CPOP-R Versus CHOP-R as First-line Therapy for Diffuse Large B-cell Lymphoma (DLBCL): A Phase 2, Randomized, Open-label, Multicenter Study

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BACKGROUND

Pixantrone (PIX) is a novel aza-anthracenedione related to the anthracycline doxorubicin (DOX), a component of CHOP-R. The standard therapy for untreated DLBCL is CHOP-R.

- Unlike DOX, PIX does not bind iron, form free radicals, or generate alcohol metabolites, activities associated with the cardiotoxicity of DOX. [1,2]
- PIX has enhanced efficacy compared with DOX in preclinical lymphoma models.
- PIX has less cardiotoxicity in preclinical studies. [3]

Phase 1-2 study tested a regimen similar to CHOP, CPOP (cyclophosphamide, PIX, vincristine, and prednisone), in patients with relapsed aggressive B cell NHL (predominantly DLBCL) and prior CHOP±R therapy. [4]

- In phase 1, PIX doses of 80-240 mg/m^2 were tested; 150 mg/m^2 selected for phase 2.
- In phase 1 (n=35), CR/CRu rate was 57% and overall response rate (ORR) was 80%.
- In phase 2 (n=30), CR/CRu rate was 47%, ORR 73%, and median progression-free survival (PFS) 8.2 months.

CPOP response rates and durability were encouraging and indicated a comparative trial of CPOP-R and CHOP-R in high-risk patients with first-line DLBCL was appropriate.

STUDY OBJECTIVES

The primary objective of the study reported here was to show that CPOP-R is not inferior to CHOP-R with respect to the CR/CRu rate.

The secondary objective was to assess whether CPOP-R is less cardiotoxic than CHOP-R.

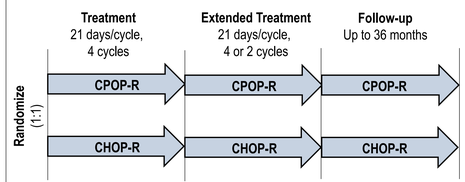
METHODS

Key Eligibility Criteria

- Untreated and histologically confirmed CD 20+ DLBCL non-Hodgkin lymphoma (NHL).
- Stage II, III, or IV disease
- ECOG performance status ≤2
- LVEF ≥50% determined by MUGA scan
- No prior chemotherapy or radiotherapy
- No history of indolent lymphoma
- No serious intercurrent infection
- Age >18 years

Study Design

- Randomized (1:1), multicenter, open label, comparative phase 2 study
- First-line treatment for patients with DLBCL
- Disease response of intent-to-treat (ITT) population assessed by an independent assessment panel (IAP)
- Extended treatment – up to 4 cycles if PR achieved 21 days after cycle 4 of treatment or up to 2 cycles if CR achieved.
- Because of resource constraints, enrollment ended before the planned enrollment was reached; the study was no longer powered to detect non-inferiority.
- The results presented here are based on the preliminary analysis of end-of-study data.



Cardiac Assessments

- Cardiac symptom update at end of treatment (EOT) and follow-up months 3, 6, 9, 12, 15, 18, 21, and 24.
- Cardiac function assessed by MUGA scan or ECHO at baseline (BL), after cycles 2, 4, and 6, at EOT, every 6 months for 1 year and at 24 months and 36 months after EOT.
- Serum troponin T was measured at BL, end of cycle 6, EOT, and 6 months after EOT.

RESULTS

Patient Characteristics

	CPOP-R (n=61)	CHOP-R (n=63)
Median age, years (min-max)	68 (38-88)	68 (31-87)
≥65 years, n (%)	38 (62.3)	37 (58.7)
Male gender, n (%)	29 (47.5)	34 (54.0)
Median DLBCL duration, months (min-max)	0.9 (0.1-3.5)	0.9 (0.1-2.4)
ECOG , n (%)		
0	18 (29.5)	26 (41.3)
1	34 (55.7)	26 (41.3)
2	9 (14.8)	11 (17.5)
IPI score, n (%)		
<3	33 (54.1)	30 (47.6)
≥3	28 (45.9)	33 (52.4)
No. of extranodal sites, median (min-max)	1 (0-4)	1 (0-5)
No. of patients with ≥3 comorbidities (%)	12 (19.7)	7 (11.1)
No. of patients with cardiac history [a]	8	2

[a] Includes coronary artery disease, congestive heart failure (CHF), or myocardial infarction

Patient Disposition

	CPOP-R	CHOP-R
Intent-to-treat Patients, n (%)	61 (100)	63 (100)
Treated patients	59 (96.7)	63 (100)
Completed Study Treatment, n (%)	45 (73.8)	45 (71.4)
Discontinued Treatment, n (%)	16 (26.2)	18 (28.6)
Progressive/relapsed disease	2 (3.3)	2 (3.2)
Adverse event	7 (11.5)	8 (12.7)
Withdraw consent	0	1 (1.6)
Other	7 (11.5)	7 (11.1)
All Deaths, n (%)	18 (29.5) [a]	9 (14.3)
Deaths within 30 days of last dose	3 (4.9)	0

[a] Includes one patient who died prior to therapy

- Most deaths occurred several months after the last dose and were attributed to complications of follow-up therapies, conditions unrelated to underlying NHL, or progressive disease (PD).
- PD was the proximate cause of death for 7 patients in each treatment group.
- The death of one patient on CPOP-R was related to study drug.
- Median overall survival follow-up time was 41.6 months for both treatment groups.

CR/CRu Rate

	CPOP-R (n=61)	CHOP-R (n=63)	Difference [a]	95% CI of the Difference
CR/CRu	46 (75.4%)	53 (84.1%)	8.7%	-5.4, 22.8

[a] Difference=CHOP-R percentage – CPOP-R percentage.

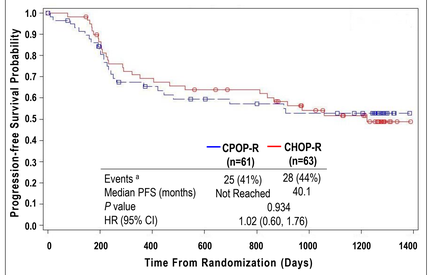
Because the study enrollment was stopped after 124 patients enrolled instead of the planned enrollment of 280 patients, the study was not sufficiently powered to determine whether, on the basis of the CR/CRu rate, the CPOP-R regimen was not inferior to the CHOP-R regimen.

Overall Response Rate

	CPOP-R (n=61)	CHOP-R (n=63)	Difference [a]	95% CI of the Difference
ORR				
(CR+CRu+PR)	50 (82.0%)	57 (90.5%)	8.5%	-3.6, 20.6

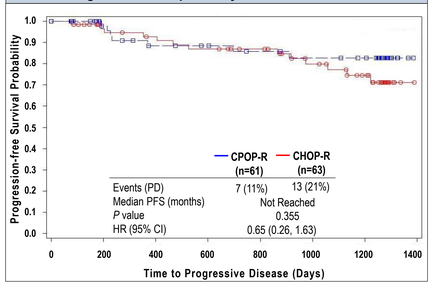
[a] Difference=CHOP-R percentage – CPOP-R percentage.

Progression-free Survival

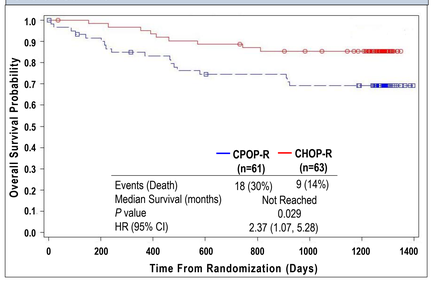


[a] Events include PD or death or subsequent therapy without PD

Time to Progression — Exploratory



Overall Survival



Three-year Survival Rate

	CPOP-R		CHOP-R	
	n	% (95% CI)	n	% (95% CI)
Overall	61	69 (57, 81)	63	85 (77, 94)
IPI Score				
≤2	33	84 (72, 97)	30	87 (75, 99)
3	18	58 (33, 82)	23	91 (79, 100)
≥3	28	51 (32, 70)	33	84 (72, 97)
Age (years)				
<65	23	91 (78, 100)	26	92 (82, 100)
≥65	38	57 (41, 73)	37	81 (68, 93)

Drug Exposure

	CPOP-R	CHOP-R
Safety Population	59	63
Median number of cycles (min-max)	8.0 (1.0-8.0)	6.0 (1.0-8.0)
No. patients received >6 cycles (%)	39 (66)	31 (49)
No. patients with dose reduction (%)	8 (13.6)	7 (11.1)

- Overall, hematologic AEs were frequent in both treatment groups occurring in 78.0% of patients on CPOP-R and in 81.0% of patients on CHOP-R.
- Neutropenia was the most frequently reported AE occurring in 64.4% of patients on CPOP-R and in 68.3% of patients on CHOP-R.

Grade 3/4 Adverse Events

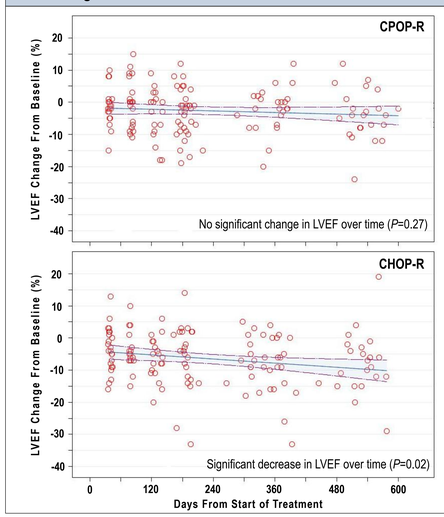
	CPOP-R (n=59)	CHOP-R (n=63)
All Grade 3/4 Adverse Event, n (%) [a]	50 (84.7)	54 (85.7)
Neutropenia	36 (61.0)	39 (61.9)
Leukopenia	17 (28.8)	15 (23.8)
Febrile neutropenia	9 (15.3)	10 (15.9)
Lymphopenia	10 (16.9)	6 (9.5)
Anemia	7 (11.9)	3 (4.8)
Fatigue	5 (8.5)	6 (9.5)

[a] Includes AEs with incidence ≥10%

Cardiac Toxicity Assessments

	CPOP-R (n=59)	CHOP-R (n=63)	*P* value
No. patients (%)			
Any cardiac toxicity event	5 (8.5)	23 (36.5)	<0.001
Congestive heart failure	0	4 (6.3)	0.120
LVEF declines ≥20% from BL	1/53 (0.9)	9/55 (8.3)	0.016
Increase over BL in troponin T levels	4/47 (8.5)	19/55 (34.5)	0.002

LVEF Change From Baseline



DISCUSSION

- To better understand the data generated from the comparison of CPOP-R with CHOP-R, in particular OS, we conducted additional analyses using historical data as a benchmark.
- The response and survival of patients from the CPOP-R vs CHOP-R study were compared with the long-term follow-up data from the Group d'Etude des Lymphomes de l' Adulte (GELA) study in which CHOP and CHOP-R were compared as first-line therapy in patients >60 years with DLBCL. [5]
- Demographics of the patients in the two studies were similar.
- Response rates and PFS were similar. OS for CHOP-R in the CPOP-R vs CHOP-R study was much higher than the OS for the same group on the GELA study.

Summary of Response and Survival in the CPOP-R vs CHOP-R Study and GELA Study

	CPOP-R vs CHOP-R		GELA [5]
	CPOP-R (n=61)	CHOP-R (n=63)	CHOP-R (n=202)
CR	72%	79%	75%
ORR	82%	87%	82%
2-year PFS	59%	41	57%
Median PFS	NR	NR	45.6 months
2-year OS	74%	88%	70%
Median OS	NR	NR	NR

NR=not reached

CONCLUSIONS

- CPOP-R is an active regimen in first-line therapy of patients with first-line DLBCL.
- Non-inferiority of CPOP-R to CHOP-R, with respect to the CR/CRu rate, could not be demonstrated because of the decrease in the planned number of enrolled patients.
- Differences in non-disease related comorbid factors rather than lack of efficacy appeared responsible for the disparity in deaths between study arms. The 2-year survival rate of 74% for patients on CPOP-R is consistent with historical experiences in high-risk patients. [5]
- CPOP-R was significantly less cardiotoxic than CHOP-R as evidenced by the significant reduction in the number of patients with any cardiac toxic event (8.5% vs 36.5%), severe LVEF declines (0.9% vs 8.3%), or CHF (0% vs 6.3%) or by the number of patients with increase over baseline in troponin T levels (8.5% vs 34.5%).
- Larger studies are required to establish the potential role of the CPOP-R regimen as first-line therapy for DLBCL.

References

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Conflicts of Interest

Herbrecht is a consultant and advisory board member for Cell Therapeutics, Inc. (CTI). Van der Jagt is a consultant and has received research funding from CTI. Cernohous and Singer are employees of CTI. All other authors have no relevant conflicts of interest to disclose.

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