	*p*	OS HR (95% CI)	*p*
Adjusted for IPI factors						
Alemtuzumab	0.8 (0.5–1.2)	0.293	0.9 (0.6–1.4)	0.620	1.6 (1.0–2.7)	0.044
LDH > N	1.4 (0.9–2.1)	0.144	1.3 (0.9–2.1)	0.193	1.5 (0.9–2.4)	0.141
ECOG > 1	0.9 (0.6–1.6)	0.835	1.0 (0.6–1.8)	0.897	1.4 (0.8–2.5)	0.267
Stage III/IV	0.7 (0.4–1.2)	0.217	1.1 (0.6–2.0)	0.780	1.3 (0.6–2.6)	0.511
E > 1	2.5 (1.5–4.2)	0.001	2.3 (1.4–3.9)	0.002	1.8 (1.0–3.2)	0.047
Adjusted for strata and sex						
Alemtuzumab	0.7 (0.5–1.1)	0.094	0.8 (0.5–1.2)	0.271	1.4 (0.9–2.4)	0.154
LDH > N	1.4 (0.9–2.1)	0.185	1.3 (0.8–2.0)	0.256	1.5 (0.9–2.5)	0.156
ECOG > 1	1.4 (0.8–2.4)	0.281	1.5 (0.8–2.6)	0.191	2.1 (1.1–3.9)	0.024
Stage III/IV	0.7 (0.4–1.3)	0.224	1.2 (0.6–2.2)	0.639	1.3 (0.6–2.8)	0.461
E > 1	2.3 (1.4–4.0)	0.001	2.1 (1.2–3.6)	0.006	1.7 (0.9–3.0)	0.098
Bulky disease	2.2 (1.1–4.3)	0.019	2.6 (1.3–5.0)	0.006	4.7 (2.3–9.6)	<0.001
Age >70 years	0.9 (0.6–1.5)	0.760	1.1 (0.7–1.8)	0.703	1.4 (0.8–2.4)	0.196
Male sex	2.5 (1.6–4.1)	<0.001	2.5 (1.5–4.0)	<0.001	2.6 (1.5–4.7)	0.001

Table 5 Causes of death according to treatment arms.

	Patients treated with A-CHOP $n = 58$	Patients treated with CHOP $n = 58$
Lymphoma related	25/39 (64%)	22/30 (73%)
Study treatment related	4/39 (10%)	1/30 (3%)
Concomitant diseases	4/39 (10%)	2/30 (7%)
Secondary neoplasia	3/39 (8%)	2/30 (7%)
Other	0/39 (0%)	2/30 (7%)
Unknown	3/39 (8%)	1/30 (3%)
Total	39/58 (67%)	30/58 (52%)

Other causes of death were accident and stroke, respectively.

Regarding clinical efficacy of the A-CHOP regimen, our data are in line with previous experience from small phase 2 trials. In the GITIL study, where most patients received a cumulative alemtuzumab dose of 240 mg together with eight courses of CHOP, CR was achieved in 17 of 24 patients (71%), allowing PFS for 13 of 24 patients (54%) at a median follow-up of 16 months [27]. In the HOVON69 trial, where patients were to receive a higher cumulative alemtuzumab dose of 720 mg in conjunction with eight courses of CHOP-14, 13 of 20 patients (65%) reached a CR/ CRu, leading to an overall and EFS of 56% and 27% at 2 years, respectively [28]. In the DSHNHL 2003-1 trial, where patients received a cumulative alemtuzumab dose of 133 mg for consolidation after eight courses of CHO(E)P, 24 of 41 (58%) achieved a CR/ CRu, with overall and EFS estimates at 3 years of 62% and 32%, respectively [29]. Although promising, these remission rates were still in the range of response rates observed for CHOP or CHOEP alone [3, 35], prompting the randomized comparison reported here. The number of lymphoma-associated deaths in the A-CHOP arm amounted to 25, compared with 22 in the CHOP arm. A formal phase 1 clinical study to establish the optimal dose of alemtuzumab in combination with CHOP has not been performed, and the outcome of patients treated with high versus lower cumulative alemtuzumab doses were similar, arguing against dose-dependent killing of lymphoma cells, although preclinical data suggest an association of CD52 abundance and lymphoma cell susceptibility for CDC and ADCC [22]. As CD52 expression appears heterogeneous across subtypes of PTCL [9, 16, 36] and measuring expression levels remains technically challenging, in depth analyses of CD52 expression including comprehensive histopathology and genetic subgroup analysis would be mandatory to better correlate expression and treatment response.

Unfortunately, there were other reasons besides low patient numbers why the primary endpoint of the study was not met. Although our hypothesis of breaking resistance to CHOP chemotherapy by adding alemtuzumab for CD52-positive tumors may be supported by the difference in CR rates observed (60% in the A-CHOP arm compared with 43% in the CHOP arm), as well as the lower number of cases with progressive disease in the alemtuzumab arm, high doses of alemtuzumab caused untoward and partly life-threatening toxicity forcing investigators to lower the dose —thus possibly preventing patients from experiencing the full therapeutic potential of alemtuzumab. As with this phase 3 study, previous phase 1/2 studies using varying doses of alemtuzumab in different disorders had shown high infection rates, in particular from viral (CMV and EBV) and fungal agents [37], probably reflecting on-target effects of alemtuzumab on normal T cells. The trial was conducted

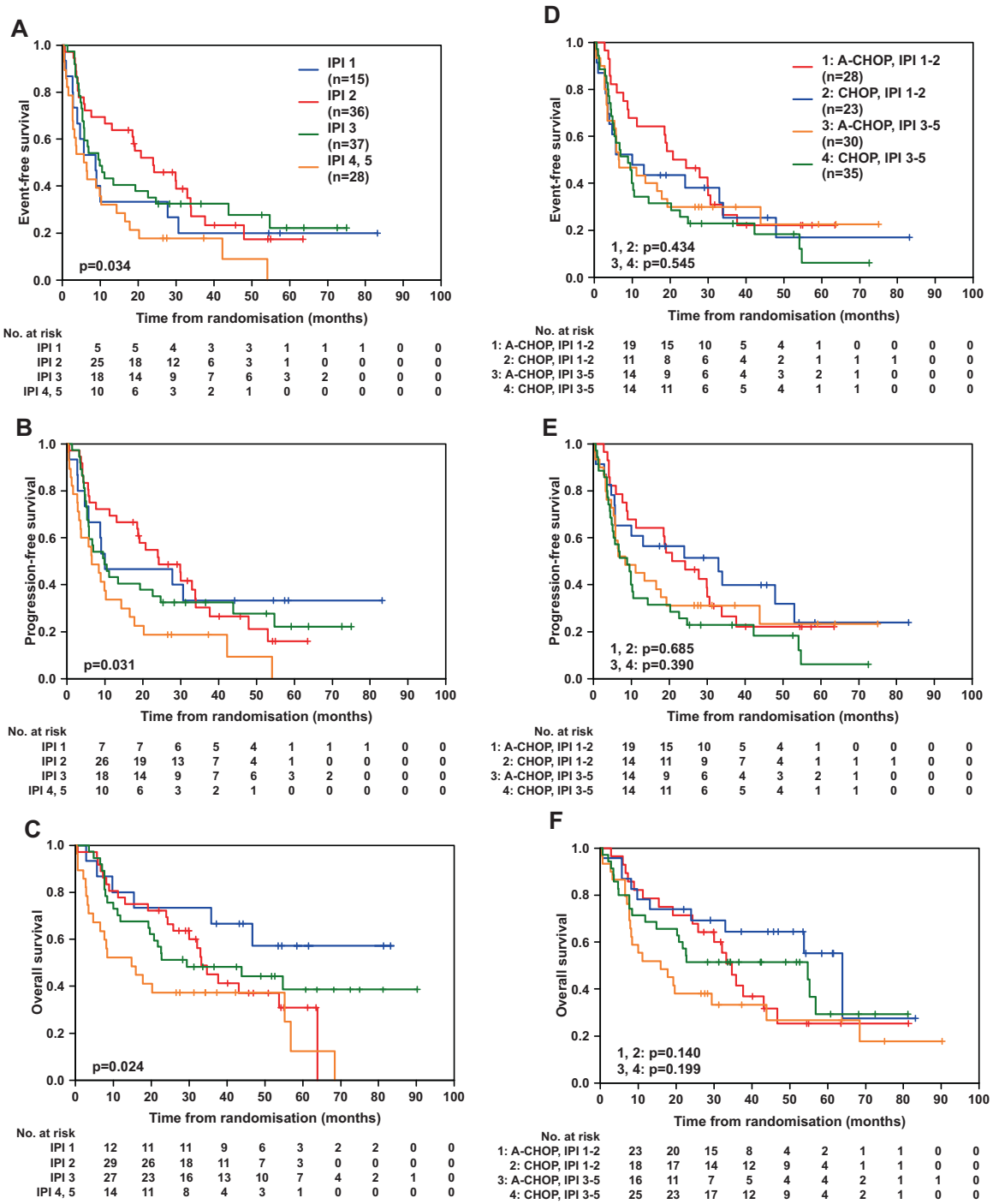

Fig. 4 Survival according to IPI. Event- free (**a**, **d**), progression-free (**b**, **e**) and overall survival (**c**, **f**) according to IPI and according to IPI and treatment arms, respectively. Please note: Patients at all stages of disease qualified for inclusion, except patients with disease Stage I N with IPI 0 (except age > 60) and without bulk.

with mandatory antiinfective prophylaxis, i.e., cotrimoxazole against pneumocystis jirovecii/toxoplasma gondii, acyclovir against herpes virus as well as recommendations for preemptive ganciclovir treatment at CMV reactivation. These measures obviously were not sufficient to prevent severe infections in some patients. Meanwhile, new effective drugs against CMV or fungal disease have become available opening the question if better CMV prophylaxis with valganciclovir [38] or letermovir [39] and anti-mycotic prophylaxis with e.g., posaconazole [40] would have prevented or ameliorated most if not all of the infectious complications seen with alemtuzumab.

The occurrence of diffuse large B-cell lymphoma is another threat to patients treated with alemtuzumab. We observed four such cases in the A-CHOP arm but none in the CHOP arm of the trial. Intriguingly, in this series DLBCL occurred exclusively in patients with AITL, where moderate EBER-positive B-cell infiltrates had been described in all four cases at diagnosis. In two patients a concurrent EBV reactivation was documented, suggesting the origin of DLBCL from opportunistic EBV-associated B-cell lymphoproliferation in a T-cell depleted host. Similar observations were reported in three of 41 patients in the HOVON69 trial [28]. EBV-positive B-cells have previously been described in about 40% of cells of primary PTCL lymphoma tissue [41] and EBV reactivation was detectable in 25–42% of PTCL patients at initial presentation [14, 42]. The occurrence of EBV-positive B-cell lymphomas has also been described during the natural course of PTCL in frequencies up to 11% [43–45], suggesting a specific biology causing the PTCL and DLBCL collision [46, 47]. While a specific EBV prophylaxis was not available at the time our trial was planned, valganciclovir might be a therapeutic option in the future. Valganciclovir suppressed EBV reactivation during alemtuzumab therapy in a study cohort of 29 patients. Albeit in that series five cases of EBV reactivation were observed, only one case of EBV-associated Hodgkin lymphoma occurred [48].

Previous studies suggested a discriminatory role for the IPI also in patients with PTCL [3, 49, 50]. The data from this prospective trial confirm the significance of the IPI for elderly PTCL patients. This appears even more noteworthy, as patients with low-risk features were under-represented in this trial: due to age >60 years as a prerequisite for inclusion there were no patients with IPI 0 in this trial, and IPI 1 patients with Ann Arbor stage I N disease and no bulk had also been excluded. In addition, this trial found bulky disease and male sex as significantly adverse prognostic factors in PTCL. Bulky disease has not been specifically addressed in most studies looking for clinical prognostic factors [51–53]. In the International T-cell Lymphoma Project, however, bulky disease defined by tumor diameter >10 cm was predictive of survival, with hazard ratios of 2.1 for OS ($p = 0.019$), and 2.5 for failure-free survival ($p = 0.003$), respectively [54]. Similarly, bulky disease—besides age >60 and thrombocytopenia—was identified as a strong, independent factor associated with inferior OS (HR: 5.3; $p = 0.019$) after multivariate adjustment in a large series of Japanese patients with PTCL-NOS [55]. Our findings are in line with these findings suggesting to take bulky disease into account as a relevant clinical prognostic factor in future PTCL trials.

The role of sex as clinical prognostic factor for treatment response in PTCL has attracted even less attendance so far. T-cell neoplasms occur more frequently in males than in females, at an overall hazard ratio of 1.8, depending on the subtype [56]. In this trial, the ratio of male to female patients was 1.4. In the planning of this trial we did not anticipate that male sex would be a significantly unfavorable prognostic factor for elderly patients with PTCL. Similarly to the findings in this trial, however, a large retrospective series of PTCL patients mainly treated with CHOP/CHOP-like regimens also found male sex to be associated with an adverse OS (HR 1.28, $p = 0.011$) as well as PFS (HR 1.26, $p = 0.014$) [35]. Thus, both data coming from this prospective trial and retrospective series suggest male sex as an independent risk factor for patients with PTCL. Beyond its biological role factor in lymphoma pathology, however, male gender may also act as a relevant confounding factor, implicating further studies for an improved understanding of the observed effects on OS.

Taken together, the addition of alemtuzumab to CHOP failed to improve the outcome for elderly patients with PTCL, because the positive effects on CR rates and primary progression were outweighed by complications of alemtuzumab therapy, namely infections and secondary DLBCL. Importantly, this study defines standards for further attempts to improve therapy because we now hold prospective survival data after CHOP chemotherapy in the elderly. The estimated 5 years OS of 39% (95% CI: 23%–56%) after treatment with CHOP is in line with registry-based observations in this patient group [35], and imposes the urgent need to find new platforms for combination approaches [12]. Ongoing molecular studies on our patients as well as on patients from the companion studies ACT-1 and AATT will shed further light on the pathogenesis of T-cell lymphoma and will hopefully open new avenues to improved treatment.

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Affiliations

Gerald G. Wulf[1] · Bettina Altmann[2] · Marita Ziepert[2] · Francesco D'Amore[3] · Gerhard Held[4] · Richard Greil[5,6] · Olivier Tournilhac[7] · Thomas Relander[8] · Andreas Viardot[9] · Martin Wilhelm[10] · Christian Wilhelm[11] · Antonio Pezzutto[12] · Josee M. Zijlstra[13] · Eric Van Den Neste[14] · Pieternella J. Lugtenburg[15] · Jeanette K. Doorduijn[15] · Michel van Gelder[16] · Gustaaf W. van Imhoff[17] · Florian Zettl[18] · Friederike Braulke[1] · Maike Nickelsen[19] · Bertram Glass[20] · Andreas Rosenwald[21] · Philippe Gaulard[22] · Markus Loeffler[2] · Michael Pfreundschuh[23] · Norbert Schmitz[24] · Lorenz Trümper[1] · for the ACT-2 study investigators

1 Hematology and Medical Oncology, University Medicine Goettingen, Goettingen, Germany

2 Institute for Medical Informatics, Statistics and Epidemiology, University Leipzig, Leipzig, Germany

3 Department of Hematology, Aarhus University Hospital, Aarhus, Denmark

4 Internal Medicine 1, Westpfalz-Klinikum, Kaiserslautern, Germany

5 Department of internal Medicine III with Haematology, Medical Oncology, Haemostaseology, Infectiology and Rheumatology, Oncologic Center, Cancer Research Institute, Salzburg, Austria

6 Laboratory for Immunological and Molecular Cancer Research (SCI-LIMCR), Paracelsus Medical University, Cancer Cluster Salzburg, Salzburg, Austria

7 Service de therapie cellullaire et Hematologie Clinique adulte, CHU Estaing, Clermont-Ferrand, France

8 Department of Clinical Sciences Lund, Lund University Hospital, Lund, Sweden

9 Department Internal Medicine III, University Hospital of Ulm, Ulm, Germany

10 Paracelsus Medical University, Medizinische Klinik 5, Klinikum Nuernberg, Nuernberg, Germany

11 Department of Hematology, University Hospital Marburg, Marburg, Germany

12 Medizinische Klinik mit Schwerpunkt Hämatologie/Onkologie Campus Virchow-Klinikum, Charite, Berlin, Germany

13 Department of Hematology, Vrije Universiteit Medisch Centrum Amsterdam, Amsterdam, The Netherlands

14 Cliniques universitaires UCL Saint-Luc, Brussels, Belgium

15 Department of Hematology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

16 Department of Hematology, Academisch Ziekenhuis Maastricht, Maastricht, The Netherlands

17 Department of Hematology, University Medical Centre Groningen, Groningen, The Netherlands

18 Klinikum Traunstein, Department Hematology and Oncology, Traunstein, Germany

19 Onkologie Lerchenfeld, Hamburg, Germany

20 HELIOS Klinikum Berlin-Buch, Berlin, Germany

21 Institute of Pathology, University of Wuerzburg and Comprehensive Cancer Centre (CCC) Mainfranken, Wuerzburg, Germany

22 Department of Pathology, Hospital Henri Mondor, APHP, Inserm U955, Université Paris-Est, Créteil, France

23 Department of Hematology and Oncology, University Hospital Saarland, Homburg, Germany

24 Department of Hematology, Oncology, Haemostaseology, and Pneumology, University Hospital, Muenster, Germany