Targeted agents plus CHOP compared with CHOP as the first-line treatment for newly diagnosed patients with peripheral T-cell lymphoma (GUIDANCE-03): an open-label, multicentre phase 2 clinical trial

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Summary

Background Peripheral T-cell lymphoma (PTCL) is a heterogeneous disease with dismal outcomes. We conducted an open-label, phase 2 nonrandomised, externally controlled study to evaluate the efficacy and safety of targeted agents plus CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) (CHOPX) for PTCL in the front-line setting.

Methods Eligible patients were ≥18 years of age and newly diagnosed PTCL. Patients in the CHOPX group received standard CHOP at Cycle 1. Specific targeted agents were added from Cycle 2, decitabine if *TP53*^{mut}, azacytidine if *TET2/KMT2D*^{mut}, tucidinostat if *CREBBP/EP300*^{mut}, and lenalidomide if without mutations above. Patients in the CHOP group received CHOP for 6 cycles. The primary endpoint was the complete response rate (CRR) at the end of treatment (EOT). Secondary endpoints included overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety. The study was registered with ClinicalTrials.gov, NCT04480099.

Findings Between July 29, 2020, and Sep 22, 2022, 96 patients were enrolled and included for efficacy and safety analysis with 48 in each group. The study met its primary endpoint. CRR at EOT in the CHOPX group was superior to the CHOP group (64.6% vs. 33.3%, OR 0.27, 95%CI 0.12–0.64; $p = 0.004$). At a median follow-up of 24.3 months (IQR 12.0–26.7), improved median PFS was observed in the CHOPX group (25.5 vs. 9.0 months; HR 0.57, 95%CI 0.34–0.98; $p = 0.041$). The median OS was similar between two groups (not reached vs. 30.9 months; HR 0.55, 95%CI 0.28–1.10; $p = 0.088$). The most common grade 3–4 hematological and non-hematological adverse events in the CHOPX group were neutropenia (31, 65%) and infection (5, 10%).

Interpretation Targeted agents combined with CHOP demonstrated effective and safe as first-line treatment in PTCL. Biomarker-driven therapeutic strategy is feasible and may lead to promising efficacy specifically toward molecular features in PTCL.

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Research in context

Evidence before this study

When we were preparing this study in May 2020, we searched PubMed for articles without data or language restrictions using the terms "peripheral T-cell lymphoma" and "treatment". Without best-of-care in peripheral T-cell lymphoma (PTCL), standard CHOP (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 [up to a maximum of 2 mg] on day 1, and oral prednisone 60 mg/m^2 [up to a maximum of 100 mg] on day 1–5) chemotherapy is still the most widely used first-line treatment, and the 5-year overall survival rate for PTCL patients excluding anaplastic large cell lymphoma (ALCL) is only 30%–40%. Recently, several targeted agents have been proven effective and safe in combination with CHOP, but none of them was used according to specific genetic alterations. Thus, we conducted this study to compare the efficacy and safety of targeted agents plus CHOP with standard CHOP in newly diagnosed patients with PTCL.

Added value of this study

Targeted agents combined with CHOP demonstrated effective and safe as first-line treatment in PTCL. It had a significantly higher complete response rate at the end of treatment and better progression-free survival than those of standard CHOP.

Implications of all the available evidence

To our knowledge, this is the first clinical trial to evaluate the efficacy and safety of biomarker-driven targeted agents plus CHOP in newly diagnosed patients with PTCL. The findings support that the biomarker-driven therapeutic strategy is feasible and may lead to promising efficacy specifically toward molecular features in PTCL.

Introduction

Peripheral T-cell lymphoma (PTCL) is a heterogeneous disease with aggressive behavior and dismal outcomes. Standard CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy is still the most widely used front-line treatment despite poor response. The complete response rate (CRR) ranges from 31% to 43% in studies using CHOP regimen.[1–4] With the exception of anaplastic large cell lymphoma (ALCL), the 5-year overall survival (OS) rate is approximately 30%–40% for most subtypes of PTCL patients,[5,6] remaining an unmet medical need in this disease. Brentuximab vedotin has proven its efficacy and safety for newly diagnosed CD30-positive PTCL,[5] inspiring the application of targeted agents combined with standard chemotherapy in the front-line setting.

Genomic profiling in PTCL may improve biological understanding and identify therapeutic targets.[7–9] *TP53* is a key tumor-suppressor gene and *TP53* mutation occurs in 15%–28% of PTCL.[10–12] DNA methyltransferase inhibitor decitabine was first found effective in treating AML and MDS with *TP53*^{mut}.[13] Recently, decitabine has demonstrated its anti-lymphoma activities when combined with R–CHOP in *TP53*^{mut} diffuse large B-cell lymphoma (DLBCL) through modulating endogenous retrovirus-dependent epigenetic mechanism.[14,15] *TET2* (Ten Eleven Translocation 2) is the most frequently mutated gene in PTCL, especially in up to ~80% of nodal T-follicular helper cell lymphomas (nTFHLs),[16] including angioimmunoblastic T-cell lymphoma (nTFHL-AI), follicular T-cell lymphoma (nTFHL-F), or peripheral T-cell lymphoma with TFH phenotype (nTFHL-NOS) according to the 5th WHO Classification.[17] It converts 5-methylcytosine to 5-hydroxymethylcytosine, which plays an essential role in transcriptional silencing by DNA modification.[18,19] DNA methyltransferase inhibitor azacytidine plus CHOP has achieved CRR of 75% and 88.2% in PTCL and TFHL, respectively.[20] *KMT2D* is another gene related to histone methylation and predicts adverse outcomes.[1] Demethylation agents can increase the interaction of *KMT2D* with transcription factor PU.1 in vitro, significantly inhibit tumor growth, and induce cell apoptosis through *KMT2D*/H3K4me axis in *KMT2D*^{mut} T-lymphoma.[21] Both azacytidine and decitabine are potentially targeted agents based on epigenetic theory. While decitabine is exclusively incorporated into DNA, azacytidine is mostly incorporated into RNA.[22] As the main epigenetic genes involving histone acetylation, *CREBBP/EP300* are mutated in around 12% of PTCL and associated with inferior progression-free survival time (PFS), which could be overcome by histone deacetylase inhibitor (HDACi) tucidinostat.[1,21] Lenalidomide is an immunomodulatory agent and shown to have activity in both untreated PTCL and heavily pretreated patients with nTFHL-AI.[23,24]

We conducted an open-label, multicenter, non-randomised, externally controlled, phase 2 trial, comparing the efficacy and safety of targeted agent selection strategy by genetic mutations plus CHOP (CHOPX) with CHOP in newly diagnosed patients with PTCL, aiming to explore the possibility of biomarker-driven therapeutic approach in this hard-to-treat population.

Methods

Study design and participants

This phase 2 trial was conducted at 7 centers (Supplementary Table S1) in China within a cooperative network of the Multicenter Hematology-Oncology Programs Evaluation System (M-HOPES) and included consecutive patients at the same time window without selection. Patients in the CHOPX group were included from the leading site, while patients in the control CHOP group were from the other 6 sites as contemporary external control.

Eligible patients were ≥18 years of age with newly diagnosed, histologically confirmed PTCL according to 2017 (the 4th) WHO classifications,[25] including peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma and other nodal lymphomas of TFH cell origin (nTFHL-AI, nTFHL-F, nTFHL-NOS according to the 5th WHO Classification), ALCL-aplastic lymphoma kinase (ALK)-negative (ALK-ALCL), monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), subcutaneous panniculitis-like T-cell lymphoma, and hepatosplenic T-cell lymphoma (HSTL) with enough tumor tissues for the next generation sequencing, have radiologically measurable disease, and an Eastern Cooperative Oncology Group (ECOG) performance status ≤2. Patients were excluded if subtypes like ALK + ALCL, NK/T-cell lymphoma, and others defined in the protocol, previous anti-lymphoma treatment, previous autologous hematopoietic stem-cell transplantation (HSCT), malignancies history except for curable disease as defined in the protocol, uncontrollable cardiocerebrovascular, coagulative, autoimmune, or serious infectious disease, primary central nervous system (CNS) lymphoma, left ventricular ejection fraction ≤50%, other uncontrollable medical condition that may interfere with their participation in the study, inadequate renal, hepatic or bone marrow functions, pregnant/lactation, or active infection, as defined in protocol in detail. The protocol flow chart was shown in Supplementary Fig. S1.

The study was approved by the Institutional Review Boards of all centers. Informed consent was obtained from all patients in accordance with the Declaration of Helsinki. The study was registered on ClinicalTrial.gov (NCT04480099) (https://clinicaltrials.gov/ct2/show/NCT04480099) on July 21, 2020. The trial was overseen by trial management and trial steering committees. The study protocol is provided in the Supplementary Files.

Targeted sequencing

Genomic DNA was extracted from frozen or paraffin tumor samples of all PTCL patients using a QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. PCR primers were designed by Primer 5.0 software. Multiplexed libraries of tagged amplicons from PTCL tumor samples were generated by Shanghai Yuanqi Bio-Pharmaceutical Multiplex-PCR Amplification System. Deep sequencing was performed using established Illumina protocols on HiSeq 4000 platform (Illumina).

Randomization and masking

Randomization and blinding did not apply since it was an open-label study with 48 patients in the CHOPX group from the leading site and other 48 patients in the CHOP group from 6 sites. Investigators and patients were not masked to treatment assignment due to different ways of administration by each treatment group.

Procedures

Patients in the CHOPX group received intravenous cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 (up to a maximum of 2 mg) on day 1, and oral prednisone 60 mg/m^2 (up to a maximum of 100 mg) on day 1–5 every 21 days at Cycle 1. A specific targeted agent was added from Cycle 2 as follows, intravenous decitabine 10 mg/m^2 on day −5 to −1 if with *TP53* mutation,[26] Subcutaneous azacytidine 100 mg on day −7 to −1 if with *TET2/KMT2D* mutation,[27] Oral tucidinostat 20 mg on day 1, 4, 8, 11 if with *CREBBP/EP300* mutation,[28] and oral lenalidomide 25 mg on day 1–10 if without mutations above.[29] When patients had more than two of the above mutations, we chose the most high-risk gene mutations like *TP53*^{mut} and *CREBBP/EP300*^{mut}, which have been reported to be associated with inferior survival in PTCL.[10,30] Patients in the control group received CHOP regimen. Each cycle was administered `every 21 days for a total of 6 cycles. Autologous HSCT (auto-HSCT) or allogeneic HSCT (allo-HSCT) was performed if complete response (CR) or partial response (PR) was achieved per the site's clinical practice. Salvage treatment was considered if a patient failed to respond to first-line treatment at interim evaluation.

Prophylaxis long-acting granulocyte-colony stimulating factor was mandatory from the second cycle in the CHOPX group. Second prophylaxis was also allowed in the CHOP group as supportive treatment if grade ≥3 neutropenia occurred after the first cycle of CHOP. Consolidation radiotherapy was allowed if patients had residual disease at the end of treatment (EOT). CNS prophylaxis was planned on patients with involvement of bone marrow, nasal/paranasal sinuses, orbit, breast, or testis in the protocol as a recommendation, using intrathecal methotrexate (MTX) 10 mg, cytarabine 50 mg, and dexamethasone 5 mg.

Assessments

PET-CT was evaluated at baseline, interim (after three cycles), and final evaluation (6–8 weeks after completion of therapy) according to 2014 Lugano criteria for non-Hodgkin lymphoma.[31] Central response assessment of

PET-CT images was performed by Shanghai Ruijin Hospital radiologists, who were not informed of the treatment group. During the follow-up period, CT scans with contrast of the neck, thorax, abdomen, and pelvis were repeated every three months during the first year, then every six months in the next two years, and yearly thereafter for up to 5 years. The severity of adverse events (AEs) was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Baseline clinical laboratory tests and examinations included complete blood cell count (CBC), serum lactate dehydrogenase (LDH), virus testing (HBV-DNA, HIV, etc.), coagulation function including APTT, PT and fibrinogen, bone marrow examination including aspiration and trephine biopsy, electrocardiography, echocardiography, PET-CT scan. Vital signs were recorded at each visit. International Prognostic Index (IPI) and Prognostic Index for T-cell lymphoma (PIT) were also collected at baseline.

Outcomes

The primary endpoint in this study was CRR (calculated by the proportion of patients who achieve CR) at EOT, measured by PET-CT according to the 2014 Lugano classification. The secondary endpoints included overall response rate (ORR, calculated by the proportion of patients who achieve CR or PR) at EOT, PFS (defined as the duration time between the date of enrollment and the date of disease progression or death from any cause), OS (defined as the duration time between the date of enrollment and the date of death from any cause), and the toxicity, evaluated according to the National Cancer Institute Common Terminology Criteria of Adverse Events, version 4.0.

Sample size and statistical analysis

The objective of this study was to evaluate the efficacy and safety of the biomarker-driven strategy of targeted agents plus CHOP as CHOPX regimen in newly diagnosed patients with PTCL. For sample size, we estimated the CRR of 62% in the CHOPX group compared with the CRR of 32% in the control CHOP group referred from national NHL-003 study in China.[1] Forty-eight patients per group were required to show this difference with 5% significance (two-sided) and 85% power, with no plan for interim analysis. The sample size was calculated by PASS 11 (NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).

Propensity score matching would be used if patients' baseline characteristics between each group were observed unbalanced during analysis. The number of patients achieving CR at EOT was reported by the treatment group with odds ratio (OR) by the logistic regression model. We planned subgroup analysis to assess treatment response in the pre-defined subgroups with results displayed as ORs [95%CI] in a Forest plot. Kaplan–Meier methods were used and survival between groups was compared by a log-rank test. Additionally, a Cox proportional analysis in the intent-to-treatment (ITT) population combining both study groups was performed. ITT population was defined as subjects who accepted at least one dose of treatment. The data analysis was generated using SPSS Statistics version 26 and GraphPad Prism 9. The Transparent Reporting of Evaluations With Nonrandomized Designs (TREND) reporting guidelines was followed. The trial was overseen by trial management and trial steering committees.

Role of the funding source

The funding source did not have any role in study design, data collection, data analysis, interpretation of the results, or writing of the report. All authors had full access to all the data and accepted responsibility to submit for publication.

Results

Patient characteristics

Between July 29, 2020, and September 22, 2022, 96 patients were enrolled in this study. A total of 108 patients were assessed for eligibility. Ten patients met the exclusion criteria and 2 patients withdrew informed consent before treatment. Therefore, 48 patients in the CHOPX group and 48 patients in the CHOP group were included as the ITT population for efficacy and safety analysis. The baseline characteristics like age, sex, Ann Arbor Stage, ECOG, serum LDH, IPI and PIT, Epstein–Barr Virus load (EBV-DNA), and pathological subtypes were comparable between the two groups (Table 1). The histological subtypes were as follows: nTFHL-AI (61/96, 64%), PTCL-NOS (18/96, 19%), ALK-ALCL (7/96, 7%), MEITL (8/96, 8%) and HSTL (2/96, 2%).

Protocol adherence

Thirty patients discontinued treatment due to progressive disease (PD) (n = 15), stable disease (SD) (n = 14), and toxicity (n = 1). In the CHOX group, 12 patients discontinued treatment due to response failure (n = 11, including 5 with PD and 5 with SD based on interim PET-CT, and 1 with PR at interim PETCT and then experienced PD after 5 cycles of azacytidine plus CHOP), as well as toxicity (n = 1, due to pulmonary infection after 5 cycles of azacytidine plus CHOP). In the CHOP group, 18 patients discontinued treatment due to failure to respond (n = 18, including 1 with clinical progressive disease quickly after the first cycle, 8 with PD, and 9 with SD based on interim PET-CT). Sixty-six patients completed the 6 cycles of treatment and response evaluation at EOT (Fig. 1). In our study, only 5 patients received CNS prophylaxis, which was well tolerated.

Eighteen patients (18.8%) underwent HSCT, including 15 auto-HSCT and 3 allo-HSCT. In the

Characteristic	No. (%)		p value[a]
	CHOPX (N = 48)	CHOP (N = 48)	
Age, median (IQR), years	63 (14.8)	63 (13.0)	0.836
≤60 years	21 (43.8)	19 (39.6)	
>60 years	27 (56.2)	29 (60.4)	
Sex			1.000
Male	31 (64.6)	31 (64.6)	
Female	17 (35.4)	17 (35.4)	
Ann arbor stage			0.433
I–II	11 (22.9)	7 (14.6)	
III–IV	37 (77.1)	41 (85.4)	
ECOG performance status			0.386
0–1	43 (89.6)	39 (81.3)	
2	5 (10.4)	9 (18.7)	
Serum LDH			0.352
Normal	10 (20.8)	15 (31.3)	
Elevated LDH	38 (79.2)	33 (68.7)	
IPI score			0.054
0	2 (4.2)	0 (0.0)	
1	2 (4.2)	6 (12.5)	
2	17 (35.4)	11 (22.9)	
3	22 (45.8)	17 (35.4)	
4	4 (8.3)	12 (25.0)	
5	1 (2.1)	2 (4.2)	
PIT score			0.595
0	3 (6.3)	3 (6.3)	
1	11 (22.9)	14 (29.2)	
2	25 (52.1)	20 (41.7)	
3	8 (16.7)	11 (22.9)	
4	1 (2.1)	0 (0.0)	
EBV-DNA, n (%)			0.535
Undetectable	28 (58.3%)	25 (52.1%)	
Detectable	20 (41.7%)	23 (47.1%)	
Pathological subtypes, n (%)			
nTFHL-AI	32 (67%)	29 (60.4)	0.661
PTCL-NOS	8 (16.7)	10 (20.8)	
ALK-ALCL	3 (6.3)	4 (8.3)	
MEITL	5 (10.4)	3 (6.3)	
HSTL	/	2 (4.2)	

nTFHL-AI, T-follicular helper cell lymphoma, angioimmunoblastic-type; ALK-ALCL, anaplastic large-cell lymphoma, anaplastic lymphoma kinase-negative; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; EBV, Epstein–Barr virus; ECOG, Eastern Cooperative Oncology Group; HSTL, hepatosplenic T-cell lymphoma; IPI, International Prognostic Index; LDH, lactate dehydrogenase; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; PIT, Prognostic Index for PTCL-NOS; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified. [a]No statistically significant difference baseline characteristics (all $p > 0.05$).

Table 1: **Baseline characteristics.**

CHOPX group, 9 patients underwent HSCT, including 7 auto-HSCT and 2 allo-HSCT. Among 7 patients who underwent auto-HSCT, 6 patients received auto-HSCT as consolidative treatment after CR. One patient with auto-HSCT and 2 with allo-HSCT received transplantation after salvage therapy. In the CHOP group, 9 patients underwent HSCT, including 8 auto-HSCT and 1 allo-HSCT. Among 8 patients who underwent auto-HSCT, 5 patients received auto-HSCT as consolidative treatment after CR. Three patients with auto-HSCT and 1 with allo-HSCT received transplantation after salvage therapy. Among the 37 patients that achieved CRR at EOT and did not undergo HSCT, the reasons were: age ≥65 years (21/37, 57%), patient's decision (12/37, 33%), early relapse (2/37, 5%) and stem-cell mobilization failure (2/35, 5%).

Response to treatment

Treatment response is summarized in Table 2. CRR at EOT in the CHOPX group (31/48, 64.6%; 95%CI,

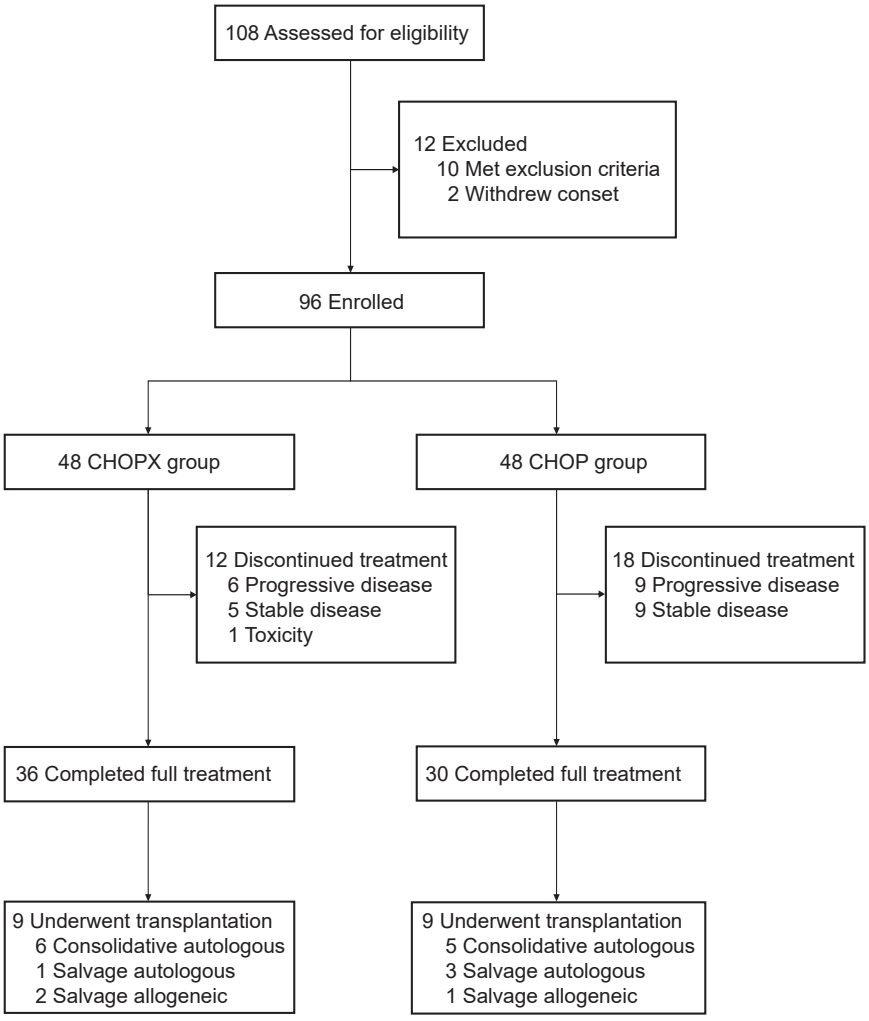

***Fig. 1:* GUIDANCE-03 trial profile.** CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone.

	No. (%)			
	CHOPX (N = 48)	CHOP (N = 48)	*p* value	OR (95% CI)
Interim evaluation				
Complete response	33 (68.8)	16 (33.3)	0.001	0.23 (0.10–0.54)
Partial response	5 (10.4)	14 (29.2)	0.039	3.54 (1.17–10.81)
Stable disease	5 (10.4)	9 (18.8)	0.386	1.99 (0.61–6.43)
Progressive disease	5 (10.4)	9 (18.8)	0.386	1.99 (0.61–6.43)
Overall response	38 (79.2)	30 (62.5)	0.115	0.44 (0.18–1.09)
End of treatment evaluation				
Complete response[a]	31 (64.6)	16 (33.3)	0.004	0.27 (0.12–0.64)
Partial response	1 (2.1)	9 (18.8)	0.015	10.85 (1.32–89.39)
Stable disease	5 (10.4)	9 (18.6)	0.386	1.99 (0.61–6.43)
Progressive disease	11 (22.9)	14 (29.2)	0.642	1.39 (0.55–3.46)
Overall response	32 (66.7)	25 (52.1)	0.212	0.54 (0.24–1.24)

[a]Primary endpoint: $p = 0.004$. OR 0.27 (95% CI 0.12–0.64).

***Table 2:* Treatment response.**

51.5%–78.1%) was superior to the CHOP group (16/48, 33.3%; 95%CI, 20.0%–46.7%; OR 0.27, 95%CI 0.12–0.64; p = 0.004), which met the study primary endpoint. The potential confounding variables like age, sex, Ann Arbor Stage, ECOG, and serum LDH were included in the multiple logistic regression and the adjusted p-value of CRR at EOT between was 0.009 (OR 0.30, 95% CI 0.12–0.74). ORR was 66.7% (32/48) in the CHOPX group and 52.1% (25/48) in the CHOP group, respectively. As for interim evaluation, CRR and ORR in the CHOPX group were 68.8% and 79.2%, compared with 33.3% and 62.5% in the CHOP group. Sixty-eight (70.8%) patients achieved response at interim evaluation in total. Among 49 patients with interim CR, 44 (89.8%) patients remained CR, 1 (2.0%) patient had PR and 4 (8.2%) had progressive disease at EOT. Of the 19 patients with interim PR, 3 (15.8%) patients achieved CR, 9 (47.4%) patients remained PR, and 7 (36.8%) had progressive disease at EOT. The median PFS in the interim CR group was not reached compared with 9.0 months (95% CI 5.8–12.2) in the interim PR and SD group. The median OS in the interim CR group was not reached compared with 31.4 months (95% CI 8.5–54.3) in the interim PR and SD group.

Prespecified subgroup analysis of CRR showed better CRR of CHOPX group in patients with age ≤60 years (OR 0.22, 95%CI 0.06–0.85; p = 0.031), age > 60 years (OR 0.31, 95%CI 0.10–0.92; p = 0.037), male (OR 0.19, 95%CI 0.06–0.57; p = 0.001), Ann Arbor stage III-IV (OR 0.25, 95%CI 0.10–0.65; p = 0.006), ECOG = 2 (OR NA, 95%CI NA–NA; p = 0.005), elevated serum LDH (OR 0.26, 95%CI 0.10–0.71; p = 0.009), nTFHL-AI subtype (OR 0.15, 95%CI 0.05–0.46; p = 0.001), IPI 2–5 (OR 0.21, 95%CI 0.08–0.52; p = 0.001) and PIT 2–4 (OR 0.22, 95%CI 0.08–0.64; p = 0.006) (Fig. 2). There was no interaction effect between each factor.

In the CHOPX group, CRR was 100.0% (4/4) with decitabine, 68.7% (22/32) with azacytidine, 50.0% (2/4) with tucidinostat, and 37.5% (3/8) with lenalidomide, respectively. In terms of pathological subgroups, higher CRR of the CHOPX group was observed in nTFHL-AI patients (75.0% vs. 31.0%; OR 0.15, 95%CI 0.05–0.46; p = 0.001). Similar CRR was observed in other pathological groups (Fig. 3A).

Targeted agents with pathological subtypes

In the CHOPX group, 32 patients with nTFHL-AI received X agents including azacytidine (n = 25, 78.1%), tucidinostat (n = 3, 9.4%), lenalidomide (n = 3, 9.4%), and decitabine (n = 1, 3.1%); 8 patients with PTCL-NOS received X agents including azacytidine (n = 4, 50.0%), lenalidomide (n = 3, 37.5%), and decitabine (n = 1, 12.5%); 3 patients with ALK-ALCL received X agents including azacytidine (n = 2, 66.7%) and decitabine (n = 1, 33.3%); 5 patients with MEITL received X agents including azacytidine (n = 1, 20.0%), tucidinostat (n = 1, 20.0%), lenalidomide (n = 2, 40.0%), and decitabine (n = 1, 20.0%). Due to the high incidence of *TET2* mutation in nTFHL-AI, azacytidine was mostly administrated in patients with nTFHL-AI (p = 0.038).

Mutation status

The biological function of selected mutated genes was identified through RNA sequencing data available from 186 patients in our database (viewed in NODE http://www.biosino.org/node by pasting the accession OEP003154 into the text search box). A significant difference in relevant gene expression signature calculated with ssGSEA method[32] between the mutant and the wild type was observed in 1) $TP53^{mut}$ with upregulated methyltransferase activity, 2) $TET2^{mut}$ with upregulated DNA Methylation-Dependent Heterochromatin Formation, TCR Signaling, Cytosine Methyltransferase Activity, and Histone H3K4 Trimethylation, as well as $KMT2D^{mut}$ with the same gene set features, 3) $CREBBP^{mut}$ and $EP300^{mut}$ with up-regulated Histone Deacetylase Regulator Activity and Histone H3K14 Acetylation (Supplementary Table S2). As revealed by gene set enrichment analysis (GSEA), the pathway related to the response to the decitabine pathway was significantly upregulated in $TP53^{mut}$ subtype (p = 0.022, Supplementary Fig. S2A), indicating the potential response to decitabine. DNA Methylation-Dependent Heterochromatin Formation pathway was significantly up-regulated in $TET2/KMT2D^{mut}$ subtype (p = 0.049, Supplementary Fig. S2B), indicating the potential response to azacytidine. Histone H3 acetyltransferase activity pathway was significantly down-regulated in $CREBBP/EP300^{mut}$ subtype (p = 0.026, Supplementary Fig. S2C), indicating the potential response to tucidinostat. In addition, increased resting NK cells (p = 0.006) and decreased activated NK cells (p = 0.035) in the immune microenvironment cell infiltration were found in patients without the above mutations (Supplementary Fig. S2D), indicating the potential response to lenalidomide.[33]

Assessed by targeted DNA sequencing, gene mutations were identified in 93 of 96 (96.9%) patients, including DNA methylation (e.g., *TET2, DNMT3A,* and *IDH2*), TCR signaling (e.g., *RHOA, CARD11,* and *FYN*), PI3K-AKT signaling (e.g., *VAV1, PI3KR1,* and *ITPR3*), histone modification (e.g., *KMT2C, KMT2D, CREBBP,* and *EP300*), tumor suppressor (e.g., *TP53, ATM,* and *MGA*), JAK-STAT signaling (e.g., *SOCS1, JAK3,* and *STAT3*), immune surveillance (e.g., *HLA-A* and *HLA-B*), chromatin remodeler (e.g., *ARID1A, ARID1B,* and *ARID2*), as well as NOTCH signaling (e.g., *NOTCH1* and *NOTCH3*). The incidence of $TP53^{mut}$, $TET2/KMT2D^{mut}$, $CREBBP/EP300^{mut}$, and others were 14% (13/96), 70% (67/96), 8% (8/96), and 21% (20/96), respectively. There were 65 patients in 1 genetic group (6 with $TP53^{mut}$, 57 with $TET2/KMT2D^{mut}$, 2 with $CREBBP/EP300^{mut}$, and 20 without any mutations above), 10 patients in 2 genetic groups (5 with concurrent $TP53^{mut}$ and $TET2/KMT2D^{mut}$, 1 with

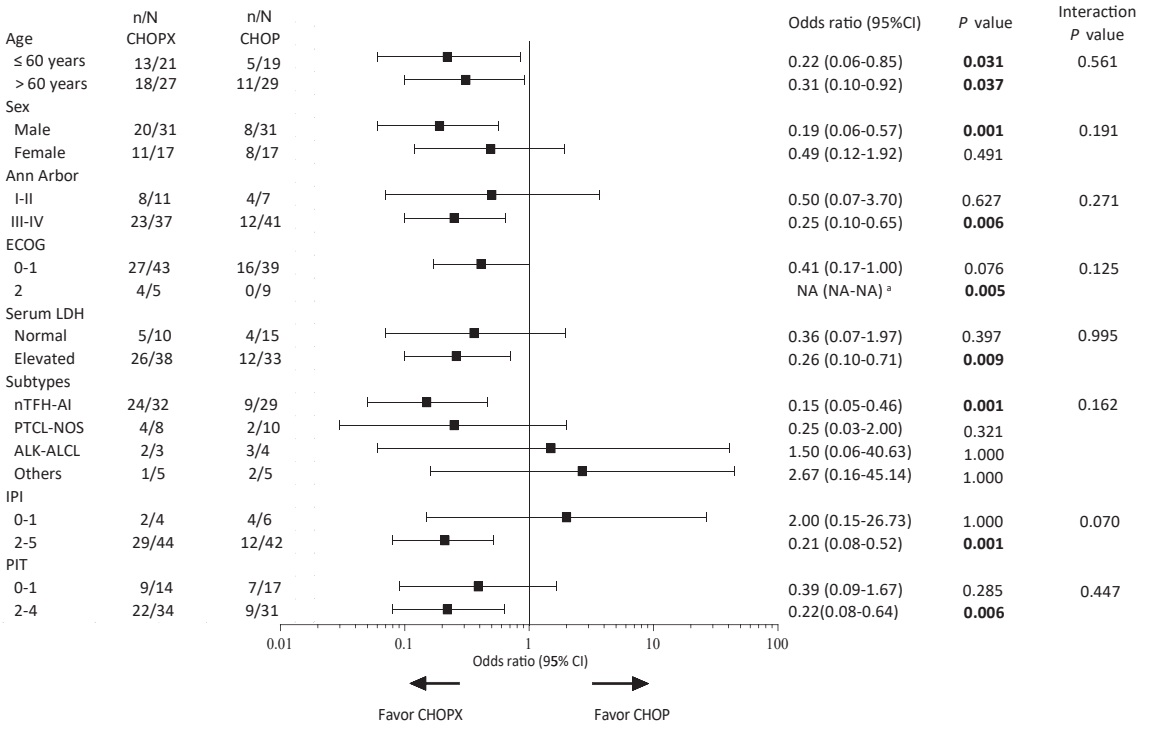

Fig. 2: **Forest plot of subgroup analysis for complete response at the end of treatment.** nTFHL-AI, nodal T-follicular helper cell lymphoma, angioimmunoblastic-type; ALK-ALCL, anaplastic large-cell lymphoma, anaplastic lymphoma kinase-negative; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NA, not available; PIT, Prognostic Index for PTCL-NOS; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified. [a]Odds ratio and confidence intervals were not available in patients with ECOG 2 from logistic regression.

concurrent *TP53*^{mut} and *CREBBP/EP300*^{mut}, 4 with concurrent *TET2/KMT2D* ^{mut} and *CREBBP/EP300* ^{mut}), 1 patient in 3 genetic groups (concurrent *TP53*^{mut}, *TET2/KMT2D* ^{mut} and *CREBBP/EP300* ^{mut}).

Of note, the CRR of the CHOPX group was higher in 35 patients with *TET2/KMT2D* mutation (68.6% vs. 28.1%, OR 0.18, 95%CI 0.06–0.51; $p = 0.001$), including 2 patients who received tucidinostat due to concurrent *CREBBP/EP300* mutation and 1 patient who received decitabine due to concurrent *TP53* mutation. All 4 patients with *TP53* mutation achieved CR (4/4, 100%). Similar CRR was observed between two groups in patients with *CREBBP/EP300* mutation and the other group (Fig. 3B).

Survival analysis

As of August 30, 2023, the median follow-up time was 24.3 months (IQR 12.0–26.7). The median PFS in the CHOPX group was 25.5 months (95%CI 8.5–42.5), as compared to 9.0 months (95%CI 3.5–14.5) in the CHOP group (HR 0.57, 95%CI 0.34–0.98; $p = 0.039$, Fig. 4A), corresponding to a 2-year PFS rate of 53.2% (95%CI 38.7–67.7) and 28.0% (95%CI 13.6–42.3), respectively. Meanwhile, the median OS was not reached in the CHOPX group, as compared to 30.9 months (95%CI 11.0–50.8) in the CHOP group (HR 0.55, 95%CI 0.28–1.10; $p = 0.088$, Fig. 4B), corresponding to a 2-year OS rate of 68.0% (95%CI 53.0–82.9) and 60.8% (95%CI 45.2–76.3), respectively.

Transplantation

Among 11 patients (6/48 [12.5%] in the CHOPX group and 5/48 [10.4%] in the CHOP group) who underwent consolidative auto-HSCT, 8 had long-term survival and 3 patients had progressive disease after auto-HSCT. Among 4 patients underwent auto-HSCT after salvage therapy, 2 died due to progressive disease. The 3 patients who underwent allo-HSCT had CR and are still alive, even though all of them had primary resistance to the front-line chemotherapy and had non-responsive disease before the HSCT. The median OS was not reached in patients with HSCT, and 30.9 months (95% CI 24.9–36.8) in patients with non-HSCT, respectively (Supplementary Fig. S3).

Toxicities

AEs of both hematological and non-hematological toxicity were listed in Table 3. Safety was assessed in

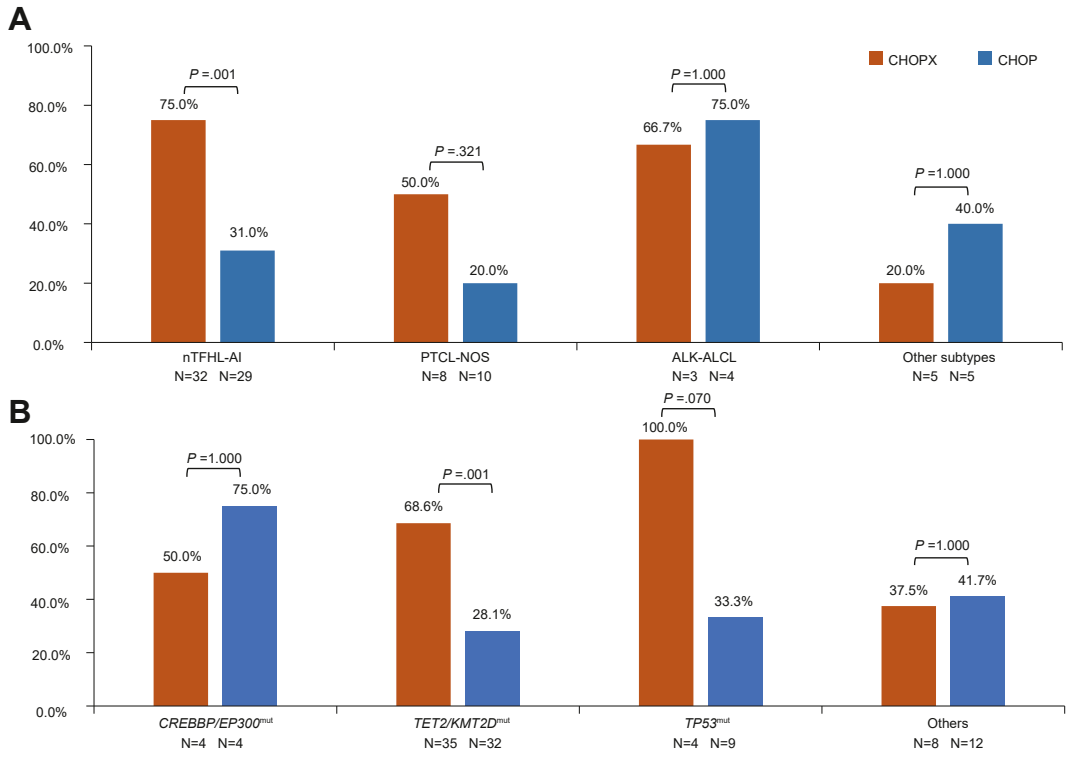

***Fig. 3:* Complete response rate of subgroups.** Complete response rate according to (A) genetic subgroups and (B) pathological subgroups.

96 patients who received at least one dose of study treatment. Neutropenia was the most common event in both groups (82% in the CHOPX group and 73% in the CHOP group). One patient who received CHOP combined with azacytidine was unable to finish the 6th cycle due to pulmonary infection. The most common grade 3–4 hematological AEs in the CHOPX group were neutropenia (31, 65%), febrile neutropenia (11, 23%),

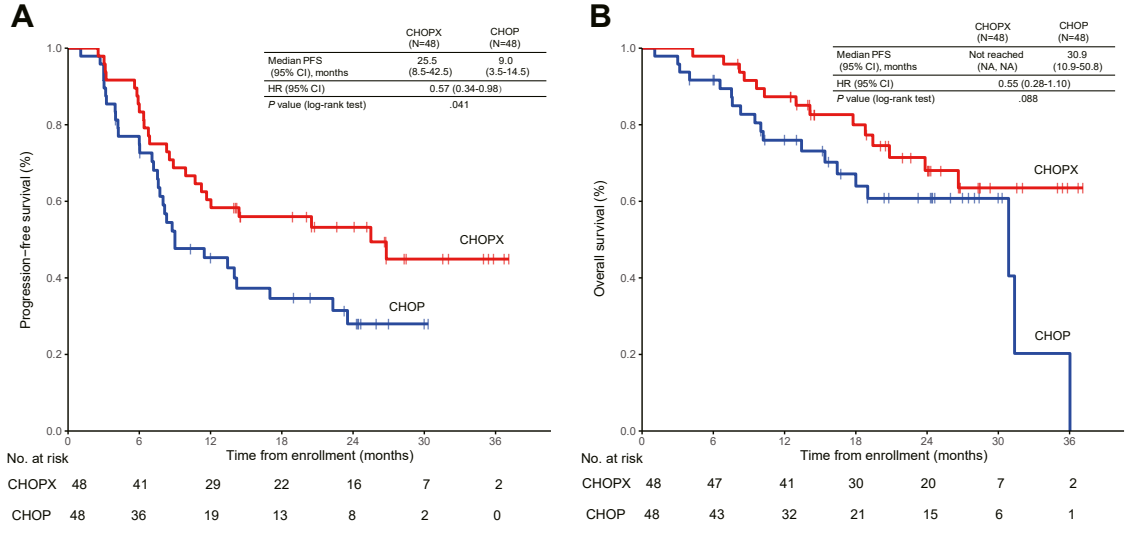

***Fig. 4:* Survival curves according to treatment groups.** Kaplan–Meier estimates of (A) progression-free survival and (B) overall survival according to treatment groups.

	CHOPX (N = 48)			CHOP (N = 48)			p value[a]	p value[b]
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4		
Hematological event								
Neutropenia	8 (17%)	13 (27%)	18 (38%)	10 (21%)	11 (23%)	14 (29%)	0.794	0.214
Thrombocytopenia	12 (25%)	5 (10%)	2 (4%)	11 (23%)	4 (8%)	0 (0%)	1.000	0.336
Anemia	25 (52%)	11 (23%)	0 (0%)	22 (46%)	8 (17%)	0 (0%)	0.683	0.442
Febrile neutropenia	0 (0%)	11 (23%)	0 (0%)	0 (0%)	9 (19%)	0 (0%)	NA	0.615
Non-hematological events								
Infection	14 (29%)	5 (10%)	0 (0%)	12 (25%)	2 (4%)	0 (0%)	0.819	0.239
Rash	5 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.056	NA
Nausea or vomiting	23 (48%)	2 (4%)	0 (0%)	14 (29%)	1 (2%)	0 (0%)	0.093	0.558
Increased aminotransferase	13 (27%)	2 (4%)	0 (0%)	10 (21%)	1 (2%)	0 (0%)	0.633	0.558
Mucositis	17 (35%)	0 (0%)	0 (0%)	13 (27%)	0 (0%)	0 (0%)	0.509	NA
Fatigue	18 (38%)	1 (2%)	0 (0%)	20 (42%)	1 (2%)	0 (0%)	0.835	1.000

Data are n (%). All patients who received at least one dose of the study drug were included in the safety analysis. NA = not available. [a]p value indicates the difference of Grade 1–2 AEs among CHOPX and CHOP groups. [b]p value indicates the difference of Grade 3–4 AEs among CHOPX and CHOP groups.

Table 3: **Incidence of adverse events.**

and anemia (11, 23%). For non-hematological AEs, CHOPX was associated with rash of all grades (5, 10%), which was mainly observed in patients who received lenalidomide, as well as the gastrointestinal reaction of all grades (25, 52%), which was mainly observed in patients received azacytidine and tucidinostat, but mostly grade 1–2 (23, 48%). The most common grade 3–4 non-hematological AEs in the CHOPX group were infection (5, 10%), gastrointestinal reaction (2, 4%) and increased aminotransferase (2, 4%). The most common grade 3–4 hematological AEs in the CHOP group were neutropenia (25, 52%), febrile neutropenia (9, 19%), and anemia (8, 17%). The most common grade 3–4 non-hematological AEs in the CHOP group were infection (2, 4%), gastrointestinal reaction (1, 2%), increased aminotransferase (1, 2%), and fatigue (1, 2%). Grade 3–4 hematological and non-hematological AEs were similar between the two groups. No patients in the CHOPX experienced long-lasting neutropenia for more than 14 days or targeted agent dose adjustment.

Despite increased AE rates, the two groups maintained similar dose intensity of chemotherapy (Supplementary Table S3). In the CHOPX group, dose interruption of tucidinostat was reported in 3 patients due to 1 for grade 3 thrombocytopenia, 2 for grade 4 neutropenia, and completed the planned treatment after recovery. Dose interruption was not reported in patients treated with decitabine, azacytidine, and lenalidomide. Dose reduction of lenalidomide, tucidinostat, and decitabine were not reported. The proportion of patients who received ≥90% overall dose intensity was similar between two groups.

Discussion

PTCL is highly aggressive, causing high treatment failure rates with limited therapeutic options, besides Brentuximab vedotin as the only targeted agent effective in CD30+ PTCL, especially ALCL. Brentuximab vedotin was not marketing available in China until August 2020, approved to treat relapsed or refractory ALCL as an indication. It was not allowed to be used in frontline settings based on the regulatory situation of national insurance. Thus, 7 patients with ALK-ALCL were also allowed to be enrolled in our study. To our knowledge, this is the first clinical trial to evaluate the efficacy and safety of targeted agents plus CHOP based on specific gene mutations in newly diagnosed PTCL. This study met its primary end point. CHOPX has superior CRR with good tolerability, as compared to CHOP. The selection of target agents is based on gene mutations and is not related to pathological subtypes in the CHOPX group in this study. In subgroup analysis, we reported a superior CRR of the CHOPX group in the nTFHL-AI subtype and *TET2/KMT2D*^{mut} group, with an overlapping mainly due to the high incidence of *TET2*^{mut} in nTFHL-AI.[16] Our study results are consistent with the single-arm phase 2 study, showing improved response in patients with TFHL treated with azacytidine plus CHOP.[20] However, a recent phase 3 ORACLE trial failed to meet its primary endpoint as PFS to compare oral azacytidine with the investigator's choice standard therapy (i.e., gemcitabine, bendamustine, or romidepsin) in patients with relapsed or refractory TFHL.[34] The negative results of this trial indicated the importance of targeted agent selection based on different gene mutations, or azacytidine in combination with other agents in this hard-to-treat disease. Meanwhile, decitabine or tucidinostat plus R–CHOP shows promising efficacy and safety profile in DLBCL, with the adverse prognosis of *TP53*^{mut} or *CREBBP/EP300*^{mut} conquered by epigenetic mechanisms.[15,35] In our study, all 4 patients with *TP53*^{mut} treated with decitabine and 2 of 4 patients with

CREBBP/EP300^{mut} received tucidinostat achieved CR. However, results from subgroup analysis should be interpreted with caution due to the small sample size without enough power, and needs to be confirmed in future studies.

The incidence of nTFHL-AI and *TET2/KMT2D* mutations in our study was 64% (61/96) and 70% (67/96), respectively. In another large prospective cohort of PTCL from Asian countries,[36] the most common subtype is nTFHL-AI (54%,120/221), excluding NK/T-cell lymphoma, ALCL and other rare subtypes, in consistent with our results. Other studies have also demonstrated that nTFHL-AI is geographically more common in Asian countries than in Western countries.[37,38] Although *TET2* is the most frequently mutated gene, it varies from 58% to 82% based on different studies.[16,39] Therefore, we believe that it is still necessary to test *TET2* in TFH lymphoma, considering that nTFHL is a highly heterogeneous disease.

Overall, the safety profile of the different targeted agents plus CHOP was as previously reported.[15,20,35,40] No treatment-related deaths were observed. The most common grade 3–4 hematological AE was neutropenia without increasing risk of severe infection. The most common grade 3–4 AE was infection but comparable to the CHOP group. No additional safety concerns were observed in the CHOPX group, in consistent with our previous studies using tucidinostat, decitabine, or lenalidomide with R–CHOP in DLBCL.[14,15,26,35] However, considering the limited patient number, more data is needed to further confirm the safety profile of additional targeted agents like decitabine, tucidinostat, or lenalidomide in PTCL.

Auto-HSCT is the best consolidation treatment in chemo-sensitive PTCL, especially for patients with advanced stage and high-risk factors.[41,42] Our results showed that even with a small sample size, the median OS in 11 patients with consolidative auto-HSCT was not reached, which is consistent with the current consensus that consolidative auto-HSCT is encouraged as standard treatment in PTCL once responses are achieved. Increased CRR in our study may translate to a higher rate of consolidative auto-HSCT. Patients with relapsed or refractory PTCL should also be offered allo-HSCT.[43] Interestingly, all 3 patients with primary refractory disease achieved disease control and long-term survival after salvage allo-HSCT. Meanwhile, with the beneficial impact of allo-HSCT on salvage therapy, further study needs to explore consolidative allo-HSCT for specific subtypes of PTCL.

Limitations to this study include the open-label, nonrandomised design and limited sample size, which could lead to potential confounders between the two treatment groups. Propensity score matching was planned once unbalanced baseline characteristics were observed during analysis, while specified key factors were similar between the two groups without statistical significance. Moreover, all other 6 sites were hospitals with equal clinical quality for care and practice as leading site. The percentage of nTFHL-AI was relatively higher in our study than in Western cohort, but comparable to other Asian studies.[36,37]

This is the first clinical trial to explore a biomarker-driven strategy on CHOP-based chemotherapy in PTCL. Although individualization of targeted agents was not powered in each X subgroup, we have already noticed higher efficacy in patients with *TET2/KMT2D* mutations. Based on our recent molecular analysis with a large cohort in PTCL, this disease may be categorized into distinct molecular subtypes with different but targetable oncogenic signaling pathways.[44] A multicenter, randomised, phase 2 trial (NCT05675813) according to genetic subtypes and related mechanism research is currently ongoing.

In summary, in this nonrandomised clinical trial, targeted agents plus CHOP showed better efficacy without additional safety concerns. The findings provide preliminary data to support that the biomarker-driven therapeutic strategy is feasible and may lead to promising efficacy specifically toward molecular features in PTCL.

Contributors

M–CC designed the study, collected and analyzed clinical data, and wrote the article. SC and YL designed the study, analyzed the data, and wrote the article. H-MJ, G-HC, TN, J-ZS, LH, XW, and LW recruited patients and collected study data. Y-HH gathered detailed clinical information and performed sequencing analysis. P-PX designed the study, wrote the protocol and the article, and was responsible for statistical review. W-LZ conceived, designed, directed, and supervised the study and wrote the manuscript. All authors contributed to the critical review and approved the final manuscript.

Data sharing statement

The study protocol is included as a data supplement available with the online version of this article. For proposals requesting individual participant data that underlie the results reported in this article (after de-identification), a steering committee involving all principal investigators will evaluate the request and make the decision before sending the database to academic partners. For data requests, please contact zhao.weili@yahoo.com. RNA sequencing data available are deposited in NODE (http://www.biosino.org/node) with accession number OEP003154.

Declaration of interests

All authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101160.

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