

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)

Emmanuel Bachy, MD, PhD^{1,2}; Vincent Camus, MD³; Catherine Thieblemont, MD, PhD⁴; David Sibon, MD, PhD⁵; René-Olivier Casasnovas, MD⁶; Loïc Ysebaert, MD, PhD⁷; Gandhi Damaj, MD, PhD⁸; Stéphanie Guidez, MD⁹; Gian Matteo Pica, MD¹⁰; Won Seog Kim, MD, PhD¹¹; Soon Thye Lim, MBBS¹²; Marc André, MD¹³; Alejandro Martín García-Sancho, MD, PhD¹⁴; Maria Jesus Penarrubia, MD, PhD¹⁵; Philipp B. Staber, MD, PhD¹⁶; Judith Trotman, MBChB¹⁷; Andreas Hüttmann, MD¹⁸; Vittorio Stefani, MD, PhD¹⁹; Alessandro Re, MD²⁰; Philippe Gaulard, MD²¹; Marie-Helene Delfau-Larue, MD, PhD²²; Laurence de Leval, MD, PhD²³; Michel Meignan, MD, PhD²⁴; Ju Li, PhD²⁵; Franck Morschhauser, MD, PhD²⁶; and Richard Delarue, MD^{5,27}

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/m², 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.

J Clin Oncol 40:242-251. © 2021 by American Society of Clinical Oncology

ASSOCIATED CONTENT

See accompanying editorial on page 221

[Data Supplement Protocol](#)

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on October 25, 2021 and published at ascopubs.org/journal/jco on November 29, 2021; DOI <https://doi.org/10.1200/JCO.21.01815>

INTRODUCTION

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous 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 etoposide⁵ or etoposide, ifosfamide, and cisplatin alternating with doxorubicin, bleomycin, vinblastine, and dacarbazine⁶ 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/m² 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 ≤ 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, ≤ 1 v > 1), and age (≤ 60 v > 60 years). Patients received six 21-day cycles of either CHOP (day 1 included cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m² [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/m² once daily) alone or with intravenous romidepsin 12 mg/m² 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)

(continued in next column)

TABLE 1. Patient Characteristics (continued)

Parameter	Ro-CHOP (n = 211)	CHOP (n = 210)	Total (N = 421)
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.

^aLDH 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 lymphomas³ 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

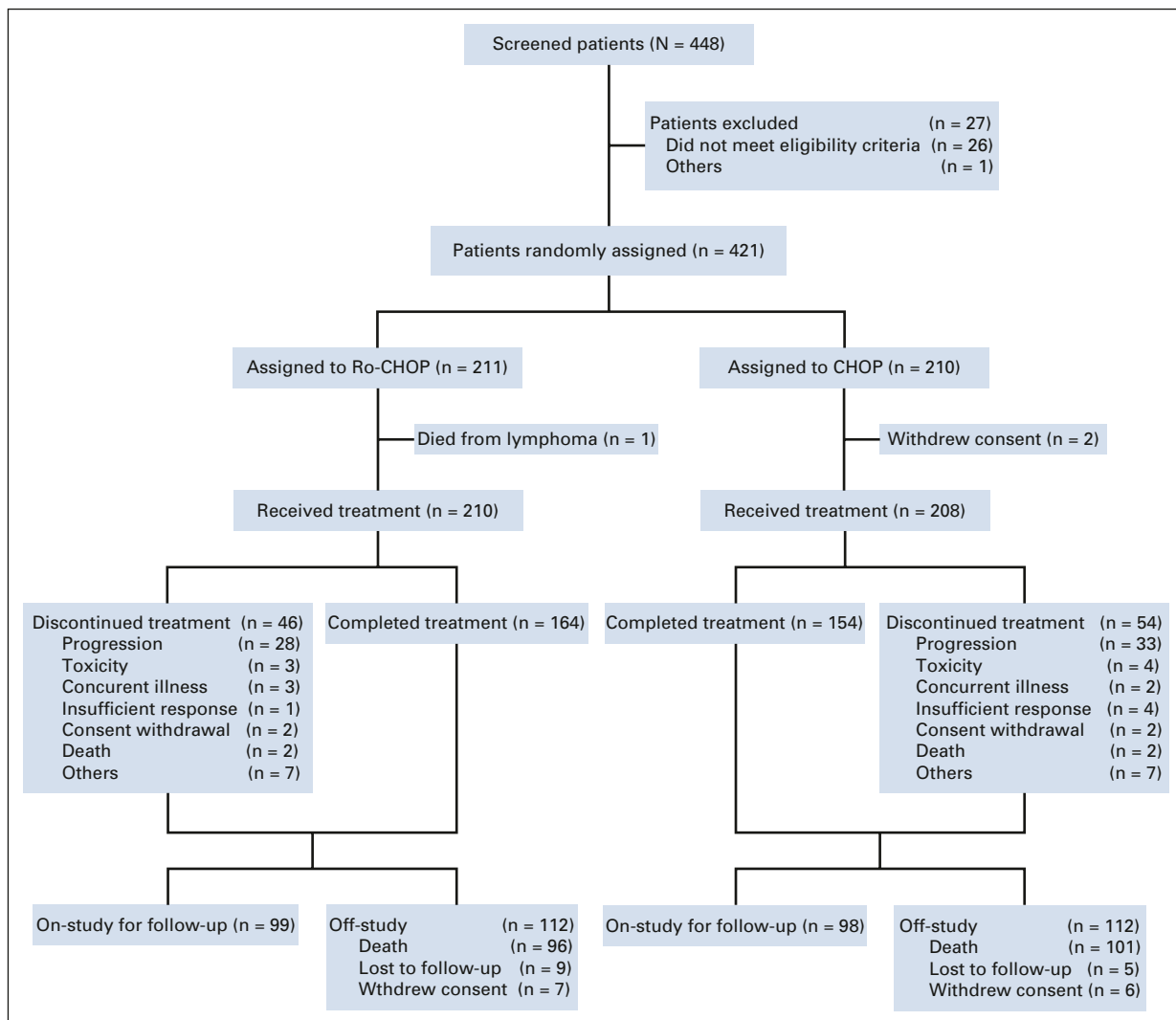


FIG 1. CONSORT diagram. CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; Ro-CHOP, romidepsin with cyclophosphamide, doxorubicin, vincristine, and prednisone.

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](https://clinicaltrials.gov/ct2/show/study/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

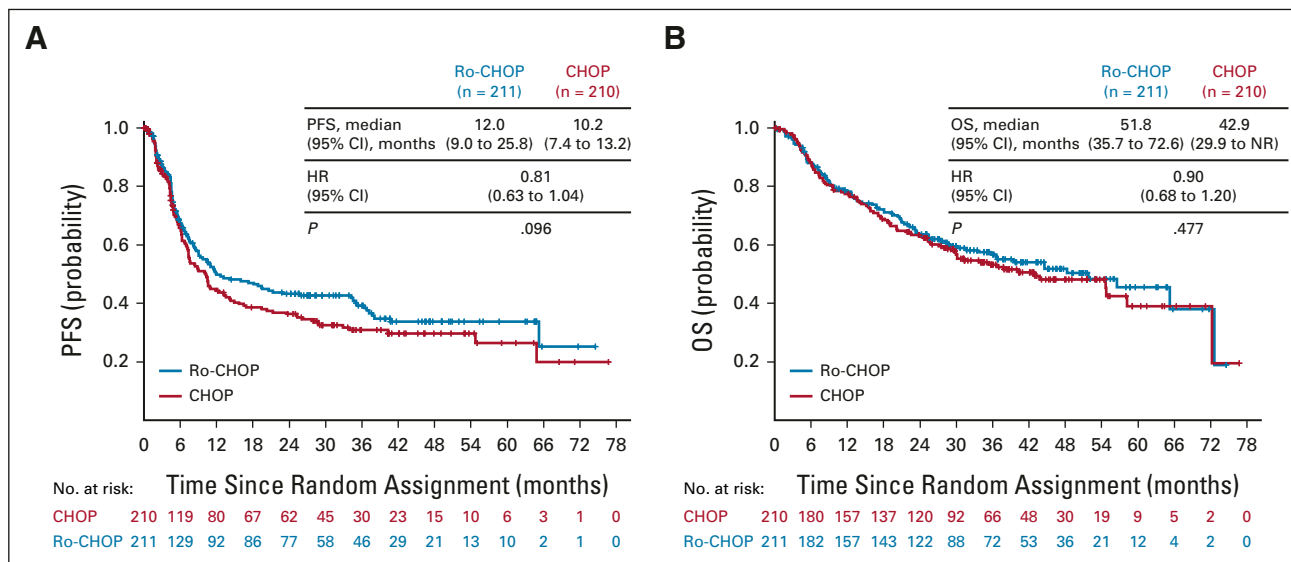


FIG 2. Kaplan-Meier estimates of (A) PFS and (B) OS in the Ro-CHOP and CHOP group. CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; HR, hazard ratio; NR, no response; OS, overall survival; PFS, progression-free survival; Ro-CHOP, romidepsin with cyclophosphamide, doxorubicin, vincristine,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

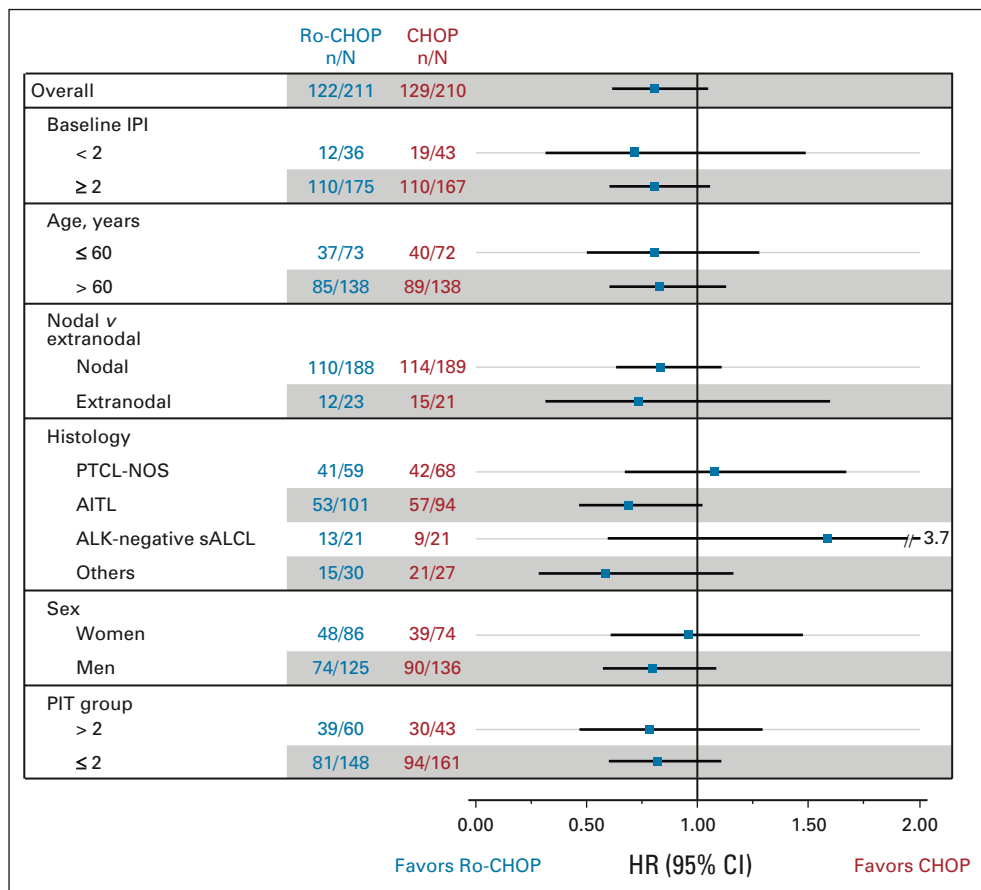


FIG 3. PFS according to prespecified subgroup analysis. AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; HR, hazard ratio; IPI, International Prognostic Index; PFS, progression-free 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 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.

^aSystem 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.

^bTEAEs included AEs that started or worsened or became serious between the date of first dose and 30 days after the date of last dose.

^cSeverity 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/m² 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 CHOP 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 + CHOP 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 of 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.

AFFILIATIONS

¹Hospices Civils de Lyon, Lyon, France

²Claude Bernard Lyon 1 University, Lyon, France

³Department of Hematology, Centre Henri Becquerel, Rouen, France

⁴APHP, Hôpital Saint-Louis, Service d'hémo-oncologie, DMU DHI, Université de Paris, Paris, France

⁵Service d'Hématologie adultes, Hôpital Universitaire Necker Enfants Malades, AP-HP, Paris, France

⁶Department of Hematology, CHU Dijon-Bourgogne and INSERM 1231, Dijon, France

⁷IUCT Oncopole, Toulouse, France

⁸Hematology Institute, University Hospital, Normandy University, School of Medicine, Caen, France

⁹Service d'Hématologie, CHU de Poitiers, Poitiers, France

¹⁰Department of Hematology, Centre Hospitalier Métropole Savoie Chambéry, Chambéry, France

¹¹Samsung Medical Center, Seoul, South Korea

¹²National Cancer Centre Singapore, Singapore

¹³Department of Hematology, CHU UCL Namur, Yvoir, Belgium

¹⁴Hospital Universitario de Salamanca, IBSAL, CIBERONC, Salamanca, Spain

¹⁵Hospital Clinico Universitario de Valladolid, Valladolid, Spain

¹⁶Division of Hematology, Department of Medicine I, Medical University of Vienna, Vienna, Austria

¹⁷Concord Repatriation General Hospital, University of Sydney, Concord, Australia

¹⁸Department of Hematology and Stem Cell Transplantation, West German Cancer Center Essen, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

¹⁹Polislinico Sant'Orsola-Malpighi, Bologna, Italy

²⁰Hematology Division, Spedali Civili di Brescia, Brescia, Italy

²¹Department of Pathology and Inserm U955, University Hospital Henri Mondor, Créteil, France

²²Department of Immunobiology and Inserm U955, Université Hôpital Henri Mondor, Créteil, France

²³Institute of Pathology, Lausanne University Hospital, Lausanne University, Lausanne, Switzerland

²⁴LYSA Imaging, APHP, Hôpital Henri Mondor, Université Paris Est, Créteil, France

²⁵Bristol Myers Squibb Company, Princeton, NJ

²⁶Univ. Lille, CHU Lille, ULR 7365 – GRITA – Groupe de Recherche sur les Formes Injectables et les Technologies Associées, Lille, France

²⁷Celgene, a Bristol Myers Squibb Company, Boudry, Switzerland

CORRESPONDING AUTHOR

Emmanuel Bachy, MD, PhD, Hematology Department, Lyon Sud Hospital, Building 1F – 3rd floor, 165 Chemin du Grand Revoyet, 69495 Pierre-Bénite Cedex, France; e-mail: emmanuel.bachy@chu-lyon.fr.

SUPPORT

Supported by the LYSARC, with funding provided by Celgene/BMS. Writing and editorial assistance were provided by Benjamin Levine, PhD, of Bio Connections LLC, funded by Bristol Myers Squibb Company.

CLINICAL TRIAL INFORMATION

NCT01796002

REFERENCES

1. Vose J, Armitage J, Weisenburger D, et al: International peripheral T-cell and natural killer/T-cell lymphoma study: Pathology findings and clinical outcomes. *J Clin Oncol* 26:4124-4130, 2008
2. Laurent C, Baron M, Amara N, et al: Impact of expert pathologic review of lymphoma diagnosis: Study of patients from the French Lymphopath Network. *J Clin Oncol* 35:2008-2017, 2017
3. Swerdlow SH, Campo E, Harris NL, et al (eds): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, in WHO Classification of Tumors, Volume 2. Lyon, France, IARC, 2017
4. Gleeson M, Peckitt C, To YM, et al: CHOP versus GEM-P in previously untreated patients with peripheral T-cell lymphoma (CHEMO-T): A phase 2, multicentre, randomised, open-label trial. *Lancet Haematol* 5:e190-e200, 2018
5. Nickelsen M, Ziepert M, Zeynalova S, et al: High-dose CHOP plus etoposide (MegaCHOEP) in T-cell lymphoma: A comparative analysis of patients treated within trials of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). *Ann Oncol* 20:1977-1984, 2009
6. Simon A, Pech M, Casassus P, et al: Upfront VIP-reinforced-ABVD (VIP-rABVD) is not superior to CHOP/21 in newly diagnosed peripheral T cell lymphoma. Results of the randomized phase III trial GOELAMS-LTP95. *Br J Haematol* 151:159-166, 2010
7. d'Amore F, Leppä S, Silva MGD, et al: Final analysis of the front-line phase III randomized ACT-1 trial in younger patients with systemic peripheral T-cell lymphoma treated with CHOP chemotherapy with or without Alemtuzumab and consolidated by autologous hematopoietic stem cell transplant. *Blood* 132:998, 2018
8. Wulf GG, Altmann B, Ziepert M, et al: Alemtuzumab plus CHOP versus CHOP in elderly patients with peripheral T-cell lymphoma: The DSHNHL2006-1B/ACT-2 trial. *Leukemia* 35:143-155, 2020
9. Horwitz S, O'Connor OA, Pro B, et al: Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHOLON-2): A global, double-blind, randomised, phase 3 trial. *Lancet* 393:229-240, 2019
10. Coiffier B, Pro B, Prince HM, et al: Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. *J Clin Oncol* 30:631-636, 2012
11. Dupuis J, Morschhauser F, Ghesquieres H, et al: Combination of romidepsin with cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated patients with peripheral T-cell lymphoma: A non-randomised, phase 1b/2 study. *Lancet Haematol* 2:e160-5, 2015
12. Cheson BD, Horning SJ, Coiffier B, et al: Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol* 17:1244, 1999
13. Whittaker SJ, Demierre MF, Kim EJ, et al: Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. *J Clin Oncol* 28:4485-4491, 2010

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI <https://ascopubs.org/doi/full/10.1200/JCO.21.01815>.

AUTHOR CONTRIBUTIONS

Conception and design: Emmanuel Bachy, Vittorio Stefoni, Michel Meignan, Ju Li, Richard Delarue

Provision of study materials or patients: Emmanuel Bachy, Loïc Ysebaert, Gandhi Damaj, Won Seog Kim, Soon Thye Lim, Marc André, Alejandro Martín García-Sancho, Philipp B. Staber, Judith Trotman, Laurence de Leval, Franck Morschhauser

Collection and assembly of data: Emmanuel Bachy, Vincent Camus, Catherine Thieblemont, David Sibon, René-Olivier Casasnovas, Loïc Ysebaert, Gandhi Damaj, Stéphanie Guidez, Gian Matteo Pica, Soon Thye Lim, Marc André, Alejandro Martín García-Sancho, Maria Jesus Penarrubia, Philipp B. Staber, Judith Trotman, Andreas Hüttmann, Vittorio Stefoni, Alessandro Re, Philippe Gaulard, Marie-Helene Delfau-Larue, Laurence de Leval, Michel Meignan, Ju Li, Franck Morschhauser

Data analysis and interpretation: Emmanuel Bachy, Vincent Camus, David Sibon, René-Olivier Casasnovas, Gandhi Damaj, Won Seog Kim, Marc André, Alejandro Martín García-Sancho, Philippe Gaulard, Laurence de Leval, Michel Meignan, Ju Li, Franck Morschhauser, Richard Delarue

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We would like to thank all the patients, families, and caregivers who participated in the study. We also acknowledge LYSARC for sponsoring the trial, coordinating the study sites, and conducting the analysis and every research team and nurse in the participating centers.

14. Ghione P, Faruque P, Mehta-Shah N, et al: T follicular helper phenotype predicts response to histone deacetylase inhibitors in relapsed/refractory peripheral T-cell lymphoma. *Blood Adv* 4:4640-4647, 2020
15. Pro B, Horwitz SM, Prince HM, et al: Romidepsin induces durable responses in patients with relapsed or refractory angioimmunoblastic T-cell lymphoma. *Hematol Oncol* 35:914-917, 2017
16. Schmitz N, Trumper L, Ziepert M, et al: Treatment and prognosis of mature T-cell and NK-cell lymphoma: An analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. *Blood* 116:3418-3425, 2010
17. d'Amore F, Relander T, Lauritzsen GF, et al: Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. *J Clin Oncol* 30:3093-3099, 2012
18. Fossard G, Broussais F, Coelho I, et al: Role of up-front autologous stem-cell transplantation in peripheral T-cell lymphoma for patients in response after induction: An analysis of patients from LYSA centers. *Ann Oncol* 29:715-723, 2018
19. Schmitz N, Truemper LH, Bouabdallah K, et al: A randomized phase 3 trial of auto vs. allogeneic transplantation as part of first-line therapy in poor-risk peripheral T-NHL. *Blood* 137:2646-2656, 2020
20. Falchi L, Ma H, Klein S, et al: Combined oral 5-azacytidine and romidepsin are highly effective in patients with PTCL: A multicenter phase 2 study. *Blood* 137:2161-2170, 2021



ASCO® Meetings

ASCO offers premier scientific events for oncology professionals, patient advocates, industry representatives, and major media outlets worldwide.

View upcoming meetings and symposia at meetings.asco.org

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)**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/nwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](#)).

Emmanuel Bachy

Honoraria: Gilead Sciences, Roche, Amgen, Janssen-Cilag

Consulting or Advisory Role: Roche, Gilead Sciences, Incyte, Takeda

Research Funding: Amgen Foundation (Inst)

Travel, Accommodations, Expenses: Janssen-Cilag, Roche, Gilead Sciences, Incyte

Vincent Camus

Honoraria: Roche/Genentech, Incyte, Janssen, Gilead Sciences, Novartis

Consulting or Advisory Role: Roche

Research Funding: iQone Healthcare (Inst)

Travel, Accommodations, Expenses: Pfizer, Roche

Catherine Thieblemont

Honoraria: Celgene, AbbVie, Bayer, Janssen, Roche, Incyte, Novartis, Gilead Sciences

Research Funding: Roche

Travel, Accommodations, Expenses: Roche, Janssen-Cilag, Kite/Gilead, Novartis

David Sibon

Consulting or Advisory Role: Takeda, iQone Healthcare, Janssen, Roche, AbbVie

Travel, Accommodations, Expenses: Takeda, Janssen

René-Olivier Casasnovas

Honoraria: Roche/Genentech, Takeda, Gilead Sciences, Bristol Myers Squibb, Merck, AbbVie, Celgene, Janssen, Amgen

Consulting or Advisory Role: Roche/Genentech, Takeda, Gilead Sciences, Bristol Myers Squibb, Merck, AbbVie, Celgene, Janssen, Incyte

Research Funding: Roche/Genentech (Inst), Gilead Sciences (Inst), Takeda (Inst)

Travel, Accommodations, Expenses: Roche/Genentech, Takeda, Gilead Sciences, Janssen

Loïc Ysebaert

Honoraria: AbbVie

Consulting or Advisory Role: AbbVie, Janssen-Cilag, Roche, Gilead Sciences

Research Funding: Roche (Inst), Janssen-Cilag (Inst), Gilead Sciences (Inst)

Gandhi Damaj

Consulting or Advisory Role: Roche/Genentech, Takeda, iQone

Research Funding: Takeda

Travel, Accommodations, Expenses: PFIZER, Roche/Genentech, AbbVie

Stéphanie Guidez

Consulting or Advisory Role: Kite/Gilead

Travel, Accommodations, Expenses: Janssen

Marc André

Consulting or Advisory Role: Takeda, BMSi

Research Funding: Takeda (Inst), Roche (Inst)

Travel, Accommodations, Expenses: Roche, Celgene, Gilead Sciences

Alejandro Martín García-Sancho

Honoraria: Roche, Janssen-Cilag, Celgene, Servier, Gilead Sciences, Takeda

Consulting or Advisory Role: Roche, Celgene, MorphoSys, Kyowa Hakko Kirin, iQone, EUSA Pharma, Gilead Sciences, Novartis, Servier, Incyte

Expert Testimony: Gilead Sciences

Travel, Accommodations, Expenses: Roche, Celgene, Servier

Maria Jesus Penarrubia

Honoraria: AbbVie, Celgene, Servier, Takeda, Roche

Consulting or Advisory Role: Gilead Sciences, Novartis, Celgene, AbbVie, Takeda, Clinigen Group

Research Funding: Celgene

Travel, Accommodations, Expenses: Amgen, Servier, Novartis, Janssen, Celgene, Takeda

Philipp B. Staber

Honoraria: Roche, Amgen, Takeda, Abbott/AbbVie, Janssen Oncology, Incyte, Celgene, Bristol Myers Squibb/Pfizer, MSD Oncology, AstraZeneca

Research Funding: Roche (Inst)

Judith Trotman

Research Funding: BeiGene (Inst), Roche/Genentech (Inst), Pharmacycics (Inst), Janssen-Cilag (Inst), Takeda (Inst), Celgene (Inst)

Travel, Accommodations, Expenses: Roche/Genentech

Andreas Hüttmann

Honoraria: Takeda

Consulting or Advisory Role: Takeda

Travel, Accommodations, Expenses: Roche Pharma AG

Philippe Gaulard

Honoraria: Takeda, Gilead Sciences

Consulting or Advisory Role: Takeda

Research Funding: Takeda (Inst), Innate Pharma (Inst), Sanofi (Inst)

Travel, Accommodations, Expenses: Roche

Marie-Helene Delfau-Larue

Honoraria: Gilead Sciences, Amgen

Research Funding: Roche, Celgene

Travel, Accommodations, Expenses: Mundipharma

Laurence de Leval

Honoraria: Novartis (Inst)

Consulting or Advisory Role: Lunaphore Technologies (Inst), Bayer (Inst)

Michel Meignan

Honoraria: Roche

Travel, Accommodations, Expenses: Roche

Ju Li

Employment: Bristol Myers Squibb/Celgene

Stock and Other Ownership Interests: Bristol Myers Squibb/Celgene

Research Funding: Bristol Myers Squibb/Celgene

Travel, Accommodations, Expenses: Bristol Myers Squibb/Celgene

Franck Morschhauser

Consulting or Advisory Role: Roche/Genentech, Gilead Sciences, Celgene, Bristol Myers Squibb, AbbVie, Epizyme, Servier

Speakers' Bureau: Roche

Expert Testimony: Roche/Genentech

Richard Delarue

Employment: Celgene/Bristol Myers Squibb, BeiGene

Stock and Other Ownership Interests: Celgene/Bristol Myers Squibb, BeiGene

No other potential conflicts of interest were reported.