original reports

# Romidepsin Plus CHOP Versus CHOP in Patients With Previously Untreated Peripheral T-Cell Lymphoma: Results of the Ro-CHOP Phase III Study (Conducted by LYSA)

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abstract

**PURPOSE** Romidepsin, a histone deacetylase inhibitor, has demonstrated activity in relapsed or refractory peripheral T-cell lymphoma (PTCL) as a single agent. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy is widely used as first-line treatment of PTCL; however, it has limited efficacy. Results from a phase Ib and II study showed the feasibility of combining romidepsin with CHOP (Ro-CHOP).

**METHODS** This study is a randomized phase III study of Ro-CHOP versus CHOP in adult patients with previously untreated PTCL. All patients received CHOP in 3-week cycles for six cycles. Romidepsin, 12 mg/m$^2$, was administered intravenously over a 4-hour period on days 1 and 8 of each 3-week cycle for six cycles. The primary end point was progression-free survival (PFS) according to International Working Group 1999 criteria.

**RESULTS** Between January 2013 and December 2017, 421 patients were enrolled (Ro-CHOP, n = 211; CHOP, n = 210). The median PFS for Ro-CHOP versus CHOP was 12.0 months (95% CI, 9.0 to 25.8) versus 10.2 months (95% CI, 7.4 to 13.2) with a hazard ratio of 0.81 ($P$ = .096). In the Ro-CHOP versus CHOP arms, the median overall survival was 51.8 versus 42.9 months and the objective response rate was 63% versus 60% with complete response plus unconfirmed complete response rates of 41% versus 37% ($P > .1$ in all comparisons), respectively. Grade 3 or 4 treatment-emergent adverse events occurring in ≥ 30% of patients in the Ro-CHOP arm included thrombocytopenia (50% *v* 10% in the Ro-CHOP *v* CHOP arms, respectively), neutropenia (49% *v* 33%), anemia (47% *v* 17%), and leukopenia (32% *v* 20%).

**CONCLUSION** The addition of romidepsin to CHOP did not improve PFS, response rates, nor overall survival and increased the frequency for grade ≥ 3 treatment-emergent adverse events. Ro-CHOP does not represent a significant advance in the standard of care for patients with previously untreated PTCL.

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## INTRODUCTION

Peripheral T-cell lymphomas (PTCLs) are a heterogenous group of lymphoid malignancies that account for 15%-20% of aggressive lymphomas and 5%-10% of all non-Hodgkin lymphomas in the Western world.[1-3] Common subtypes of PTCL include angioimmunoblastic T-cell lymphoma (AITL), anaplastic large-cell lymphomas (ALCLs), and PTCL not otherwise specified (PTCL-NOS). Despite aggressive chemotherapy, the majority of patients with PTCL have relatively dismal clinical outcomes compared with B-cell lymphoma with a 5-year overall survival (OS) of approximately 30%-40% for AITL and PTCL-NOS, the most frequent subtypes in Western countries.[1]

Because of the rarity and the heterogeneity of the disease, randomized trials are scarce in PTCL. In frontline, trials aiming to replace cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with another chemotherapy regimen, such as gemcitabine in association with cisplatin and methylprednisolone, failed to demonstrate superiority.[4] Similarly, building on CHOP for more intensive treatments like high-dose CHOP plus etoposide[5] or etoposide, ifosfamide, and cisplatin alternating with doxorubicin, bleomycin, vinblastine, and dacarbazine[6] did not lead to more favorable outcomes and was associated with significantly higher toxicity. Finally, adding an anti-CD52 antibody to a CHOP backbone did not further improve survival.[7,8]

## CONTEXT

**Key Objective**

The prognosis of peripheral T-cell lymphoma (PTCL) is poor. Almost no improvement over the standard first-line cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen has been made for decades apart from the recent approval of brentuximab vedotin for CD30+ PTCL by the US Food and Drug Administration. The Ro-CHOP phase III trial aimed at comparing standard CHOP with romidepsin plus CHOP.

**Knowledge Generated**

Romidepsin plus CHOP is not superior to CHOP alone in the first-line treatment of PTCL and is associated with significantly higher toxicity. Exploratory analyses pinpoint a higher efficacy in follicular helper phenotype PTCL already suggested by noncomparative retrospective studies, although the trial was not designed to specifically assess differences among histologic subgroups.

**Relevance (*J.W. Friedberg*)**

The results of this trial do not support the addition of romidepsin to CHOP. Subset analyses validate previous findings of heterogeneity between subtypes of T-cell lymphoma. Future trials should incorporate these findings into novel clinical trial designs in this disease.*

*Relevance section written by *JCO* Editor-in-Chief Jonathan W. Friedberg, MD.



Over the past two decades, the only novel agent approved in the first-line setting has been brentuximab vedotin (BV) for CD30+ PTCL in the United States and Japan and for ALCL in Europe, in association with cyclophosphamide, doxorubicin, and prednisone (CHP) on the basis of the results of the ECHELON-2 trial.[9] Subgroup analyses show that the overall benefit of BV in addition to CHP is largely driven by efficacy of the antibody drug conjugate in ALCL entities, accounting for 70% of the enrolled population.

Romidepsin is a potent, selective, class I histone deacetylase inhibitor. As a single agent in relapsed or refractory (R/R) PTCL, romidepsin was associated with 25% response rate including 15% of complete response (CR) or unconfirmed complete response (CRu).[10] Results from a phase Ib and II study showed the feasibility of combining romidepsin with cyclophosphamide, doxorubicin, vincristine, and prednisone (Ro-CHOP).[11] Romidepsin given intravenously over 4 hours at a dose of 12 mg/m$^2$ on days 1 and 8 of each 3-week cycle was the recommended phase II dose.

In 2013, the Lymphoma Study Association started a phase III randomized trial comparing Ro-CHOP with CHOP in patients with previously untreated PTCL (Ro-CHOP study). Presented here is the analysis of this phase III randomized study.

## METHODS

### Study Design and Participants

In this open-label randomized phase III study, patients age 18-80 years were eligible if they presented with PTCL-NOS, AITL, systemic anaplastic lymphoma kinase (ALK)–negative ALCL, enteropathy-associated T-cell lymphoma, hepatosplenic T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, primary cutaneous gamma-delta T-cell lymphoma, primary cutaneous CD8+ aggressive epidermotropic lymphoma, primary cutaneous CD4+ small or medium T-cell lymphoproliferative disorder, and other nonclassifiable T-cell lymphoma. Patients with an Eastern Cooperative Oncology Group performance status $\leq 2$ and stage I-IV disease were eligible. Consolidation strategy with stem-cell transplant was not allowed per the Protocol (online only). Patients with ALK-positive ALCL, known to experience a far better prognosis than those with other PTCL subtypes using chemotherapy alone, were not included in the study.

The Protocol was approved by local or national ethics committees according to the laws of each country, and the study was undertaken in accordance with the Declaration of Helsinki. Patients were required to provide written informed consent before registration.

### Procedures

Patients were randomly assigned in a 1:1 ratio to CHOP or Ro-CHOP at 98 centers from nine countries in Europe, Asia, and Australia. Random assignment was stratified for histology type according to local pathology assessment (nodal *v* extranodal histologies), International Prognostic Index (IPI, $\leq 1$ *v* $> 1$), and age ($\leq 60$ *v* $> 60$ years). Patients received six 21-day cycles of either CHOP (day 1 included cyclophosphamide 750 mg/m$^2$, doxorubicin 50 mg/m$^2$, and vincristine 1.4 mg/m$^2$ [maximum 2 mg at the discretion of the investigator and maximum 1.5 mg if age $> 70$ years] by intravenous infusion, and days 1-5 included oral prednisone 40 mg/m$^2$ once daily) alone or with intravenous romidepsin 12 mg/m$^2$ at days 1 and 8 (once daily). Granulocyte colony-stimulating factor was mandatory for all patients at each cycle whatever the treatment arm.

Computed tomography (CT) scans were performed at screening and after three cycles. After completion of study

**TABLE 1.** Patient Characteristics

| Parameter | Ro-CHOP (n = 211) | CHOP (n = 210) | Total (N = 421) |
|---|---|---|---|
| Median age, years (range) | 65 (26-80) | 65 (25-81) | 65 (25-81) |
| Age group, years | | | |
| ≤ 60 | 73 (34.6) | 72 (34.3) | 145 (34.4) |
| > 60 | 138 (65.4) | 138 (65.7) | 276 (65.6) |
| Sex | | | |
| Male | 125 (59.2) | 136 (64.8) | 261 (62.0) |
| Female | 86 (40.8) | 74 (35.2) | 160 (38.0) |
| Histologic diagnosis (local pathology) | | | |
| AITL | 101 (47.9) | 94 (44.8) | 195 (46.3) |
| PTCL-NOS | 59 (28.0) | 68 (32.4) | 127 (30.2) |
| ALCL ALK–negative type | 21 (10.0) | 21 (10.0) | 42 (10.0) |
| Others | 30 (14.2) | 27 (12.9) | 57 (13.5) |
| ECOG performance status | | | |
| 0 | 72 (34.1) | 90 (42.9) | 162 (38.5) |
| 1 | 91 (43.1) | 92 (43.8) | 183 (43.5) |
| 2 | 47 (22.3) | 28 (13.3) | 75 (17.8) |
| 3 | 1 (0.5) | 0 | 1 (0.2) |
| Ann Arbor stage at enrollment | | | |
| I | 8 (3.8) | 8 (3.8) | 16 (3.8) |
| II | 22 (10.4) | 24 (11.4) | 46 (10.9) |
| III | 40 (19.0) | 52 (24.8) | 92 (21.9) |
| IV | 141 (66.8) | 126 (60.0) | 267 (63.4) |
| B symptoms | | | |
| Yes | 98 (46.4) | 100 (47.6) | 198 (47.0) |
| No | 113 (53.6) | 110 (52.4) | 223 (53.0) |
| Extranodal involvement | | | |
| < 2 sites | 108 (51.2) | 118 (56.2) | 226 (53.7) |
| ≥ 2 sites | 100 (47.4) | 89 (42.4) | 189 (44.9) |
| Missing | 3 (1.4) | 3 (1.4) | 6 (1.4) |
| LDH elevated[a] | | | |
| Yes | 127 (60.2) | 108 (51.4) | 235 (55.8) |
| No | 84 (39.8) | 101 (48.1) | 185 (43.9) |
| Missing | 0 | 1 (0.5) | 1 (0.2) |
| IPI score (derived) | | | |
| 0 | 9 (4.3) | 6 (2.9) | 15 (3.6) |
| 1 | 27 (12.8) | 36 (17.1) | 63 (15.0) |
| 2 | 43 (20.4) | 54 (25.7) | 97 (23.0) |
| 3 | 60 (28.4) | 59 (28.1) | 119 (28.3) |
| 4 | 51 (24.2) | 42 (20.0) | 93 (22.1) |
| 5 | 18 (8.5) | 9 (4.3) | 27 (6.4) |
| Missing | 3 (1.4) | 4 (1.9) | 7 (1.7) |

NOTE. Data are No. (%) unless noted otherwise.

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; Ro-CHOP, romidepsin with cyclophosphamide, doxorubicin, vincristine, and prednisone.

[a]LDH elevated was defined as LDH > upper limit of normal.

treatment, a final restaging assessment was scheduled between 3 and 5 weeks after the last dose administration. Follow-up CT scans were performed every 3 months during the first year, every 4 months during the second year, and every 6 months thereafter. All patients were to be followed after completion of treatment for progression-free survival (PFS) and OS with clinic visits every 3 months for the first year, every 4 months for the next year, and then every 6 months thereafter.

Any suspicion of progression had to be confirmed by a blinded central review of the CT scan and clinical data by the Response Adjudication Committee (RAC). If the progressive disease was not confirmed by RAC, the Protocol required the patient continue treatment or follow-up as per the Protocol.

The diagnosis of a specific PTCL histology was assigned locally before the random assignment. Central pathology review was required for all patients registered and was performed by at least two expert hematopathologists, and a consensus diagnosis according to the WHO 2017 classification of lymphomas[3] was retrospectively registered in the database. Dose adjustment recommendations for anticipated toxicities are described in the Data Supplement (online only).

## Outcomes

The primary end point was PFS assessed by RAC, defined from the date of random assignment to the date of first documented relapse, progressive disease, or death because of any cause, whichever came first. Secondary end points included PFS assessed by the investigator, OS, objective response rate (ORR), CR + CRu, duration of response (DOR), and safety. Exploratory end points included PFS according to the centrally confirmed histologic subgroup (94% of cases were centrally reviewed by expert pathologists; P.G. and L.D.L.). Lymphoma response and progression were assessed centrally by RAC assessment according to International Working Group 1999 criteria.[12] The intent-to-treat (ITT) population included all patients randomly assigned regardless of study drug being received or not. The ITT population was used for the primary efficacy

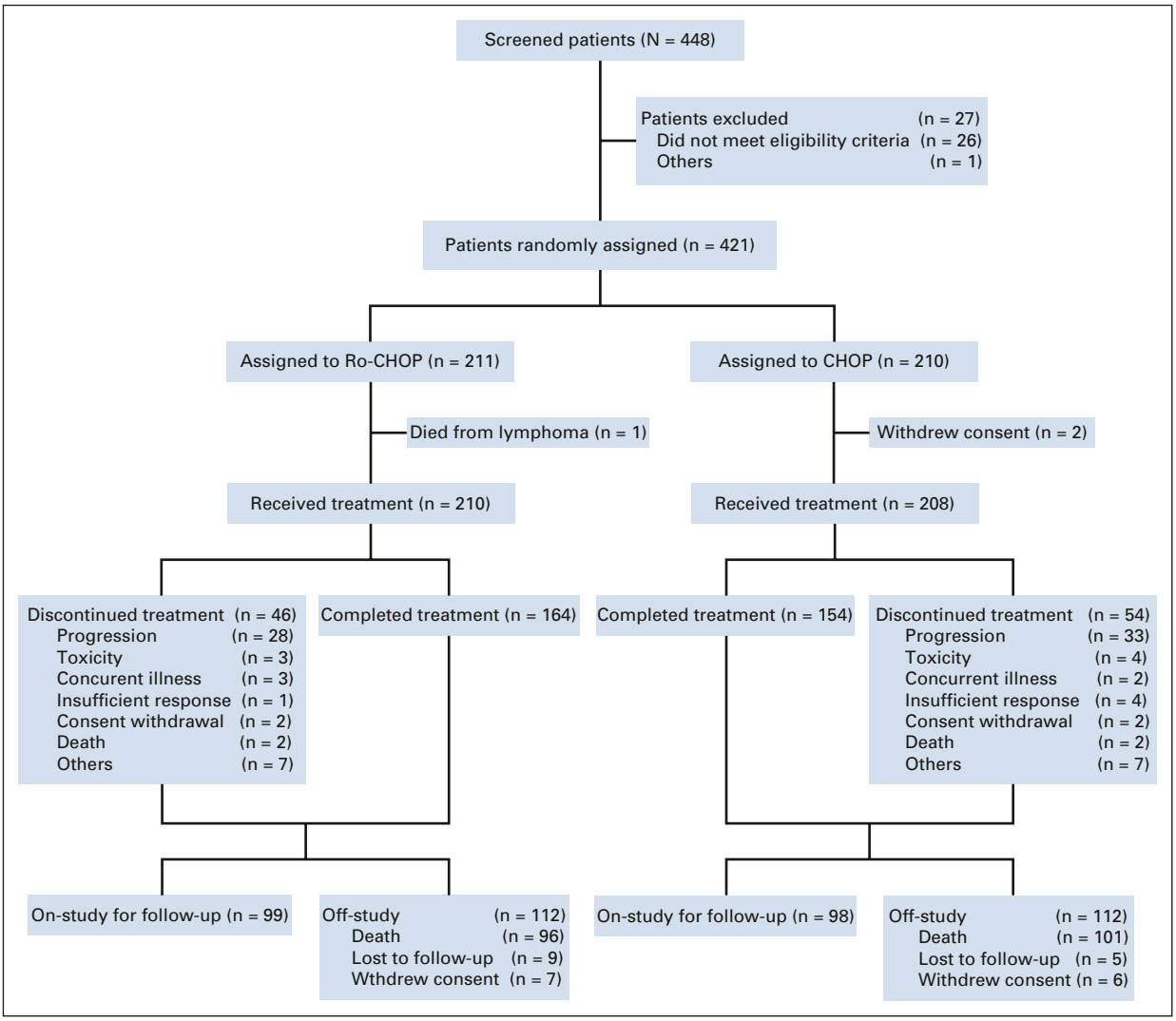


**FIG 1.** CONSORT diagram. CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; Ro-CHOP, romidepsin with cyclophosphamide, doxorubicin, vincristine, and prednisone.



analysis and for secondary end points. Patients were analyzed according to the treatment arm to which they were initially assigned. Safety outcomes were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 4.03).

### Statistical Analyses

Sample size determination was based on the primary efficacy end point (PFS). To provide 80% power to detect a hazard ratio (HR) of 0.7143 for Ro-CHOP versus CHOP with a one-sided alpha (type I error) of .025, a total of 278 progression/death events from both arms were required. An HR of 0.7143 corresponded to a 40% improvement in median PFS (from 12 months in control to 16.8 months in testing arms). This resulted in a total of 420 evaluable patients to be randomly assigned to the two treatment arms (210 in each arm), assuming a 10% drop-out rate per year. One interim analysis for futility was performed at 30% of the total number of planned events (approximately 84 cumulative progression/death events), and the Independent Data Monitoring Committee meeting advised that the study continues as planned. The stratified log-rank test by random assignment stratification factors was used to compare PFS difference between arms. A two-sided $P$ value $< .05$ was considered significant. Survival curves were generated using the Kaplan-Meier method. All statistical analyses were performed using SAS software version 9.3. This trial is registered at ClinicalTrials.gov (identifier: NCT01796002).

## RESULTS

Between January 2013 and December 2017, 448 patients were screened and 421 were enrolled in the study (211 in the Ro-CHOP arm and 210 in the CHOP arm).

Baseline characteristics were mostly similar between the two arms (Table 1). The median age was 65 years (range, 25-81

years). Diagnosis by local pathology determined that 195 (46.3%) patients had AITL, 127 (30.2%) had PTCL-NOS, 42 (10.0%) had ALK-negative ALCL, and 57 (13.5%) were categorized as others (Data Supplement). Despite IPI stratification at random assignment (≤ 1 *v* > 1), patients in the Ro-CHOP arm presented with more aggressive features compared with those in the CHOP arm with respect to both Eastern Cooperative Oncology Group performance status ≥ 2 (22.7% *v* 13.3%) and elevated lactate dehydrogenase (60.2% *v* 51.4%) and, as a result, IPI score 4 or 5 (32.7% *v* 24.3%).

Disposition of patients is presented in Figure 1. In the treated population (n = 418), 46 (21.9%) patients from the Ro-CHOP arm and 54 (26.0%) from the CHOP arm prematurely discontinued treatment. In both arms, the primary reason for discontinuation was disease progression (n = 28 in the Ro-CHOP arm and n = 33 in the CHOP arm).

As of December 13, 2019, after a median follow-up of 27.5 months, the primary end point of PFS assessed by a central review committee was not met and did not demonstrate superiority of Ro-CHOP compared with CHOP, with an HR of 0.81 (95% CI, 0.63 to 1.04; *P* = .0962, Fig 2A). The median PFS was 12.0 months (95% CI, 9.0 to 25.8) in the Ro-CHOP arm and 10.2 months (95% CI, 7.4 to 13.2) in the CHOP arm. PFS rates at 6 months, 1 year, and 2 years were 67.4%, 49.8%, and 43.2%, respectively, in the Ro-CHOP arm and 65.9%, 44.3%, and 36.3%, respectively, in the CHOP arm. Prespecified sensitivity analysis of PFS by the local investigator did not meet statistical significance either (Data Supplement). The median OS for Ro-CHOP versus CHOP was 51.8 months (95% CI, 35.7 to 72.6) versus 42.9 months (95% CI, 29.9 to not reached, Fig 2B). The OS rates at 1 year and 2 years were 78.2% and 63.6%, respectively, in the Ro-CHOP arm and 77.5% and 63.4%, respectively, in the CHOP arm with a HR of 0.90 (95% CI, 0.68 to 1.20; *P* = .4767). The ORR of Ro-CHOP versus CHOP at the end of treatment was 63.0% versus 60.5% with CR + CRu rates of 41.2% versus 37.1% (Data Supplement). In patients who achieved CR, CRu, or PR, the median DOR was 36.3 months (95% CI, 29.5 to not reached) in the Ro-CHOP arm compared with 23.7 months (95% CI, 8.8 to 50.1) in the CHOP arm (*P* = .032; Data Supplement).

Preplanned PFS analyses were conducted in subgroups with potential prognostic or predictive factors for the ITT population. There was no statistically significant difference in PFS between the Ro-CHOP and CHOP arms for any subgroup analyzed (Fig 3).

Histology was centrally reviewed in 398 of 421 patients (94.5%). After central review, diagnoses were AITL or related neoplasms of follicular helper T-cell (TFH) derivation (follicular T-cell lymphoma or nodal PTCL with TFH phenotype) in 201 (47.7%) patients, PTCL-NOS in 66 (15.7%) patients, ALK-negative ALCL in 34 (8.1%) patients, and others in 97 (23.0%) patients. The main reason for the absence of central histologic review was insufficient biopsy material. In 23 patients (5.4%), the initial diagnosis could not be confirmed on the submitted material or there was a major change of diagnosis (Data Supplement), but those patients were part of the ITT population that was based on local diagnosis.

Exploratory analysis of PFS in centrally confirmed TFH lymphomas (AITL and related entities) identified prolonged PFS in the Ro-CHOP arm (n = 103) compared with the CHOP arm (n = 98). The median PFS was 19.5 months (95% CI, 11.5 to 37.8) in the Ro-CHOP arm and 10.6 months

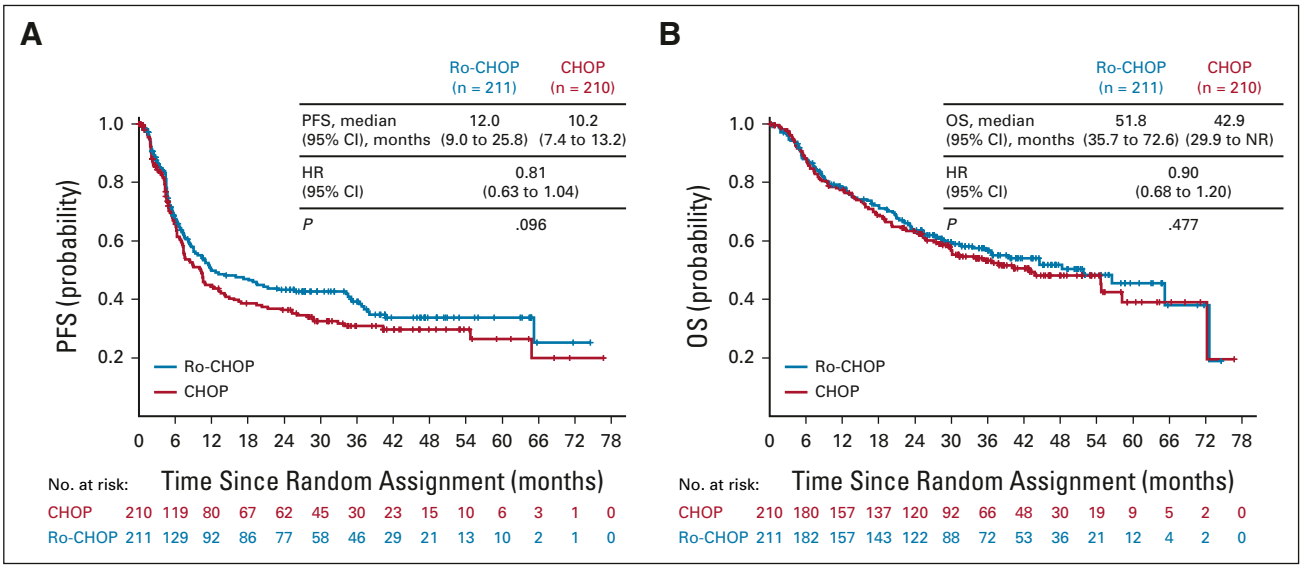


**FIG 2.** Kaplan-Meier estimates of (A) PFS and (B) OS in the Ro-CHOP and CHOP group. CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; HR, hazard ratio; NR, no response; OS, overall survival; PFS, progression-free survival; Ro-CHOP, romidepsin with cyclophosphamide, doxorubicin, vincristine, and prednisone.

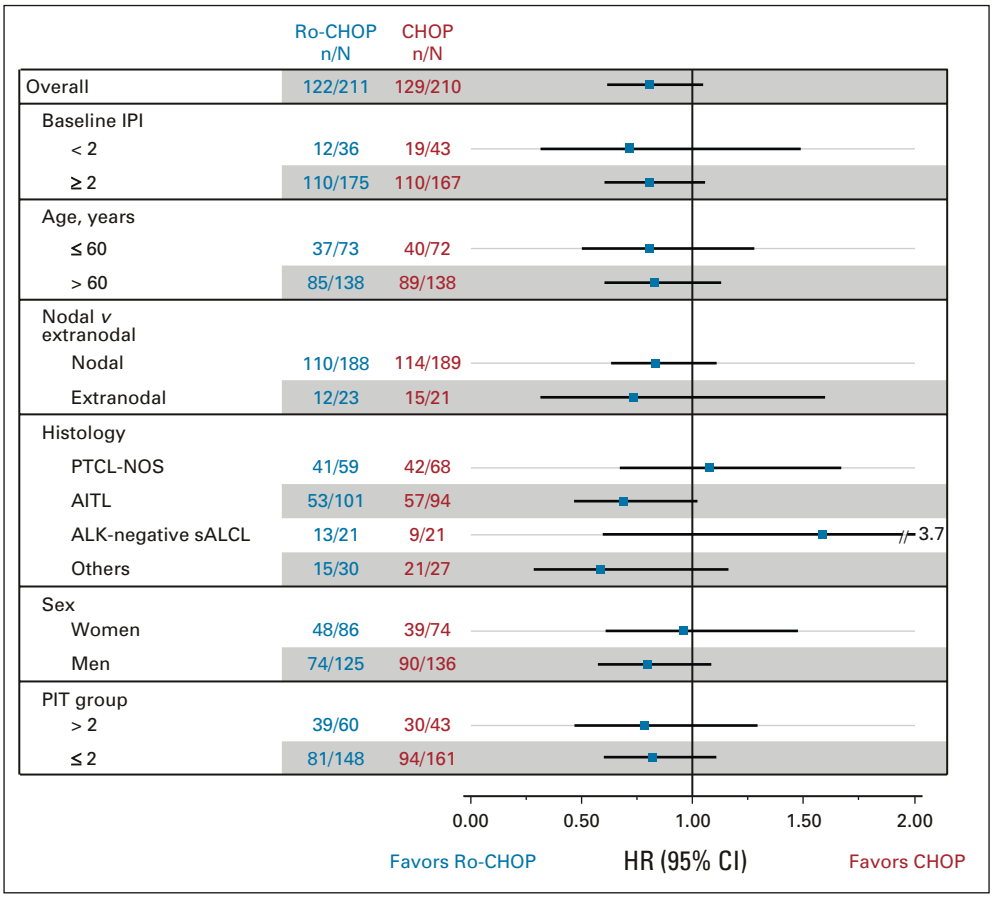


**FIG 3.** PFS according to prespecified subgroup analysis. AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; HR, hazard ratio; IPI, International Prognostic Index; PFS, progression-free survival; PIT, prognostic index for T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; Ro-CHOP, romidepsin with cyclophosphamide, doxorubicin, vincristine, and prednisone.

(95% CI, 7.4 to 14.9) in the CHOP arm with a HR of 0.69 (95% CI, 0.48 to 1.00; $P = .046$; Data Supplement).

In the safety population, the percentage of patients with at least one treatment-emergent adverse event (TEAE) of any grade was similar between the two treatment arms (99% for Ro-CHOP *v* 98% for CHOP), but grade 4 as maximum severity was higher in the Ro-CHOP arm versus CHOP arm (74% *v* 42%). The frequency of grade ≥ 3 TEAEs was higher in the Ro-CHOP arm versus CHOP arm (93.8% *v* 69.7%) with a difference ≥ 10% observed between the two treatment arms for thrombocytopenia (50.0% *v* 10.1%), neutropenia (49.0% *v* 32.7%), anemia (46.7% *v* 17.3%), leukopenia (31.9% *v* 19.7%), platelet count decreased (27.6% *v* 1.4%), neutrophil count decreased (26.2% *v* 15.4%), white blood cell count decreased (23.3% *v* 11.5%), and febrile neutropenia (21.0% *v* 9.6%, Table 2). In the Ro-CHOP arm, TEAEs led to romidepsin discontinuation in 8.1% of patients, dose reduction in 36.7%, and interruption in 62.9%. A total of 112 (53.3%) patients in the Ro-CHOP arm and 125 (60.1%) patients in the CHOP arm completed the six cycles without dose reduction or interruption for CHOP. The percentage of patients with relative dose intensity (calculated as the average of the three drugs: cyclophosphamide, doxorubicin, and vincristine) < 90% was higher in the Ro-CHOP arm (15.3%) compared with the CHOP arm (9.2%).

Death rates were similar in the two treatment arms (44.8% in the Ro-CHOP arm *v* 48.1% in the CHOP arm). The most common cause of death was lymphoma in both arms (Data Supplement). The majority of deaths occurred during the post-treatment period. Grade 5 TEAEs occurred in one patient in the Ro-CHOP arm (Escherichia coli sepsis assessed as not related to study treatments) and two patients in the CHOP arm (colitis assessed as related to CHOP treatment by the investigator and acute cholecystitis assessed as not related to study treatments).

## DISCUSSION

To our knowledge, the Ro-CHOP study is the largest randomized trial in first-line setting across various PTCL

**TABLE 2.** TEAEs in the Safety Population Reported in at Least 5% of Patients (grade 3 or higher) in Either Treatment Arm

| System Organ Class<br>Preferred Term[a] | Ro-CHOP (n = 210) | | CHOP (n = 208) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥ 3 | Any Grade | Grade ≥ 3 |
| Patients with at least 1 TEAE[b,c] | 208 (99.0) | 197 (93.8) | 203 (97.6) | 145 (69.7) |
| Blood and lymphatic system disorders | 186 (88.6) | 170 (81.0) | 126 (60.6) | 97 (46.6) |
| Thrombocytopenia | 110 (52.4) | 105 (50.0) | 35 (16.8) | 21 (10.1) |
| Neutropenia | 107 (51.0) | 103 (49.0) | 77 (37.0) | 68 (32.7) |
| Anemia | 140 (66.7) | 98 (46.7) | 80 (38.5) | 36 (17.3) |
| Leukopenia | 69 (32.9) | 67 (31.9) | 47 (22.6) | 41 (19.7) |
| Febrile neutropenia | 45 (21.4) | 44 (21.0) | 20 (9.6) | 20 (9.6) |
| Lymphopenia | 40 (19.0) | 40 (19.0) | 27 (13.0) | 22 (10.6) |
| Investigations | 133 (63.3) | 88 (41.9) | 92 (44.2) | 46 (22.1) |
| Platelet count decreased | 67 (31.9) | 58 (27.6) | 17 (8.2) | 3 (1.4) |
| Neutrophil count decreased | 56 (26.7) | 55 (26.2) | 38 (18.2) | 32 (15.4) |
| WBC count decreased | 49 (23.3) | 49 (23.3) | 33 (15.9) | 24 (11.5) |
| Lymphocyte count decreased | 34 (16.2) | 34 (16.2) | 27 (13.0) | 19 (9.1) |
| Metabolism and nutrition disorders | 105 (50.0) | 40 (19.0) | 33 (15.9) | 12 (5.8) |
| Decreased appetite | 54 (25.7) | 13 (6.2) | 11 (5.3) | 1 (0.5) |
| Hypokalemia | 30 (14.3) | 11 (5.2) | 8 (3.8) | 1 (0.5) |
| Gastrointestinal disorders | 179 (85.2) | 32 (15.2) | 128 (61.5) | 9 (4.3) |
| Vomiting | 85 (40.5) | 12 (5.7) | 20 (9.6) | 2 (1.0) |
| General disorders and administration site conditions | 139 (66.2) | 25 (11.9) | 115 (55.3) | 8 (3.8) |
| Asthenia | 61 (29.0) | 11 (5.2) | 50 (24.0) | 3 (1.4) |

NOTE. Data are No. (%).

Abbreviations: AE, adverse event; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CTCAE, Common Terminology Criteria for Adverse Events; Ro-CHOP, romidepsin with cyclophosphamide, doxorubicin, vincristine, and prednisone; TEAE, treatment-emergent adverse event.

[a]System organ classes and preferred terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (Version 22.0). A patient was counted only once for multiple events within preferred term/system organ class.

[b]TEAEs included AEs that started or worsened or became serious between the date of first dose and 30 days after the date of last dose.

[c]Severity graded according to CTCAE, version 4.03.



histologies excluding ALK+ ALCL, a known subgroup with a more favorable outcome. A total of 421 patients, predominantly with AITL, PTCL-NOS, or ALK-negative ALCL, were enrolled and randomly assigned to either six 3-week interval cycles of standard CHOP regimen or CHOP with romidepsin 12 mg/m$^2$ once daily on days 1 and 8. The study did not demonstrate a PFS advantage for romidepsin added to CHOP compared with CHOP alone in first-line PTCL (HR = 0.81, $P$ = .0962) and confirmed the overall very poor outcome in these patients.

Secondary end point analyses showed that DOR was significantly prolonged by the addition of romidepsin to CHOP, suggesting that quality of response, despite overlapping ORR and CR/CRu rates at the end of induction as per Cheson 1999 criteria, could be slightly better in the romidepsin arm of treatment. The borderline statistical significance of this secondary end point analysis and the large proportion of patients failing to achieve a response at the end of treatment likely explain why DOR prolongation did not translate into statistically longer PFS. Furthermore, given the low level of evidence because of multiple testing on this subgroup of the ITT patient population, this result should be interpreted with caution.

Main severe (grade ≥ 3) adverse events with romidepsin in association with CHOP compared with CHOP alone were of hematologic, gastrointestinal, or nutritional origin, in agreement with the previously known safety profile of the drug used as a single agent or in association with CHOP in the phase Ib and II study.[11] Of concern, the addition of romidepsin led to more frequent dose reduction or interruption and a lower dose intensity of the CHOP backbone compared with the CHOP-alone control arm, which could explain at least in part the absence of significant benefit of adding romidepsin. Cardiac toxicity was monitored as an adverse event of special interest because of previously reported early cardiac events or T-wave abnormalities with romidepsin.[11,13] Importantly, no difference was observed between the two treatment arms despite more frequent metabolism disorders and especially grade ≥ 3 hypokalemia in the Ro-CHOP arm.

In an exploratory analysis in the centrally confirmed histologic subgroup of PTCL of putative TFH origin, as defined by the latest WHO classification,[3] a significant PFS prolongation was observed in the Ro-CHOP arm. Although statistical considerations preclude any firm conclusion, this is in line with previous reports showing prolonged response duration in patients with R/R AITL treated with romidepsin and a recent retrospective study finding a benefit of histone deacetylase inhibitors in PTCL exhibiting a TFH phenotype.[14,15]

The median PFS and OS were 10 and 43 months in the CHOP arm compared with 12 and 52 months in the Ro-CHOP arm, respectively. At 2 years, the PFS and OS were 36% and 63% in the CHOP arm compared with 43% and 64% in the Ro-CHOP arm. These figures are comparable with the previously reported survival in a randomized trial comparing CHOP with an intensified chemotherapy regimen in patients with PTCL (ALK+ ALCL excluded) where the median event-free survival (EFS) was 12 months, the 2-year EFS was 43%, and the median OS was 42 months.[6] In the international peripheral T-cell and natural killer/T-cell lymphoma study, 5-year failure-free survivals were 20%, 18%, and 36% in patients with PTCL-NOS, AITL, and ALK-negative ALCL, respectively. Corresponding 5-year OS rates were 32%, 32%, and 49%, respectively.[1] In the study published by the German group in patients treated with standard or intensified CHOP with or without etoposide, the 3-year EFS and OS were 41% and 54% for PTCL-NOS, 50% and 67% for AITL, and 46% and 62% for ALK-negative ALCL.[16] Altogether, results appear comparable with those reported in the present study.

In recent years, first-line regimens built on a CHOP-like backbone have been studied in three randomized trials. Alemtuzumab in association with CHOP did not show any superiority in young nor in elderly patients.[7,8] The addition of BV to CHP was associated with a prolonged PFS and OS in PTCL with more than 10% CD30+ tumoral cells by immunohistochemistry.[9] A limitation of the study was the low number of patients with non-ALCL histology, and consequently, BV + CHP has been approved by the US Food and Drug Administration and in Japan in first-line CD30+ PTCL (whatever the percent of positive cells) and approved by the European Medicines Agency for adult patients with previously untreated systemic ALCL.

In the Ro-CHOP study, autologous stem-cell transplant (ASCT) was not allowed according to the trial Protocol. The role of ASCT in first line is still highly controversial. A large prospective trial from the Nordic Lymphoma Group has reported long PFS with a median of more than 30 months after six cycles of CHOEP (CHOP plus etoposide) and ASCT following the conditioning regimen.[17] However, the lack of random assignment against a control arm without ASCT consolidation precluded drawing firm conclusions. Our group did not find any superior outcome favoring ASCT in first-line PTCL in a large retrospective propensity score-matching analysis for patients in response after induction.[18] Recently, no superiority of allogeneic stem-cell transplant over ASCT in first line was observed in the randomized phase III AATT trial conducted by the Lymphoma Study Association and the German Lymphoma Alliance.[19]

In conclusion, the addition of romidepsin to CHOP in first-line PTCL did not translate into significantly prolonged PFS and was associated with higher toxicity, leading to lower dose intensity in the CHOP backbone. Higher toxicity was expected from the phase I and II study results, but benefit was expected to override potential drug discontinuation or dose modification. The Ro-CHOP study could help further refine balance between toxicity and expected potency before embarking into such a large phase III study. The suggested benefit in TFH-like histologies (AITL and TFH PTCL) was marginal but in line with data in the R/R setting and warrants further investigation. Ancillary analyses combining positron emission and CT, cell-free DNA response assessment, and biomolecular markers could refine the identification of patients likely to benefit from romidepsin in the first-line or R/R setting. Recent data demonstrated impressive ORR and complete response rates from the combination or romidepsin and oral azacytidine for AITL in frontline setting with much lower toxicity than observed with the combination of CHOP and romidepsin.[20] Such strategies using drug synergy with specific activity in well-delineated PTCL subtypes will probably pave the way for achieving better outcome and overcome the poor survival associated with the disease. However, a CHOP-like regimen (with or without the addition of BV in CD30+ cases) remains for now the standard treatment for PTCL in first line. Thus, identifying better treatments remains a major unmet need for most patients with PTCL.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Romidepsin Plus CHOP Versus CHOP in Patients With Previously Untreated Peripheral T-Cell Lymphoma: Results of the Ro-CHOP Phase III Study (Conducted by LYSA)**

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