Supplementary Material

Supplemental table 1. **Detailed histological diagnoses (by local pathologist)**

	Treatment Arm		ITT Set
	Ro-CHOP	CHOP	
	N=211	N=210	N=421
Histological diagnosis (local)			
Nodal	**181 (85.8%)**	**183 (87.1%)**	**364 (86.5%)**
PTCL, not otherwise specified	59 (28.0%)	68 (32.4%)	127 (30.2%)
Angioimmunoblastic T-cell lymphoma	101 (47.9%)	94 (44.8%)	195 (46.3%)
Anaplastic large cell lymphoma, ALK-negative type	21 (10.0%)	21 (10.0%)	42 (10.0%)
Extra-Nodal	**15 (7.1%)**	**16 (7.6%)**	**31 (7.4%)**
Enteropathy-associated T-cell lymphoma	5 (2.4%)	11 (5.2%)	16 (3.8%)
Hepato-splenic T-cell lymphoma	1 (0.5%)	1 (0.5%)	2 (0.5%)
Subcutaneous panniculitis-like T-cell lymphoma	7 (3.3%)	2 (1.0%)	9 (2.1%)
Primary cutaneous gamma-delta T-cell lymphoma	1 (0.5%)	1 (0.5%)	2 (0.5%)
Primary cutaneous CD8 positive aggressive epidermotropic lymphoma	1 (0.5%)	0 (0.0%)	1 (0.2%)
Primary cutaneous CD4 positive small/medium T-cell lymphoma	0 (0.0%)	1 (0.5%)	1 (0.2%)
Other non classifiable peripheral T-cell lymphoma	**14 (6.6%)**	**11 (5.2%)**	**25 (5.9%)**
Other histological diagnosis	**1 (0.5%)**	**0 (0.0%)**	**1 (0.2%)**

Data are n (%).

ALK, anaplastic lymphoma kinase; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; PTCL, peripheral T-cell lymphoma; Ro-CHOP, romidepsin, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Supplemental table 2. **Response rates at the end of induction according to investigator's assessment (intent-to-treat population)**

Parameter	Ro-CHOP Arm	CHOP Arm
	N = 211	**N = 210**
Response at the end of treatment period*		
Complete Response	72 (34.1)	55 (26.2)
Unconfirmed Complete Response	15 (7.1)	23 (11.0)
Partial Response	46 (21.8)	49 (23.3)
Stable Disease	5 (2.4)	7 (3.3)
Progressive Disease	56 (26.5)	51 (24.3)
Not Evaluated	17 (8.1)	25 (11.9)
Complete response rate (CR + CRu)	87 (41.2)	78 (37.1)
95% CI†	(34.5, 48.2)	(30.6, 44.1)
p-value‡	0.2146	
Objective response rate (CR + CRu + PR)	133 (63.0)	127 (60.5)
95% CI†	(56.1, 69.6)	(53.5, 67.1)
p-value‡	0.4758	

Data are n (%).

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CI, confidence interval; CR, complete response; CRu, unconfirmed complete response; IPI, international prognostic index; NHL, non-Hodgkin lymphoma; PR, partial response; Ro-CHOP, romidepsin, cyclophosphamide, doxorubicin, vincristine, and prednisone.

*Response at the end of treatment was based on the International Working Group response criteria for NHL (Cheson, 1999).

†Exact CI for binomial distribution.

‡Two-sided p-value obtained from Cochran-Mantel-Haenszel test adjusting for all 3 stratification factors: derived baseline IPI (< 2, ≥ 2); Age (≤ 60, > 60 years); derived histology by investigator (Nodal vs Extranodal).

Percentage is based on the total number of patients in each treatment arm.

Supplemental table 3. **Reclassification of local histology diagnosis by central review leading to major PTCL subtype reclassification or diagnosis change**

Initial diagnosis	Final diagnosis
Mycosis fungoides	Lymphomatoid papulosis
Peripheral T-cell lymphoma not otherwise specified	Extranodal NK/T cell lymphoma- nasal type
ALK-negative anaplastic large cell lymphoma	Enteropathy-associated T-cell lymphoma
Peripheral T-cell lymphoma not otherwise specified	Enteropathy-associated T-cell lymphoma
Peripheral T-cell lymphoma not otherwise specified	Monomorphic epitheliotropic intestinal T-cell lymphoma
Angioimmunoblastic T-cell lymphoma	Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder
Angioimmunoblastic T-cell lymphoma	Bone marrow biopsy with possible involvement
Angioimmunoblastic T-cell lymphoma	Bone marrow biopsy with possible involvement
Angioimmunoblastic T-cell lymphoma	Unclassifiable diffuse large cell lymphoma
Peripheral T-cell lymphoma not otherwise specified	Unclassifiable diffuse large cell lymphoma
Angioimmunoblastic T-cell lymphoma	Unclassifiable diffuse large cell lymphoma
Peripheral T-cell lymphoma not otherwise specified	Unclassifiable diffuse large cell lymphoma
Angioimmunoblastic T-cell lymphoma	Classical Hodgkin lymphoma
ALK-negative anaplastic large cell lymphoma	Classical Hodgkin lymphoma
Peripheral T-cell lymphoma not otherwise specified	Nodular sclerosis classical Hodgkin lymphoma
Angioimmunoblastic T-cell lymphoma	Histiocyte-rich Hodgkin
Diagnosis of tumour uncertain	Diagnosis of tumour uncertain
Follicular T-cell lymphoma	Diagnosis of tumour uncertain
Diagnosis of tumour uncertain	Diagnosis of tumour uncertain
Peripheral T-cell lymphoma not otherwise specified	Non tumoral (lesion)
Hepatosplenic T-cell lymphoma	Non tumoral (lesion)
Angioimmunoblastic T-cell lymphoma	Non tumoral (lesion)
Peripheral T-cell lymphoma not otherwise specified	Non tumoral (lesion)

Supplemental table 4. **Causes of death according to treatment arm in the safety population**

Primary Cause	Ro-CHOP (n=210)	CHOP (n=208)
Overall number of deaths	**94 (44.8%)**	**100 (48.1%)**
Cause of Death*		
Lymphoma	72 (34.3%)	74 (35.6%)
Concurrent illness (including unrelated cancer)	8 (3.8%)	14 (6.7%)
Other reason	7 (3.3%)	3 (1.4%)
Toxicity of additional treatment	2 (1.0%)	4 (1.9%)
Toxicity of study treatment (including related cancer)	1 (0.5%)	2 (1.0%)
Unknown	4 (1.9%)	3 (1.4%)
Deaths		
On Treatment†	**5 (2.4%)**	**3 (1.4%)**
Lymphoma	4 (1.9%)	1 (0.5%)
Concurrent illness (including unrelated cancer)	1 (0.5%)	1 (0.5%)
Toxicity of study treatment (including related cancer)	0	1 (0.5%)
Off Treatment‡	**89 (42.4%)**	**97 (46.6%)**
Lymphoma	68 (32.4%)	73 (35.1%)
Concurrent illness (including unrelated cancer)	7 (3.3%)	13 (6.3%)
Other reason	7 (3.3%)	3 (1.4%)
Toxicity of additional treatment	2 (1.0%)	4 (1.9%)
Toxicity of study treatment (including related cancer)	1 (0.5%)	1 (0.5%)
Unknown	4 (1.9%)	3 (1.4%)

Data are n (%).

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; Ro-CHOP, romidepsin, cyclophosphamide, doxorubicin, vincristine, and prednisone.

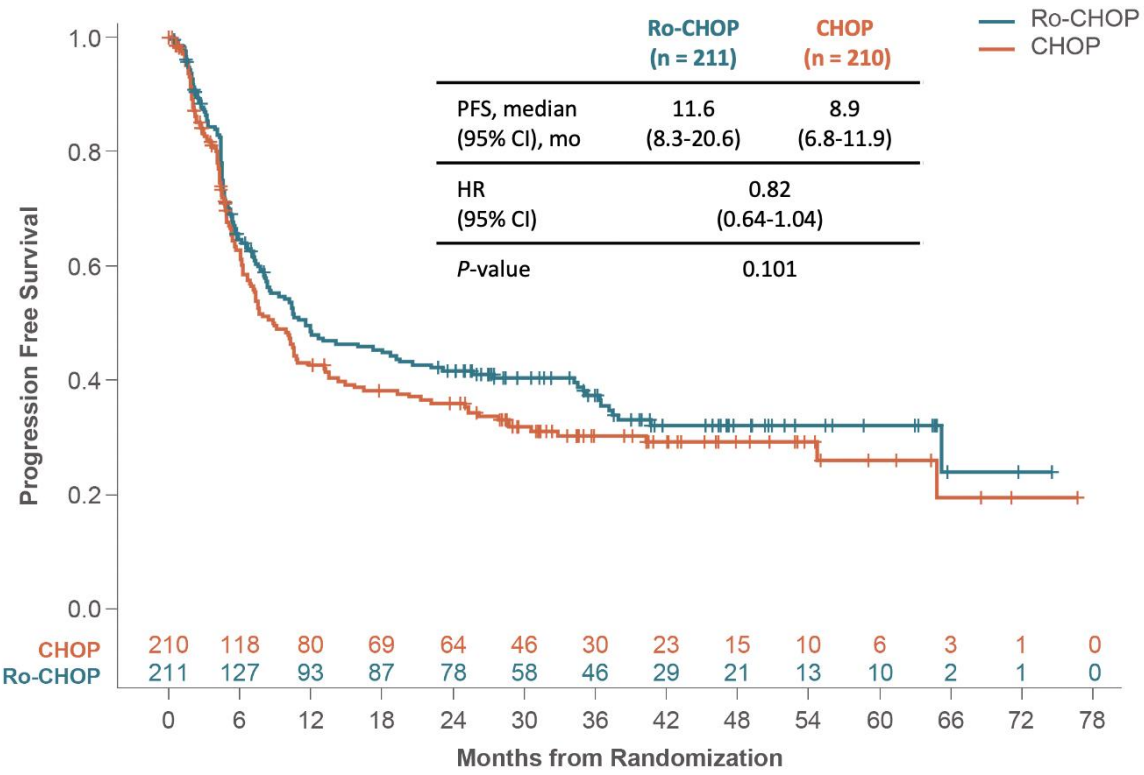
*Only deaths that occurred after the first dose of study treatment are included.

†On treatment includes deaths that occurred from the first dose of study treatment until 30 days after the last dose of study treatment.

‡Off treatment includes deaths that occurred more than 30 days after the last dose of study treatment.

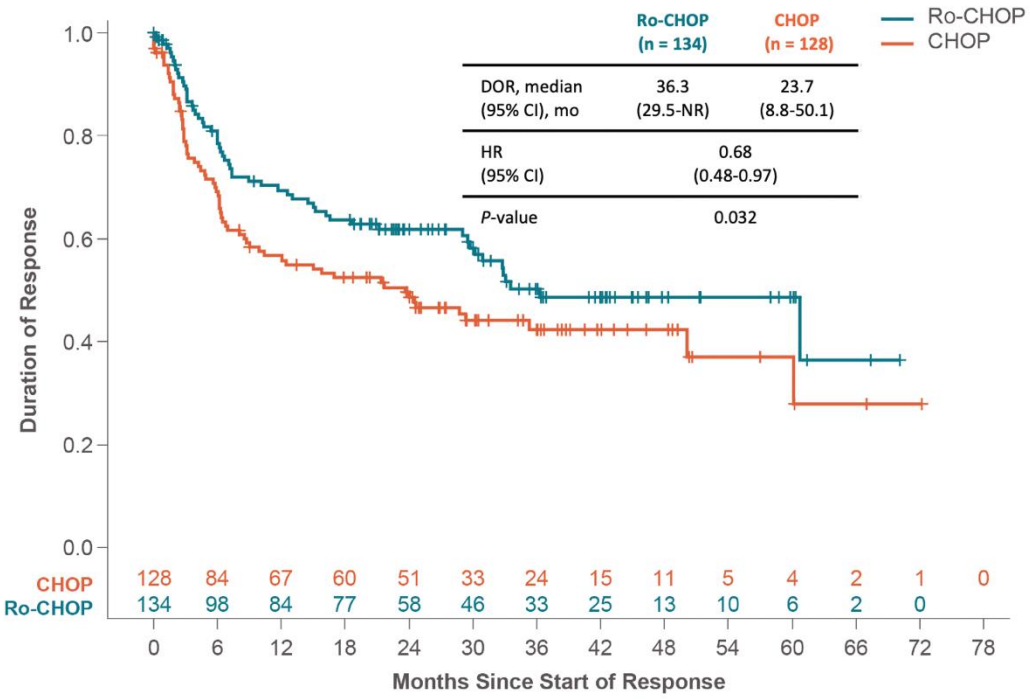
Frequencies are listed in descending order for the Ro-CHOP arm. Percentage is based on the total number of patients in each arm.

Supplemental figure 1. **Progression-free survival according to treatment arm (assessed by local investigator)**



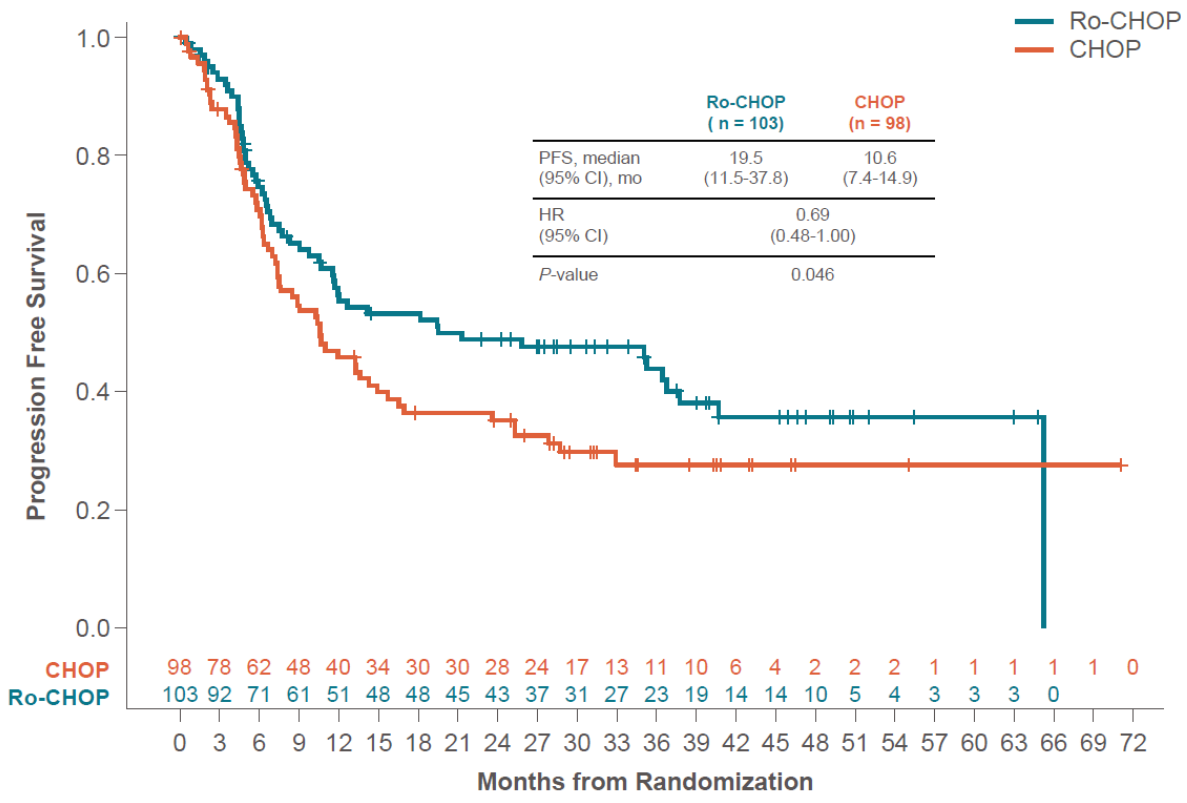
CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; HR, hazard ratio; PFS, progression-free survival; Ro-CHOP, romidepsin, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Supplemental figure 2. **DOR according to treatment arm**



CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; DOR, duration of response; HR, hazard ratio; Ro-CHOP, romidepsin, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Supplemental figure 3. **PFS according to treatment arm in the centrally confirmed AITL and related TFH PTCL histological subgroup**



AITL, angioimmunoblastic T-cell lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; HR, hazard ratio; PFS, progression-free survival; Ro-CHOP, romidepsin, cyclophosphamide, doxorubicin, vincristine, and prednisone; TFH PTCL, T follicular helper peripheral T-cell lymphoma.

DOSE MODIFICATION GUIDANCE

Hematological toxicities

Ro-CHOP arm, day 1:

- ANC ≥ 1 x 10^9/L and platelets ≥ 75 x 10^9/L within three days: no change
- ANC < 1 x 10^9/L or platelets < 75 x10^9/L: administration of chemotherapeutic drugs delayed for 1 week.
    - After 1-week delay:
        - If ANC ≥1 x 10^9/L and platelets ≥ 75 x 10^9/L, chemotherapy was administered without dose reduction.
        - If ANC < 1 x 10^9/L or platelets < 75 x 10^9/L, chemotherapy delayed 1 additional week.
    - After 2 weeks delay: bone marrow (by myelogram) verified.
        - If bone marrow is not involved:
            - If ANC ≥ 1 x 10^9/L and platelets ≥ 75 x 10^9/L, romidepsin dose reduced by 2 mg/m^2 for D1 and D8, and cyclophosphamide and doxorubicin reduced by 20% each.
            - If ANC < 1 x 10^9/L or platelets < 75 x 10^9/L, romidepsin stopped permanently and cyclophosphamide and doxorubicin reduced by 20% each.
        - If bone marrow was involved and involved at baseline: the patient could continue on the same dose or be considered as stable/progressive and terminate the study.
- If febrile neutropenia (ANC < 1 x 10^9/L associated with fever (single temperature >38.3°C/101°F or a sustained temperature of > 38°C/100.4°F for more than one hour) in previous cycle: romidepsin also reduced by 2 mg/m^2 for day 1 and day 8 and cyclophosphamide and doxorubicin reduced by 20% each.

Ro-CHOP arm, day 8:

- Platelets ≥ 50 x 10^9/L: no change
- Platelets < 50 x 10^9/L: Day 8 romidepsin dose skipped in that cycle.
    - If day 8 platelet count was < 50 x 10^9/L in two consecutive cycles, romidepsin reduced by 2 mg/m^2 for Day 1 and day 8 of each cycle.
    - If day 8 platelet count was < 25 x 10^9/L in two consecutive cycles, romidepsin reduced by 2 mg/m^2 for Day 1 of each cycle and romidepsin permanently discontinued at day 8.

CHOP arm, day 1:

- ANC ≥ 1 x 10^9/L and platelets ≥ 75 x 10^9/L within three days: no change
- ANC < 1 x 10^9/L or platelets < 75 x10^9/L: chemotherapeutic drug administration was delayed 1 week.
    - After 1-week delay:
        - If ANC ≥ 1 x 10^9/L and platelets ≥ 75 x 10^9/L, chemotherapy was administered without dose reduction.
        - If ANC < 1 x 10^9/L or platelets < 75 x 10^9/L, chemotherapy delayed 1 additional week.
    - After 2 weeks delay: verify bone marrow.
        - If bone marrow was not involved: cyclophosphamide and doxorubicin reduced by 20% each.
        - If bone marrow was involved and involved at baseline: the patient could continue on the same dose or be considered as stable/progressive and terminate the study.
- If febrile neutropenia (ANC < 1 x 10^9/L associated with fever (single temperature >38.3°C/101°F or a sustained temperature of > 38°C/100.4°F for more than one hour) in previous cycle: cyclophosphamide and doxorubicin reduced by 20% each.

Cardiac toxicities

Ro-CHOP arm: a cumulative dose of doxorubicin was not allowed to exceed 300 mg/m^2 in this study.

- Evidence of new or worsening > Grade 2 congestive heart failure: doxorubicin should be discontinued.
- QTc ≥ 501 msec, ventricular arrhythmia: VT (≥ 3 beats in a row), or new occurrence of > Grade 2 atrial fibrillation or flutter: next dose of romidepsin held and cardiologist consulted. At next dose:
    - If resolved, romidepsin restarted and reduced by 2mg/$m^{2.}$
    - If not resolved or if toxicity recurs, romidepsin and doxorubicin discontinued.
- Ventricular fibrillation (VF) including Torsade de Pointes: doxorubicin and romidepsin stopped permanently.
- If other cardiac toxicities (whatever type of toxicity and >grade 2)
    - If resolved at time of next cycle: restarted with same dose.
    - If not resolved at time of next cycle or if toxicity recurs: romidepsin reduced by 2mg/m^2 and doxorubicin by 20% for the next cycles.

CHOP arm: a cumulative dose of doxorubicin was not allowed to exceed 300 mg/m^2 in this study.

- Evidence of new or worsening > Grade 2 congestive heart failure: doxorubicin should be discontinued.
- QTc ≥ 501 msec, ventricular arrhythmia: VT (≥3 beats in a row), or new occurrence of > Grade 2 atrial fibrillation or flutter: next dose held. At next dose:
    - If resolved, no change.
    - If not resolved or if toxicity recurs, doxorubicin discontinued.
- Ventricular fibrillation (VF) including Torsade de Pointes: doxorubicin stopped permanently.
- If other cardiac toxicities (whatever type of toxicity and >grade 2)
    - If resolved at time of next cycle: restarted with same dose.
    - If not resolved at time of next cycle or if toxicity recurs: doxorubicin reduced by 20% for the next cycles.

Neurological toxicities

Both Ro-CHOP and CHOP arms:

- > Grade 1 neurological toxicity related to vincristine (sensory or motor neuropathy, constipation, visual or auditory changes): vincristine reduced to 1mg flat dose by cycle. If neurological toxicity increased despite dose reduction, vincristine was permanently stopped.

Other toxicities

Both Ro-CHOP and CHOP arms:

- Development of > Grade 3 hematuria: cyclophosphamide held until resolution. 50% reduction of cyclophosphamide considered for the next cycle. Re-escalation of cyclophosphamide at next cycle to the initial full dose was recommended if symptoms did not recur in that cycle.
- All other non-hematologic toxicities: Patients who developed clinically relevant non-hematologic adverse events CTC-Grade > 2 should have had their next cycle of treatment delayed in 1-week increments for up to a maximum of 14 days until the event resolved to severity grade <2. Patients who experienced a delay exceeding 14 days in the initiation of the next planned cycle of treatment were removed from study treatment.

Ro-CHOP arm:

- In case of gastrointestinal events CTC-Grade > 2:
    - with appropriate prophylactic anti-emetics, the romidepsin dose was permanently reduced by 2 mg/m².
    - without prophylactic anti-emetics, an appropriate prophylaxis was administered without romidepsin dose reduction.
- All other non-hematologic toxicities: Patients who developed clinically relevant non-hematologic adverse events CTC-Grade > 2 should have had their next cycle of romidepsin delayed in 1-week increments for up to a maximum of 14 days until the event resolved to severity grade ≤2. If Grade > 2 toxicity recured, the romidepsin dose was permanently reduced by 2 mg/m². Patients who experienced a delay exceeding 14 days in the initiation of the next planned cycle of treatment were removed from study treatment.

A maximum of 2 romidepsin dose reductions were allowed. If a patient has had dose reduction, dose re-escalation was not permitted at any time.

If lowest dose could not be tolerated, romidepsin was stopped but the patient continued on CHOP alone until the 6th cycle or progression whichever came first.

Dose modification for CHOP was modified according to the clinical practice for the investigator's institution, where applicable and in line with approved prescribing information.